MSDA 2014

9th Metabolic Syndrome, Type 2 Diabetes and Atherosclerosis Congress

Program & Abstract Book

Kyoto, Japan

Friday, September 12 – Sunday, September 14, 2014

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Contents

Welcome Address 2

Scientific and Organizing Committees 3

Acknowledgements 4

Program-at-a-Glance 5

General Information 6

Floor Map 9

Access Map 10

Detailed Program 11

Poster Abstract List 16

Abstracts 37

Author Index 89

Welcome address

Dear colleagues,

We are delighted to invite you to participate in the 9th edition of The MSDA (Metabolic Syndrome, Type 2 Diabetes and Atherosclerosis) Congress to be held from September 12 to 14, 2014 in Kyoto, Japan.

The MSDA congress is an international scientific event, which is organized every year and welcomes a wide number of participants from all over the world, involved in diabetes, atherosclerosis and cardiovascular diseases fields.This annual meeting covers every item from evolution to definition, from basic research to the latest therapeutic managements and prevention.

This meeting will provide an opportunity for health professionals to come and share the recent findings from research, and debate the main issues in practice and education to improve the quality of cardiometabolic care.

The venue is in the beautiful city of Kyoto, the acclaimed cultural center in Japan.

We are all looking forward to seeing you in Kyoto, Japan.

Jean-Charles Fruchart
President and Co-Chair

Takashi Kadowaki
Co-Chair
Japan Diabetes Society

Tamio Teramoto
Co-Chair
Japan Atherosclerasis Society

Masato Kasuga
Co-Chair
Japan Society for the Study of Obesity

Scientific and Organizing Committees

Scientific Committee

President and Co-chair

Jean-Charles Fruchart

Honorary Chairmen

Yuji Matsuzawa

Toru Kita

Co-Chairs

Takashi Kadowaki

Tamio Teramoto

Masato Kasuga

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Acknowledgements

Under the aegis of

Society for the Study of Obesity Japan

Japan Atherosclerosis Society

The Japan Diabetes Society

R3i Residual Risk Reduction initiative

International Atherosclerosis Society

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MSDA 2014 Program-at-a-Glance

7:00	Friday, September 12	Saturday, September 13	Sunday, September 14
8:00		7:30-8:20 **Morning Seminar 1** Sponsored By Boehringer Ingelheim, Lilly **Pathology and Treatment of Diabetes with Metabolic Syndrome** Chair: Naoko Tajima (Japan) Hiroaki Masuzaki (Japan)	7:30-8:20 **Morning Seminar 2** Sponsored By **New Horizons in Diabetes Therapy** Chair: Kazuyuki Tobe (Japan) Tadahiro Kitamura (Japan)
9:00		8:20-8:30 Break	8:20-8:30 Break
10:00		8:30-10:10 **Symposium 1** Sponsored By Astellas **Novel Molecular Target for the Treatment of Diabetes** Chairs: Masakazu Haneda (Japan) Jiro Nakamura (Japan) Yoshikatsu Kanai (Japan) Yasuo Terauchi (Japan) Kohei Kaku (Japan)	8:30-10:10 **Symposium 5** Sponsored By **Current and Future Approaches to Residual Lipid Risk Management** Chairs: Toru Kita (Japan) Jean Davignon (Canada) Jean-Charles Fruchart (France) Shun Ishibashi (Japan) Koutaro Yokote (Japan) M. John Chapman (France)
11:00		10:10-11:50 **Symposium 2** **Recent Progress in Understanding Pathogenesis of Type 2 Diabetes** Chairs: Philip J. Barter (Australia) Eiichi Araki (Japan) Ira Tabas (USA) Domenico Accili (USA) Mitsuo Fukushima (Japan) Liping Zhao (China)	10:10-11:50 **Symposium 6** **Macro and Microvascular Complications in Type 2 Diabetes: An Update** Chairs: Raul D. Santos (Brazil) Hidenori Arai (Japan) Alberto Zambon (Italy) Michel Hermans (Belgium) Henry Ginsberg (USA) May Faraj (Canada)
12:00		11:50-12:00 Break	11:50-12:00 Break
13:00		12:00-13:00 **Luncheon Seminar 1** Sponsored By Daiichi-Sankyo **Comprehensive Risk Management for Prevention of Atherosclerotic Disease** Chair: Shizuya Yamashita (Japan) Kohjiro Ueki (Japan)	12:00-13:00 **Luncheon Seminar 2** Sponsored By **Implication of GLP-1 Therapy in Type 2 Diabetes** Chair: Yuichiro Yamada (Japan) Yutaka Seino (Japan)
14:00		13:00-13:10 Break 13:10-14:10 **Poster Viewing**	13:00-13:10 Break 13:10-14:50 **Symposium 7** Sponsored By **New Insights into Immunological and Hormonal Aspects of Atherosclerosis** Chairs: Nobuya Inagaki (Japan) Tatsuhiko Kodama (Japan) Peter Libby (USA) Ken-ichi Hirata (Japan) Norio Harada (Japan) Hirotaka Watada (Japan)
15:00		14:10-15:50 **Symposium 3** Sponsored By **Abdominal Fat and Life Style Diseases** Chairs: Masato Kasuga (Japan) Yuji Matsuzawa (Japan) Hiroshi Itoh (Japan) Hiroshi Maegawa (Japan) Jean-Pierre Després (Canada) Ichiro Tatsuno (Japan)	
16:00		15:50-17:30 **Symposium 4** **Obesity Research Update in East and West** Chairs: Masayuki Yokode (Japan) Yasushi Saito (Japan) Tohru Funahashi (Japan) Jesús Millán Núñez-Cortés (Spain) Toshimasa Yamauchi (Japan) Jay D. Horton (USA)	14:50-16:30 **Symposium 8** **Cutting-Edge Topics of Inflammation and Lipid Metabolism in Atherosclerosis** Chairs: Yasufumi Sato (Japan) Hisao Ogawa (Japan) Ichiro Manabe (Japan) Christopher K. Glass (USA) Hitoshi Shimano (Japan) Jonathan C. Cohen (USA)
17:00			
18:00	17:00-17:20 **Opening Ceremony** 17:20-18:00 **Plenary Lecture 1** **Recent Progress of iPS Cell Research and Application** Chair: Takashi Kadowaki (Japan) Shinya Yamanaka (Japan)	17:30-17:40 Break 17:40-18:40 **Evening Seminar** Sponsored By **Role of Oral Hypoglycemic Agent and Future Prospects of Diabetes Management** Chair: Iichiro Shimomura (Japan) Masato Odawara (Japan)	
19:00	18:00-18:40 **Plenary Lecture 2** **PCSK9: From Discovery to Clinical Applications** Chair: Tamio Teramoto (Japan) Nabil G. Seidah (Canada)		
20:00	18:40- **Welcome Reception** **Venue: Lobby, 1F, AnnexHall** **Kyoto Int'l Conference Center**	18:50- **Banquet** **Venue: "Swan"** **1F, Kyoto Int'l Conference Center**	

General Information

Period

September 12-14, 2014

Venue

Kyoto International Conference Center

Address: Takaragaike, Sakyo-ku, Kyoto, Japan, 606-0001

Tel: +81-75-705-1205 Web: http://www.icckyoto.or.jp/

Language

The official language of the congress is English. Sessions and posters will be presented in English. Simultaneous interpretation will not be provided.

Registration & Information

The Registration & Information will be located on the lobby of Annex Hall, Kyoto International Conference Center.

Open Hours

Friday, September 12	16:00 ～ 18:40
Saturday, September 13	7:00 ～ 18:40
Sunday, September 14	7:00 ～ 15:00

Registration Fee

	Early	Regular	On-site
PHYSICIAN	JPY30,000	JPY30,000	JPY30,000
ABSTRACT AUTHOR	JPY20,000	JPY20,000	JPY20,000
STUDENTS	JPY10,000	JPY10,000	JPY10,000
ONE-DAY			JPY10,000

Notes: One-Day ticket is available on-site only for each day of the congress.

The method of payment for On-site Registration MUST BE PAID IN CASH ONLY.

Name Badge

All congress participants are kindly requested to wear their name badges at all times in order to attend the Reception, Scientific Sessions, Luncheon Seminars, Morning Seminars, Evening Seminar and Exhibition.

For Chairpersons

On your first day of arrival at the conference site, please go to the registration desk signed “Chairs/Invited Speakers”.
Chairpersons are requested to be in the session room, preferably 15 minutes in advance of the scheduled start time.

Information for Speakers

Speakers for oral sessions are requested to visit PC Operator in the session room to submit and check your presentation data.

If you bring your own laptop, both Windows and MAC, in order to avoid trouble arising from software incompatibility, speakers are requested to use their own laptop computer with an analog VGA (mini D-SUB 15 pin) connector for data projection.

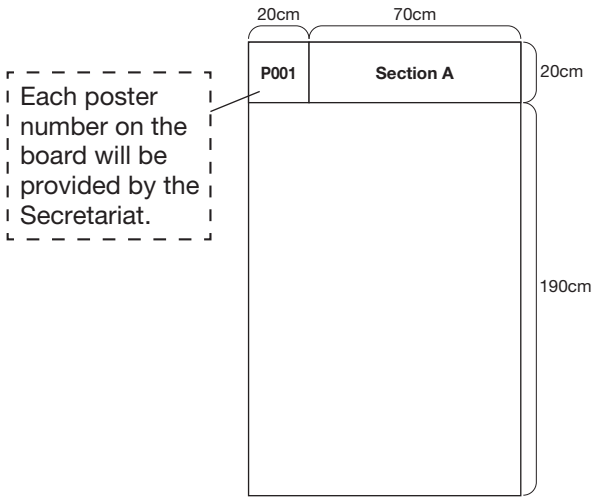
For Poster Presentation

Posters will be displayed from 17:00, Friday, September 12 to 16:00, Sunday, September 14.

	Poster Mounting Time	Poster Viewing Time	Poster Removing Time
Friday, September 12	17:00 ～ 19:00		
Saturday, September 13	7:30 ～ 13:00	13:10 ～ 14:10	
Sunday, September 14			16:00 ～ 17:00

*Please note that any posters left on the poster board after the poster removing time will be removed and discarded without notice.
*The congress organizer is not responsible for any loss or damage to each poster.

Poster board measures W90cm×H210cm (Vertical).
Presentation numbers will be posted in the upper left of the board.
Please prepare a list of your abstract title, name and affiliation of presenter sized W70cm×H20cm to be put next to the presentation number (in Section A).



Exhibition

The Exhibition will be held in Annex, located on the first floor. Any participants who registered for MSDA2014 are welcomed to visit the Exhibition Hall. They will have the opportunity to acquire the cutting-edge and innovative knowledge in the field of metabolic syndrome, type2 diabetes and atherosclerosis.

The Exhibition Will Be Open during the Following Hours

Friday, September 12	17:00 ～ 18:40
Saturday, September 13	9:00 ～ 18:00
Sunday, September 14	9:00 ～ 16:00

Information Board

Information of congress program, lost and found items, etc. will be displayed on the information boards, located in the Registration & Information area.

Congress Bag

Congress bags will be distributed at the Registration on the first floor.

Congress Regulations

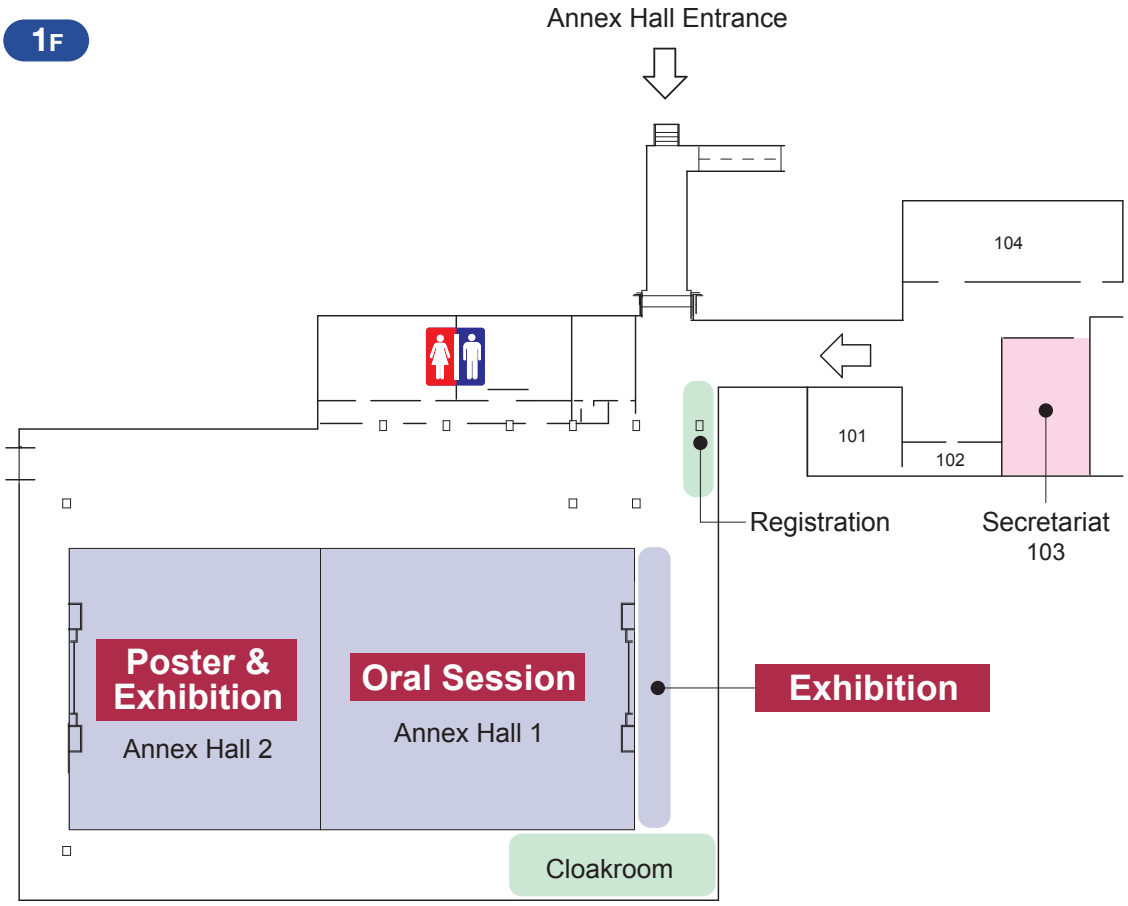
- Smoking is prohibited in the congress venue.
- Mobile phone must be turned off during oral sessions.
- No photography and/or recording is allowed in any sessions, including posters.

Credits in Japan

日本糖尿病学会専門医更新単位　３単位
日本動脈硬化学会認定専門医更新単位　５単位
日本肥満学会肥満症専門医単位　３単位

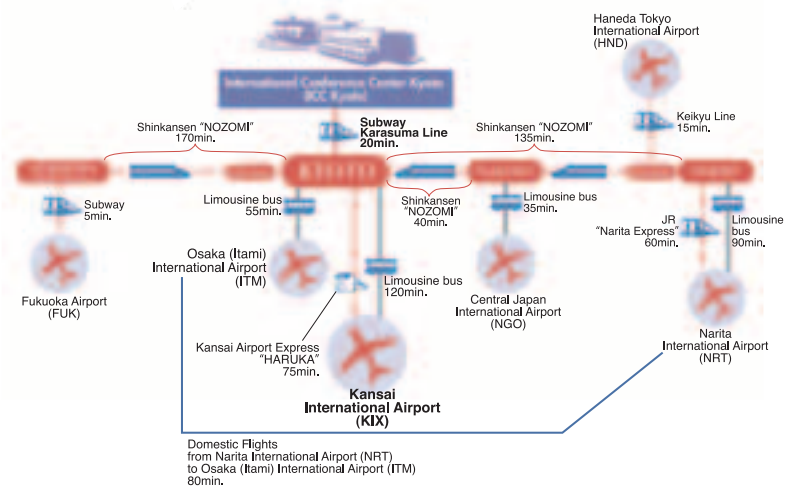
Floor Map

Annex Hall,
Kyoto International Conference Center



Access Map

How to get to ICC Kyoto



❑ About 75 minutes by Airport Shuttle Train "HARUKA" from Kansai International Airport to Kyoto Station.
❑ About 55 minutes by Limousine bus from Osaka (Itami) International Airport to Kyoto Station.
❑ 2 hours 15 minutes by Shinkansen (Bullet Train) "NOZOMI" from Tokyo Station to Kyoto Station.

※Please note that we shall not be responsible for any changes.

Friday, September 12, 2014

Annex Hall

17:20 pm
18:00 pm

Plenary Lecture 1

Chair: Takashi Kadowaki (The University of Tokyo, Tokyo, Japan)

- Recent Progress of iPS Cell Research and Application ..... Shinya Yamanaka
  Center for iPS Cell Research and Application, Kyoto University, Kyoto, Japan PL1

18:00 pm
18:40 pm

Plenary Lecture 2

Chair: Tamio Teramoto (Teikyo University, Tokyo, Japan)

- PCSK9: From Discovery to Clinical Applications ..... Nabil G. Seidah
  Clinical Research Institute of Montreal, Montreal, Canada PL2

Saturday, September 13, 2014

Annex Hall

07:30 am – 08:20 am

Morning Seminar 1

Boehringer Ingelheim / Lilly

Chair: Naoko Tajima (The Jikei University School of Medicine, Tokyo, Japan)

- Pathophysiology and Treatment of Diabetes with Metabolic Syndrome ..... Hiroaki Masuzaki
  University of the Ryukyus, Okinawa, Japan **MS1**

08:30 am – 10:10 am

Symposium 1

Novel Molecular Target for the Treatment of Diabetes

astellas

Chair: Masakazu Haneda (Asahikawa Medical University, Hokkaido, Japan)
Jiro Nakamura (Aichi Medical University, Aichi, Japan)

- Molecular Physiology of SGLT2 and Basic Pharmacology of SGLT2 Inhibitors ..... Yoshikatsu Kanai
  Osaka University, Osaka, Japan **SY1-1**
- Cancelled **SY1-2**
- Effect of SGLT2 Inhibitor on Nonalcoholic Fatty Liver Disease (NAFLD) and Adipose Tissue Volume ..... Yasuo Terauchi
  Yokohama City University, Kanagawa, Japan **SY1-3**
- New Directions in Treatment of Type 2 Diabetes in Japan~A Role of SGLT2 Inhibitors~ ..... Kohei Kaku
  Kawasaki Medical School, Okayama, Japan **SY1-4**

10:10 am – 11:50 am

Symposium 2

Recent Progress in Understanding Pathogenesis of Type 2 Diabetes

The Japan Diabetes Society

Chair: Philip J. Barter (University of New South Wales, Sydney, Australia)
Eiichi Araki (Kumamoto University, Kumamoto, Japan)

- Calcium Signaling and ER Stress in Obesity and Type 2 Diabetes ..... Ira Tabas
  Columbia University, New York, USA **SY2-1**
- Insulin Resistance, Hyperglycemia, and Atherosclerosis: Mechanisms and Interventions ..... Domenico Accili
  Columbia University, New York, USA **SY2-2**
- Insulin Secretory Defect and Insulin Resistance in the Development of Type 2 Diabetes ..... Mitsuo Fukushima
  Okayama Prefectural University, Okayama, Japan **SY2-3**
- Can We Follow Koch's Postulates for Hunting Down Human Obesity Bugs in Gut Microbiota?..... Liping Zhao
  Shanghai Jiao Tong University, Shanghai, China **SY2-4**

12:00 am – 13:00 pm

Luncheon Seminar 1

Comprehensive Risk Management for Prevention of Atherosclerotic Disease

Daiichi-Sankyo

Chair: Shizuya Yamashita (Osaka University, Osaka, Japan)

- Comprehensive Risk Management for Prevention of Caridiovascular Complications of Type 2 Diabetes ..... Kohjiro Ueki
  The University of Tokyo, Tokyo, Japan **LS1**

Saturday, September 13, 2014

Annex Hall

14:10 pm – 15:50 pm

Symposium 3

Abdominal Fat and Life Style Diseases

Chair: Masato Kasuga (National Center for Global Health and Medicine, Tokyo, Japan)
Yuji Matsuzawa (Sumitomo Hospital, Osaka, Japan)

- Possible Linkage of Visceral Fat Deposition and Hyperaldosteronism---Existence of Aldosterone Production-Stimulating Factor in the Serum of Idiopathic Hyperaldosteronism (IHA) Patients ..... Hiroshi Itoh
  Keio University, Tokyo, Japan **SY3-1**
- Lifestyle Disease and Abdominal Fat Distribution ..... Hiroshi Maegawa
  Shiga University of Medical Science, Shiga, Japan **SY3-2**
- Obesity as a CVD Risk Factor: Weight Loss Is Not the Optimal Target ..... Jean-Pierre Després
  Québec Heart and Lung Institute, Montreal, Canada **SY3-3**
- Abdominarl Fat and Dyslipidemia ..... Ichiro Tatsuno
  Toho University Sakura Medical Center, Chiba, Japan **SY3-4**

15:50 pm – 17:30 pm

Symposium 4

Obesity Research Update in East and West

Chair: Masayuki Yokode (Kyoto University, Kyoto, Japan)
Yasushi Saito (Chiba Life Science Research Support Center, Chiba, Japan)

- New Insights in Visceral Fat Syndrome and Adiponectin ..... Tohru Funahashi
  Osaka University, Osaka, Japan **SY4-1**
- Perspectives on Obesity, Anthropometry and Cardiovascular Risk ..... Jesús Millán Núñez-Cortés
  University of Madrid, Madrid, Spain **SY4-2**
- Development of a Small-Molecule AdipoR Agonist for Type 2 Diabetes and Short Life in Obesity ..... Toshimasa Yamauchi
  The University of Tokyo, Tokyo, Japan **SY4-3**
- Molecular Mediators of Nonalcoholic Fatty Liver Disease ..... Jay D. Horton
  UT Southwestern Medical Center at Dallas, Dallas, USA **SY4-4**

17:40 pm – 18:40 pm

Evening Seminar

Chair: Iichiro Shimomura (Osaka University, Osaka, Japan)

- Role of Oral Hypoglycemic Agent and Future Prospects of Diabetes Management ..... Masato Odawara
  Tokyo Medical University, Tokyo, Japan **ES**

Sunday, September 14, 2014

Annex Hall

07:30 am
08:20 am

Morning Seminar 2

New Horizons in Diabetes Therapy

Chair: Kazuyuki Tobe (University of Toyama, Toyama, Japan)

- Diabetes Therapy by Focusing on Plasma Glucagon and Body Weight ..... Tadahiro Kitamura
  Gunma University, Gunma, Japan **MS2**

08:30 am
10:10 am

Symposium 5

Current and Future Approaches to Residual Lipid Risk Management

Chair: Toru Kita (Kobe City Medical Center General Hospital, Hyogo, Japan)
Jean Davignon (Institut de Recherches Cliniques de Montreal, Montreal, Canada)

- SPPARM α : the Next Generation of Selective Drugs Targeting Peroxisome Proliferator-activated receptor α for Residual Vascular Risk Management ..... Jean-Charles Fruchart
  R3i Foundation / Pasteur Institute of Lille / University of Lille, Lille, France **SY5-1**
- Cholesterol Ester Hydrolysis in Macrophages: New Therapeutic Target for Residual Risk Reduction ..... Shun Ishibashi
  Jichi Medical University, Tochigi, Japan **SY5-2**
- Statin in Lipid Management of Diabetes: Effect on Dyslipidemia and Beyond ..... Koutaro Yokote
  Chiba University, Chiba, Japan **SY5-3**
- Statin Therapy in Prediabetes: New Insights from Lipidomics in the CAPITAIN Study ..... M. John Chapman
  INSERM, Paris, France **SY5-4**

10:10 am
11:50 am

Symposium 6

Macro and Microvascular Complications in Type 2 Diabetes: An Update

Chair: Raul D. Santos (University of Sao Paulo Medical School, Sao Paulo, Brazil)
Hidenori Arai (Kyoto University, Kyoto, Japan)

- Triglycerides and Dense LDL : Stars or Second Leads? ..... Alberto Zambon
  University of Padua, Padua, Italy **SY6-1**
- Residual Microvascular Risk : the Next Frontier in Diabetes ..... Michel P. Hermans
  Cliniques Universitaires St-Luc, Brusseles, Belgium **SY6-2**
- Regulation of ApoA-I Synthesis by Insulin Signaling ..... Henry N. Ginsberg
  Columbia University, New York, USA **SY6-3**
- HyperapoB and Insulin Resistance ..... May Faraj
  University of Montreal / Clinical Research Institute of Montreal, Montreal, Canada **SY6-4**

Sunday, September 14, 2014

Annex Hall

12:00 am – 13:00 pm

Luncheon Seminar 2

Chair: Yuichiro Yamada (Akita University, Akita, Japan)

- Implication of GLP-1 Therapy in Type 2 Diabetes ..... Yutaka Seino
  Kansai Electric Power Hospital, Osaka, Japan LS2

13:10 pm – 14:50 pm

Symposium 7

New Insights into Immunological and Hormonal Aspects of Atherosclerosis

Chair: Nobuya Inagaki (Kyoto University, Kyoto, Japan)
Tatsuhiko Kodama (The University of Tokyo, Tokyo, Japan)

- Inflammation: a Unifying Mechanism in Diabetes, Metabolic Syndrome, and Atherosclerosis ..... Peter Libby
  Brigham and Women's Hospital, Boston, USA SY7-1
- Immune System and Gut Microbiota Are Novel Therapeutic Targets for Atherosclerosis. ..... Ken-ichi Hirata
  Kobe University, Hyogo, Japan SY7-2
- The Role of GIP in High Fat Diet-induced Obesity ..... Norio Harada
  Kyoto University, Kyoto, Japan SY7-3
- The Role of Autophagic Failure in Beta Cell Dysfunction in Type2 Diabetes Mellitus ..... Hirotaka Watada
  Juntendo University, Tokyo, Japan SY7-4

14:50 pm – 16:30 pm

Symposium 8

Cutting-Edge Topics of Inflammation and Lipid Metabolism in Atherosclerois

Chair: Yasufumi Sato (Tohoku University, Miyagi, Japan)
Hisao Ogawa (Kumamoto University, Kumamoto, Japan)
(National Cerebral and Cardiovascular Center, Osaka, Japan)

- Lipotoxicity and Immune Regulation of Homeostasis and Inflammation in Adipose Tissue ..... Ichiro Manabe
  The University of Tokyo, Tokyo, Japan SY8-1
- A Genome-wide View of Macrophage Activation ..... Christopher K. Glass
  University of California, San Diego, USA SY8-2
- New Aspect of Organ Lipids in Metabolic Diseases and Atherosclerosis from Quantity to Quality: Lessons from Elovl6 ..... Hitoshi Shimano
  University of Tsukuba, Ibaraki, Japan SY8-3
- Role of ANGPTL3 and 8 in Lipid Metabolism ..... Jonathan C. Cohen
  The University of Texas Southwestern Medical Center, Dallas, USA SY8-4

List of Poster Abstracts

Poster 1 : Atherosclerosis

Chair : Makoto Kinoshita (Internal Medicine, Teikyo University School of Medicine)

P001 Serum HDL-C decreases in microRNA-33b knock-in mice for an intron of sterol regulatory element-binding factor 1 (Srebf1).

Takahiro Horie, Tomohiro Nishino, Osamu Baba, Yasuhide Kuwabara, Tetsushi Nakao, Masataka Nishiga, Shunsuke Usami, Masayasu Izuhara, Takeshi Kimura, Koh Ono

Department of Cardiovascular Medicine, Kyoto University, Japan

P002 Plasma macrophage inhibitory cytokine-1 (MIC-1) is associated with atherosclerosis in subjects with normal glucose tolerance

Osamu Ebisui[1], Keizo Ohno[1], Hitto Tokunaga[1], Teruhisa Ueda[1], Kazuyuki Akesaka[2], Mizune Tamaki[2]

1 Department of Diabetes and Endocrinology, Ehime Prefectural Central Hospital, Japan
2 Department of General Medicine, Ehime Prefectural Central Hospital

P003 PUFA and MUFA suppress MCP-1 secretion in LPS-stimulated THP-1 macrophages

Wao Tsutsui, Hideo Ohira, Ren Miyagi, Rie Mamoto, Masako Nishida, Miki Ito, Sayaka Yamaguchi, Yoshio Fujioka

Division of Clinical Nutrition, Faculty of Nutrition, Kobe Gakuin University, Japan

P004 SREBP-1c regulates hypertriglyceridemia in apoA5 deficiency

Hiroaki Okazaki[1], Mikio Takanashi[1], Hiroki Yoshida[1], Pengfei Xu[1], Akari Noda[1], Asahi Uni[1], Sachiko Okazaki[1], Satoru Takase[1], Yoko Iizuka[1], Guosheng Liang[2], Takashi Kadowaki[1]

1 Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, Japan
2 University of Texas Southwestern Medical Center at Dallas

P005 MicroRNA-33 deficiency reduces atherosclerotic plaque progression in apoE knockout mice

Osamu Baba[1], Takahiro Horie[1], Koh Ono[1], Yasuhide Kuwabara[1], Naoya Sowa[1], Koji Hasegawa[2], Noriaki Kume[1], Masayuki Yokode[1], Toru Kita[3], Takeshi Kimura[1]

1 Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Japan
2 Kyoto Medical Center
3 Kobe City General Holspital

P006 CTRP9, a paralog of adiponectin, reduces atherosclerosis in apolipoprotein E-deficient mice

Yoshihisa Okamoto[1,2], Harumi Katsumata[2], Masaaki Okamoto[2], Koji Ohashi[3], So Ishii[2], Makoto Fukushima[2], Shiro Minami[2], Noriyuki Ouchi[3]

1 Endocrinology and Diabetes, Yokohama City University Medical Center, Japan
2 Nippon Medical School
3 Nagoya University Graduate School of Medicine

List of Poster Abstracts

Poster 2 : Atherosclerosis

Chair : Hideaki Bujo (Department of Clinical-Laboratory and Experimental-Research Medicine, Toho University Sakura Medical Center)

P007 Sleep apnea syndrome as an emerging risk factor for type 2 diabetes and atherosclerosis: evidence and underlying mechanism

Yoji Kyotani, Hiroyo Ota, Asako Hironaka, Akiyo Yamauchi, Sumiyo Tsuchida, Jing Zhao, Kosuke Nagayama, Kentaro Ozawa, Shin Takasawa, Hiroshi Kimura, Masanori Yoshizumi

Pharamacology, Nara Medical University, Japan

P008 Activation of AdipoR1 in hematopoietic cells leading to anti-inflammation and R2 in endothelial cells leading to reduced oxidative stress prevent cardiovascular diseases

Masato Iwabu, Toshimasa Yamauchi, Miki Iwabu, Tetsuya Kubota, Naoto Kubota, Takashi Kadowaki

Department of Diabetes and Metabolic Diseases, The University of Tokyo, Japan

P009 Ttc39b deficiency increases HDL production and impairs non-HDL absorption in intestinal enterocytes

Masahiro Koseki[1,2], Joanne Hsieh[2], Emi Yakushiji[2], Carrie Welch[2], Jahangir Iqbal[3], Mahmood Hussain[3], Shunichi Takiguchi[4], Daniel J Rader[4], Yasushi Sakata[1], Alan R Tall[2], Shizuya Yamashita[1]

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P010 Inhibition of local macrophage growth ameliorates focal inflammation in the plaque and suppresses atherosclerosis in ApoE-deficient mice.

Takafumi Senokuchi[1,2], Sarie Yamada[1], Emi Negita[3], Takeshi Matsumura[1], Takeshi Nishikawa[1,2], Eiichi Araki[1]

1 Department of Metabolic Medicine, Faculty of Life Sciences, Kumamoto University, Japan
2 Department of Molecular Diabetology, Faculty of Life Sciences, Kumamoto University
3 School of Medicine, Kumamoto University

P011 Relationship between RDW (red blood cell distribution width) and vascular screening tests : a cross-sectional study.

Teruaki Sugiyama, Yusuke Kabeya, Kiyoe Kato, Masaya Osawa, Yoshihiro Atsumi, Mari Okisugi, Masuomi Tomita, Takeshi Katsuki, Yoichi Oikawa, Akira Shimada

Diabetes and Endcrinology, Tokyo Saiseikai Central Hospital, Japan

P012 Clinical applications of serum apolipoprotein B-48 measurement to evaluate the accumulation of chylomicron remnants and residual risk status in atherosclerotic cardiovascular diseases

Daisaku Masuda[1], Manabu Okubo[2], Takuya Kobayashi[1], Kazuhiro Nakatani[1], Masahiro Koseki[1], Tohru Ohama[1,3], Hiroyuki Hanada[2], Makoto Nishida[1,3], Yasushi Sakata[1], Shizuya Yamashita[1,4]

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List of Poster Abstracts

Poster 3 : Atherosclerosis

Chair : Hidenori Arai (Department of Human Health Sciences, Kyoto University Graduate School of Medicine)

P013 Inflammation and shedding of receptor for AGE (RAGE): roles of ER stress

Hidenori Koyama[1], Masayo Monden[1], Takuhito Shoji[1], Yasuhiko Yamamoto[2], Hiroshi Yamamoto[2], Masaaki Inaba[3], Mitsuyoshi Namba[1]

1 Department of Internal Medicine, Division of Diabetes, Endocrinology and Metabolism, Hyogo College of Medicine, Japan
2 Kanazawa University
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P014 Is pentraxin 3 a biomarker, a player, or both in the context of coronary atherosclerosis?

Shinichiro Miura, Ayumi Nakamura, Yuhei Shiga, Yuiko Miyase, Asuka Nakayama, Sayo Tomita, Kenji Norimatsu, Keijiro Saku

Department of Cardiology, Fukuoka University School of Medicine, Japan

P015 LR11, a cell migration regulator, is a novel biomarker for pathological vascular intimal smooth muscle cells

Meizi Jiang

Department of Experimental Research and Medicine, Toho University Sakura Medical Center, Japan

P016 Unbalanced M1/M2 phenotypes of monocytes and hyperglycemia associate with M1/M2 macrophages in the carotid atherosclerotic plaque in the patients with obesity and diabetes undergoing carotid endarterectomy

Masashi Tanaka[1], Yoshiyuki Matsuo[1], Yousuke Sasaki[1], Hajime Yamakage[1], Kazuya Muranaka[1], Tetsuya Tsukahara[2], Akira Shimatsu[1], Noriko Satoh Asahara[1]

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P017 Investigation of the vascular protective function of AMPK in *in vivo* models using endothelium-specific AMPK mutant transgenic mice

Daisuke Nagata

Department of Nephrolgy, Jichi Medical University, Japan

P018 Serum uric acid is a novel risk factor for the vulnerability of carotid atheromatous plaque in diabetic patients

Hiroki Kagaya

Division of Generel Internal Medicine, Chiba Cerebral and Cardiovascular Center, Japan

P019 Correlation between lipid profile and level of circulating endothelial progenitor cells (EPCs) in metabolic syndrome patients in saiful anwar general hospital, malang, indonesia

Destiansyah Aulia Rifqi[1], Arsana Moda Putu[1,2], Arthamin Zulhaidah Maimun[1,3]

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List of Poster Abstracts

Poster 4 : Atherosclerosis

Chair : Tomoya Yamashita (Kobe University Graduate School of Medicine, Division of Cardiovascular Medicine)

P020 Vascular and metabolic effects of different dosages of omega-3 fatty acids in patients with hypertriglyceridemia

Kwang K Koh, Pyung C Oh, Seung H Han, Seungik Lee, Myeong gun Kim

Cardiology, Gachon Uni Gil Medical Center, Korea, South

P021 AMAP1 as a negative-feedback regulator of nuclear factor-kappaB

Noboru Ashida[1], Dat Tien Nguyen[1,2], Ayumu Yoshikawa[3], Ari Hashimoto[3], Hisataka Sabe[3], Kaeko Kamei[2], Hidenori Arai[1], Toru Kita[4], Takeshi Kimura[1], Masayuki Yokode[1]

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3 Hokkaido University Graduate School of Medicine
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P022 The mechanism underlying the association between 5'-flanking region of neuropeptide Y2 receptor gene variant and plasma HDL-cholesterol levels

Mio Okada, Masami Nagai, Akiko Hamaue, Hidesuke Kaji

Division of Physiology and Metabolism, University of Hyogo, Japan

P023 Lysophospholipids in atherosclerosis and thrombosis

Makoto Kurano

Clinical Laboratory Medicine, The University of Tokyo, Japan

P024 Molecular dissection of hypoapoC-II caused by defective apoC-II mRNA transcription

Satoru Takase[1], Hiroyuki Ishiura[1], Jun Mitusi[1], Hayato Fujita[1], Kazuo Hara[1], Mikio Takanashi[1], Jun ichi Osuga[2], Shun Ishibashi[2], Shoji Tsuji[1], Takashi Kadowaki[1], Hiroaki Okazaki[1]

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P025 Effect of linagliptin on AVI and API, indices of vascular stiffness evaluated by an automatic blood pressure monitor

Anna Sakashita, Reie Yoshinaga, Yoshimi Abe, Chieko Morisawa, Tomoko Morita, Yoshitaka Akiyama, Masafumi Matsuda

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List of Poster Abstracts

Poster 5 : Atherosclerosis

Chair : Masayuki Yoshida (Tokyo Medical and Dental University)

P026 Resistin like molecule beta stimulates CB1 expression in monocytes/ macrophages through CAP1-related signaling pathways

Yuna Kim, KI HOON HAN

Medicine and Cardiology, Asan Medical Center, University of Ulsan, Korea, South

P027 Lipidomic analysis approach to reveal molecular mechanism of endothelial function in clinical study

Fumiyuki Nakagawa[1,4], Katsutaro Morino[1], Keiko Kondo[1], Atsushi Ishikado[1,2], Nikami Fumio[2], Makoto Suwa[2], Motonobu Matsumoto[2], Taketoshi Makino[2], Yoshihiko Nishio[3], Satoshi Ugi[1], Hiroshi Maegawa[1]

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P028 Pioglitazone ameliorates cuff induced neointimal formation by both adiponectin dependent and independent pathways

Tetsuya Kubota[1,2], Naoto Kubota[1,2], Mariko Inoue[2], Iseki Takamoto[2], Toshimasa Yamauchi[2], Kohjiro Ueki[2], Takashi Kadowaki[2]

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P029 Relationships of elevated levels of serum hepatic enzymes and alcohol intake with arterial stiffness in Japanese men

Hirokazu Uemura, Sakurako Kamano, Miwa Yamaguchi, Kokichi Arisawa

Department of Preventive Medicine, Institute of Health Biosciences, The University of Tokushima Graduate School, Japan

P030 Progranulin plays a crucial role in the development of atherosclerosis

Ryota Kawase[1], Tohru Ohama[1], Akifumi Matsuyama[2], Yinghong Zhu[1], Takeshi Okada[1], Kazuhiro Nakatani[1], Daisaku Masuda[1], Masahiro Koseki[1], Makoto Nishida[1], Yasushi Sakata[1], Shizuya Yamashita[1]

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2 Foundation for Biomedical Research and Innovation

P031 Rapid HPLC method for measurement of cholesterol levels in major lipoprotein classes and estimation of lipoprotein profiles in male volunteers without overt diseases

Hiroshi Yoshida[1], Yuji Hirowatari[2], Daisuke Manita[2], Norio Tada[3]

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List of Poster Abstracts

Poster 6 : Atherosclerosis

Chair : Yoshio Fujioka (Division of Clinical Nutrition Faculty of Nuftition, Kobe Gakuin University)

P032 Newly developed apolipoproteinA-I mimetic peptide decreased native and modified high-density lipoprotein-induced aldosterone synthesis in adrenocortical cells

Yoshino Matsuo, Shinichiro Miura, Asuka Nakayama, Sayo Tomita, Yasunori Suematsu, Ayumi Nakamura, Yuiko Miyase, Yuhei Shiga, Keijiro Saku

Department of Cardiology, Fukuoka University School of Medicine, Japan

P033 Protective effect of semaphorin 3G on atherosclerosis development

Masaya Yamaga, Harukiyo Kawamura, Kazuki Kobayashi, Hirotake Tokuyama, Takahiro Ishikawa, Ryoichi Ishibashi, Kenichi Sakamoto, Akiko Hattori, Peng He, Minoru Takemoto, Koutaro Yokote

Department of Clinical Cell Biology and Medicine, Chiba University Graduate School of Medicine, Japan

P034 Long-term effects of VCRESC® (a vitamin micronutrient beverage) on vitamin and homocysteine (Hcy) levels in patients with coronary atherosclerosis

Kouji Kajinami[1], Michiyo Sasagawa[2], Kayo Yamamoto[2], Akihiko Nakagawa[2]

1 Cardiology, Kanazawa Medical University, Japan
2 Kanazawa Medical University Hospital

P035 Effects of eicosapentaenoic acid (EPA) on lipid accumulation in lipoprotein-loaded macrophages

Rie Mamoto, Hideo Ohira, Takafumi Hatano, Wao Tsutsui, Miki Ito, Masako Nishida, Sayaka Yamaguchi, Yoshio Fujioka

Division of Clinical Nutrition, Faculty of Nutrition, Kobe Gakuin University, Japan

P036 Normal calorific diet enriched fat and fructose leads to multiple metabolic disorders and enhances atherosclerosis in WHHL rabbits

Bo Ning[1], Xiaoyan Wang[1], Ying Yu[1], Bilal Waqar[1], Masashi Shiomi[2], Jianglin Fan[1]

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P037 Collateral damage: A case of chronic total occlusion of the left main coronary artery

Neil Wayne C. Salces, Carolyn K. Fermin, Wilfredo M. Ypil

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List of Poster Abstracts

Poster 7 : Diabetes

Chair : Hideaki Kaneto (Division of Diabetes, Metabolism and Endocrinology, Kawasaki Medical School)

P038 A small-molecule AdipoR agonist ameliorates type 2 diabetes and prolongs the shortened lifespan

Miki O. Iwabu, Toshimasa Yamauchi, Masato Iwabu, Takashi Kadowaki

Department of Diabetes and Metabolic Diseases, The University of Tokyo, Japan

P039 Role of chronic inflammation in diabetic nephropathy through glucolipotoxicity and intraglomerular crosstalk

Takashige Kuwabara[1], Kiyoshi Mori[1], Hideki Yokoi[1], Motoko Yanagita[1], Kazuwa Nakao[1], Masashi Mukoyama[1,2]

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P040 Withdrawn

P041 Histone acetyltransferase GCN5 regulates hepatic gluconeogenesis through CITED2-dependent substrate switch

Mashito Sakai[1], Masato Kasuga[2], Michihiro Matsumoto[1],

1 Department of Molecular Metabolic Regulation, Diabetes Research Center, Research Institute, National Center for Global Health and Medicine, Japan
2 National Center for Global Health and Medicine

P042 The combination of quantity and quality of sleep and the risk of diabetes in Japanese employees with prediabetes

Kayo Godai[1], Azusa Shima[1,2], Yuichiro Kawatsu[2], Akiko Morimoto[1], Yukako Tatsumi[3], Nao Sonoda[1], Naomi Miyamatsu[1]

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P043 A mouse model of tetrahydrobiopterin deficiency induces progression of diabetes and obesity

Yasuo Oguri[1], Yoshihito Fujita[1], Abulizi Abudukadier[1], Akio Obara[1], Futoshi Furuya[1], Akiko Ohashi[2], Toru Fukushima[1], Shunsuke Yamane[1], Masahito Ogura[1], Hiroyuki Hasegawa[2], Nobuya Inagaki[1]

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List of Poster Abstracts

Poster 8 : Diabetes

Chair : Naoya Yahagi (Department of Internal Medicine (Endocrinology and Metabolism), Faculty of Medicine, University of Tsukuba)

P044 Long-range transactivation of C/EBP α gene expression by PPAR γ through distal enhancers during adipocyte differentiation

Tomohisa Aoyama[1,2], Hironori Waki[1,3], Toshimasa Yamauchi[1], Kenichi Wakabayashi[4], Tsuyoshi Inoue[5], Masahiro Nakamura[1], Youichiro Wada[1], Tatsuhiko Kodama[5], Juro Sakai[6], Hiroyuki Aburatani[4], Takashi Kadowaki[1]

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4 Genome Science Division, Research Center for Advanced Science and Technology, The University of Tokyo
5 Laboratory for Systems Biology and Medicine, Research Center for Advanced Science and Technology, The University of Tokyo
6 Division of Metabolic Medicine, Research Center for Advanced Science and Technology, The University of Tokyo

P045 Useful models of pancreatic endocrine progenitor cell line Tec-3p and dual-labeled Ngn3-eGFP/Ins-DsRed2 mice for the identification of the key driving regulators during pancreatic endocrine differentiation

Masahito Matsumoto[1], Yzumi Sugawara-Yamashita[3], Satomi Suzuki[1], Yukiko Yatsuka[1], Masataka Hirasaki[2], Yoichi Yasunami[4], Wylie Vale[3], Yasushi Okazaki[1]

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3 Salk Institute for Biological Studies
4 Fukuoka University

P046 Deletion of Elovl6 ameliorates hyperglycemia in db/db mice

Takashi Matsuzaka, Yuta Nakano, Zhao Hui, Marii Suzuki, Tang Nie, Yoshimi Nakagawa, Naoya Yahagi, Nobuhiro Yamada, Hitoshi Shimano

Department of Internal Medicine (Endocrinology and Metabolism), Faculty of Medicine, University of Tsukuba

P047 Plaque score of ultrasound analysis of carotid arteries is a useful reference index for cerebro-cardiovascular events in patients with type 2 diabetes

Shigeru Okuya[1,2], Kyoko Ariyoshi[2], Kimie Matsunaga[2], Yuko Nagao[2], Ryuta Nomiyama[2], Komei Takeda[2], Yukio Tanizawa[2]

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P048 Loss of Tcf21 in podocytes leads to enhanced diabetic nephropathy

Yoshiro Maezawa[1], Tuncer Onay[2], Rizaldy Scott[2], Minoru Takemoto[1], Koutaro Yokote[1], Susan E Quaggin[2]

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2 Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada, and Feinberg Cardiovascular Research Institute and Division of Nephrology, Northwestern University, Chicago, United States

P049 Blockade of Kv2.1 channels potentiates GLP-1-induced insulin release in mouse islet β -cells

Rauza S. Rita, Katsuya Dezaki, Toshihiko Yada

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List of Poster Abstracts

Poster 9 : Diabetes

Chair : Kazunori Utsunomiya (Division of Diabetes and Endocrinology, Department of Internal Medicine, The Jikei University School of Medicine)

P050 Role of N-type calcium channel in diabetic nephropathy

Shoko Ohno[1], Hideki Yokoi[1], Masato Kasahara[2], Kiyoshi Mori[3], Tomohiro Numata[4], Koichiro Kuwahara[5], Akira Sugawara[6], Yasuo Mori[4], Motoko Yanagita[1], Kazuwa Nakao[3], Masashi Mukoyama[1,7]

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7 Department of Nephrology, Graduate School of Medical Sciences, Kumamoto University

P051 Plasma brain-derived neurotrophic factor, cardiac autonomic function and nocturnal changes in blood pressure: implications in nocturnal hypertension in diabetes

Manabu Kadoya, Hidenori Koyama, Masafumi Kurajoh, Miki Hatayama, Hirokazu Okazaki, Takuhito Shoji, Yuji Moriwaki, Tetsuya Yamamoto, Mitsuyoshi Namba

Department of Internal Medicine, Division of Diabetes, Endocrinology and Metabolim, Hyogo College of Medicine, Japan

P052 Bone and mineral metabolism and incident diabetes: A prospective study

ChingLung Cheung, ChorWing Sing, Annie WC Kung, Bernard MY Cheung, Ian CK Wong, Kathryn CB Tan

Medicine, The University of Hong Kong, Hong Kong

P053 MafA is important for maintenance of the mature beta-cell phenotype

Wataru Nishimura, Miho Kawaguchi, Haruhide Udagawa, Nobuaki Funahashi, Takao Nammo, Kazuki Yasuda

Department of Metabolic Disorder, Diabetes Research Center, Research Institute, National Center for Global Health and Medicine, Japan

P054 Associations of chemerin and FGF21 with subclinical atherosclerosis and adverse lipid metabolism in type 2 diabetes

Hyeongkyu Park, Hyejung Kim, Dongwon Byun, Kyoil Suh, Myunghi Yoo

Soonchunhyang University Hospital, Korea, South

P055 The critical role of heat shock protein 72 in diabetic pathophysiology

Rina Matsuyama, Tatsuya Kondo, Sayaka Kitano, Rieko Goto, Kaoru Ono, Motoyuki Igata, Junji Kawashima, Takeshi Matsumura, Hiroyuki Motoshima, Eiichi Araki

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List of Poster Abstracts

Poster 10 : Diabetes

Chair : Naoto Kubota (Departmant of Diabetes and Metabolic Diseases, Graduate School of Medicine University of Tokyo)

P056 Predictors for mild and severe hypoglycemia in Japanese outpatients with insulin-treated diabetes: a 6-month follow-up study

Nao Sonoda[1], Akiko Morimoto[1], Satoshi Ugi[2], Kayo Godai[1], Katsutaro Morino[2], Osamu Sekine[2], Ken-ichi Nemoto[2], Hiroshi Maegawa[2], Naomi Miyamatsu[1]

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P057 Effect of sitagliptin and vildagliptin, dipeptidyl peptidase-4 inhibitors, on M1/M2-like phenotypes of peripheral blood monocytes and arterial stiffness in type 2 diabetic patients

Noriko SatohAsahara, Masashi Tanaka, Yoshiyuki Matsuo, Hajime Yamakage, Kazuya Muranaka, Yousuke Sasaki, Shinji Odori, Shigeo Kono, Akira Shimazu

Division of Diabetic Research, Clinical Research Institute, National Hospital Organization, Kyoto Medical Center, Japan

P058 A novel podocyte gene, R3h domain containing-like inhibits non-canonical TGF- β signaling

Takahiro Ishikawa[1], Minoru Takemoto[1], Yoshiro Maezawa[1], Yoshiro Akimoto[2], Kunimasa Yan[3], Ryoichi Ishibashi[1], Peng He[1], Kenichi Sakamoto[1], Chirster Betsholtz[4], Karl Tryggvason[5], Koutaro Yokote[1]

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4 Department Immunology, Genetics and Pathology, Rudbeck Laboratory, Uppsala University
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P059 Diabetes risk score in Bangladesh: A simple non-invasive tool for detecting undiagnosed type 2 diabetes in a Bangladesh population

Bishwajit Bhowmik

Department of International Community Health, University of Oslo, Norway

P060 Timing of hypoglycemia is associated with increased mortality and length of stay among patients with diabetes admitted to internal medicine departments

Mona Boaz[1,2], Julio Wainstein[2], Zohar Landau[2], Yosefa Bar Dayan[2], Eyal Leibovitz[2]

1 Department of Nutrition, School of Health Sciences, Ariel University, Israel
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P061 Impact of comorbid depression on glycemic control and family functioning in treatment-resistant patients with type 2 diabetes: a 6-month follow-up study

Toshinari Saeki[1,2], Miki Takaishi[2,3], Kazufumi Ishida[3], Tomoyuki Komo[4], Susumu Tazuma[2], Shigeto Yamawaki[2]

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List of Poster Abstracts

Poster 11 : Diabetes

Chair : Yuichiro Yamada (Department of Endocrinology, Diabetes,and Geriatric Medicine, Akita University Graduate School of Medicne)

P062 Efficacy of DPP-4 inhibitors on serum lipid profile according to glycemic control in Japanese patients with type 2 diabetes

Masataka Kusunoki[1], Daisuke Sato[2], Tana Chen[3], Yukie Natsume[3], Hideyo Tsutsui[4], Takao Nakamura[2], Tetsuro Miyata[5], Yoshiharu Oshida[6]

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3 Graduate School of Medicine, Nagoya University
4 Teikyo University School of Medicine
5 Vascular Disease Center, Sanno Medical Center
6 Research Center of Health, Physical Fitness and Sports, Nagoya University

P063 Statins improve glucose tolerance in high fat-fed mice possible through PPAR γ activation in adipocytes

Kazuki Fukuda, Takeshi Matsumura, Norio Ishii, Hiroyuki Kinoshita, Saiko Murakami, Sarie Yamada, Takafumi Senokuchi, Tatsuya Kondo, Hiroyuki Motoshima, Takeshi Nishikawa, Eiichi Araki

Metabolic Medicine, Kumamoto University, Japan

P064 Sitagliptin add on therapy rapidly improved daily glycaemic excursion within 24 hours in the type 2 diabetic patients with secondary failure to sulfonylureas. SUNSHINE Study

Satoshi Ugi[1], Katsutaro Morino[1], Katsuya Egawa[2], Yasushi Omura[3], Takaaki Nakamura[4], Masataka Nishimura[1,5], Noriko Takahara[6], Akio Kish[7], Yasuo Kida[7], Yoshihiko Nishio[8], Hiroshi Maegawa[1]

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4 Omihachiman community medical center
5 Nagahama city hospital
6 Akoh city hospital
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P065 Change of urinary angiotensinogen predicts progression of diabetic nephropathy

Ahn Kang Hee, Kim Sang Soo, Song Sang Heon, Nam Yoon Jeong, Park Soo Bin, Kim Jong Ho, Kim Won Jin, Jeon Yun Kyung, Kim Bo Hyun, Kim In Joo

Department of Internal Medicine, Pusan National University Hospital, Korea, South

P066 Association between serum fatty acid compositions and clinical and nutritional factors in Japanese patients with type 2 diabetes

Nao Kawabata, Toshiko Sato, Rie Furusawa, Megumi Furuuchi, Atsuko Onoguchi, Mayako Miyahara, Daisuke Nagata, Shun Ishibashi

Department of Clinical Nutrition, Jichi Medical University Hospital, Japan

P067 Clinical factors that influence the long term efficacy of sitagliptin in patients with type 2 diabetes

Tatsuya Fujikawa, Sayaka Chinju, Yasunari Yoshida, Masaki Horiguchi, Kentaro Inoue, Taiji Yonei

Mitoyo General Hospital, Japan

List of Poster Abstracts

Poster 12 : Diabetes

Chair : Atsunori Kashiwagi (Kusatsu General Hospital)

P068 A critical role of hormone-sensitive lipase in streptozotocin-induced diabetic hypertriglyceridemia

Mikio Takanashi[1], Satoru Takase[1], Akari Noda[1], Yoshino Taira[1], Sachiko Okazaki[1], Futoshi Shionoiri[1], Yoko Ilzuka[1], Junichi Osuga[2], Shun Ishibashi[2], Takashi Kadowaki[1], Hiroaki Okazaki[1],

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P069 Reconstituting pancreas development from purified progenitor cells reveals genes essential for islet differentiation

Takuya Sugiyama[1,2,3], Toshimasa Yamauchi[1], Yusuke Hirota[1], Hironori Waki[1,2], Miki Okada Iwabu[1], Masato Iwabu[1], Takashi Kadowaki[1], Seung K Kim[3],

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2 Functional Regulation of Adipocytes, Graduate School of Medicine, University of Tokyo
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P070 Metabolic status in lean and overweight type 2 diabetes mellitus

Shilpa B. Asegaonkar, Ishrat Kareem, Jayshree S. Bavikar, Sunita Aghade, Avinash Pagdhune, Anand P. Thorat, Mangala Borkar

Biochemistry, Government Medical College Aurangabad Maharashtra India, India

P071 Voluntary exercise under a food restriction condition decreases blood branched-chain amino acids levels, in addition to improvement of glucose and lipid metabolism, in *db* mice, type 2 diabetes animal model

Ancah C.N. Marchianti[1,2], Emi Arimura[1,3], Miharu Ushikai[1], Masahisa Horiuchi[1]

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2 Jember University Faculty of Medicine
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P072 Use second trimester prenatal screening markers for down syndrome to predicting gestational diabetes mellitus

Hui Chuan Shen[1], Ting Chun Hung[1], Chieh Tien Wang[1], Li Ching Wu[1], Sheng Hsien Chen[2]

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P073 Relation of an elderly diabetes and frailty -Classification by the Kihon Checklist-

Sayuri SABLE MORITA, Syosuke SATAKE, Takahisa TANIKAWA, Syuji KAWASHIMA, Yasumoto MATSUI, Haruhiko TOKUDA, Aushi HARADA

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List of Poster Abstracts

Poster 13 : Diabetes

Chair : Ryo Suzuki (Dept. of Diabetes and Metabolic Diseases, Graduate School of Medicine The University of Tokyo)

P074 Type 2 diabetes, obesity and malnutrition risk in adults hospitalized in internal medicine departments

Mona Boaz[1,2], Julio Wainstein[2], Zohar Landau[2], Yosefa Bar Dayan[2], Sami Giyres[3], Eyal Leibovitz[2]

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3 Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

P075 Blend of sesame and rice bran oils as cooking oil improves glucose and lipid metabolism in type 2 diabetes mellitus-An open label dietary approach study

Sankar Devarajan[1], Ravinder Singh[2], Biprabuddha Chatterjee[3], Bo Zhang[4]

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2 Department of Non-communicable Diseases, Indian Council of Medical Research
3 Research & Development, Adani Wilmar Limited
4 Department of Biochemistry, School of Medicine, Fukuoka University

P076 Anagliptin affects lipid metabolism in patients with type 2 diabetes mellitus and dyslipidemia

Yasuhiro Hotta[1], Setsuya Okubo[2], Takehiko Ichikawa[2], Yutaka Yano[1]

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2 Kuwana East Medical Center

P077 Differences in the clinical characteristics between young onset adult type 1 and type 2 diabetes mellitus under insulin treatment

Rei Hashimoto[1], Yuko Okano[1], Yasuhiro Hotta[1], Mei Uemura[1], Taro Yasuma[1], Yuki Onishi[1], Toshinari Suzuki[1], Noriko Furuta[1], Rika Araki[2], Yutaka Yano[1], Yoshiyuki Takei[3]

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P078 The relationship between medial temporal lobe atrophy and diabetes mellitus

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P079 Ultra-long-acting insulin degludec improved the nadir of the nocturnal plasma glucose by fitting to basal insulin secretion in type 2 diabetes

Gendai Lee, Mina Nishiura, Youko Katamine, Aya Yoshida, Natsumi Matsui, Emi Tokumoto, Izumi Harada, Akiko Obata

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List of Poster Abstracts

Poster 14 : Diabetes

Chair : Toshimasa Yamauchi (Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, the University of Tokyo)

P080 Preclinical study of cytopiloyne as an anti-diabetic novel phytocompound

WenChin Yang[1], Cicero L. T. Chang[2]

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P081 The role of survivin and Raf-1 kinase against enhancement of pancreatic beta cell apoptosis in patients with type 2 diabetes mellitus

Eva Decroli, Asman Manaf, Syafril Syahbuddin

Internal Medicine, Faculty of Medicine, Andalas University, Indonesia

P082 Clinical results of hospitalization according to a two-week clinical path in diabetic patients with visceral fat accumulation

Takashi Ohoshi[1], Junko Kanamoto[1], Yoshihisa Hiromine[2], Fumimaru Niwano[2], Yuzuru Kishitani[3], Kenichi Ogawa[4], Takashi Akamizu[5], Kishio Nanjo[6]

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P083 Serum insulin-like growth factor-1 is related to lipoprotein(a) level in patients with type 2 diabetes mellitus

Dooman Kim, Juri Park, Yoonjung Kim, Hoyoung Son

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P084 Study on the expansion of a Japanese-style medical diabetes service in China

Yoko Iizuka[1], Yiwen Wang[2], Shinobu Shirakawa[3], Hongwooi Thor[4], Yumiko Ohashi[1], Makoto Oe[1], Kyoko Inoue[5], Yoshiyuki Hisai[6], Jian Fu[7], Weiping Jia[8], Takashi Kadowaki[1]

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5 Tokyo Securities Industry Health Insurance Society Clinic
6 Terumo Corporation
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P085 The importance of appropriate insulin treatment in aging society- from the standpoint of hypoglycemia-

Yasunari Yoshida, Tatsuya Fujikawa, Masaki Horiguchi, Kentarou Inoue, Taiji Yonei

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List of Poster Abstracts

Poster 15 : Diabetes

Chair : Shinji Kihara (Osaka University)

P086 Effect of acupuncture for appetite control in type 2 diabetes with obesity- a pilot study

Chulyun Park[1], Jeon Eonju[1], Euidal Jung[1], Mina Kwak[2], Imhee Shin[1], Seokbong Kang[2], Hosang Shon[1]

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P087 Withdrawn

P088 The transcriptional coregulator CITED2 regulates adipocyte differentiation by interacting with retinoblastoma protein

Michihiro Matsumoto, Tomoko Hayakawa, Mashito Sakai, Daisuke Yamaji, Takashi Yagi, Hiroyuki Yano, Masaru Mitsushima, Masato Kasuga

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P089 Differences in vasodilation via protease-activated receptor-2 in various arteries from SHRSP.Z-*Lepr*^{fa}/IzmDmcr rats with metabolic syndrome

Kana Maruyama[1], Satomi Kagota[1], Hirokazu Wakuda[1], John J McGuire[2], Noriko Yoshikawa[1], Kazuki Nakamura[1], Kazumasa Shinozuka[1]

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P090 Phenotypic shift of bone marrow monocytes into a pro-inflammatory subset in obese diabetes and established obesity

Battsetseg Batchuluun[1], Toyoshi Inoguchi[1,2], Baigalmaa Batchuluun[1], Noriyuki Sonoda[1,2], Yuka Sakaki[1], Kana Kudo[1], Ryoichi Takayanagi[1]

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P091 FABP5 is an essential modulator of fatty acid-induced GIP secretion in enteroendocrine K cells

Kimitaka Shibue[1,2], Shunsuke Yamane[1], Norio Harada[1], Akihiro Hamasaki[1], Kazuyo Suzuki[1], Erina Joo[1], Kanako Iwasaki[1], Daniela Nasteska[1], Takanari Harada[1], Yasuhiro Adachi[3], Yuji Owada[4], Ryoichi Takayanagi[2], Nobuya Inagaki[1]

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List of Poster Abstracts

Poster 16 : Obesity

Chair : Hironori Waki (Department of Diabetes and Metabolic Diseases, Functional Regulation of Adipocytes, Graduate School of Medicine The University of Tokyo)

P092 Butyrate suppresses inflammatory responses generated by the interaction of adipocytes and macrophages

Hideo Ohira, Wao Tsutsui, Miki Ito, Masako Nishida, Sayaka Yamaguchi, Rie Mamoto, Yoshio Fujioka

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P093 Sarcopenia is associated with non-alcoholic fatty liver disease regardless of obesity and metabolic syndrome: Nationwide surveys (KNHANES 2008-2011)

Bong Soo Cha[1], Yong ho Lee[1], Hye Jin Yoon[1], Kyu Jeung Ahn[2], Byung Wan Lee[1], Eun Seok Kang[1], Hyun Chul Lee[1]

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P094 Genome-wide profiling of brown fat-specific open regulatory regions identifies NFIA as a transcriptional regulator of brown fat muscle cell lineage specification

Hironori Waki[1,2], Yuta Hiraike[1], Jing Yu[1], Kana Miyake[1], Masahiro Nakamura[1], Ken Suzuki[1], Kohjiro Ueki[1], Shuichi Tsutsumi[2], Hiroyuki Aburatani[2], Toshimasa Yamauchi[1], Takashi Kadowaki

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P095 Anthropometric indices of obesity and type 2 diabetes in a rural Bangladeshi population

Tasnima Siddiquee

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P096 The change of the prevalence of metabolic syndrome this ten years in Okinawa

Kenichiro Wakuta[1], Yoko Maekawa[1], Kurando Watanabe[1], Norihumi Kamiya[1], Tomohiro Yara[1], Isao Shiroma[2]

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P097 Withdrawn

List of Poster Abstracts

Poster 17 : Obesity

Chair : Yukihiko Ueda (KKR Hirakata Kohsai Hospital)

P098 Visceral fat area is significantly related with hepatic steatosis assessed by controlled attenuation parameter

Kwang Joon Kim[1], Jae Hyuk Lee[2], See Hoon Lee[3], Han Seok Choi[4], Dong Yeob Shin[1]

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P099 Comparison of changes in metabolic markers after Roux-en-Y gastric bypass between non-obese and obese patients

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P100 The serine protease prostasin regulates hepatic insulin sensitivity by modulating TLR4 signaling

Kohei Uchimura[1], Manabu Hayata[1], Teruhiko Mizumoto[1], Yoshikazu Miyasato[1], Yutaka Kakizoe[1], Kazuki Fukuda[2], Tatsuya Kondo[2], Takeshi Matsumura[2], Eiichi Araki[2], Masashi Mukoyama[1], Kenichiro Kitamura[1]

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P101 Sexually dimorphic, fat depot-dependent expression of a fibrogenic adipokine, thrombospondin 1 (THBS1) in human obesity

Yoshiyuki Matsuo[1], Masashi Tanaka[1], Yousuke Sasaki[1], Hajime Yamakage[1], Kazuya Muranaka[1], Iwao Ikai[2], Hiroaki Hata[2], Akira Shimatsu[1], Mayumi Inoue[3], Tae Hwa Chun[3], Noriko Satoh Asahara[1]

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P102 Enriched environment reverses food preference for fat over carbohydrate involving leptin signaling

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P103 A prospective study of serum leptin and incident metabolic syndrome: The ARIRANG study

Jang Young Kim, Song Vogue Ahn, Sang Baek Koh

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List of Poster Abstracts

Poster 18 : Obesity

Chair : Tohru Ohama (Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine)

P104 EP4 receptor regulates obesity-related inflammation and insulin sensitivity

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P105 Withdrawn

P106 An eight-week high complex carbohydrate, energy restricted dietary intervention is associated with weight loss and a reduction of inflammation markers

Olga Raz[1,3], Arie Steinvil[2,3], Tovit Rosenzweig[1], Shlomo Berliner[2,3], Itzhak Shapira[2,3], Mona Boaz[1]

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P107 Lycopene attenuates high fat diet-induced adipose tissue inflammation and insulin resistance by regulating both macrophage recruitment and M1/M2 status

Naoto Nagata, Yinhua Ni, Mayumi Nagashimada, Liang Xu, Fen Zhuge, Shuichi Kaneko, Tsuguhito Ota

Kanazawa University Brain/Liver Interface Medicne Research Center, Japan

P108 Hepatic CREB3L3 controls whole-body energy homeostasis and improves obesity and insulin resistance

Aoi SATHO[1,2], Yoshimi NAKAGAWA[1], Takashi MATSUZAKA[1], Hitoshi IWASAKI[1], Kazuto KOBAYASHI[1], Shigeru YATOH[1], Naoya YAHAGI[1], Hiroaki SUZUKI[1], Nobuhiro YAMADA[1], Hitoshi SHIMANO[1,2]

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P109 Relationship between body fat distribution and cardiometabolic risk factors in nonobese Japanese subjects

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List of Poster Abstracts

Poster 19 : Others

Chair : Koh Ono (Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine)

P110 Can children intervene on reducing tobacco in the community where they live? Health promotion tool to reduce tobacco consumption in low socioeconomic communities in Sri Lanka

Chamil P Senevirathne[1], Nayana D Dhanapala[2], Shalika Thennakoon[3], Prasad Katulanda[4], Manoj Fernando[5], Shanika Malalgoda[6]

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P111 Treatment of familial LCAT deficiency syndrome by self-transplantation of therapeutic-enzyme secreting adipocytes

Yasuyuki Aoyagi[1], Masayuki Kuroda[1], Sakiyo Asada[1], Masayuki Aso[2], Koutaro Yokote[1], Yasushi Saito[1], Hideaki Bujo[1,3]

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P112 MicroRNA-451 is involved in diabetic cardiomyopathy through suppression of the LKB1/AMPK pathway

Yasuhide Kuwabara[1], Takahiro Horie[1], Osamu Baba[1], Masataka Nishiga[1], Shunsuke Usami[1], Masayasu Izuhara[1], Tetsushi Nakao[1], Tomohiro Nishino[1], Toru Kita[2], Takeshi Kimura[1], Koh Ono[1]

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P113 MicroRNA-33, embedded in *Srebf2* intron, regulate fatty acid synthesis through targeting SREBP-1 *in vivo*

Tomohiro Nishino[1], Takahiro Horie[1], Osamu Baba[1], Yasuhide Kuwabara[1], Masayuki Yokode[1], Toru Kita[1], Takeshi Kimura[2], Koh Ono[1]

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2 Kobe City Medical Center General Hospital

P114 Targeted next-generation sequencing and fine linkage disequilibrium mapping reveals association of *PNPLA3* and *PARVB* with the severity of nonalcoholic fatty liver disease

Kikuko Hotta[1], Takuya Kitamoto[1], Aya Kitamoto[1], Masato Yoneda[2], Hideyuki Hyogo[3], Hidenori Ochi[3], Takato Ueno[4], Kazuaki Chayama[2], Atsushi Nakajima[3]

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P115 Lipoprotein subfractions highly associated with renal damage in familial LCAT deficiency

Masayuki Kuroda[1], Adriaan G Holleboom[2], Erik S.G. Stroes[2], Sakiyo Asada[1], Yasuyuki Aoyagi[1], Kouju Kamata[3], Shizuya Yamashita[4], Shun Ishibashi[5], Yasushi Saito[1], Hideaki Bujo[1,6]

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6 Toho University

List of Poster Abstracts

P116 Apolipoprotein A-V Gly185Cys is a possible risk factor for severe hypertriglyceridemia in patients with normal circulating lipoprotein lipase protein concentrations

Takeyoshi Murano[1], Daiji Nagayama[2], Atsuhito Saiki[2], Ichiro Tatsuno[2], Kohji Shirai[2], Hideaki Bujo[1]

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List of Poster Abstracts

Poster 20 : Others

Chair : Tetsuo Shoji (Department of Geriatrics and Vascular Medicine, Osaka City University Graduate School of Medicine)

P117 Autoimmune severe hypertriglyceridemia induced by anti-apolipoprotein C-II antibody

Hiroyasu Yamamoto, Minoru Tanaka, Satomi Yoshiga, Tohru Funahashi, Iichiro Shimomura, Shinji Kihara

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P118 Plasma fetuin-A levels are associated with insulin resistance in a general population in Uku-town

Aya Obuchi[1], Hisashi Adachi[2], Mika Enomoto[1], Ako Fukami[1], Kyoko Ohbu[1], Ayako Yoshimura[1], Sachiko Nakamura[1], Yume Nohara[1], Erika Nakao[1], Tsutomu Imaizumi[3], Yoshihiro Fukumoto[1]

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P119 Urinary liver-type fatty acid binding protein is associated with microalbuminuria as well as insulin resistance in a general population

Ako Fukami[1], Hisashi Adachi[2], Mika Enomoto[1], Eita Kumagai[1], Sachiko Nakamura[1], Ayako Yoshimura[1], Aya Obuchi[1], Erika Nakao[1], Yoshihiro Fukumoto[1]

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P120 Association between lifestyle and the prevalence of chronic kidney disease: the Saku study

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P121 Serum ferritin and oxidative stress biomarkers in Japanese with and without metabolic syndrome

Noriko Sakano[1], Nobuyuki Miyatake[2], Suketaka Iwanaga[3], Kazuhisa Taketa[4], Wang Da Hong[5], Sakiko Kanbara[6], Tomohiro Hirao[7], Keiki Ogino[8]

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P122 Intervention to reduce childrens television time and get their participation to improve the knowledge on NCDs in a middle income community, Sri Lanka

Chamil P Senevirathne[1], Nayana Dhanapala[2], Prasad Katulanda[3]

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P123 Relationship between cognitive function and oxidative stress

Mika Enomoto, Hisashi Adachi, Ako Fukami, Eita Kumagai, Sachiko Nakamura, Aya Obuchi, Ayako Yoshimura, Yume Nohara, Erika Nakao, Yoshihiro Fukumoto

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PL1 Recent Progress of iPS Cell Research and Application

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Induced pluripotent stem cells (iPSCs) were originally generated from mouse and human fibroblasts by the retroviral transduction of four genes, *Oct3/4, Sox2, c-Myc* and Klf4. The iPSCs have the ability to proliferate almost indefinitely, and to differentiate into multiple lineages. iPSCs can be made using various somatic cells, which may come from genetically characterized individuals, providing better opportunities for versatile medical applications. As a result, cell-based therapies, disease mechanisms and new drug development are being studied worldwide using iPSCs, and the iPSC technology has evolved at an accelerating pace.

We are currently trying to establish optimally safe and efficient technologies for iPSC generation, which could be made the world standard to realize medical applications in accordance with GMP. In terms of the safety of iPSC derivation, we have reported an integration-free method that does not result in any chromosomal damage using episomal vectors. In extended studies of iPSC-inducing factors, we proposed the use of L-Myc as an alternative to the oncogenic c-Myc in order to reduce the risk of tumorigenicity, while keeping the high efficiency. In order to avoid the need for conventional feeder cells or culture materials from different species, and to make them more suitable for the GMP setting, feeder cells were replaced with a recombinant laminin-based matrix and a culture medium free of animal-derived constituents (xeno-free) was developed. Regarding the quality control, some marker genes for neural differentiation-defective clones were identified, indicating that there may be a possibility of screening out the low-quality iPSCs before use, such as prior to their application for regenerative medicine. Thus, many improvements have been achieved in iPSC production in terms of both safety and efficiency.

This year, the world's first clinical research using iPSCs was initiated to study the transplantation of iPSC-derived RPE (retinal pigment epithelium) sheets for age-related macular degeneration. In addition, iPSC studies have recently shown major progress for other conditions, such as corneal diseases, blood diseases and Parkinson's disease, suggesting that these human conditions may also be treated using iPSC-based regenerative medicine in the near future. From a broad perspective, we are proceeding with an iPSC stock project in which iPSC clones are being established from donors with a homologous HLA haplotype, which is associated with a decreased immune response, in order to provide quality-assured iPSCs for future cell transplantation.

Another application of iPSCs is to provide more effective systems for drug screening, toxicity studies and the elucidation of disease mechanisms using disease-specific iPSCs from patients with intractable diseases. In addition, using individual iPSCs may make it possible to predict the patient condition and provide a preemptive therapeutic approach to protect against the onset of the disease or personalized medicine. Moreover, it is expected that the repositioning of drug candidates which used to be categorized as false-positive or false-negative with conventional testing may be feasible.

PL2 PCSK9: From Discovery to Clinical Applications

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During 1960-1970's it was firmly established that many bioactive secretory proteins, including polypeptide hormones and enzymes, are initially produced as inactive precursors that are transformed into bioactive moieties by limited proteolysis, as illustrated by the processing of pro-opiomelanocortin (POMC) into ACTH and β-endorphin, and pro-insulin into insulin. From 1990-1999 eight mammalian PCs were discovered and shown to be responsible for the tissue-specific processing of various secretory precursors. Substrates of these PCs include hormones, growth factors, receptors, metalloproteases, membrane-bound transcription factors and surface glycoproteins. Thus, depending on their site of action and protease activities, PCs are vitally involved in different physiological and clinically relevant processes resulting in activation/inactivation events, some of which impact on cardiovascular health.

An exhaustive PCR-based screen for a new mammalian PC led to the discovery of the 9th and last member of the family, known as proprotein convertase subtilisin kexin 9 (PCSK9), which was reported in early 2003. In rodents, PCSK9 was found to be expressed mostly in adult liver hepatocytes, much less so in the small intestine and kidney, and transiently expressed in the developing central nervous system. Because of its rich expression in liver hepatocytes and the localization of its gene (PCSK9) on human chromosome 1p32, a region linked to familial hypercholesterolemia (FH) in some French families, it was suspected and soon confirmed to represent the 3rd FH locus, with the low density lipoprotein receptor (LDLR) and apolipoprotein B (ApoB) genes being the other two.

Secreted into the plasma by the liver, the proteinase K-like serine protease PCSK9 binds the LDLR at the surface of hepatocytes, thereby preventing its recycling and enhancing its degradation in endosomes/lysosomes, resulting in reduced LDL-cholesterol (LDLc) clearance. The [PCSK9≡LDLR] complex involves the tight interaction of the catalytic subunit of PCSK9 with the EGF-A domain of the LDLR. Surprisingly, in a non-enzymatic fashion PCSK9 enhances the intracellular degradation of all its target proteins, including the LDLR, VLDLR and ApoER2 and LRP1. The escort and degradation of the [PCSK9 ≡ LDLR] complex in endosomes/lysosomes is regulated by a variety of proteins including PCSK9 and LDLR themselves, ApoB, sec24a, and most likely, other undefined and transitory partners that would interact with this complex along the secretory route, even as early as the endoplasmic reticulum (ER). Furthermore, the proprotein convertase Furin cleaves PCSK9 at $Arg_{218}\downarrow$ at the surface of hepatocytes and likely results in its *in vivo* inactivation, suggesting that some proteases could regulate PCSK9 activity. PCSK9 seems to be unique compared to other PCs in the sense that it is the only convertase that has only one enzymatic substrate, itself. It seems that this relatively more recent and polymorphic convertase was selected for its [protein ≡ protein] interaction with LDLR-like receptors, rather than as a protease, as the inhibitory prosegment remains tightly bound to the catalytic subunit.

Rare gain-of-function (GOF) PCSK9 variants lead to higher levels of LDLc and increased risk of cardiovascular disease (CVD); more common loss-of-function (LOF) PCSK9 variants are associated with reductions in both LDLc and risk of CVD. The highly active Anglo-Saxon D374Y PCSK9 variant is the most remarkable GOF mutation, while the heterozygote African nonsense LOF mutation C679X correlates with an amazing 88% reduction in CVD risk compared to non-carriers. Such LDLc lowering effects are also found in subjects with a dominant negative Q152H mutation, which prevents proPCSK9 autocatalytic cleavage into PCSK9 in the ER. Additionally, two complete LOF mutations causing marked hypocholesterolemia were found to be compatible with life and result in an amazingly low level of circulating LDLc levels of ~0.4 mM. Indeed, mammals can survive and stay healthy without PCSK9, as also confirmed in Pcsk9 knockout (KO) mice. Recent studies in mice revealed that the absence of PCSK9 protects against the development of atherosclerosis and aortic calcification associated with high LDLc.

The realization that a complete LOF PCSK9 mutation and/or inhibition of plasma PCSK9 result in rock-bottom cholesterol levels, suggested that PCSK9 inhibitors could be the next blockbuster drug to combat hypercholesterolemia, which would be a harbinger of things to come. Accordingly, it took 9 years to elaborate powerful new PCSK9-based therapeutic approaches to reduce circulating levels of LDLc. Presently, subcutaneous injection of monoclonal antibodies (mAbs, every 2 or 4 weeks) that inhibit the PCSK9 function on the LDLR are evaluated in phase III clinical trials. So far, the data revealed a significant 60-70% reduction of LDLc that lasts over a year and a ~30% reduction in the levels of the highly atherogenic Lp(a), suggesting that PCSK9 targets one of the hepatic Lp(a) receptors for degradation. This presentation will address the biochemical, cellular, genetic and clinical aspects associated with PCSK9's biology and pathophysiology in cells, rodents and human, and the clinical benefits of silencing the expression/activity of PCSK9 as a new modality in the treatment of hypercholesterolemia and associated pathologies.

SY1-1 Molecular Physiology of SGLT2 and Basic Pharmacology of SGLT2 Inhibitors

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In kidney, glucose in glomerular filtrate is completely reabsorbed in the renal proximal tubules, so that it does not appear in urine. In the process of glucose reabsorption, glucose in the luminal fluid is taken up by tubular epithelial cells via the sodium/glucose cotransporters (SGLT) in the apical membrane and then leaves the epithelial cells through the facilitative glucose transporters (GLUT) in the basolateral membrane to blood stream. SGLT mediates sodium-dependent active transport that transports glucose against its concentration gradient, whereas GLUT mediates passive transport transporting glucose along its concentration gradient. It has been well established that a low-affinity/high-capacity transport machinery localized in the early portion of proximal tubules (proximal convoluted tubules or S1 segment) that transports Na^+ and glucose with the coupling ratio of 1:1 reabsorbs 90% of glucose filtered in glomerulus, whereas, the high-affinity/low-capacity transport machinery in the late portion of proximal tubules (proximal convoluted tubules or S3 segment) transporting Na^+ and glucose with the coupling ratio of 2:1 reabsorbs remaining 10% of glucose.

In 1987, the first SGLT (SGLT1) was identified in small intestine by functional expression cloning approach. In kidney, SGLT1 was expressed in S3 segment of renal proximal tubules. Its functional properties corresponded well with those of the proximal straight tubules. By using SGLT1 cDNA as a probe, we screened human kidney cDNA library and identified second SGLT (SGLT2) in 1994. The expression of SGLT2 was kidney specific and localized in S1 segment of the proximal tubules. The functional properties of SGLT2 were those of proximal convoluted tubes. In contrast to SGLT2 with the concentrating capacity of 140, SGLT1 can concentrate glucose ~20,000 fold because of coupling with two Na^+, which is critical to reabsorb glucose completely at the proximal straight tubules. The benefit of SGLT2 is, in contrast, to absorb glucose with low energy consumption because SGLT2 is coupled with one Na^+.

The first chemical compound that affects SGLTs was phlorizin, which decreases blood glucose level, recovers insulin secretion and improves insulin tolerance when administered to diabetic animal model. However, phlorizin cannot be used orally because it is degraded by glycosidase in intestine. Furthermore, phlorizin has little selectivity to SGLT2. Because of such disadvantages, phlorizin itself was not developed as a therapeutics drug. The first chemical compound designed for therapeutics by modifying phlorizin was T-1095. T-1095 is an ester-type pro-drug activated in liver by esterase. Because of this property, T-1095 can act on renal glucose reabsorption with less affecting intestinal glucose absorption. Additionally, T-1095 is relatively resistance to glycosidase in intestine, so that it can be administered orally. T-1095, in fact, played an important role to establish the concept of SGLT2 inhibitors in the early stage of the development. As expected from the pharmacological effect of phlorizin, T-1095 increased urinary glucose excretion and decreased blood glucose and HbA1c levels when administered to diabetic animal. T-1095, furthermore, recovered insulin secretion and insulin response and reduced urinary albumin excretion as well as histo-pathological changes in kidney associated with diabetic nephropathy. T-1095 is an *O*-glycoside similar to florizin, so it still suffered from digestion by glycosidase. Now 6 selective SGLT2 inhibitors have been developed for the treatment of type 2 diabetes. These compounds have *C*-glycoside structures in which sugar and aglycons are directly connected so that they are more resistant to glycosidase. Beside improved half life in blood, they are designed to be highly selective to SGLT2 and with high affinity to SGLT2. They have been established as anti-diabetic drugs with new mechanisms of action to reduce blood glucose without depending on insulin and to recover or prevent symptoms and pathological changes associated with diabetes.

SY1-2

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SY1-3 Effect of SGLT2 Inhibitor on Nonalcoholic Fatty Liver Disease (NAFLD) and Adipose Tissue Volume

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The sodium–glucose cotransporter 2(SGLT2) is responsible for most glucose reabsorption in the kidney and has been proposed as a novel therapeutic target for the treatment of type 2 diabetes. Selective SGLT2 inhibitors are able to reduce hyperglycemia in patients with type 2 diabetes by increasing urinary glucose excretion, and weight loss and improved liver function are consistent associated findings. Here, I would like to focus on the effect of SGLT2 inhibitor on nonalcoholic fatty liver disease (NAFLD) and adipose tissue volume.

SGLT2 inhibitors have been shown to improve obesity and liver steatosis in animal models with type 2 diabetes. For example, ipragliflozin was examined in high-fat diet and streptozotocin–nicotinamide-induced type 2 diabetic mice. Four-week repeated administration of ipragliflozin improved not hyperglycemia but also hepatic steatosis and obesity with a concomitant increase in urinary glucose excretion. In addition, ipragliflozin reduced plasma and liver levels of oxidative stress biomarkers and inflammatory markers, such as interleukin 6, TNF α, MCP-1 and CRP. On the other hand, canagliflozin reportedly decreased blood glucose, body weight gain, epididymal fat, and liver weight in obese animal models of type 2 diabetes. These animal results suggest that SGLT2 selective inhibitors improve not only hyperglycemia but also diabetes/obesity-associated NAFLD in human subjects with type2 diabetes.

Studies of body composition assessing changes in fat mass and lean mass have been conducted for a number of antidiabetic treatments in patients with type 2 diabetes. For example, the increase in body weight seen with thiazolidinediones is largely attributable to an increase in total fat mass and total body water. Bolinder et al. investigated whether weight loss with dapagliflozin was accounted for by changes in fat or fluid components. This was a 24-wk, international, multicenter, randomized, parallel-group, double-blind, placebo-controlled study. Included were 182 patients with type 2 diabetes (mean values: women 63.3 and men 58.6 yr of age; hemoglobin A1c 7.17%, body mass index 31.9 kg/m^2, and body weight 91.5 kg) inadequately controlled on metformin. Dapagliflozin 10 mg/d or placebo was added to open-label metformin for 24 wk. In a subset of patients, magnetic resonance assessment of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) volume and hepatic lipid content were also evaluated. Dapagliflozin reduced total body weight, predominantly by reducing fat mass, VAT and SAT. The same investigators also reported that, over 102 weeks, dapagliflozin improved glycaemic control, and reduced weight and fat mass without affecting markers of bone turnover or bone mineral density in patients with type 2 diabetes inadequately controlled on metformin.

Taken together, SGLT2 selective inhibitors are expected to improve not only hyperglycemia but also diabetes/obesity-associated metabolic abnormalities in human subjects with type2 diabetes.

SY1-4 New Directions in Treatment of Type 2 Diabetes in Japan ～ A Role of SGLT2 Inhibitors ～

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Type 2 diabetes mellitus (T2DM) is a chronic and progressive disorder associated with an increased risk of micro- and macrovascular complications. Despite the wide lineup of available medications, many patients do not achieve the target level of glycemic control. Most antihyperglycemic drugs aim at a reduction in insulin resistance or an enhancement of insulin secretion. Inhibitors of sodium glucose co-transporter 2 (SGLT2) are a new class of oral antihyperglycemic drugs (OADs), and its efficacy is independent of insulin sensitivity and secretion. Healthy kidneys filter approximately 180 g of glucose daily, the majority of that is reabsorbed in the proximal tubule by SGLT2. The SGLT2 inhibitors increase the excretion of glucose in the urine (glucosuria), resulting in a reduction of blood glucose level. The increase in glucosuria and osmotic diuresis results in body weight reduction.

Ipragliflozin, the first product of this class, has appeared into a clinical stage of T2DM in Japan at the end of April, 2014, and another 5 products (dapagliflozin, tofogliflozin, luceogliflozin, canagliflozin and empagliflozin) have been launched at this time or will be launched by the end of 2014. A systematic review and meta-analysis of SGLT2 inhibitors (Ann Intern Med. 2013) reported a favorable effect on HbA1c level (mean difference vs. placebo, -0.66% [95% CI, -0.73% to -0.58%] and a significant reduction of body weight (mean difference, -1.80 kg [CI, -3.50 to -0.11 kg]) and systolic blood pressure (mean difference, -4.45 mm Hg [CI, -5.73 to -3.18 mm Hg]). In Japanese patients with T2DM, the efficacy of SGLT2 inihibitors on glycemic parameters and body weight has been demonstrated over 24 to 52 weeks. A significant HbA1c reduction is observed not only in monotherapy, but also in combination with other any kind of oral antidiabetic drug such as SU, glinide, DPP4 inhibitor, metformin, pioglitazon or α-glucosidase inihibitor. In addition, dyslipidemia (high triglyceride and low HDL-cholesterol) and hyperuricemia frequently observed in T2DM were significantly improved in Japanese population.

In general, the safety and tolerability of SGLT2 inhibitors reported in Japanese patients were similar to those reported in patients outside of Japan. However, the value of weight loss in Japanese population is similar to that reported in Caucasian, whereby the impact on safety and tolerability of this drug may be higher than Caucasian. The reduction of lean body mass and undesirable increase in ketone body would become potential risk in lean or insulin-dependent patients who are not uncommon in Japanese population. Pharmaceuticals and Medical Devices Agency (PMDA) strongly recommends to collect the PMS data of elderly patients (65 years or more) who are thought to be a higher risk of this class of drugs.

A role of SGLT2 inhibitors as a treatment of T2DM in the Japanese population is discussed based on the clinical trial data in comparison with those conducted outside of Japan.

SY2-1 Calcium Signaling and ER Stress in Obesity and Type 2 Diabetes

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Glucagon signaling and endoplasmic reticulum (ER) stress contribute to the metabolic disturbances of obesity and type 2 diabetes (T2D), but the precise mechanisms remain to be elucidated. We recently described a novel pathway involving glucagon-induced hepatic glucose production (HGP) and hyperglycemia in obesity (Ozcan et al., Cell Metabolism 2012). This pathway is triggered by PKA-mediated activation of IP3 receptor, leading to a cascade of calcium release, calcium-calmodulin-dependent protein kinase II (CaMKII) and p38 activation, FoxO1 nuclear translocation, and stimulation of HGP. We have recently shown that the CaMKII-p38 pathway also suppresses insulin signaling in hepatocytes in a manner that is distinct from its effects on nuclear FoxO1 and HGP (Ozcan et al., Cell Metabolism 2013). In particular, genetic suppression of the pathway by targeting CaMKII, p38, or the P38 substrate MAPKAPK2 (MK2) improves insulin-induced AKT phosphorylation in palmitate-treated hepatocytes and in the liver of obese mice. Interestingly, the mechanism does not involve increased tyrosine phosphorylation and activation of insulin receptor (IR) or insulin receptor substrate (IRS) proteins. Rather, CaMKII-p38-MK2 activates the ER stress effector ATF4, leading to increased Tribble 3 (Trb3) and suppression of insulin-induced p-AKT. As such, the improvement in insulin signaling that we observe in hepatocytes or obese mice lacking CaMKII is abrogated by genetically restoring ATF4 or Trb3. In new work, we have evidence that the mechanism of ATF4-TRB3 activation by CaMKII-P38-MK2 involves co-repressor-mediated inhibition of Atf6 expression, leading to a decrease in the chaperone P58IPK and subsequent activation of the PERK-ATF4 branch of the Unfolded Protein Response. In summary, CaMKII-P38-MK2 signaling is involved in two major hallmarks of T2D, excessive hepatic glucose production and defective hepatic insulin signaling. Thus, therapeutically targeting the CaMKII-P38-MK2 pathway may provide a new therapeutic approach to T2D.

SY2-2 Insulin Resistance, Hyperglycemia, and Atherosclerosis: Mechanisms and Interventions

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Treatment advances in type 2 diabetes have significantly curtailed the prevalence, severity, and costs associated with its microvascular complications. Disappointingly, progress in treating atherosclerotic macrovascular complications lags behind, partly because–unlike microvascular disease–their development appears to be impervious to glycemia control. Indeed, considerable epidemiological evidence indicates that insulin resistance can promote atherosclerosis independent of hyperglycemia. We have been interested in studying the genetic, cellular, and biochemical mechanisms by which insulin resistance promotes atherosclerosis. We will review two areas that affect different aspects of the atherogenic process: hepatic dyslipidemia and endothelial dysfunction. In liver, we have recently shown that a key function of insulin is to determine the balance of different species of bile acids. In experimental animal models, the insulin-resistant state is associated with the preferential synthesis of non-12α-hydroxylated (hydrophilic) bile acids. The latter turn out to be poor ligands for the bile acid receptor, FXR, leading to decreased intestinal cholesterol absorption and increased hepatic triglyceride synthesis. Both features contribute to a pro-atherogenic lipid profile, with elevated secretion of TG-rich lipoproteins from the liver. In endothelial cells insulin resistance has pleiotropic manifestations that include decreased NO production, increased chemotaxis, inflammation, and generation of hydroxyl radicals. We have recently shown that these actions are mediated through a single effector, transcription factor Foxo (encoded by three isoforms, 1, 3a, and 4), and that genetic ablation of these effectors results in a striking protection from atherosclerosis. As Foxo factors are also principally responsible for insulin regulation of bile acid synthesis, we will review evidence suggesting that Foxo inhibitors are beneficial for the treatment of metabolic disorders, with an eye toward reducing the excess CVD risk in type 2 diabetics.

SY2-3 Insulin Secretory Defect and Insulin Resistance in the Development of Type 2 Diabetes

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Diabetes mellitus is a heterogeneous disorder characterized by decreased insulin secretion and insulin resistance. Evaluation of insulin secretory capacity and insulin sensitivity is essential for elucidation of pathophysiology, prevention, classification, and therapeutic choice in patients with diabetes. We have analyzed insulin secretory capacity and insulin sensitivity according to the results of OGTT, minimal model analysis and glucose clamp studies in Japanese and compared with Caucasian studies. We have revealed insulin secretory capacity is decreased, and indices of insulin sensitivity is widely distributed from low to high in Japanese diabetic patients. In contrast, Caucasian diabetic patients had decreased insulin sensitivity, and insulin secretory capacity was widely distributed from low to high. In Korean and Chinese studies, similar phenotypic characters are found with Japanese in view of insulin secretory capacity and insulin sensitivity in the published evidences. There are big differences between mean BMIs of Japanese (around 24) compared with Caucasian (around 30) type 2 diabetic patients, however, the prevalence of diabetes in Japanese are similar with USA. Taken together with these results, East Asians are considered vulnerable to diabetes due to reduced reserve capacity of insulin secretion with a little impairment of insulin sensitivity in contrast with Caucasian diabetes with strong insulin resistance. The therapeutic, diagnostic and preventive strategies should be constructed with the consideration of phenotypic characteristic of type 2 diabetes.

SY2-4 Can We Follow Koch's Postulates for Hunting Down Human Obesity Bugs in Gut Microbiota?

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The gut microbiota has been linked with chronic diseases in humans such as obesity and diabetes. Accumulating evidence indicates that gut microbiota may play a pivotal role in onset and progression of adiposity and insulin resistance, the core conditions of metabolic syndrome (MetS) via two different but complementary pathways, i.e. regulation of energy metabolism and provocation of chronic inflammation. However, these mechanistic findings are obtained almost exclusively with rodent models. Their relevance to humans still remains a question. It is also controversial whether the obesity-associated changes of gut microbiota happen at broad taxonomic-level or are more relevant with specific phylotypes. Thus, the demonstration of causality between constituents of the microbiota and specific diseases remains an important challenge in the field. In this presentation, using Koch's postulates as a conceptual framework, I explore the chain of causation from alterations in the gut microbiota, particularly the endotoxin-producing members, to the development of obesity in both rodents and humans. Three components are essential for identifying the causative agents of obesity in the human microbiota: 1) microbiome-wide association studies; 2) isolation of the putative agents and disease reproduction in gnotobiotic animals; 3) mechanistic analysis of host responses to establish the molecular chain of causation.

We have employed this strategy in dietary therapy of morbid obesity/diabetes in humans to show that specific bacterial phylotypes, which are more relevant with MetS, can be identified, isolated and demonstrated in gnotobiotic models to be causatively contributing to MetS development in humans.

SY3-1 Possible Linkage of Visceral Fat Deposition and Hyperaldosteronism---Existence of Aldosterone Production-stimulating Factor in the Serum of Idiopathic Hyperaldosteronism (IHA) Patients

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Metabolic syndrome is recognized to be the complex of glucose intolerance, high blood pressure and dyslipidemia caused by visceral fat deposition. Recently, because of the progress of diagnostic procedure, the occurrence of primary aldosteronism（PA）has been increasing and PA patients are estimated up to 5~15% of total hypertensives. PA mainly consist of two subtypes; aldosterone-producing adenomas (APA) and idiopathic hyperaldosteronism (IHA). APA are usually the unilateral and surgically curable disease and recent studies revealed that several genetic mutations in KCNJ5, ATP1A1 and others have been identified as causative abnormalities. In contrast, the etiology of IHA has not yet been elucidated so far. In the review of our clinical database, daily urinary excretion of aldosterone was highly correlated to BMI, waist circumference, HbA1c and HOMA-R in IHA patients (n=85), but not in PA patients (n=35) or non-PA patients (n=57). We evaluated patients' sera for aldosterone production-stimulating activity in vitro by the two methods; one is CYP11B2 (aldosterone synthase) promotor-driven luciferase reporter assay and the other is ELSA measurement of supernatant aldosterone concentration of cultured aldosterone-producing adrenocortical cells. IHA patients' sera had significantly higher potentials to enhance CYP11B2-promotor activity and aldosterone production than non-PA patients' sera. The difference was more obvious when obese patients with BMI more than 25 were sorted for analysis. The in vitro aldosterone production-stimulating activity of IHA patients' sera was positively correlated with urinary aldosterone excretion and also with visceral fat area estimated by CT scan, while no significant correlation was observed in non-PA patients' sera. These results all together indicate that some humoral factor(s) to stimulate aldosterone production is present in IHA patients' sera and it might be associated with the accumulation of visceral fat in IHA patients. Since aldosterone possesses direct deteriorating action on cardiovascular system, the association of metabolic syndrome and IHA might cause poorer prognosis. We propose that the adipose tissue can be the therapeutic target for IHA.

SY3-2 Lifestyle Disease and Abdominal Fat Distribution

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Abdominal fat distribution may affect lifestyle diseases such as diabetes, hypertension, and dyslipidemia. Japanese have been reported to develop Type 2 diabetes with less obese compared with Caucasian. We will present 2 topics in this symposium. First topic is the comparison of obesity and abdominal fat distribution between Japanese and American men and their impacts of developing metabolic derangements. Second is the impact of obesity and visceral obesity on management of type 2 diabetes in Japan.

ERA-JUMP study has been conducted by Prof. Ueshima (Shiga University of Medical Science) collaborated with Prof. Sekikawa (University of Pittsburg). The aim of this study is to clarify the relationship between risk factors for ischemic heart diseases and subclinical arthrosclerosis in American and Japanese men aged 40-49. In this study, we found that Japanese have larger visceral adipose tissue area with similar waist circumference compared with American. Furthermore, Japanese have easily developed metabolic derangement with obesity and mild visceral obesity compared with American.

Next, we will present the impact of obesity on the management of type 2 diabetes in Japan. Shiga Medical Association conducted the survey for diabetes patients in Shiga prefecture at 2012. This survey revealed that diabetic patient became obese, especially in younger generations, and obese patients have poor control in diabetes, hypertension and dyslipidemia, even though receiving each medication. Finally, we examined the abdominal fat distribution (subcutaneous and visceral fat) in diabetic patients in outpatient clinic of Shiga university hospital using the dual-impedance method (Dural Scan), and found that visceral obesity deteriorates control in diabetes, hypertension and dyslipidemia.

These data suggest that visceral fat accumulation may deteriorate the lifestyle disease control in the diabetic patients, and the management of obesity and visceral obesity is critical to improve the future prognosis.

SY3-3 Obesity as a CVD Risk Factor: Weight Loss Is Not the Optimal Target

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There is now considerable evidence supporting the notion that obesity is a heterogeneous condition and that it can no longer be solely defined on the basis of an excess of total body fat. Indeed, there are remarkable individual differences in regional body fat accumulation at any given body mass index (BMI) value or amount of total body fat. Such variation in regional lipid accumulation has been shown to be a key factor in the determination of the complications associated with a given excess of total body fat. On that basis, it can be questioned whether or not the magnitude of weight loss in response to a lifestyle modification program still represents the most relevant therapeutic target for the management of cardiometabolic risk in sedentary abdominally obese patients.
For instance, it is relevant to point out that both a high level of physical activity and a good level of cardiorespiratory fitness (as an objective marker of regular participation to vigorous physical activities /exercises) are associated with a reduced risk of type 2 diabetes and of cardiovascular disease and that such relationship is partly independent from the concomitant variation in body weight/adiposity. For instance, data from the EPIC-Norfolk prospective study have clearly shown that individuals who reported to be very active were characterized by a reduced risk of coronary heart disease (by about 50%) even if they were abdominally obese with the features of the metabolic syndrome. Accordingly, a high level of cardiorespiratory fitness has been associated with a reduced mortality from cardiovascular disease, even among patients with type 2 diabetes or overweight/obese individuals. Thus, regular vigorous physical activity/exercise is associated with a reduced cardiometabolic risk and this association is partly independent from weight loss. This finding has led to the introduction of the "fat and fit individual" concept. In this regard, MRI and CT imaging studies have clearly shown that physically active/fit individuals are characterized by lower levels of visceral/ectopic fat than sedentary/unfit individuals, even after control for BMI or total adiposity. Accordingly, results of lifestyle modification programs have shown that regular endurance exercise can induce a selective mobilization of visceral adipose tissue/liver fat which is greater than the magnitude of weight loss. Further, regular endurance exercise can induce a selective loss of visceral adipose tissue/ectopic fat even in the absence of changes in body weight. On that basis, it is proposed that beyond weight loss, which remains a legitimate therapeutic target, we should aim for 1- improvement in cardiorespiratory fitness as an objective marker of participation to vigorous physical activity/exercise and 2- reduction in waist circumference and of circulating triglyceride levels as simple markers of loss of visceral/ectopic fat.

SY3-4 Abdominarl Fat and Dyslipidemia

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Obesity (especially abdominal obesity) is a major component of metabolic syndrome, which is based on insulin resistance caused by visceral fat accumulation, and is known as a strong risk factor for cardiovascular diseases. Despite the increased awareness of health risks associated with obesity and its attendant metabolic disorders, the prevalence of obesity has increased rapidly in the past 30 years in Japan. As Asian populations develop negative health consequences at a lower BMI than Caucasians, obesity is defined as any BMI greater than 25 kg/m2 in Japan. The National Health and Nutrition Survey Japan 2011 demonstrated that the prevalence of obesity has increased to 30.3% in male, especially young generation, on the other hand, those in female has been relatively stable at 21.5%.
Dyslipidemia is an obesity-related disorder and one of major risk factors for cardiovascular disease. With extra caloric intake and low exercise, the excess energy is stored as fat at not only subcutaneous but also visceral fat. Visceral fat is associated with higher insulin resistance to promote increased hormone-sensitive lipase activity and excess lipolysis of stored triglycerides from adipocytes, with excess release of free fatty acids (FFAs). The FFA flux stimulates hepatic production of VLDL to cause hypertriglyceridemia. Exchange of triglycerides from VLDL for cholesterol esters of HDL-C by cholesterol ester transfer protein results in rapid clearance of HDL-C. Excess triglycerides also are transferred to LDL, and results in small dense LDL particles.
For the prevention and/or treatment of the obesity-related dyslipidemia, the reduction of body weight, particularly abdominal fat, is essential, and achieved by keeping negative energy balance with caloric restriction and increased physical activity. Formula diet (FD) is characterized by its unique dietary macronutirent composition; high protein, low fat and low carbohydrate, and helpful for the treatment of obesity. Our recent findings indicate that FD has beneficial effects by reducing visceral fat and improving glucose metabolism and lipid profiles, probably through modulating adipose tissue function. The lifestyle modification is not sometimes enough and the anti-obese drugs might be necessary. Cetilistat, an inhibitor of lipase, is recently approved and waited to use the treatment for the obese adults (BMI ≥ 25) with type 2 diabetes and dyslipidemia in Japan. Lorcaserin hydrochloride, a selective 5-HT2C receptor agonist, is approved for use in obese adults (BMI ≥ 30) or adults (BMI ≥ 27) with weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia in USA. It is also appropriate to target on the treatment for the atherogenic dyslipidemia by drugs including fibrates and fish oils. For the treatment of severe obesity (BMI > 35), the bariatric surgery is effective to reduce the body weight and cardiovascular risk. In this session, I am focusing on the obesity-related dyslipidemia, and discussing the necessity of multidisciplinary therapy including nutrition, exercise, drug and surgery.

SY4-1 New Insights in Visceral Fat Syndrome and Adiponectin

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Atherosclerotic cardiovascular disease (CVD) has become a major life-threatening disorder both in West and East. Hyper LDL cholesterolemia is a strong risk factor and strategy has been almost established. A second target is a cluster of multiple risk factors even though the degree of each is week. With the life-styles of physical inactivity and overeating, obesity has become an inevitable physical status, although the average BMI is still quite lower in East Asia compared to Western countries. The prevalence of diabetes mellitus, hypertension and dyslipidemia is explosively increasing also in East where many people live. Accumulation of intra-abdominal visceral fat frequently associates with multiple risk factors, and found in approximately 40% of patients with coronary artery disease (CAD) even though their BMI ranged between 23-25. We named such atherogenic condition associated with multiple risk factors downstream of visceral fat accumulation as visceral fat syndrome (VFS).

Recent researches exploited that inflammatory process plays an important role in the progression of CVD. However, triggers of systemic inflammation remain unknown. Adipose tissue functions as self-defense system against starvation and also produces a variety of biologically acitive substances conceptualized as 'adipocytokines' including members of immune system such as complements. Dysfunction of adipocyte occurs in VFS, and adipocyte oversecretes various proinflammatory adipocytokines and non-protein substances like free fatty acids and reactive oxygen species. Macrophages are recruited to remove damaged adipocytes and to maintain normal function. The inflamed adipose tissue must be an origin of fire in systemic inflammation.

We identified S100A8 mRNA in microarray analysis of adipose expressed genes. S100A8 forms calprotectin with S100A9 and works as an endogenous ligand for an immune system. S100A8 mRNA was expressed in mature adipocyte fraction and upregulated in obese mice. On the other hand, its counterpart (or stabilizer), S100A9 was expressed in stromal vascular fraction (SVF) of adipose tissue. S100A8 may work as early alarming signal to activate and draw macrophages into adipose tissue.

Adiponectin is an adipocyte-derived protein structurally related with complement C1q, which we discovered in human adipose cDNAs, having anti-atherogenic, anti-inflammatory and anti-diabetic activities. Remarkable characteristics of the protein is that 1) adiponectin is present abundantly in plasma but its plasma level is decreased in VFS, and 2) accumulates in injured or atherosclerotic arteries. Hypoadiponectinemia along with overproduction of proinflammatory substances from inflamed adipose tissue may accelerate the progression of atherosclerosis together with a cluster of multiple risk factors.

To clarify the target organs of adiponectin, we injected serum of wild type (WT) mice to adiponectin knockout (KO) mice and performed western blotting of organs. Surprisingly, the tissue, where the exogenous adiponectin accumulated most abundantly, was adipose tissue with no endogenous adiponectin. Exogenous adiponectin was more abundant in SVF of obese mice. Retention or return of adiponectin to born site may play some role in inflamed adipose tissue and mechanism of hypoadiponectinemia in obesity.

Robust exogenous adiponectin was also detected in the aorta. Western blotting showed adiponectin was present in intima of aorta without periaortic adipose tissue. Immunofluorescence study confirmed adiponectin immunoreactivity was observed in aortic endothelial cells co-localized with CD31. Immunoelectromicroscopic study demonstrated adiponectin mainly existed on the luminal surface of aortic endothelial cells. Interestingly, adiponectin was also localized in intracellular vesicles. In apoE KO mice, adiponectin was detected on the surface of vascular smooth muscle cells in the intima of atherosclerotic plaque. Furthermore, adiponectin was also observed on the cell surface of monocytes adjacent to atherosclerotic lesions.

Prevention of CVD is important issue for the management of visceral fat syndrome. We evaluated 1) systemic arteriosclerosis (abdominal aorta, carotid, renal, and common iliac arteries) qualitatively using by vascular ultrasonography, 2) visceral fat area by bioelectrical impedance method and 3) life-style coaching to reduce visceral fat when they have visceral fat accumulation in type 2 diabetics. Polyvascular lesions were detected in 63% patients, and the presence of VFS correlated with polyvascular lesions. Vascular score of ≥ 2 was associated with the presence of CAD.

Although CAD occurs either of diabetics with or without visceral fat accumulation, strategy focusing on the reduction of accumulated visceral fat in VFS and VFS type diabetes.

SY4-2 Perspectives on Obesity, Anthropometry and Cardiovascular Risk

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In Spain, several studies have examined the importance of cardiovascular risk factors; however, DORICA was the first to analyze the role of each of them individually, thus revealing how much each risk factor contributes to cardiovascular morbidity and mortality.

In terms of weight, 40.12% of men and 48.87% of women were classified as normal according to their BMI; 13.2% of men and 17.5% of women were classified as obese. As for cholesterol, 57.3% of men and 53% of women had levels greater than 200 mg/dl, 23% of men and 17.95% of women had LDL-cholesterol levels higher than 160 mg/dl, whereas 15% of men and 6% of women had HDL-cholesterol levels below 40 mg/dl. Hypertriglyceridemia (>150 mg/dl) was detected in 28% of men and 13% of women. Systolic blood pressure was greater than 140 mmHg in 30% of men and in 21% of women; diastolic pressure was higher than 90 mmHg in 23.2% of men and in 13.6% of women. Baseline blood sugar levels were above 126 mg/dl in 11.2% of men and in 7.2% of women aged more than 55; the prevalence of diabetes in this age group was 5.3% and 2.4%, respectively. Smokers accounted for 39% of the study population, and this proportion was higher in men (48.1% of the population compared with 30.2% women).

The prevalence of metabolic syndrome was 10.87% overall (12.15% in men and 9.9% in women). The number of participants with at least 1 major cardiovascular risk factor (arterial hypertension, dyslipidemia, diabetes) was higher in participants with a BMI >27 than in those whose BMI was normal. In terms of waist circumference, 25% of those individuals with risk factors (>102 cm in men and >88 cm women) presented at least 1 major cardiovascular risk factor ($\chi^2 = 56.970$; $P<0.001$). Receiver operating characteristic (ROC) curves were used to compare the sensitivity and specificity of the different anthropometric indicators and estimate the presence of cardiovascular risk factors associated with obesity.

The individual importance of each cardiovascular risk factor in our setting was evaluated by calculating the attributable risk fraction. The attributable fraction for arterial hypertension was 26.7% for men and 22.9% for women. The prevalence of hypercholesterolemia was 20.7% for men and 18.2% for women, with an attributable fraction of 15.7% and 12.7%, respectively. The prevalence of obesity was 13.2% for men and 17.5% for women, with an attributable fraction of 4% and 5%, respectively. Smoking was third in men, with an attributable

SY4-3 Development of a Small-molecule AdipoR Agonist for Type 2 Diabetes and Short Life in Obesity

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Adiponectin is an anti-diabetic and anti-atherogenic adipokine, which binds to adiponectin receptors AdipoR1 and AdipoR2, and exerts beneficial effects on metabolic syndrome via activation of AMPK/SIRT and PPAR-α pathways, respectively, leading to increased mitochondria as well as decreased ectopic fat accumulation, oxidative stress and inflammation (***Nature*** 423:762, 2003; ***Nature Med.*** 13:332, 2007; ***Nature*** 464:1313, 2010). Levels of adiponectin in plasma are reduced in obesity, which causes insulin resistance, type 2 diabetes, fatty liver and atherosclerosis (***Nature Med.*** 7:941, 2001; ***Nature Med.*** 8:1288, 2002; ***Cell Metab.*** 17:185, 2013). Thus, orally active small molecules that bind to and activate AdipoR1 and AdipoR2 could ameliorate obesity-related diseases such as type 2 diabetes, NASH and atherosclerosis.

Here we report the identification of orally active synthetic small-molecule AdipoR agonists (***Nature*** 503:493, 2013). One of these compounds, AdipoR agonist (AdipoRon), bound to both AdipoR1 and AdipoR2 in vitro. AdipoRon showed very similar effects to adiponectin in muscle, liver and adipose tissue, such as activation of AMPK and PPAR-α pathways, and increased exercise endurance and energy expenditure, and ameliorated fatty liver, insulin resistance and glucose intolerance in mice fed a high-fat diet, which was completely obliterated in AdipoR1 and AdipoR2 double-knockout mice. Moreover, AdipoRon ameliorated diabetes of genetically obese rodent model db/db mice, and prolonged the shortened lifespan of db/db mice on a high-fat diet.

Thus, orally active AdipoR agonists such as AdipoRon are a promising therapeutic approach for the treatment of obesity-related diseases such as type 2 diabetes, NASH and atherosclerosis.

SY4-4 Molecular Mediators of Nonalcoholic Fatty Liver Disease

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Obesity and insulin resistance are strongly associated with the development of nonalcoholic fatty liver disease (NAFLD). The excess triglyceride that accumulates in hepatocytes is derived from multiple sources, one of which is de novo lipogenesis. Lipogenesis in liver is regulated by SREBP-1c, a transcription factor that activates genes involved in fatty acid synthesis. The first committed enzyme in fatty acid synthesis, acetyl-CoA carboxylase (ACC), is also regulated by phosphorylation/dephosphorylation, and protein polymerization. Previously, we showed that MIG12, a 22 kDa cytosolic protein, binds to ACC and lowers the threshold for citrate-induced ACC activation. In vitro, recombinant MIG12 induced recombinant ACC polymerization and increased ACC activity by >50-fold. In vivo, adenoviral overexpression of MIG12 induced ACC polymerization, increased fatty acid synthesis, resulting in triglyceride accumulation and fatty liver. A second protein, Spot14 (S14) shares significant homology with MIG12, is also highly expressed in liver and is regulated by SREBP-1c. The mechanism for S14's ability to modulate lipogenesis has not been elucidated. Recombinant S14 homodimers had no effect on ACC polymerization or activity. In vitro biochemical studies and in vivo studies show that S14 can form a heterodimer with MIG12. Recombinant MIG12;S14 heterodimeric proteins also had no effect on ACC polymerization or activity. Conversely, reducing S14 levels in rat primary hepatocytes using siRNA increased ACC polymerization and activity. However, despite increased ACC activity, the knockdown of S14 ultimately reduced overall flux through the fatty acid synthesis pathway, suggesting that S14 has an additional role in regulating fatty acid synthesis. Here, we further explore the interrelated molecular and physiological functions of lipogenic regulators in the development of NAFLD.

SY5-1 SPPARM α : the Next Generation of Selective Drugs Targeting Peroxisome Proliferator-activated Receptor α for Residual Vascular Risk Management

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Significant HDL-C and TG-related risk remains even in patients that attain a low LDL-C target. This suggests that HDL-C and TG levels should be modified in addition to LDL-C.

PPARα transactivation /transrepression modulates potentially atherogenic pathways. PPARα transactivation leads to increased expression of genes involved in FFA uptake and b oxidation, LPL and apoAV and to decreased expression of apoCIII. The net effects of these actions are increases in HDL production, VLDL clearance and LDL particle size and decreases in VLDL production. PPARα activation can also transpress transcription factors involved in vascular inflammation NFKB or AP-1 and reduce the synthesis of proteins such as matrix metalloproteinases, vascular cell adhesion molecules and tissue factor. The inhibition of NFKB and AP-1 activation reduce inflammation and thrombogenesis.

PPARα activation mediates also inhibition of fibrinogen transcription and decreases this independent risk factor for atherosclerosis.

Future developments in the field of PPARα modulators are aimed at developing selective agents, which elicit tissue-specifying desirable biological effects at low doses and are devoid of negative side effects. Each drug has characteristic cofactor binding pattern. The pharmalogical profiling of a selective PPARα modulator compound can be assessed using a number of in vitro and in vivo techniques.

A new generation of potent, selective PPARα agonists (SPPARMα) should have the potential to improve the management of dyslipidemia, CVD and prevent the development/progression of atherosclerosis of diabetic macro- and microvascular complications.

The ideal SPPARMa should be potent, highly selective and should have a reduced side-effect profile.

SY5-2 Cholesterol Ester Hydrolysis in Macrophages: New Therapeutic Target for Residual Risk Reduction

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Because cholesterol ester (CE)-laden macrophage foam cells are the hallmark of atherosclerosis, inhibitors of cholesterol ester formation have been eagerly developed. Although some ACAT inhibitors were shown to be atheroprotective in animal models, their efficacy has not been proven clinically. Theoretically, stimulating the hydrolysis of CE is the alternate way to reduce CE load in macrophage foam cells. However, the molecular identity of the enzymes hydrolyzing CE has been elusive. We have identified neutral cholesterol ester hydrolase 1 (NCEH1), an ER anchored enzyme belonging to the lipase superfamily, as the major enzyme that catalyzes this reaction. Inhibition of NCEH1 causes accumulation of CE in macrophages. Mice transplanted with Nceh1-deficient bone marrow develop more advanced atherosclerotic lesions than those transplanted with wild-type bone marrow. Incubation of Nceh1-deficient macrophages with 25-hydroxycholesterol, a side-chain oxysterol, causes activation of ER stress signaling followed by apoptotic cell death. Esterifed 25-hydroxycholesterol markedly accumulates in the ER, which may directly activate ER stress. Consistently, inhibition of ACAT1 but not ACAT2 completely reverses the effect of 25-hydroxycholesterol. Since activation of toll-like receptor 4 markedly induces cholesterol 25-hydrolase (CH25H) in macrophages, thereby increasing the production of 25-hydroxycholesterol, it is tempting to speculate that NCEH1 protects against immunological activation of ER stress and may be a new therapeutic target for residual risk reduction.

SY5-3 Statin in Lipid Management of Diabetes: Effect on Dyslipidemia and Beyond

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Diabetes is a major risk factor of atherosclerotic cardiovascular diseases (CVD). Patients with diabetes tend to show atherogenic lipid profiles related to impaired insulin action including the appearance of small dense low-density lipoprotein (LDL), increase in the amount of remnant lipoproteins, and decrease in and functional disability of high-density lipoproteins (HDL). Diabetes often accompanies renal dysfunction which is also known to increase risk of CVD. Cholesterol-lowering therapy by use of statin has been well established to prevent CVD in subjects with diabetes. On the other hand, recent data suggest that statin usage is associated with increased risk of developing diabetes in non-diabetic population.

The 2014 American College of Cardiology (ACC)/American Heart Association (AHA) guideline for cholesterol treatment defined diabetes as one of four “statin-benefit groups”. In this guideline, patients with diabetes aged 40-75 and LDL-C≥70 mg/dl are recommended to take either moderate- or high-intesity statin. However, further discussion is required how to overcome residual lipid risk.

Among various statins, pitavastatin is characterized for its potent LDL-C-lowering as well as TG-lowering and stable HDL-C-elevating effects. Renoprotective effects of pitavastatin has also been reported. Moreover, clinical trials performed in Europe and Japan so far have not shown adverse effect of pitavastatin on glucose metabolism. In this presentation, the role of statin in lipid management as well as other potential effects in patients with diabetes will be discussed.

SY5-4 Statin Therapy in Prediabetes: New Insights from Lipidomics in the CAPITAIN Study

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Statin therapy favours normalisation of elevated atherogenic lipoprotein levels and of subnormal HDL-C concentrations in the dyslipidemia of Metabolic syndrome (MetS), a prediabetic state. Beyond the standard lipid profile, plasma lipoproteins transport >300 distinct lipid species, which can be identified and quantitated by mass spectrometric technology. Whether such analysis can identify statin-mediated changes in the plasma lipidome which may negatively or positively impact risk of development of type 2 diabetes is indeterminate. This question is of considerable relevance to public health in view of the putative diabetogenic action of the statin class.

Twelve insulin-resistant males displaying MetS (IDF criteria) with an atherogenic lipid profile involving elevated levels of triglyceride-rich lipoproteins, remnants and LDL-C, and subnormal HDL-C were recruited into the CAPITAIN study after dietary stabilisation. Participants were treated with pitavastatin (4mg/day) for 180 days, resulting in reductions of atherogenic non-HDL-C (-39%), triglycerides (-41%) and remnant cholesterol (-55%), and increase in HDL-C (4%). For lipidomic analyses, age-matched, non-obese, normolipidemic males (n=12) were used as controls. Plasma lipidomic profiles, including molecular species of ceramides, glycosphingolipids, sphingomyelins, phospholipids, lysophospholipids, plasmalogens, cholesteryl esters and glycerolipids were measured using ESI-MS/MS. Differences were assessed by t-tests, adjusted for multiple comparisons. Hypergeometric analysis was applied to compare statin-mediated changes in the plasma lipidome to the lipidomic profile characteristic of type 2 diabetes as determined from two large, independent cohort studies (AusDiab and SAFHS; Meikle et al, PLOS One, 2013, 8:e74341).

At baseline and prior to normalization to allow for statin-mediated changes in lipid levels, the concentrations of 232 of the 330 species in the plasma lipidome were significantly different between the MetS and control groups. Following pitavastatin treatment, the plasma levels of 138 lipid species were significantly increased and two decreased, of which 119 were shifted towards concentrations in healthy controls. These lipids were dominated by alkyl, alkenyl (plasmalogen) and lyso species of phosphatidylcholine and phosphatidylethanolamine (59 species) as well as sphingomyelin and other sphingolipids (35 species). Plasma lipid profiles were normalised to non-HDL-C to rigorously define the compositional differences between groups; statin-mediated modifications in the plasma lipidome of MetS subjects were then compared by hypergeometric analysis to the plasma lipidomic profile characteristic of type 2 diabetes. Importantly, this analysis revealed that plasma lipid species which were both prominently associated with type 2 diabetes and equally present at elevated levels in the diabetic lipidome were enriched among those that were targeted and normalised by pitavastatin treatment. Importantly, several lipid species whose concentrations were normalized by statin treatment are implicated in biological processes central to the pathophysiology of insulin resistance and cardiovascular disease in MetS and type 2 diabetes, including insulin signaling, inflammation, oxidative stress, and atherosclerotic plaque formation.

Pitavastatin treatment of MetS patients resulted in a significant degree of normalisation of the plasma lipidomic profile associated with prediabetes and type 2 diabetes. Such modifications may afford insight into the neutral or even anti-diabetogenic action of pitavastatin in individuals with impaired glucose tolerance as in a cohort displaying impaired glucose tolerance (J-PREDICT trial), and in MetS subjects (CAPITAIN, PREVAIL-US and LIVES studies).

SY6-1 Triglycerides and Dense LDL: Stars or Second Leads?

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Cardiovascular disease (CVD) remains the leading cause of death and a major cause of disability affecting quality of life. Despite best evidence-based strategies, including high-dose statin therapy, it is clear that an unacceptably high residual risk of CV events persists. This clinical challenge is exacerbated by the pandemics of obesity, metabolic syndrome and type 2 diabetes. Atherogenic lipoprotein phenotype (ALP), defined as the imbalance between proatherogenic apoB-containing lipoproteins (increased triglyceride-rich lipoproteins, TRL, and dense LDL particles) and antiatherogenic apo A-I-lipoproteins (contained in HDL), is a key contributor to residual CV risk Epidemiological studies suggest that a high level of HDL-C is protective against CVD. Contemporary data does not support the hypotheses that increasing HDL-C reduces additional CVD risk when fenofibrate or niacin are used in combination with statin. Another class of drugs, cholesteryl ester transfer protein (CETP) inhibitors, clearly increase HDL-C by as much as 50% and do not reduce CVD events. A recent analysis using a Mendelian randomisation approach showed that lifelong exposure to higher plasma levels of HDL-C did not translate to reduction in myocardial infarction risk, and there was no association between an increase in HDL-C and risk for MI. Recent studies on HDL metabolism would suggest that HDL-C is a rather crude and inadequate measure of the antiatherogenic potential of these lipoproteins, while evidence is mounting that HDL "functionality" is also a relevant parameter to account for their atheroprotective effect. A possible alternative explanation of this conflicting evidence is that remnant lipoproteins (dense VLDL and IDL) and small, dense LDL are clinically more relevant than the effect on HDL-C levels.

ALP included hypertriglyceridemia, increased small, dense LDL particles and low HDL cholesterol. Increased small LDL and decreased HDL-C were both found to predict future CVD in the Quebec Cardiovascular Study of randomly selected men followed for 13 years and more recently ALP again was demonstrated to be predictive of CVD in 4594 healthy men and women in Sweden followed for 12 years. In the Multi-Ethnic Study of Atherosclerosis the adjusted risk for developing CVD in 4387 individuals was increased in those with small LDL. ALP was an entity independent of risk associated with isolated increased LDL-C levels or isolated decreased HDL-C levels. There has also been re-evaluation of the importance of TRL as a driver of residual CV risk, especially in the context of cardiometabolic disease. Genetic studies show that variants associated with triglyceride-related pathways (for example the APOA5 variant 1131T>C), are associated with coronary risk. Triglycerides per se might not be atherogenic but instead represent a marker of CV risk because of their association with atherogenic TRL and their remnants. A Mendelian randomisation design was used to overcome confounding between remnant cholesterol and other risk factors including HDL, a major flaw in previous observational studies. The genes studied were those affecting levels of HDL, LDL and triglycerides. In this study, a 1 mmol/L (39 mg/dL) increase in estimated levels of non-fasting remnant cholesterol was associated with a 2.8-fold causal risk for ischaemic heart disease; this was double the risk based on observational data alone.

Patients with high TGs have a greater residual CVD risk but also a greater CVD benefit than those with normal-low plasma triglycerides from a statin-fenofibrate or statin–niacin combination approach, by maximizing the benefits associated with the LDL-C reduction with a significant decrease of TG-rich VLDL, their remnants and dense LDL particles. Normo-triglyceridemic individuals do not have the lipid phenotype with increased lipoprotein remnants and dense LDL, thereby limiting the potential benefits on coronary stenosis and CVD events associated with pharmacological changes in these lipoproteins.

SY6-2 Residual Microvascular Risk : the Next Frontier in Diabetes

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In T2DM, macro-/microvascular complications represent the major cause for morbi/mortality, decreased quality of life and healthcare costs. Microangiopathy ("diabetic complications") are diabetes-specific long-term complications of hyperglycemia (retinopathy, glomerular nephropathy or neuropathy), whereas other vascular complications (PAD, TIA/stroke, (non)glomerular CKD or erectile dysfunction) arise from a combination of macro-/microangiopathies.

Residual vascular risk (RVR) in T2DM is defined as "residual risk of incident vascular events or progression of established vascular damage persisting in patients treated with current evidence-based recommended care, including risk from established risk factors (RFs), such as dyslipidemia, hypertension, hyperglycemia, inflammation and unhealthy lifestyles, and risk related to emerging or newer RFs". Current standards of care in T2DM recommend multifactorial intervention on conventional modifiable RFs to achieve recommended glucose, LDL-C and BP levels. Yet, a minority of T2DM patients attain such targets, most patients not at target being left with substantial RVR of incident micro-/macrovascular events and/or progression of existing complications.

Determining RVR in T2DM is of relevance, as a substantial fraction is modifiable. A major component of modifiable RVR is related to LDL/non-LDL lipids, including atherogenic dyslipidemia (AD; raised fasting TG [a marker of TG-rich lipoproteins and their remnants] and low HDL-C). AD is driven by VLDL overproduction as a result of insulin resistance (IR)/hyperinsulinemia. Epidemiological studies and RCTs show that AD contributes to RVR of micro-/macrovascular disease in T2DM, even when LDL-C and/or hyperglycaemia are controlled. Screening for AD provides an easy, clinically-relevant means to capture RVR associated with the underlying abnormalities of low HDL-C and high TG.

The presence of a metabolic syndrome (MetS) or its score (0/5 to 5/5) also hints to RVR. The presence of a MetS may be used as dichotomic state (presence vs. absence), whereas score ranking within the 6 MetS categories identifies stepwise rises in IR or CV risk (from 0/5 to 5/5), and in microangiopathy risk (from 1/5 to 5/5). Whereas MetS does not compute absolute vascular risk, its presence/score captures relative RVR from standard CV RFs underlying the current MetS definition (high BP, hyperglycemia or AD components) plus that from nonstandard cardiometabolic RFs.

Standards of care in T2DM include target attainment for major modifiable variables (HbA_{1c}, systolic BP, LDL-C) using lifestyle changes or pharmacotherapies. Other modifiable factors or cardiometabolic states associated with RVR are potential therapeutic targets: MetS phenotype, IR/hyperinsulinemia, unhealthy lifestyles, adverse anthropometrics (abnormal distribution and expansion of fat tissue, sarcopenia), low-grade systemic inflammation, endothelial dysfunction, proatherothrombotic conditions, sleep-related breathing disorders, and emerging CV RFs.

As regards non-LDL dyslipidemia, AD is best addressed by lifestyle intervention, fibrates, or nicotinic acid. In ACCORD Lipid, RVR of macrovascular events, persisting despite background statin, was substantially decreased in patients with AD by a lipid-lowering bitherapy combining fenofibrate plus simvastatin. Fenofibrate also decreased RVR of retinopathy progression, irrespective of baseline lipids (ACCORD EYE); reduced albuminuria incidence; and was associated, despite a reversible increase in serum creatinine, with lesser secular loss of eGFR (FIELD washout sub-study), hinting to paradoxical nephroprotection with raised creatinine. This, together with reductions in retinopathy and amputation risk, suggests a wider role for fenofibrate in protecting microvessels in T2DM. As regards other drugs, recent trials targeting low HDL-C/HDL pathways were disappointing.

The R^3i recommendations to reduce residual microvascular risk in T2DM are: (i) improved management of cardiometabolic RFs and attainment of all lipid goals, including non-HDL-C, apolipoprotein B_{100}, HDL-C and TG; (ii) fenofibrate should be incorporated into management algorithms for T2DM to slow progression of early-stage DRP; and (iii) improved collaboration between primary and secondary care is key to targeting preventive strategies to the earliest stages of microangiopathies. Non-HDL-C should be included in therapeutic management decisions on lipid-related RVR.

SY6-3 Regulation of ApoA-I Synthesis by Insulin Signaling

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High density lipoprotein (HDL) cholesterol (C) and apolipoprotein A-I (ApoA-I) levels are strong predictors of risk for cardiovascular disease (CVD). Low plasma levels of HDLC and ApoA-I are common in individuals who are insulin resistant, eg, with metabolic syndrome and/or type 2 diabetes mellitus (T2DM). Despite these strong clinical links between reduced levels of HDL and insulin resistance, there are few studies that have addressed how insulin signaling regulates ApoA-I and HDLC levels. We reported previously that liver specific insulin receptor (InsR) knockout (LIRKO) mice have markedly reduced plasma HDLC levels that increased significantly after restoration of hepatic Akt signaling. Therefore, we created acute LIRKO mice by injecting an albumin-Cre adenovirus (Ad-alb-Cre) into $Insr^{flox/flox}$ (f/f) mice. Knockdown of InsR induced marked reductions in the plasma level of HDLC and the hepatic mRNA levels of both ApoA-1 and Type1 iodothyronine deiodinase1 (Dio1), a selenoenzyme expressed mainly in the liver that converts thyroxine to 3,5,3'-triiodothyronine (T3) or reverse T3. Importantly, injection of LIRKO mice with an adenovirus carrying *Dio1* cDNA restored HDLC levels and significantly increased the expression of ApoA-1 mRNA. Deiodinase1 knockout mice (D1KO) have decreased plasma HDLC compared with WT controls, and ApoA-1 mRNA levels in livers of D1KO mice were significantly reduced. Plasma insulin levels were not different between D1KO and control mice, and hepatic levels of T4 and T3 were normal in D1KO mice. In vitro studies showed that knockdown of either *InsR* or *Dio1* expression significantly reduced *APOA1* expression in HepG2 cells. Overexpression of *Dio1* restored *APOA1* promoter activity that had been reduced by knockdown of InsR in HepG2 cells. Of note, knockdown of InsR in HepG2 cells decreased *APOA1* promoter activity by acting on a region which does not contain any thyroid response elements. Pulse-chase experiments in HepG2 cells showed that deficiency of insulin signaling resulted in decreased synthesis and secretion of ApoA-I. Based on these data, we conclude that defective hepatic insulin signaling leads to reduced expression of *Dio1* which, in turn, leads to reduced expression of *ApoA-1* and decreased synthesis and secretion of ApoA-I from hepatocytes. Studies are underway to identify the transcriptional pathway from *Dio1* to the *APOAI* gene expression. We believe that our studies, which identify a novel pathway linking hepatic insulin signaling, *Dio1*, and ApoA-I synthesis and secretion, could lead to new approaches for increasing HDL levels in people with defective insulin signaling.

SY6-4 HyperapoB and Insulin Resistance

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Background/ objectives: About 80% of diabetes-attributed deaths are secondary to cardiovascular disease and stroke. HyperapoB, or elevated number of apoB-lipoprotein mostly in the form of LDL, is among the most common atherogenic dyslipoproteinemia characterizing patients with insulin resistance (IR) and type 2 diabetes (T2D). In 2006, we hypothesized that hyperapoB was not a mere consequence of T2D but an active player in its pathophysiology. Indeed since then, epidemiological studies confirmed the link of elevated plasma apoB to the development of T2D over 6-10 years in many populations independent of other risk factors including central adiposity and glycemia. However, the mechanisms involved were yet to be elucidated. Our objectives were to establish the mechanisms by which apoB-lipoproteins promote IR and accordingly T2D in humans using *in vivo*, *ex vivo* and *in vitro* models.
Methods: Eighty one non-diabetic obese subjects (45-74 years, BMI ≥ 27 kg/m^2, 33 men and 48 post-menopausal women, no chronic disease, no hormone replacement therapy or medication affecting metabolism) were recruited between 2010 and 2014 at our clinical research unit in Montréal. Insulin sensitivity and secretion were measured *in vivo* using a combination of 1-hour intravenous glucose tolerance test followed by a 3-hours hyperinsulinemia euglycemia clamp. The clearance and oxidation of dietary fat was measured in breath and blood using ^{13}C-triolein-labeled high fat meal. The function of subcutaneous white adipose tissue (WAT) was measured *ex vivo* by assessing the hydrolysis, uptake and storage of synthetic ^{3}H-triolein-labeled triglyceride-rich lipoproteins by subjects' WAT samples obtained by needle biopsy.
Results: We demonstrated in this population of normoglycemic subjects that; 1) plasma apoB predicted IR and compensatory glucose-stimulated hyperinsulinemia in women and men. 2) plasma apoB predicted the activation of IL-1 β system, measured as plasma IL-1 receptor antagonist. 3) Subjects with high plasma apoB had delayed postprandial plasma clearance of dietary fat *in vivo* and dysfunctional subcutaneous WAT *ex vivo*. 4) Four-hours incubation of subjects' WAT samples *ex vivo* with their own LDL reduced WAT function and increased fatty acid accumulation in the medium. There was no sex difference in the relation of apoB-lipoproteins to the metabolic abnormalities explored in this population.
In parallel to the human data, *in vitro* studies demonstrated that 7-day differentiation of adipocytes with elevated, but physiological, concentrations of LDL (1.4 g/L apoB) reduced adipocytes differentiation and function. Moreover, acute incubation of normally-differentiated adipocytes with LDL for 4 hours also reduced adipocytes function. Finally, LDL-inhibition of triglyceride-rich lipoproteins clearance by the adipocytes was, at least in part, secondary to the inhibition of lipoprotein lipase activity by LDL in a concentration dependent manner.
Conclusion and significance: HyperapoB promotes the development of T2D in humans by promoting WAT dysfunction and associated delayed dietary fat clearance, chronic inflammation hyperinsulinemia and IR. Targeting the reduction of plasma apoB may prevent the development of both cardiovascular disease and T2D.

SY7-1 Inflammation: A Unifying Mechanism in Diabetes, Metabolic Syndrome, and Atherosclerosis

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Atherosclerotic disease and obesity share common pathophysiological features. Inflammation mediates all stages of atherogenesis—from early lesion development to atheroma complication—and associates with obesity, insulin resistance, and type 2 diabetes. Inflammation constitutes a mechanistic link between obesity and atherosclerosis: adipokines and free fatty acids released by adipose tissue favor insulin resistance, dyslipidemia, endothelial dysfunction, hypercoagulability, and systemic inflammation, all of which can promote atherosclerosis. Both the innate and adaptive limbs of the immune response operate during obesity and atherosclerosis. The accumulation of heterogeneous macrophage populations, T-cell activation and the effects of numerous cytokines and chemokines characterize both atherosclerosis and obesity. Cytokines such as gamma interferon elaborated by the less numerous T lymphocytes critically regulate macrophages in both obesity and atherosclerosis. Gamma interferon and tumor necrosis factor can also promote insulin resistance, contributing to dysglycemia and diabetes development. Pro-inflammatory cytokines produced by adipose tissue can stimulate the acute phase response, and thus elevate hepatic synthesis of fibrinogen, the precursor of thrombi, and of plasminogen activator inhibitor-1, the major endogenous inhibitor of thrombolysis. Thus, obesity can alter the “fluid phase” of blood in a way that tips the balance toward clot formation and persistence when atheroma disrupt. Obesity elevates blood levels of inflammatory biomarkers, such as high-sensitivity C-reactive protein, itself an acute phase reactant, which can predict cardiovascular events and guide therapy, reflecting the pathophysiological links between atherosclerosis and obesity and its associated metabolic disorders.

SY7-2 Immune System and Gut Microbiota Are Novel Therapeutic Targets for Atherosclerosis

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Atherosclerosis has been recognized as a chronic inflammatory disease, and it has become apparent that various types of inflammatory cells participate in the initiation and progression of atherosclerosis. An intervention to the inflammatory process could be novel therapeutic strategies for preventing cardiovascular diseases. Regulatory T cells (Tregs) and tolerogenic dendritic cells (tDCs) play key roles in atherosclerosis as well as inflammation. We have been focusing on Tregs and tDCs that are considered to down-regulate the activation of T cell responses, and to be activated in the gut, and skin. We have previously shown that oral administration of anti-CD3 antibody or an active form of vitamin D_3 reduced atherosclerotic lesion formation in mice by inducing Tregs and/or tDCs in the gut-associated lymphoid tissues. In addition, we have also demonstrated that ultraviolet B (UVB) irradiation significantly reduced atherosclerotic lesion formation and plaque inflammation. Interestingly, UVB-irradiated mice showed systemic expansion of $CD4^+Foxp3^+$ Tregs with suppressed pathogenic T-cell immune responses. These findings implied that the gut and skin immune systems could be novel therapeutic targets for preventing atherosclerosis. We would like to apply this notion to clinical therapy.

Recently, we also investigated the relationship between the gut commensal bacteria (gut flora), which are reported to be highly associated with the intestinal immunity, and the susceptibility to atherosclerosis. Bacterial DNAs from fecal samples were analyzed by using terminal restriction fragment length polymorphisms in patients with coronary artery diseases and control volunteers. There was no difference in the diversity of microbiota between the coronary artery disease (CAD) and control group. However, characteristic changes of gut microbiota were observed in CAD patients. The order Lactobacillales was increased, the phylum Bacteroidetes (Bacteroides+ Prevotella) was decreased in CAD group. In addition, there was also an association between the percentage of Lactobacillales and the severity of coronary atherosclerotic lesions. These results suggest that CAD was associated with a change in the composition of gut microbiota. Changes in the quality and structure of the Lactobacillales community may cause the initiation and/or progression of CAD. These results suggest that modifying the composition of gut microbiota may be a candidate for novel therapy for CAD. We would like to present our data in this research area.

SY7-3 The Role of GIP in High Fat Diet-induced Obesity

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GIP is an incretin secreted from the enteroendocrine K-cells into the circulation after nutrient ingestion and is involved in glucose-dependent insulin secretion, bone formation, and adipose tissue modification through GIP receptor (GIPR) activation. GIP has a role in compensatory insulin secretion and fat storage into adipose tissue in high fat diet (HFD)-induced obesity. Therefore, GIP has a direct and indirect effect on fat accumulation into adipose tissue.
GIP secretion is induced in response to glucose, protein, and fat ingestion. Especially, fat ingestion strongly induces GIP secretion. However, the molecular mechanisms of GIP secretion remain unclear, due to difficulties in separating K-cells from other intestinal epithelial cells in vivo. We established GIP-GFP knock-in (GIP-GFP) mice that enable us to visualize K-cells by EGFP. Flow cytometry analysis using GIP-GFP heterozygous mice ($GIP^{gfp/+}$) showed that GFP-positive cells (K-cells) were expressed in upper and lower small intestine, but not in stomach and colon. The number of K-cells was significantly greater in upper small intestine than those in lower small intestine (0.052% vs. 0.028% of intestinal epithelial cells; $P<0.05$). GIP mRNA expression and GIP content were greater in K-cells of upper small intestine than that in lower small intestine, indicating that K-cells of upper small intestine are more important to regulate GIP secretion in response to nutrients than those of lower small intestine. Expression levels of free fatty acid receptor GPR120 mRNA were exclusively high in K-cells of upper small intestine, while expression levels of GPR40 and GPR43 mRNA were exclusively high in K-cells of lower small intestine. GPR120-knockout mice had a lower GIP secretion (75% reduction) during oral lard tolerance test (OLTT) compared to wild-type mice (WT), but not during oral glucose tolerance test (OGTT), indicating that GPR120 plays a critical role in lipid-induced GIP secretion from K-cells population.
GIPR-knockout mice showed that inhibition of GIPR signaling ameliorates HFD-induced obesity. However, it remains unclear whether lowering GIP secretion decreases adiposity in vivo. $GIP^{gfp/+}$ showed decreased GIP secretion (50%) compared to WT, while GIP levels were below detectable range in GIP-GFP homozygous mice ($GIP^{gfp/gfp}$) during OGTT. Hence, we evaluated the effects of GIP on HFD-induced obesity in $GIP^{gfp/+}$ and $GIP^{gfp/gfp}$. Under normal fat diet condition, insulin levels after glucose loading were significantly lower in $GIP^{gfp/+}$ and $GIP^{gfp/gfp}$ compared to WT. Bone histomorphometry showed that bone volume and trabecular number did not statistically differ in $GIP^{gfp/+}$ compared to WT. However, they were significantly decreased in $GIP^{gfp/gfp}$. During 8 weeks of HFD feeding, body weight gain was suppressed in HFD-fed $GIP^{gfp/+}$ and $GIP^{gfp/gfp}$. OGTT showed no significant changes in blood glucose levels among three types of mice. HFD-fed $GIP^{gfp/+}$ and $GIP^{gfp/gfp}$ had significantly lower insulin levels than WT. Total body fat was significantly decreased in HFD-fed $GIP^{gfp/+}$ compared to WT. Insulin levels were significantly lowest total body fat in HFD-fed $GIP^{gfp/gfp}$. These results suggest that decreased GIP levels inhibit hypersecretion of insulin and fat accumulation in adipose tissue under HFD-induced obesity. In conclusion, GIP is associated with HFD-induced obesity and lowering GIP secretion has a beneficial role in reducing obesity and insulin resistance without impairing glucose tolerance in HFD-induced obesity.

SY7-4 The Role of Autophagic Failure in Beta Cell Dysfunction in Type2 Diabetes Mellitus

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Progressive decline of beta cell function is one of typical features observed in Type2 diabetes mellitus. Reduced total amount of insulin caused by progressive loss of beta cells eventually results in difficulty to control blood glucose level without hypoglycemia even using intensive insulin treatment. This state is regarded to be highly associated with the onset of vascular complications. Thus, to prevent vascular complications in type 2 diabetes mellitus, it is important to elucidate the mechanism of beta cell dysfunction and to find the new strategy to prevent the progressive decline of beta cell dysfunction based on its pathophysiology.
Although it has been postulated that large-scale protein synthesis and degradation is ongoing within the pancreatic beta cells, the mechanism underlying the dynamic protein turnover in beta cells remains largely unknown. We found that low level of constitutive autophagy was observed in beta cells of C57BL/6 mice fed standard diet; however, it was markedly up-regulated when mice were fed high-fat diet. On the other hand, accumulation of p62 that may suggest the presence of insufficient autophagic flux were observed in islets of diabetic db/db mice and the patients with type 2 diabetes mellitus (Abe H. et al. Endocrinology 2013). This result clearly suggest the association between autophagic failure and beta cell dysfunction. To elucidate the causal relationship between autophagic failure and beta cell dysfunction, we analyzed beta-cell-specific Atg7 knockout mice. This Autophagy-deficient mice showed degeneration of beta-cells and impaired glucose tolerance with reduced insulin secretion. While high-fat diet stimulated beta-cell autophagy in control mice, it induced profound deterioration of glucose tolerance in beta-cell autophagy-defecient mutants, partly because of the lack of compensatory increase in beta-cell mass (Ebato C. et al. Cell Metabolism 2008). These results suggest that the degradation of unnecessary cellular components by autophagy is essential for the maintenance of architecture and function of beta cells. Autophagy also serves as a crucial element of stress responses to protect beta cells under insulin resistant states. Recently, we found that human IAPP that causes amyloid deposition in islets of type 2 diabetes mellitus could be a critical substrate of autophagy (Shigihara N. et al. J. Clin. Invest. 2014). Thus, enhancement of autophagy in beta cells may be potential strategy for the treatment for type 2 diabetes.

SY8-1 Lipotoxicity and Immune Regulation of Homeostasis and Inflammation in Adipose Tissue

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Obesity has reached epidemic proportions in most industrialized countries. Visceral obesity, in particular, is centrally involved in the increased risk of metabolic and cardiovascular disease. Recent studies have shown that obesity is associated with active inflammation within visceral adipose tissue, which in turn increases proinflammatory cytokine production as well as adipocyte lipolysis and release of free fatty acids (FFAs). These adipose tissue-derived cytokines and FFAs are thought to play key roles in the development of cardiovascular and metabolic complications, in part by activating inflammatory processes in distant tissues. Accumulation of excess lipids in metabolic tissues, including liver and muscle, leads to insulin resistance, cellular dysfunction and cell death, which is collectively termed “lipotoxicity”. We recently showed that the major long-chain saturated fatty acid, palmitate, markedly aggravated neointima formation partly by inducing proinflammatory phenotypes in smooth muscle cells in the murine carotid artery ligation model. “Vascular lipotoxicity” is likely to contribute to the development of vascular diseases, such as atherosclerosis, at least partly by promoting vascular inflammation. We also found that palmitate induces β cell dysfunction in vivo by activating inflammatory processes within pancreatic islets. These results suggest that inflammation that has been initiated in visceral adipose tissue leads to activation of inflammation in distant tissues, and that the expansion of chronic inflammation may underlie cardiovascular and metabolic diseases in obese subjects. In that regard, it is important to elucidate how inflammation is regulated in adipose tissue. We found that regulatory B cells maintain homeostasis. Interestingly, adipose tissue regulatory B cells are activated by FFAs, suggesting that B cells are the negative regulatory limb of the response to FFAs in the adipose immune cell network.

SY8-2 A Genome-wide View of Macrophage Activation

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Our recent studies utilized a combination of genome-wide and genetic approaches to define the molecular mechanisms that underlie the development of classically activated and alternatively activated macrophage phenotypes. These studies suggest a relatively simple model of hierarchical interactions between lineage-determining and signal-dependent transcription factors that are required to select functional regulatory elements. To test specific aspects of this model at the level of the DNA template, we used natural genetic variation as an *in vivo* mutagenesis screen to assess the genome-wide effects of sequence variation on lineage- and signal-specific transcription factor binding, epigenomics, and transcriptional outcomes in primary macrophages from different mouse strains. We found substantial genetic evidence supporting the concept that LDTFs define epigenetic and transcriptomic states by selecting enhancer-like regions in the genome in a collaborative fashion and facilitating binding of signal-dependent factors. Our findings set the stage for a much more ambitious approach to exploit natural genetic variation as a means of decoding transcriptional regulatory mechanisms in any cell type. In addition, these findings provide a conceptual basis for understanding how natural genetic variation is likely to affect responses of innate immune cells in the context of chronic inflammatory diseases.

SY8-3 New Aspect of Organ Lipids in Metabolic Diseases and Atherosclerosis from Quantity to Quality: Lessons from Elovl6

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Insulin resistance and lipotoxicity are major pathogenetic factors that precipitate metabolic syndrome, type2 diabetes, and atherosclerosis. To date, well-known established therapeutic approach is improved energy balance towards amelioration of obesity and hepatosteatosis. It should be stressed that abnormal tissue lipids involves two aspects: quantity and quality SREBP-1c is a bHLH type transcription factor (TF) that controls lipid synthesis and is induced during over-nutrition to facilitate the conversion of glucose to fatty acids and triglycerides for storage of the excess energy. Activation of nuclear SREBP-1c in the liver causes hepatosteatosis, hypertriglyceridemia, hepatic insulin resistance through direct suppression of insulin signaling pathways and causes atherosclerosis. SREBP-1c seems to be linked to pancreatic β cell dysfunction, and several diabetic complications. In contrast, CREB3l3 is starvation-induced TF in the opposite direction to SREBP-1c and activates a series of metabolic pathways involved in energy depletion such as lipolysis, insulin sensitization, ketogenesis in a coordinated manner with PPARα, showing protective effects on obesity, diabetes, and atherosclerosis.
While this scenario in lipotoxicity represents quantitative aspect of tissue lipids in obesity-related diseases focusing gene expression, quality of tissue lipids is another important factor to be considered. Aside from a well-known factor: desaturation of lipids such as saturated and unsaturated fatty acids, we have shown that hepatic fatty acid composition focusing on side chain length is a novel determinant for insulin sensitivity independent of tissue lipid contents. We have focused on Elovl6: the long fatty acid elongase that catalyzes conversion of palmitate to stearate and regulates long fatty acid composition around C16-C18. Mice deficient for Elovl-6 become obese and develop hepatosteatosis to the similar levels to controls when fed a high-fat diet or when mated to leptin-deficient ob/ob mice. However, they exhibited marked protection from hepatic insulin resistance (Nat Med 2007). Furthermore, Elovl6 absence completely ameliorated diabetes through protection from loss of pancreatic beta cell mass and impaired insulin secretion (BBRC 2014), atherosclerosis through inhibition of foam cell formation (ATVB 2011), suppressed non-alcoholic steato-hepatitis through inhibition of inflammasome (Hepatology 2012), which temps us to investigate which organ Elovl6 are important and what are the molecular mechanisms using tissue-specific KO mice. Elovl6 seems to play certain roles in various signaling pathways occurring both in membrane and cytoplasmic lipids not only in parenchymal cells such as hepatocytes and beta cells, but also in non-parenchymal cells like macrophages involved in inflammation and fibrosis, contributing to protection from lipotoxic ROS and cell stresses. Meanwhile, Elovl6 is crucial for normal functions of some organs. Lung Elovl6 is important for surfactant with unique fatty acid composition, and related to bleomycin-induced lung fibrosis (Nature Commun 2013). Elovl6 is highly expressed in brain and KO mice exhibit increased brain and hippocampus weights with a variety of marked abnormalities in food preference and behaviors in trends of depression and anxiety, accompanying neuronal changes suggesting involvement of Elovl6 in neuronal signaling and interaction between glia cells and neurons (unpublished data). These new findings in brain could be a hint of most unmet therapeutic issues in this field: behavior change.
Diversity of fatty acid composition in different organs and tissues is now revealed in metabolomics and should be related to different physiologic and pathphysiologic issues. The roles of this unique elongase encompasses emerging diverse functions of fatty acids: signaling through receptors, membrane phospholipid remodeling, and fluxes from storage lipids and should be involved in lipotoxicity and can be a new therapeutic target for insulin resistance, diabetes, and cardiovascular risks circumventing obesity.

SY8-4 Role of ANGPTL3 and 8 in Lipid Metabolism

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Energy homeostasis is maintained by a complex regulatory network that synchronizes fuel metabolism with nutrient availability. During fasting, hormonal and neuronal signals ensure an uninterrupted energy supply to oxidative tissues by promoting the release of fatty acids from and adipose tissue into the circulation. Upon refeeding, the flux of energy substrates is reversed, and the reservoirs of glycogen in liver, and triglyceride (TG) in adipose tissue are replenished. The diurnal flux of circulating TG is controlled by three members of the angiopoeitin-like family of proteins, ANGPTL3, 4, and 8, which are potent post-translational inhibitors of lipoprotein lipase. Genetic ablation of any one of these proteins results in a striking reduction of plasma TG levels, but differences in their temporal and tissue-specific patterns of expression suggest different metabolic roles. The role of ANGPTL4 is the most clearly defined: In WAT, fasting induces the expression of ANGPTL4 which inhibits LPL activity and directs VLDL-TG to oxidative tissues. Here we will discuss recent progress towards elucidating the functions of

MS1 Pathophysiology and Treatment of Diabetes with Metabolic Syndrome

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An urgent task we must undertake to prepare for the coming super-aging society is to establish an active and healthy lifestyle for senior adults, (we Japanese sometimes call them the grand generation), which allows them to enjoy their own lives while passing on their knowledge and experience to the next generation, and to build medical and social systems to support it. Okinawa, which was once an island of the longest-lived people in the world, has ranked near the top of all Japanese prefectures in terms of the proportion of obese people and patients with type 2 diabetes mellitus in the recent decade, and the average lifespan of people in Okinawa has been rapidly decreasing in the same period (the Okinawa crisis). Analysis of the sudden deterioration in disease statistics and the current situation in Okinawa will provide a lot of information that will help us to envision a future of long and healthy lives in Japan as well as Asian countries.
A high-fat diet induces enhanced insulin resistance and excessive/prolonged secretion of insulin, increasing the risk for obesity and type 2 diabetes mellitus. High-fat meals, which are rare in the wild, disrupt the appetite control mechanism of the brain and cause hyperphagia, i.e., eating more than the calories the body needs. The similarity between the dependence on high-fat meals and drug addiction is also attracting attention. A patient with drug dependence increases the dose of his/her drug as the threshold of the brain reward system has been increased and his/her brain is no longer satisfied with the blood level of the drug at the time. Rats fed with high-fat meals, like ones with induced narcotic addiction, exhibit an increase in the stimulus threshold of the brain reward system and cannot feel the rewards of eating in their brain. Reward signals (information on whether the brain is satisfied or not) are mainly processed by dopamine neurons, but obese people exhibit reduced activity of dopamine D2 receptors in the striatum, the core of the reward system. A study in people with severe obesity based on functional MRI analysis revealed that their striatal neurons were not excited even after meals, demonstrating that they could not feel satisfied with eating in their brain.
In my presentation, I strive to make a brief on the scientific front of the obesity-diabetes syndrome, and also I would like to introduce you our challenge of natural food-based novel approach toward the prevention and treatment of obesity-diabetes syndrome. Our research focused on fermentation-based brain control and related epigenetic analyses will also be presented.

MS2 Diabetes Therapy by Focusing on Plasma Glucagon and Body Weight

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Over the past two decades insulin resistance has been considered to be the most essential factor for the development of type 2 diabetes mellitus (T2DM). However, insulin resistance does not lead to T2DM unless it is accompanied by pancreatic islet cell dysfunction. Among islet cell types, much less attention has been paid to α cells than to β cells, but glucagon, the product of α cells, has been shown to play a major role in the development of hyperglycemia in T2DM. Recent clinical application of DPP4 inhibitor and GLP-1 receptor agonist (these drugs control blood glucose by increasing insulin secretion and decreasing glucagon secretion) gave attention to glucagon again. Furthermore, recently Metformin has been also reported to suppress glucagon's function on hepatic glucose production. One of the critical issues in the glucagon research is the poor specificity and low sensitivity of current assay systems. We therefore developed a new glucagon sandwich ELISA that has higher specificity and sensitivity than the conventional assays. Using this new system, we showed that T2DM patients have more severe hyperglucagonemia than currently assumed.
On the other hand, recent large-scale clinical trials revealed that intensive diabetes therapy does not always lead to better quality of life in diabetes patients. Now we have to consider the quality of the treatment, e.g. we should not increase body weight during the treatment of diabetes, otherwise the beneficial effects of lowering blood glucose are canceled by the bad influence of body weight gain. Among diabetes drugs, GLP-1 receptor agonist, α -GI and SGLT2 inhibitor have evidence of lowering body weight. So, these drugs should be used preferentially to obese diabetes patients.
Thus, in the future diabetes treatment, we should pay more attention to plasma glucagon levels and body weight change in diabetes patients.

LS1 Comprehensive Risk Management for Prevention of Caridiovascular Complications of Type 2 Diabetes

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A rapid increase in the prevalence of diabetes is a growing and threatening health issue in Asian countries as well as other regions. Indeed, people with diabetes have been shown to have a significantly shorter life expectancy compared to that of general population, partly due to the increased risk of cardiovascular complications. Regarding the blood glucose control, results of the recent clinical trials have suggested that strict control starting as early as the onset of the disease is effective to prevent the cardiovascular complications. However, it also turns out that hypoglycemia, hyperinsulinemia and body weight gain frequently associated with anti-hyperglycemic therapy could increase cardiovascular events and mortality especially for the patients with long history of diabetes and advanced atherosclerosis. On the other hand, accumulating evidence has indicated that strict control of blood pressure and lipids by ARBs (ACEIs) and statins is quite effective to prevent cardiovascular events of diabetic subjects. Indeed, Steno 2 study has revealed that multifactorial intervention including blood glucose, blood pressure and lipids is effective for prevention of cardiovascular complications and mortality, although its sample size was relatively small. In Japan, we are conducting a multifactorial intervention trial, J-DOIT3, in which 2542 patients were randomly allocated into conventional therapy group and intensive therapy group. The targets of HbA1c, BP and Lipids in conventional therapy group just follow the domestic guideline, while in intensive therapy group, the target of A1c is below 6.2%, the BP target is lower than 120/75 mmHg and the LDL cholesterol target is below 80mg/dl. Since the achievement rates of these targets are relatively high with a very low rate of severe hypoglycemic episodes, J-DOIT3 is expected to provide a further evidence of the efficacy of the comprehensive care of diabetes and a basis of the new guideline of the treatment of type 2 diabetes.

LS2 Implication of GLP-1 Therapy in Type 2 Diabetes

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Almost 90 years have already been passed from discovery of incretin concept which is glucose regulations by gastrointestinal hormones, GIP and GLP-1. During recent several years, the newer treatments for type 2 diabetes, incretin-based therapies that include the glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP4) inhibitors have been become widely used in type 2 diabetes treatments not only in Japan and Asia but also the United States and Europe.

In clinical trials of GLP-1 receptor agonists in Japanese, Asian and also Caucasian populations, treatment with GLP-1 receptor agonists is associated with sustained improvements in glycaemic control, weight reduction with lower risk of hypoglycaemia. And in some clinical trials, GLP-1 receptor agonists have shown favourable effects on several parameters of beta cell function so treatment of GLP-1 receptors agonists might be suitable especially for Asian type 2 patients including Japanese patients with predominantly impaired insulin secretion.

During 4 years' experiences in clinical practice, we confirmed clinical benefit of GLP-1 receptor agonists with HbA1c control and weight reduction and efficacy for blood glucose control was well correlated to residual insulin secretory capacity in Liraglutide treatment.

Also we confirmed the challenge of GLP-1 receptor agonists which are that how we maintain the efficacy of GLP-1 receptors agonists and how we find appropriate patients for these agents.

In this lecture, our consideration regarding appropriate use of GLP-1 receptors agonists will be shown based on the results from clinical trials and experiences in clinical practice of Liraglutide.

ES Role of Oral Hypoglycemic Agent and Future Prospects of Diabetes Management

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"Annual Health, Labour and Welfare Report 2011" announced in March 2013 reported that Japanese citizens who are "highly suspicious of being diabetic" or "cannot deny the possibility of being diabetic" reaches up to a total of 27%, that is to say more than one out of four are diabetic or likely to become one. Therefore, developing prevention and treatment strategies for diabetes are becoming a national issue.

Along with this movement, goal for diabetes treatment has been modified in May 2013 and following goals were proposed; < 6.0% for normalization of blood glucose level, < 7.0% for prevention of complications, and < 8.0% when intensive treatment seems difficult. Improved glycemic control is without doubt highly effective, not only for prevention of microangiopathies but also of macroangiopathies.

Methods for attaining improved glycemic control are diet, exercise and medical treatment. There has been spectacular progress in especially medical treatment, and recently various diabetic drugs have been developed and used in clinical practices. DPP4 inhibitor was the most epoch-making OHA. DPP4 inhibitors rarely cause hypoglycemia as a monotherapy, and it is expected to protect β cell and to reduce CV event risks. It became an indispensable to achieve glycemic goal. With new insulin regimens and GLP-1 receptor agonists, treatment options are rapidly broadening.

While these drugs contribute to improving glycemic control, several issues still remain unsolved. Increasing risks of hypoglycemia and weight gain may be reducing the effect of lowering blood glucose as observed in ACCORD trial. From these points of view, by lowering only HbA1c is not sufficient and a "high quality glycemic control" without causing hypoglycemia and weight gain is thought to be necessary for diabetes treatment.

Under these circumstances, SGLT2 inhibitor is now available in Japan. SGLT2 inhibitor lowers blood glucose by excreting urinary glucose, which is a completely different OHA with a new mechanism of action. There is high expectation with many benefits; low risk of hypoglycemia as monotherapy, possibility when added-on to other OHAs as well and weight loss effect. In this lecture, I would like to look at the current situation and issues of type 2 diabetes patient care, and express my expectations towards the future diabetes treatment.

P001 Serum HDL-C decreases in microRNA-33b knock-in mice for an intron of sterol regulatory element-binding factor 1 (Srebf1)

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Background: MicroRNAs (miRs) are small non-protein-coding RNAs that bind to specific mRNAs and inhibit translation or promote mRNA degradation. Recent reports, including ours, indicated that miR-33 (miR-33a) located within the intron of sterol regulatory element-binding protein (SREBP) 2 controls cholesterol homeostasis and can be a possible therapeutic target for treating atherosclerosis. Primates, but not rodents, express a second miR-33 gene (miR-33b) from an intron of SREBF1. To address miR-33b function in vivo, we developed humanized mice, in which a miR-33b transgene is inserted within a Srebf1 intron.
Methods: The human miR-33b sequence was introduced into intron 16 of mouse Srebf1 by conventional gene targeting methods, because miR-33b is located in intron 16 of human SREBF1 and there are high homologies in exons 16 and 17 between human and mouse.
Results: We successfully established miR-33b knock-in (KI) mice with C57BL/6 background and this miR-33b KI strategy did not alter Srebf1 intron 16 splicing, which was confirmed by RT-PCR and sequencing. The expression of miR-33b in miR-33b KI+/- mice were almost half of those in miR-33b KI+/+ mice. An LXR agonist T0901317, which induces Srebf1 expression, enhanced miR-33b expression in primary hepatocytes and the liver of miR-33 KI+/+ mice. The protein levels of known miR-33a target genes, such as ABCA1, ABCG1, and SREBP-1, were reduced compared with those in wild-type mice. Peritoneal macrophages from the miR-33b KI mice had a reduced cholesterol efflux capacity via apoA-I and HDL-C. Serum HDL-C levels were reduced by almost 35% even in miR-33b KI +/- mice compared with wild-type mice. HPLC elution analysis showed that the decreased HDL levels were mainly composed of very large-, large-, medium sized HDL, which was compatible with the previous results of miR-33a deficient mice.
Conclusions: miR-33b KI mice for an intron of Srebf1 showed reduced HDL-C level. These results indicate that miR-33b can be a potential target for raising HDL-C in humans and may account for lower HDL-C levels in humans than those in mice. It is also indicated that miR-33b is possibly utilized for a feedback mechanism to regulate its host gene SREBF1. These mice will aid in elucidating the roles of miR-33s in different disease models and in screening of the drugs that can alter miR-33a and miR-33b levels and activities.

P002 Plasma macrophage inhibitory cytokine-1 (MIC-1) is associated with atherosclerosis in subjects with normal glucose tolerance

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-Background- Macrophage inhibitory cytokine-1 (MIC-1), is also called GDF15, is a member of the transforming growth factor-beta superfamily. It is expressed in activated macrophages, the placenta, and prostate, and, to a lesser extent, in the liver, kidney, and brain. Increased plasma concentrations of MIC-1 have been reported in patients with a chronic inflammatory state, such as rheumatoid arthritis, and in many types of cancer. MIC-1 is also expressed in adipose tissue and secreted from adipocytes. On the other hand, it has been reported that adipokines, such as adiponectin, leptin, and resistin, are associated with atherosclerosis.
-Objective- The aim of this study was to investigate the relationship between plasma MIC -1 levels and the carotid intima-media thickness (C-IMT) and elucidate the association between plasma MIC-1 levels and atherosclerosis in subjects with normal glucose tolerance.-Methods- A total of 132 subjects with normal glucose tolerance underwent C-IMT measurement. Blood samples were obtained in the fasting state for the evaluation of clinical chemistry parameters. Plasma levels of MIC-1 was measured with ELISA. Spearman's rank correlation coefficient was calculated between clinical parameters. Multiple regression models were used to assess relationships among the sex, body weight, systolic blood pressure, diastolic pressure, total cholesterol, FBS, IRI, HDL-cholesterol, triglycerides, a waist circumference, creatinine, BMI, HOMA-R, plasma MIC-1 concentration, and C-IMT by stepwise analysis.-Results-(N0.1: C-IMT analysis) C-IMT was positively associated with the plasma MIC-1 levels, age and total cholesterol (r=0.252, 0.373, 0.233, P=0.004, 0.0001, 0.007, respectively). Multiple regression analysis resulted in ANOVA P<0.0001, R2=0.232; age, smoking, and total cholesterol were significant factors, their standardized regression coefficients were 0.353, 0.279, and 0.254, and P-values were 0.0001, 0.001, and 0.002,respectively. The partial correlation coefficient between C-IMT and MIC-1 adjusted for the age was -0.05 (P=0.569).(No2: MIC-1 analysis) Plasma MIC-1 levels were positively associated with the age, smoking, and creatinine (r=0.291, 0.231, 0.239, P=0.001, 0.007, 0.005, respectively). Multiple regression analysis resulted in ANOVA P<0.0001, R2=0.235; age, CRP, and sex were significant factors, their standardized regression coefficients were 0.291, 0.301, and 0.270, respectively, and all P-values were 0.0001. -Conclusion- The results suggest that MIC-1 and C-IMT became associated with an increasing age and plasma MIC-1 levels are associated with atherosclerosis.

P003 PUFA and MUFA suppress MCP-1 secretion in LPS-stimulated THP-1 macrophages

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Objective: Monocyte chemoattractant protein-1 (MCP-1) is one of the key chemokines that regulate inflammations. Fatty acid (FA) also modulates inflammatory responses. In this study, we examined the effects of various FAs on MCP-1 secretion.
Methods: THP-1 macrophages were stimulated by 0.1 microg /ml LPS with or without eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), arachidonic acid (AA) as polyunsaturated FA (PUFA), oleic acid (OA) as monounsaturated FA (MUFA), and palmitic acid (PA) and stearic acid (SA) as saturated fatty acid (SFA) for 24h. Cellular viability was examined using an MTT cell viability assay kit. MCP-1 concentration in cell culture medium was measured by ELISA. The expression of MCP-1 mRNA was quantified by real-time RT-PCR. Activation of a nuclear factor-kappa B (NF-kappaB) was determined by using assay kit.
Results: First, we confirmed cell viability under the condition with each FA (1, 10, and 100 micromol/L) with and without 100 microg/mL LPS. Every case showed the similar viability to the controls. Then, we measured MCP-1 concentrations with various kinds of 1, 10, and 100 micromol/L FA without LPS, and compared them to the controls. PUFA (EPA, DHA, and AA) could reduce MCP-1 secretion in a dose-dependent manner. OA and SFA did not reduce MCP-1 secretion at lower concentration, but OA significantly reduced MCP-1 secretion at 100 micromol/L. In contrast, SFA (PA, SA) significantly increased MCP-1 secretion at 100 micromol/L. Next, we measured MCP-1 concentrations with various kinds of 1, 10, and 100 micromol/L FA with LPS. LPS extremely increased MCP-1 secretion. Under LPS stimulation, all kinds of FA reduced MCP-1 secretion, and PUFA and MUFA reduced MCP-1 secretion in a dose dependent manner. In contrast, 100 micromol/L SFA reduced MCP-1 secretion weaker than 1 micromol/L SFA. Similar suppressing effects of PUFA and MUFA were found on MCP-1 mRNA expression, although SFA had no significant effects. LPS activated NF-kappaB, and micromol/L PUFA and MUFA inhibited NF-kappaB activation. However, SFA had no significant effects.
Conclusion: FA affects MCP-1 secretion via NF-kappaB in macrophage. Especially, PUFA and MUFA have the suppressive effect.

P004 SREBP-1c regulates hypertriglyceridemia in apoA5 deficiency

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[Background] Apolipoprotein A5 (apoA5) plays an important role in triglyceride (TG)-rich lipoprotein (TGRL) metabolism. Deficiency of apoA5 causes severe hypertriglyceridemia (HTG) in human and *APOA5* variants are associated with an increased prevalence of mild HTG as well as an increased risk of cardiovascular diseases, implicating apoA5 as a therapeutic target to rescue atherogenic HTG. The facts that not all patients develop HTG in apoA5 deficiency and that they usually develop HTG later in life suggests that there may be some gene/environmental predispositions for developing HTG in apoA5 deficiency. **[Aim]** 1) Identify the factors that induce HTG in apoA5 deficiency. 2) Identify the molecular target to treat HTG of apoA5 deficiency. **[Methods]** We took advantage of apoA5 deficient mice (*Apoa5*$^{-/-}$) which develop only moderate HTG (- 800 mg TG / dl plasma) in contrast to the severe HTG phenotype in human apoA5 deficient patients (- 7000 mg TG/ dl plasma). The detailed biochemical analysis including plasma TG measurement were performed in *Apoa5*$^{-/-}$, after challenging mice with olive oil to increase chylomicron (CM) secretion, T0901317 (an LXR agonist) to increase large VLDL production, and triton WR-1339 to block the catabolism of CM and VLDL. Because we previously identified transcription factor SREBP-1c as a critical regulator of large VLDL production (Okazaki H et al. *J Biol Chem* 2010), we crossbred *Apoa5*$^{-/-}$ with SREBP-1c deficient mice (*Srebp-1c*$^{-/-}$) to generate doubly mutant mice (*Apoa5*$^{-/-}$;*Srebp-1c*$^{-/-}$). Plasma TG levels were measured in *Apoa5*$^{-/-}$ and *Apoa5*$^{-/-}$;*Srebp-1c*$^{-/-}$ of various ages. **[Results/Conclusion]** Both olive oil gavage and T0901317 treatment aggravate HTG in *Apoa5*$^{-/-}$, suggesting the contributions of TGRL of both intestinal and hepatic origin to the HTG in *Apoa5*$^{-/-}$ mice. The absence of SREBP-1c completely reverse the severe HTG in *Apoa5*$^{-/-}$ induced by T0901317, but not by olive oil gavage, suggesting the critical role of SREBP-1c in VLDL accumulation in *Apoa5*$^{-/-}$. We also found that aged *Apoa5*$^{-/-}$ mice develop severe HTG similar to human apoA5 deficient patients. Finally, we found that the age-related HTG in *Apoa5*$^{-/-}$ is largely rescued by the deficiency of SREBP-1c. The results implicate SREBP-1c as a critical regulator of VLDL accumulation in apoA5 deficiency. SREBP-1c, activity of which increases in diabetes and metabolic syndrome, can be a promising therapeutic target to rescue atherogenic HTG due to defective apoA5 function.

P005 MicroRNA-33 deficiency reduces atherosclerotic plaque progression in apoE knockout mice

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Purpose: Despite the rapid progression of medicine in recent years, cardiovascular disease remains one of the major causes of death all over the world. It is known that atherosclerosis is responsible for those cardiovascular diseases and serum cholesterol level has close relation with atherosclerosis progression. Although lowering LDL cholesterol (LDL-C) with statin is epoch-making treatment for preventing and reducing atherosclerosis, HDL cholesterol (HDL-C) raising therapy is still not established.

On the other hand, microRNAs are small, non-protein-coding RNAs that bind to specific mRNAs and inhibit their translation or promote their degradation.

Recently, we and other groups reported that microRNA-33 reduced serum HDL-C by targeting ATP-binding cassette transporter A1 (ABCA1). In fact, microRNA-33 deficient mice which we generated showed a significant increase in serum HDL-C. In this study, we assessed the effect of microRNA-33 on atherosclerosis formation with microRNA-33 and apoE double knockout mice.

Methods and Results: We generated microRNA-33 and apoE double knockout mice by mating microRNA-33 deficient mice with apoE deficient mice. These mice were fed a western diet containing 0.15% cholesterol for 16 weeks from 6 weeks old, and then the severity of atherosclerosis was assessed. Double knockout mice showed a significant increase in serum HDL-C compared to apoE deficient mice. Atherosclerotic plaque areas at aortic root were significantly reduced in double knockout mice. Cholesterol efflux to both apoA-I and HDL-C was also significantly increased in peritoneal macrophages obtained from double knockout mice.

To assess the effect of microRNA-33 in macrophages on atherosclerosis formation, we generated apoE knockout mice that were selectively deficient in leukocyte miR-33 using bone marrow transplantation (BMT). BMT was performed at the age of 8 weeks old. These mice were fed a western diet for 12 weeks from 12 weeks old, and then severity of atherosclerosis was assessed.

Serum HDL-C levels of microRNA-33 and apoE double knockout BM recipients were the same as apoE knockout BM recipients. There was a tendency for a reduction in atherosclerotic plaque formation in double knockout BM recipients compared with apoE knockout BM recipients. On the other hand, quantification of lipid accumulation by oil red O staining showed a significant decrease in double knockout BM recipients compared with apoE knockout BM recipients.

Conclusions: MicroRNA-33 deficiency reduced atherosclerosis probably by both increasing serum HDL-C and elevating macrophage cholesterol efflux. Inhibition of microRNA-33 can be a novel therapeutical approach for atherosclerosis.

P006 CTRP9, a paralog of adiponectin, reduces atherosclerosis in apolipoprotein E-deficient mice

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(Background) The dysreguation of adipocytokines closely links to the development of metabolic syndrome and atherosclerotic cardiovascular diseases. Adiponectin (APN) is a major adipocytokine with anti-atherogenic and anti-diabetic properties. C1q/TNF-related protein 9 (CTRP9) has been recently identified as a paralog of APN, and its plasma levels are low in obesity as well as APN. Recent studies reported that CTRP9 protects myocardium from the injury following ischemia-reperfusion and attenuates neointimal formation after wire arterial injury. However, the effect of CTRP9 on spontaneous atherogenesis remains unclear. Therefore, the present study tested the hypothesis that CTRP9 may mitigate atherogenesis and sought the potential anti-inflammatory effects on macrophages, cells found in atherosclerotic lesions.

(Methods) Recombinant adenovirus expressing the full-length mouse CTRP9 (Ad-CTRP9) or β-galactosidase (Ad-βgal) were administered to male apolipoprotein E deficient (ApoE-/-, 15 weeks old) mice fed normal chow. Three days after the administration, plasma CTRP9, blood glucose, cholesterol and triglyceride were measured. Four weeks after the administration, the aortic roots of these mice were harvested. The atherosclerotic lesions were evaluated by histological analyses including staining with Oil Red O and specific antibodies for CTRP9, mac-3 and smooth muscle α-actin. In vitro, human monocyte-derived macrophages were treated with or without recombinant human CTRP9 for 24 hours, and subsequently they were stimulated with LPS for 6 hours. The mRNA expression of inflammatory-related genes, such as TNF-α, IL-6, MCP-1, IP-10 and tissue factor, an initiator of coagulation, were quantified by real-time RT-PCR methods.

(Results) Ad-CTRP9 significantly increased the plasma levels of CTRP9 in ApoE-/- mice compared to control at 3 days after administration while it did not change blood glucose and lipid parameters. The atherosclerotic lesions in Ad-CTRP9 treated mice were significantly smaller than those in Ag-βgal treated (control) mice. Interestingly, histochemical analyses revealed that CTRP9 protein localizes in atheromata with mac-3 positive / α-actin negative lesions. In addition, in LPS-stimulated macrophages, CTRP9 significantly suppressed the mRNA expression of TNF-α, IL-6, MCP-1 and IP-10, while no change in that of tissue factor.

(Conclusion) CTRP9 in blood stream may directly interact to atheromata and reduce atherosclerosis by attenuating the inflammatory response in macrophages.

P007 Sleep apnea syndrome as an emerging risk factor for type 2 diabetes and atherosclerosis: evidence and underlying mechanism

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Aims: Sleep apnea syndrome (SAS) characterized by intermittent hypoxia (IH) is known as a risk factor for diabetes and atherosclerosis. However, the underlying mechanism how IH induces diabetes and atherosclerosis is elusive. **Main methods:** Pancreatic beta cells (human 1.1B4, rat RINm5F, and hamster HIT-T15 cells), primary cultured rat pancreatic islets and aortic smooth muscle cells (RASMC) were exposed to normoxia, sustained hypoxia, or IH. Glucose-induced insulin secretion (GIS), cell proliferation, and apoptosis were measured by ELISA, WST-8 assay, and TUNEL method, respectively. Changes in mRNA expression, protein expression, and phosphorylation were measured by real-time RT-PCR and immunoblot analysis. **Linking SAS to diabetes:** After IH treatment, GIS both from HIT-T15 cells and isolated rat islets were significantly attenuated. The mRNA level of CD38, a key enzyme for GIS, in IH-treated islets was significantly lower than that in normoxia-treated islets. Reporter gene assay showed that IH attenuated transcription of CD38, and transfection of CD38 expression vector recovered the attenuation of GIS by IH. IH significantly increased cellular proliferation of HIT-T15, RINm5F, and 1.1B4 beta cells, unchanging apoptosis. Real-time RT-PCR revealed that the mRNA levels of Reg family genes, IL-6, a typical Reg family gene inducer, and HGF, an inhibitor of high-concentration of Reg protein-induced apoptosis, were increased in IH-treated cells. In addition, siRNAs against rat Reg family genes except for PAP I/Reg 2 attenuated IH-induced beta cell proliferation. **Linking SAS to atherosclerosis:** The proliferation of RASMC was significantly increased by IH without changing the level of apoptosis. IH-treated cell conditioned medium significantly increased RASMC proliferation. We next investigated the EGF family as autocrine growth factors. Among the EGF family, we found significant increases in mRNAs for epiregulin (ER), amphiregulin (AR) and neuregulin-1 (NRG1) in IH-treated cells and mature ER in IH-treated cell conditioned medium. We next investigated the changes in erbB family receptors that are receptors for ER, AR, and NRG1, and found that erbB2 receptor mRNA and protein expressions were increased by IH. Phosphorylation of erbB2 receptor at Tyr-1248, which leads cell proliferation, was increased by IH. In addition, inhibitor for erbB2 receptor suppressed IH-induced cell proliferation. **Conclusion:** IH stress directly attenuates GIS via down-regulation of CD38. IH also up-regulates Reg family genes as well as HGF gene in beta cells and EGF family genes and erbB2 receptor gene in vascular smooth muscle cells. Thus, SAS could be an important risk factor for diabetes and atherosclerosis.

P008 Activation of AdipoR1 in hematopoietic cells leading to anti-inflammation and R2 in endothelial cells leading to reduced oxidative stress prevent cardiovascular diseases

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The adipocyte-derived hormone adiponectin (Ad) has been proposed to play the central roles as antidiabetic and antiatherogenic adipokine. However, whether Ad receptors AdipoR1 (R1) and AdipoR2 (R2) have the protective roles against atherosclerosis in vivo are still undetermined.

Ad has been shown to be downregulated in obesity. Here we showed that in mice, ApoE deficiency and obesity induced by high-fat diet or leptin deficiency resulted in significantly decreased expression of R2 in aorta.

We showed that R1 knockout (KO) mice exhibited significantly more neointimal formation in response to external vascular cuff injury than wild-type (WT) mice. R2KO or R1•R2 double KO mice exhibited much more neointimal formation in response to cuff injury than R1KO mice. Interestingly, neointimal formation induced by cuff injury as well as insulin resistance were worsened by transplantation of bone marrow from R1KO but not by transplantation of bone marrow from R2KO mice, consistent with the observations that Ad could reduce inflammation via R1 in macrophages. Importantly, the extent of neointimal formation observed in endothelial (ET) cells-specific R2KO mice was almost the same as that in conventional R2KO mice. Moreover, adenovirus-mediated supplement of R2 in aorta or ET cells-specific R2 upregulation significantly attenuated neointimal proliferation. Adenovirus-mediated expression of R2 resulted in increased PPARgamma and increased oxidative stress-detoxifying enzymes such as SOD1. Conversely, targeted disruption of R2 in ET cells resulted in decreased PPARgamma and SOD1.

This study provides the direct evidence that R2 in ET cells and R1 in macrophages play the protective roles against atherosclerosis. Indeed, AdipoRs agonist could suppress inflammation in macrophages and prevent neointimal formation induced by cuff injury.

P009 Ttc39b deficiency increases HDL production and impairs non-HDL absorption in intestinal enterocytes

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TTC39B was identified in a GWAS as a novel gene influencing HDL cholesterol (HDL-C) levels. Here, we show that increased HDL-C levels in *Ttc39b*$^{-/-}$ mice. On a chow diet HDL-C levels were significantly increased by 22% and there were increases in LXR protein but not mRNA, increased expression of ABCA1 mRNA and protein and increased secretion of HDL by small intestinal enterocytes. When mice were fed with a high fat/high cholesterol/bile salt (Paigen) diet, there was a significant 42% increase in HDL-C and also decreased incorporation of dietary cholesterol and fat into chylomicrons and marked protection from steato-hepatitis; in addition to intestinal changes, there was increased LXR protein and induction of Abcg5/8 in liver. *Ldlr*$^{-/-}$*Ttc39b*$^{-/-}$ mice on the Western diet showed increased HDL-C, decreased VLDL/LDL cholesterol and decreased atherosclerosis. These studies show that Ttc39b deficiency results in increased LXR primarily in enterocytes, beneficial lipoprotein changes and reduced atherosclerosis. Moreover, *Ttc39b*$^{-/-}$ mice are protected from fatty liver, indicating that Ttc39b inhibition could be an effective strategy for reducing atherosclerosis and fatty liver.

P010 Inhibition of local macrophage growth ameliorates focal inflammation in the plaque and suppresses atherosclerosis in ApoE-deficient mice

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[Objective] Macrophages play the central role in every stage of atherosclerotic plaque progression, by mediating inflammation and lipid accumulation. Although the local macrophage proliferation in plaque has been detected and indicated to play some role in its development, pathophysiological implication of the macrophage proliferation has not been fully understood. To verify the direct evidence of involvement of local macrophage proliferation for atherosclerotic plaque formation we have generated a mouse whose macrophage proliferation is specifically suppressed, and investigated the pathophysiological significance of macrophage proliferation in atherosclerotic lesion formation. [Research design and Methods] The transgene was designed to inhibit macrophage specific growth by expressing a cyclin dependent kinase inhibitor, p27^{kip} under the control of the scavenger receptor A promoter/enhancer, and was used to generate mac-p27Tg mouse by microinjection. Apolipoprotein E-deficient mouse (ApoE$^{-/-}$) was crossed with mac-p27Tg, and the ApoE$^{-/-}$/mac-p27Tg was created. Atherosclerotic lesion area of 16 and 20-week old ApoE$^{-/-}$ and ApoE$^{-/-}$/mac-p27Tg mice was quantified in oil red O-stained aortic valve annulus sections. Macrophage proliferation was evaluated in double immunostaining of Iba1 and Ki67. The mRNA expression of macrophage marker CD68 and inflammatory cytokines (MCP-1, IL-1β) were assessed by quantitative real-time PCR in atherosclerotic lesion tissue selectively collected by laser-capture microdissection. [Results] The average plaque area of the aortic valve annulus sections at 16-week old, was significantly reduced in ApoE$^{-/-}$/mac-p27Tg, compared with that of the control ApoE$^{-/-}$ (ApoE$^{-/-}$/mac-p27Tg: 0.083 mm^2, ApoE$^{-/-}$: 0.179 mm^2, p = 0.005). Ki67-positive proliferating macrophages were barely detected, and Iba1-positive macrophages were less accumulated in ApoE$^{-/-}$/mac-p27Tg plaque area. The percentage of the necrotic core to the total advanced lesion area was also significantly decreased in ApoE$^{-/-}$/mac-p27Tg. The mRNA expression of CD68 in the lesion was significantly low, and inflammatory cytokine (MCP-1, IL-1β) mRNA expression was also reduced in ApoE$^{-/-}$/mac-p27Tg. [Conclusion] The excess inflammatory response in the atherosclerotic lesion was ameliorated by macrophage growth inhibition. Therefore, the inhibition of local macrophage growth resulted in the marked suppression of atherosclerotic plaque and necrotic core formation in ApoE$^{-/-}$ mice. These results suggest that the local macrophage proliferation plays an essential role in atherosclerotic plaque formation and progression.

P011 Relationship between RDW (red blood cell distribution width) and vascular screening tests : a cross-sectional study

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(Background)
Previous studies have shown that RDW (red blood cell distribution width) is a prognostic marker that reflects oxidative stress and chronic inflammation, which could affect the progression of vascular atherosclerosis. However, the relationship between RDW and vascular screening tests remains unclear.
(Methods)
This is a cross-sectional study performed at Tokyo Saiseikai Central Hospital. We sampled 733 participants who underwent vascular screening tests (cardio ankle vascular index (CAVI), ankle brachial index (ABI) and maximum intima media thickness (maxIMT) of carotid arteries by ultrasound) for their health checkups from January 2006 to January 2011.
They were divided into tertile according to their RDW levels (the 1st tertile, median 15.6; 2nd tertile, median 16.2; and 3rd tertile, median16.7).
We analyzed the differences in the results of vascular screening tests and other factors affecting atherosclerosis (FPG, HbA1c and LDL-C, etc) according to the RDW categories. Trend tests and analysis of variance tests were used for the comparison. Then, the relationship between carotid atherosclerosis and RDW was further analyzed using logistic regression analysis. Carotid atherosclerosis was defined as max IMT of 1.0mm or more. The odds ratio of having carotid atherosclerosis according to RDW levels were calculated with adjustments for age, gender, BMI, HbA1c, HDL-C, LDL-C, systolic blood pressure and smoking status.
(Results)
MaxIMT significantly increased with RDW levels :the 1st tertile 1.06 ± 0.6mm; 2nd tertile 1.23 ± 0.6mm; and 3rd tertile 1.42 ± 0.8mm (P<0.001 for trend, P<0.001 for ANOVA). However, ABI and CAVI did not increase with RDW levels. FPG and HbA1c levels increased modestly but not significantly with RDW levels. The logistic regression analysis showed that those with higher RDW levels had higher odds of having carotid atherosclerosis with ORs of 1.43 (95% CI, 0.97-2.12; 2nd vs. 1st tertile) and 3.27 (95% CI, 2.08-5.13; 3rd vs. 1st tertile).
(Conclusions)
The present study showed that maxIMT was independently associated with RDW levels. This result supports the past finding that RDW is an indicator of the progression of atherosclerosis. On the other hand, CAVI and ABI, which could reflect arterial stiffness rather than atherosclerosis, did not show a significant result. The disparity in the results should be further investigated. As for the non-significant association between glycemic measures and RDW levels, a study with a larger sample is required to confirm the association.

P012 Clinical applications of serum apolipoprotein B-48 measurement to evaluate the accumulation of chylomicron remnants and residual risk status in atherosclerotic cardiovascular diseases

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Fasting hypertriglyceridemia is one of independent and residual risk factors for coronary heart disease (CHD) and partially related to the postprandial hypertriglyceridemia (PH). PH is caused by the overproduction of chylomicrons (CMs) from the intestine or the impaired clearance of CM remnants (CM-Rs). Recent researches have shown that CM-R directly influences the progression of atherosclerotic plaque and CM-Rs are retained within the intima of arterial wall twice as much as VLDL remnants or LDL. Since these data indicated the atherogenic nature of CM-Rs, we established ELISA and CLEIA methods for measuring serum apolipoprotein (apo) B-48 concentration for quantitative evaluation of CM-Rs. The estimated upper reference limit of apoB-48 was 5.7 μg/mL in normolipidemia (n=332)(reference interval, 0.74 to 5.65 μg/mL). We reported that fasting apoB-48 concentrations were higher in males, obese subjects and patients with type II diabetes mellitus. Fasting apoB-48 concentrations increased according to the cumulative number of abnormal factors for dyslipidemia (hypertriglyceridemia, low HDL-cholesterolemia and high LDL-cholesterolemia). They also increased according to the cumulative number of risk factors for metabolic syndrome (MetS). ApoB-48 concentrations were high in patients with clinical and subclinical hypothyroidism. Among subjects including patients with chronic kidney disease (CKD) (n=264), serum log-apoB-48 levels were significantly higher in patients with low estimated glomerular filtration rate (eGFR) (cutoff level; 60mL/min/1.73m^2) or high eGFR with proteinuria than in those with high eGFR without proteinuria. eGFR significantly correlated with log-apoB-48 level and log-apoB-48/TG ratio, and non-HDL cholesterol and log-apoB-48 levels were significant determinants of the reduced eGFR by multiple regression analysis, suggesting that increased serum apoB-48 concentrations partly contributed to an increased risk of CKD as well as CHD. Furthermore, high fasting apoB-48 level significantly correlated with the intima-media thickness of carotid arteries in subjects with normal but relatively high TG concentrations (100<TG<150 mg/dl). Fasting serum apo B-48 levels were significantly higher in patients with CHD (n=96) than in subjects without CHD (n=67) (6.9 ± 2.6 vs. 3.9 ± 2.4 μg/mL, p<0.0001) and had the most significant correlation with the prevalence of CHD. The clustering of high fasting apoB-48 concentrations (>4.34 μg/mL, the cut-off value) and other coronary risk factor increased the prevalence of CHD. In conclusion, high apoB-48 concentrations indicate the accumulation of CM-Rs and significantly correlate with the impaired metabolism and the development of atherosclerotic cardiovascular diseases (ASCVD). Measurement of fasting apoB-48 concentrations is very important for assessment of residual and risk status for ASCVD.

P013 Inflammation and shedding of receptor for AGE (RAGE): roles of ER stress

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Receptor for advanced glycation end-products (RAGE) plays a key role in progression of atherosclerosis through regulation of inflammatory process in endothelial cells. RAGE shedding is a tightly regulated cellular process which could affect inflammatory signaling. Here, we examined cellular mechanisms underlying RAGE shedding in human microvascular endothelial cells. In RAGE-overexpressing endothelial cells, tumor necrosis factor-α (TNF-α) markedly stimulates RAGE shedding with the action dependent on ADAM10, but not on ADAM17, MMP2 and MMP9 expression. Endogenous RAGE activation appears essential for this process; the RAGE ligands, S100P and HMGB1, accelerate RAGE shedding, and TNF-α -mediated RAGE shedding was blocked by knockdown of S100P. TNF-α-stimulated RAGE shedding was suppressed by JNK- or p38-MAP kinase inhibition, but not by Erk inhibition. TNF-α significantly upregulated ATF-4, a mediator of ER stress, while it marginally increased XBP-1 protein, another ER stress pathway. Finally, knockdown of ATF-4 potently suppressed TNF-α-stimulated ADAM10 activation and RAGE shedding. Thus, TNF-α induces RAGE shedding through JNK- , p38-MAP kinase, and ATF-4 pathway in endothelial cells, which could play important roles in RAGE-mediated inflammatory process and atherosclerosis.

P014 Is Pentraxin 3 a biomarker, a player, or both in the context of coronary atherosclerosis?

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Although pentraxin 3 (PTX3) is a biomarker for the risk of vulnerable coronary plaque independent of C-reactive protein (CRP), it is unclear whether PTX3 is a biomarker, player, or both in the context of coronary atherosclerosis. To answer this question, we performed several experimental and clinical studies. First, we examined 690 consecutive patients who underwent coronary angiography with computed tomography. Plasma PTX3 levels were negatively correlated with the visceral fat area, and positively correlated with the levels of two anti-inflammatory factors: plasma adiponectin and high-density lipoprotein cholesterol (HDL-C). On the other hand, high-sensitive (hs)CRP levels were negatively associated with adiponectin and HDL-C levels. Interestingly, the levels of PTX3 and hsCRP showed opposite associations with the number of metabolic factors. Next, we noted that plasma levels of PTX3 were positively correlated with the percentage of lipid volume and negatively correlated with the percentage of fibrous volume by integrated backscatter intravascular ultrasound analysis in patients with stable angina. Since we previously reported that the administration of angiotensin II type 1 receptor blockers (ARBs) decreased plasma levels of PTX3 in patients with successful coronary intervention, we analyzed whether ARBs could directly decrease the secretion of PTX3 from human coronary artery endothelial and smooth muscle cells and adipocytes under serum starvation. As a result, ARBs significantly decreased the secretion of PTX3 from cells independent of nuclear factor kappa-B inactivation, whereas HDL stimulated the secretion of PTX3. In conclusion, the result of these experimental and clinical studies suggest that PTX3 may be not only a biomarker but also a rescue player in coronary atherosclerosis.

P015 LR11, a cell migration regulator, is a novel biomarker for pathological vascular intimal smooth muscle cells

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Migration of vascular smooth muscle cells (SMCs) from the media to the intima plays a key role in the development of atherosclerosis. Soluble form of LR11 (sLR11), an LDL receptor family member, is produced by intimal SMCs, and enhances migration of SMCs via up-regulation of urokinase-type plasminogen activator receptor (uPAR) expression. In this study, the clinical significance of the pathological intimal SMC-specific molecule as a biomarker was studied. Animal experiments showed that the intimal thickness of femoral arteries after cuff placement was decreased in Lr11-/- mice. In cultured Lr11-/- SMCs, AngII-stimulated migration was almost completely abolished. AngII accelerated membrane ruffling through an increase in sLR11-mediated complex formation with uPAR. Thus, migration of SMCs was mediated by sLR11-induced signal activation for membrane ruffle formation. In clinical studies, circulating sLR11 was increased in patients with ACS compared with stable angina pectoris (SAP). The sLR11 levels after coronary stenting of patients with SAP who were treated with PCI were increased after the procedure. Circulating levels of sLR11 in subjects with CAD were increased in those accompanied with diabetes. Taken together, circulating sLR11 most likely reflected the pathological conditions of SMCs in the course of atherosclerosis and after vascular injuries in patients. In conclusion, the animal experiments showed that migration regulator LR11 is involved in the intimal SMC pathology, and furthermore clinical studies strongly indicated that the circulating levels possibly reflect the pathological conditions of SMCs in the process of atherosclerosis.

P016 Unbalanced M1/M2 phenotypes of monocytes and hyperglycemia associate with M1/M2 macrophages in the carotid atherosclerotic plaque in the patients with obesity and diabetes undergoing carotid endarterectomy.

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OBJECTIVE: Obesity and diabetes are high risk factors for stroke as well as myocardial infarction. Monocytes/macrophages (Mϕ) play critical roles on the pathogenesis of inflammation and atherosclerosis. We previously demonstrated the unbalanced inflammatory M1/anti-inflammatory M2 phenotype of peripheral blood monocytes in obese diabetic patients (Satoh N et al., *Diabetes Care* 2010). The aim of this study was to elucidate whether the unbalanced phenotypes of monocytes and clinical variables are associated with the phenotypes of Mϕ in the carotid plaque in the patients with obesity and diabetes.
METHODS and RESULTS: We examined the expression levels and the ratio of positive cells of M1 markers (IL-6, TNF-α), M2 marker (IL-10), and activation markers (ICAM-1, VCAM-1) in monocytes and carotid plaque, respectively, from patients undergoing carotid endarterectomy (n = 23). The expressions of TNF-α and ICAM-1 in monocytes were significantly elevated, although IL-10 expression was significantly decreased in diabetic subjects (n = 11) compared to those in nondiabetic subjects (n = 12) ($p < 0.05$). We also found that VCAM-1 level in the carotid plaque was significantly higher in obese subjects (n = 6) than in nonobese subjects (n = 17) ($p < 0.05$) and that the levels of TNF-α and IL-6 in the carotid plaque were significantly higher in diabetic subjects (n = 11) than those in nondiabetic subjects (n = 12) ($p < 0.05$). Our further analyses indicated that HbA1c and FPG positively correlated with the ratio of IL-6$^+$ cells in the carotid plaque ($r = 0.489$, $p < 0.05$; $r = 0.453$, $p < 0.05$). In addition, HbA1c, FPG, and IRI showed significant negative correlations with the ratio of IL-10$^+$ cells in the carotid plaque ($r = -0.531$, $p < 0.05$; $r = -0.549$, $p < 0.05$; $r = -0.726$, $p < 0.05$). Finally, we found that the levels of IL-6 and TNF-α in monocytes showed significant positive correlations with the levels of IL-6 and TNF-α in the carotid plaque, respectively ($r = 0.420$, $p < 0.05$; $r = 0.419$, $p < 0.05$).
CONCLUSIONS: Our findings suggested that the unbalanced M1/M2 phenotype of monocytes and hyperglycemia would reflect the M1/M2 phenotypes of Mϕ in the carotid plaque in obese and diabetic patients.

P017 Investigation of the vascular protective function of AMPK in *in vivo* models using endothelium-specific AMPK mutant transgenic mice

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Background: The vascular-specific functions of AMPK *in vivo* have not been clarified yet because its vascular-specific conditional knock-out mice have not generated well. We succeeded in generating vascular-endothelium-specific dominant-negative (dn)AMPK and constitutively-active (ca)AMPK transgenic mice using Tet-On expression system. **Results:**We developed TEK-rtTA/TRE-dnAMPK and TEK-rtTA/TRE-caAMPK mice by cross-breeding endothelium-specific TEK promoter-drived rtTA mice with TRE-dnAMPK or TRE-caAMPK mice. After 3 weeks administration of deoxycorticosterone acetate (DOCA) and sodium chloride to uninephrectomised conrol, TEK-rtTA/TRE-dnAMPK, and TEK-rtTA/TRE-caAMPK mice, aorta were isolated and endothelium-dependent vasodilatation(EDVD) was estimated by relaxation responses to acetylcholine. In doxycycline-treated TEK-rtTA/TRE-caAMPK mice, EDVD responses to acetylcholine were significantly ameliorated compared to control DOCA-salt mice, however NG-Monomethyl-L-arginine monoacetate (L-NMMA) pretreatment completely canceled out such amelioration. On the contrary, EDVD responses were significantly smaller in doxycyclin-treated TEK-rtTA/TRE-dnAMPK mice than in control mice. **Conclusion:**Endothelial AMPK might protect vascular function via NO-dependent but blood-pressure-independent mechanisms.

P018 Serum uric acid is a novel risk factor for the vulnerability of carotid atheromatous plaque in diabetic patients

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Carotid-wall intima-media thickness (IMT) is a surrogate marker of atherosclerosis associated with cardiovascular risk factors and with cardiovascular outcomes. MR imaging of carotid plaque has been shown to be superior to the diagnostic assessment of plaque vulnerability at high risk of rupture. Regression of plaque has been reported by intensive statin therapy (IST). The effect of IST on the characteristics of carotid plaques, especially on the instability of plaques was determined using a combination of ultrasonography and MR imaging. In the present investigation, 630 diabetic patients having max IMT over 1.5mm were included. Among them, 492 patients had been treated on IST for more than 1 year before the study (IST group). On the other hand, 138 patients had not been treated on IST before the study (non-IST group). A horizontal cross-sectional image of plaque was taken with T1 and T2 mode. The ratio of the lesion and the submandibular gland was determined. Plaques having the ratio of T1 evaluation more than 1.25 were defined as intraplaque hemorrhage (IPH), while those below 1.25 were defined as stable. Plaques having the ratio of T2 evaluation more than 1.25 were defined as lipid core (LC), while those below 1.25 were defined as stable. In IST group, 59% of the patients have stable plaque, 7% have IPH, 24% have LC and 10% have IPH+LC. On the other hand, 49% of the patients of non-IST group have stable plaque, 5% have IPH, 34% have LC and 12% have IPH+LC. In IST group, among various parameters, only serum uric acid has strong and significant correlation with the presence of LC in carotid plaque in male (p=0.003). Odds ratio of uric acid in the presence of LC in carotid plaque is 1.530. No such correlation was observed in female. Thus, the present investigation provides a new insight into the role of uric acid in the vulnerability of carotid atheromatous plaque in diabetic patients. Also, the uricosuric action of dapagliflozin, a new sodium-glucose cotransporter 2 inhibitor, seems to be noteworthy.

P019 Correlation between lipid profile and level of circulating endothelial progenitor cells (EPCs) in metabolic syndrome patients in saiful anwar general hospital, malang, indonesia

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Prevalence of obesity in Indonesia is relatively high, around 10,3% and tend to be increased every year. Increased prevalence of obesity associated with metabolic syndrome prevalence. Metabolic syndrome, that one of the symptoms was dyslipidemia, directly associated with atherosclerosis. EPCs, due to the function of repair the damage of vascular endhotelial, could not work as expected. Therefore, aim of this study was determine whether there is any correlation between lipid profile and level of circulating endothelial progenitor cell in bloodstream. This study was a survey study with cross sectional data collection. Result of this study shown descriptively using analysis of correlation. Subjects of this study were patients of Endocrinology Division, Internal Medicine Clinic at Saiful Anwar General Hospital, Malang. Blood sample was the main material of this study. Lipid profile and EPCs level were measured and analyzed by using a Spearman Rho for correlation analysis. Correlation analysis shown that Total Cholesterol possesses a significant correlation. r: -547, p less than 0.05. on decreased number of EPCs, otherwise the other component of lipid profile such as Triglyceride, HDL and LDL did not show any correlation on EPCs level. Mechanism between increased levels of Total Cholesterol and decreased number of EPC remain unclear. This study came up with a conclusion that increased level of Total Cholesterol correlated with decreased number of EPCs.

P020 Vascular and metabolic effects of different dosages of omega-3 fatty acids in patients with hypertriglyceridemia

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Background: Experimental studies demonstrate that higher intake of omega-3 fatty acids (n-3 FA) improves insulin sensitivity, however, we reported that n-3 FA 2 g therapy, most commonly used dosage did not significantly improve insulin sensitivity despite of reducing triglycerides by 21% in patients. Therefore, we investigated the vascular and metabolic effects of different dosages of n-3 FA in patients with hypertriglyceridemia.
Methods: This was a randomized, single-blind, placebo-controlled, parallel study. Age, sex, and body mass index were matched among groups. All patients were recommended to maintain a low fat diet. Forty-four patients (about 16 had metabolic syndrome) in each group were given placebo, n-3 FA 1 (O1), 2 (O2), or 4 g (O4), respectively daily for 2 months.
Results: n-3 FA therapy dose-dependently significantly decreased triglycerides and triglycerides/HDL cholesterol and improved flow-mediated dilation, compared with placebo (by ANOVA). However, each n-3 FA therapy did not significantly decrease high-sensitivity C-reactive protein and fibrinogen, compared with placebo. O1 significantly increased insulin levels and decreased insulin sensitivity (determined by QUICKI) and O2 significantly decreased plasma adiponectin levels relative to baseline measurements. Of note, when compared with placebo, each n-3 FA therapy did not significantly change insulin, glucose, adiponectin, glycated hemoglobin levels and insulin sensitivity (by ANOVA). We observed similar results in a subgroup of patients with the metabolic syndrome.
Conclusions: n-3 FA therapy dose-dependently and significantly decreased triglycerides and improved flow-mediated dilation. Nonetheless, n-3 FA therapy did not significantly improve acute-phase reactants and insulin sensitivity in patients with hypertriglyceridemia, regardless of dosages.

P021 AMAP1 as a negative-feedback regulator of nuclear factor-kappaB

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Nuclear Factor-kappaB (NF-kappaB) is a major transcriptional factor regulating many cellular functions including inflammation, therefore it plays critical roles in the pathogenesis of atherosclerosis. The detailed mechanism of its activation has been well characterized, but that of negative regulation has been poorly understood. In this study, we found A Multiple-domain Arf-GAP Protein 1 (AMAP1) as a negative feedback regulator for NF-kappaB by binding with IKK-beta, an essential kinase in NF-kappaB signaling.
[Methods and Results] We recently reported that IKK-beta has multiple roles in regulating widespread cellular responses and cell signaling, implicating that there are still undiscovered roles of IKK-beta. In exploring them further, we identified AMAP1 as a binding protein with IKK-beta by proteomics analysis. AMAP1 is an Arf-GTPase-activating protein that functions to catalyze the hydrolysis of GTP bound to Arf, and reported to play major roles in the regulation of membrane remodeling, cytoskeletal organization and cellular migration. The role of AMAP1 in the inflammatory response is of high interest because AMAP1 is dramatically upregulated in advanced cancers, but it has been poorly understood so far. Co-immunoprecipitation study confirmed the IKK-beta-AMAP1 binding, and experiments using truncated mutation of IKK-beta and AMAP1 indicated the IKK-gamma-binding domain of IKK-beta and SH3 domain of AMAP1 are the binding sites. Previous reports showing the requirement of IKK-beta-gamma binding for the activation of NF-kappaB prompted us to examine the effect of AMAP1 on NF-kappaB activity, and we found that overexpression of AMAP1 suppressed NF-kappaB activity by interfering the binding of IKK-beta and IKK-gamma, and deletion of AMAP1 augmented NF-kappaB activity. Further, sucrose-gradient fractionation and immunocytochemistry experiments indicated that the activation of NF-kappaB by IL-1-beta induced translocation of AMAP1 to cytoplasm from cell membrane and nucleus, which resulted in augmented interaction of AMAP1 and IKK-beta.
[Conclusion] These results demonstrated a novel role of AMAP1 as a negative feedback regulator of NF-kappaB, and presented it as a possible target for treatments against inflammation, including atherosclerosis.

P022 The mechanism underlying the association between 5'-flanking region of neuropeptide Y2 receptor gene variant and plasma HDL-cholesterol levels

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In the previous report by Kuo et al., adipose tissue neuropeptide Y (NPY) and NPY 2 receptor (NPY2R) are involved in the development of visceral obesity in mice with high caloric diet under stress. We have previously reported the association between 5'-flanking region of NPY2R gene SNPs (rs6857530 A/G and rs6857715 T/C) and plasma HDL-cholesterol (HDL-C) levels in subjects coming to the city health center for health checkups (Metabolism 59, 1591-1596, 2010). Plasma HDL-C levels were lower in subjects with each SNP type G or T, and higher in those with A or C. However, the mechanism underlying the association between NPY2R gene variants and plasma HDL-C levels is still to be clarified. In the present study, we constructed pGL3-basic vector with 5' -flanking region of NPY2R gene including each SNP haplotype GT or AC, and measured luciferase activity after the transfection of these vectors in cultured HepG2 cells, macrophage differentiated from THP-1, and adipocytes differentiated from 3T3-L1. Relative luciferase activity vs. control empty pGL3-basic (mean±SD) was 1.0±0.3 at control, 1.48±0.76 at AC, and 4.9±3.0 at GT in HepG2 cells (ANOVA, $P<0.05$). On the other hand, relative luciferase activity was 1.0±0.21 at control, 2.72±0.48 at AC and 1.5±0.51 at GT in macrophage ($P<0.01$). Luciferase activity was 1.0±0.07 at control, 1.08±0.15 at AC, and 1.07 ±0.21 at GT in adipocytes ($P=0.694$). These results suggest that higher expression of NPY2R in hepatocytes and lower expression in macrophage might cause lower plasma HDL-C levels. Further studies are required to examine why NPY2R gene transcription is differently controlled among SNP genotypes as well as cell types and how the expression of molecules involved in HDL metabolism are regulated by NPY through NPY2R in each cell types.

P023 Lysophospholipids in atherosclerosis and thrombosis

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Background: Lysophospholipids (LPLs), such as sphingosine 1-phosphate (S1P) and lysophosphatidic acid (LPA), are proposed to exert important roles in the field of atherosclerosis and thrombosis from basic studies; however, the involvement of lysophospholipids in the atherosclerosis and thrombosis in human subjects remains to be elucidated.
Method: We measured the plasma LPLs (S1P, LPA, lysophosphatidylcholine [LPC], lysophosphatidylethanolamine [LPE], lysophosphatidylinositol [LPI], lysophosphatidylglycerol [LPG], and lysophosphatidylserine [LPS]) using LC-MS/MS analysis, the proteins related with LPLs (Autotaxin [ATX] and phosphatidylserine-specific phospholipase A1 [PSPLA1], a producing enzyme for LPA and LPS, respectively, and apolipoprotein M [ApoM], a carrier and modulator of S1P), and several markers for platelet activation (serotonin, β-TG, and PF4) and thrombosis (PAI-1) in 141 consecutive patients undergoing coronary angiography (acute coronary syndrome [ACS], n = 38; stable angina pectoris [SAP], n = 72; angiographically normal coronary arteries [NCA], n = 31).
Results: In the ACS subjects, the LPA, LPE, LPI, LPG, and LPS levels significantly increased. Moreover, multivariate logistic regression analyses revealed that the highest LPE and LPI tertiles were independently associated with ACS, as well as LDL cholesterol and HDL cholesterol.
Contrary to the increase in plasma LPA and LPS in ACS subjects, the producing enzymes, ATX and PSPLA1, were not elevated in ACS. ATX and PSPLA1 had only a weak correlation with LPA and LPS, respectively, while apoM had no significant correlation with S1P. These results suggest that several conditions such as platelet activation might modulate the LPLs levels in human subjects as well as these proteins related with LPLs.
Regarding the correlation between the markers for platelet activation or thrombosis and LPLs, serotonin had a significant positive correlation with LPS and S1P, β-TG and PF4 had a rather weaker correlation with most of the LPLs, and PAI-1 had a positive correlation with LPE, LPG, and LPS. When the subjects were confined to those with ACS, we observed that serotonin had a stronger correlation with LPS ($r = 0.57$) and PAI-1 with LPG ($r = 0.36$), LPS ($r = 0.35$), and S1P ($r = 0.43$), while no correlation were observed between β-TG or PF4 and LPLs.
Conclusion: Minor LPLs (LPE, LPI, LPG, and LPS) as well as LPA might be involved in the pathogenesis of ACS, especially platelet activation and thrombosis.

P024 Molecular dissection of hypoapoC-II caused by defective apoC-II mRNA transcription

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[Background] Apolipoprotein C-II (apoC-II) is a cofactor of lipoprotein lipase (LPL) that accelerates hydrolysis of triglyceride (TG) in TG-rich lipoprotein particles. ApoC-II deficiency, an autosomal recessive disease, is a well-known cause of severe hypertriglyceridemia (HTG). Most of the apoC-II deficiencies completely lack plasma apoC-II protein. In several atypical cases of apoC-II deficiency, plasma apoC-II protein was detected but markedly reduced (hereafter referred to as hypoapoC-II) due to homozygous mutations in *APOC2* that cause decreased promoter activity or improper splicing of apoC-II mRNA.
[Aim] Elucidate the molecular bases of our case of hypoapoC-II, manifesting severe HTG with recurrent episodes of acute pancreatitis.
[Methods] To examine apoC-II protein in patient's plasma which had not been detected by immunodiffusion assay, immunoblot analysis of plasma, isoelectric focusing and two-dimensional electrophoresis of TG-rich lipoprotein were performed. LPL and hepatic lipase activites in patient's post-heparin plasma (PHP) were measured using ^{3}H-triolein emulsions. Expression levels of apoC-II mRNA was investigated by Northern blot analysis using primary monocytes/macrophages derived from peripheral blood of the patient. DNA sequencing and whole-genome sequencing were carried out using genomic DNA.
[Results/Conclusion] Immunoblot assay using anti-apoC-II antibody proved reduced but detectable levels of apoC-II protein in patient's plasma. Estimated plasma concentration of apoC-II protein in patient's plasma was ca. 0.6 mg/dl, which was below the plasma levels of the apoC-II protein in heterozygous apoC-II deficiency. Isoelectric focusing and two-dimensional electrophoresis of TG-rich lipoprotein followed by immunobloting demonstrated that each isoform of patient's apoC-II protein had identical isoelectric point and molecular weight to those of a normal control subject, indicating normal amino acid structure of patient's apoC-II. Consistent with these findings, LPL activity in patient's PHP was reduced, which is restored by the addition of control plasma. All of these results were compatible with the diagnosis of hypoapoC-II. Transcription of apoC-II mRNA was decreased in the patient's monocytes/macrophages. However, sequencing of the patient's *APOC2* including splice donor sites, 3'-UTR and promoter regions revealed no rare variant. Other genes involved in plasma TG metabolism (*LPL*, *APOA5*, *APOC3*, *LMF1* and *GPIHBP1*) were sequenced, but no rare variant was found in the patient's gene. To reveal the yet-to-be-identified regulatory mechanisms of apoC2 mRNA transcription, we performed whole-genome sequencing; screening of several candidate mutations that could cause hypoapoC-II is underway.

P025 Effect of linagliptin on AVI and API, indices of vascular stiffness evaluated by an automatic blood pressure monitor

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Dipeptidyl peptidase 4 inhibitors (DPP4i) have been widely used for the treatment of type 2 diabetic patients. Effect of DPP4i on cardiovascular system is still controversial. Among drugs in this class, linagliptin has been shown to have beneficial effects to reduce incidents of cardiovascular events in an early preliminary analysis. Pasesa® blood pressure monitor (Shisei Datum, Tokyo, Japan) has received approval for medical use in Japan, and this automatic blood pressure monitoring apparatus measures blood pressure, heart rate, and pulse pressure, while simultaneously displaying the condition of central arteries near the heart (AVI) and the stiffness of peripheral blood vessels (API). In this study, we evaluated AVI and API when type 2 diabetic patients received linagliptin in clinical settings. Twenty six diabetic patients (M/F=16/10, age: 68±11y.o., duration of diabetes: 12±11yrs, HbA1c: 7.8 ±1.4%, BMI: 24±4kg/m^2, BP: 134±20/73±15mmHg) received linagliptin 5mg qd for 11.9 months on average. The application of this drug and clinical practice is conducted by physicians who practice based on clinical guidelines issued from the Japan Diabetes Society. Pasesa® was used to evaluate AVI and API on each visit. Although BP at the observation (135±21/70±14mmHg) was not different from the base line, HbA1c was reduced to 7.4±1.6% ($p<0.05$). AVI (from 23.6±8.4 to 22.6 ±6.6) and API (from 31.7±8.2 to 33.2±8.9) were not different significantly. While HDL-C was increased from 43±12 to 48±16 mg/dL, LDL-C was not decreased (from 95±21 to 102±31 mg/dL). CAROLINA study has been conducted to investigate the long term impact on cardiovascular morbidity and mortality by linagliptin. However the result will not be available until 2018. Our data indicate that there were not any deteriorate effects on AVI, API, and lipid profiles by linagliptin. Since glucose control has been improved it may be possible to expect some beneficial effects by this drug.

P026 Resistin like molecule beta stimulates CB1 expression in monocytes/macrophages through CAP1-related signaling pathways

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Background:
Resistin, a hallmark of NIDDM (type 2 diabetes), increases cellular levels of insulin resistance and produced by murine adipose tissue and by human adipocytes, myocytes, pancreatic cells and most notably monocytes/macrophages. Resistin and resistin like molecules (RELMs) alpha and beta are a cysteine-rich proteins. RELM alpha shows little expression in humans. RELM beta reportedly contributes to local immune responses and may also facilitate atherosclerosis because RELM beta is abundantly expressed in foam cells within plaques.
Recently, we found that human monocytes undergo significant upregulation of cannabinoid receptor 1(CB1) expression during differentiation into macrophages, showing that CB1 induced the generation of reactive oxygen species (ROS) and subsequent production of pro-inflammatory cytokines by macrophages.
We therefore investigate if human resistins may affect CB1 expression in human monocytes/macrophages and their functional activities.

Methods and Results:
RT-PCR, real-time PCR and immunoblotting consistenly showed that RELM beta dose-dependently induced upregulation of CB1 expression by human THP-1 macrophages. Promoter assay using Luciferase reporter system confirmed positive regulatory role of RELM beta on CB1 expression. RT-PCR and immunoblotting also showed that RELM beta-stimulated CB1 expression requires activation of MEK, MAPK and NF-kappaB signaling pathways. RELM beta dose-dependently activated adenylyl cyclase-associated protein 1 (CAP1), a novel resistin receptor, through direct binding of CAP1. Suppression of CAP1 expression by specific small interfering RNA (siRNA) abolished RELM beta-induced expression of CB1.

Conclusion: RELM beta stimulates CB1 expression in monocytes/macrophages through CAP1-related signaling pathways such as NF-kappa B.

P027 Lipidomic analysis approach to reveal molecular mechanism of endothelial function in clinical study

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Introduction:
Endothelial function is a predictor of cardiovascular events. Many epidemiological reports suggest the relationship between dietary habit and atherosclerosis. However, molecular mechanisms of endothelial dysfunction are not fully understood. Therefore, we focused on the role of lipid mediators in endothelial function using blood samples from subjects with dietary intervention of fish and brown rice. Lipid mediators are signaling molecules metabolites by enzymes such as cyclooxygenase (COX), lipoxygenase and CYP450. Polyunsaturated fatty acids become a substrate hydrolyzed from membrane phospholipid by phospholipases A2. These lipid mediators act as autocrine or paracrine and exert complex control over many bodily systems. Few reports measured lipid mediators in clinical study. Vasodilator tune signals composed with nitric oxide (NO) synthetized by eNOS, prostacyclin, endothelium-derived hyperpolarizing factor (EDHF) such as epoxyeicosatrienoic acids (EETs) in the lipid mediator. Therefore, we developed the method with comprehensive identification and quantification of lipid mediators in human plasma and serum using LC-MS/MS system to reveal how these lipid mediators play a role in vascular function.
Study design and Method:
Twenty-three type 2 diabetes mellitus (T2DM) were assigned to two month periods of either a brown rice based diet or a white rice based diet group in a randomized design. After both diets were completed, both groups in all T2DM were assigned to two month of energy control diet period. Endothelial function was measured with reactive hyperemia using strain-gauge plethysmography in 0, 2 and 4 months. This endothelial function was determined with peak forearm blood flow (Peak FBR), duration of reactive hyperemia (Duration) and flow debt repayment (FDR). Also in this period plasma samples were taken to evaluate the level of lipids mediators.
Results:
A brown rice-based dietary group improves Peak FBR (413 to 492 %, $p < 0.01$), FDR (47 to 64 %, $p < 0.05$). We identified about 65 compounds in the plasma from these subjects by LC-MS/MS. COX derivative (PGE_2, TXB_2) from arachidonic acid were significantly decreased after brown rice diets. However, 6-keto-PGF_{1a} metabolite of PGI_2 were slightly increased after brown rice diets. Thus, the ratio 6-keto-PGF_{1a}/TXB_2 significantly increased in after 2 month of brown rice diets. Furthermore, EETs were increased in brown rice diet group compared with white rice diet group during follow-up period.
Further study is necessary to investigate the relationship between these lipid mediators and endothelial function.

P028 Pioglitazone ameliorates cuff induced neointimal formation by both adiponectin dependent and independent pathways

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Thiazolidinediones (TZDs) have known to ameliorate atherosclerosis. Adiponectin also has anti-atherogenic properties in vivo and in vitro. We previously demonstrated the adiponectin deficient mice exhibited increased neointimal formation in response to cuff-injury, and adiponectin transgenic ApoE-deficient mice showed amelioration of atherosclerosis. TZDs have been shown to upregulate adiponectin expression, and these upregulations have been proposed to be a major mechanism of the TZDs-induced suppression of atherosclerosis. However it remains unclear to what degree adiponectin is indeed involved in the TZDs-mediated amelioration of atherosclerosis. In this study we investigated neointimal formation in the adiponectin deficient (adipo-/-) mice by pioglitazone treatment. In the normal diet, the adipo-/- mice showed substantially more neointimal formation than the wild-type mice as previously reported. 3 weeks of pioglitazone reduced significantly the neointimal formation in the wild-type mice with upregulation of serum adiponectin levels, but 3 weeks of pioglitazone fail to reduce the neointimal formation in the adipo-/- mice. Moreover, the proliferation of vascular smooth muscle cell (VSMC) was significantly increased in the wild-type mice after 3 weeks of pioglitazone treatment. Adiponectin significantly suppressed the proliferation of VSMC via AMPK activation in the cultured human aortic smooth muscle cells. 3 weeks of pioglitazone suppressed the neointimal formation in an adiponectin-dependent fashion, at least in part via the suppression of proliferation of VSMC. On the other hand, 8 weeks of pioglitazone exhibited similar significant reductions in neointima formation in both wild-type and adipo-/- mice. The proliferation of VSMC was significantly increased in the adipo-/- mice, which was completely normalized after 8 weeks of pioglitazone. Morover, inflammatory cytokines and lipid profiles significantly improved in the adipo-/- mice after 8W of pioglitazone. 8 weeks of pioglitazone suppressed the neointimal formation independent of adiponectin, at least in part via the suppression of proliferation of VSMC, inflammatory cytokines and lipid profiles. Thus, pioglitazone-induced suppression of atherosclerosis occurs both dependently and independently of adiponectin.

P029 Relationships of elevated levels of serum hepatic enzymes and alcohol intake with arterial stiffness in Japanese men

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Objective:
Elevations in serum alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT), surrogate markers for liver injury, have been shown to predict cardiovascular diseases and events in prospective studies independent of conventional cardiovascular risk factors. However, detailed reports about the relationships between serum elevated levels of hepatic enzymes and arterial stiffness are few. Moreover, alcohol intake might have a modifying effect on the relationship between serum levels of hepatic enzymes and arterial stiffness. We evaluated the relationships of elevated serum ALT and GGT levels with arterial stiffness in Japanese men. In addition, whether alcohol intake had a modifying effect on the relationships was further evaluated.
Methods:
A total of 647 eligible Japanese men aged 35-69 years who were enrolled in the baseline survey of a prospective cohort study in Tokushima Prefecture, Japan and in whom brachial-ankle pulse wave velocity (baPWV) as an index of arterial stiffness was measured at the baseline survey were included in this cross-sectional study. Serum biochemical factors including ALT and GGT were determined, and information on individual medical histories and lifestyle characteristics over the past year was obtained through a structured self-administered questionnaire. Serum ALT and GGT levels were divided into tertiles, and their associations with baPWV values were evaluated by general linear models.
Results:
The mean age and body mass index of the study subjects were 48.8 years and 24.5 kg/m^2, respectively. The mean baPWV of the study subjects was 1,438 cm/s. Elevated serum ALT and GGT levels were proportionally associated with increased baPWV after adjusting for the multivariate covariates (P values for trend, 0.004 and 0.003, respectively). Further analyses revealed that the proportional associations between serum levels of hepatic enzymes and baPWV were striking in the subjects without alcohol intake but not in those with alcohol intake. The effect of the interaction between serum GGT level (continuous, log-transformed) and alcohol intake (dichotomous, current or others) on baPWV was significant (P for interaction, 0.042).
Conclusions:
Our study demonstrates that elevated serum ALT and GGT levels are associated with increased arterial stiffness, independent of the classical atherosclerotic risk factors in Japanese men, and that the association of elevated serum GGT level with arterial stiffness differs according to alcohol intake.

P030 Progranulin plays a crucial role in the development of atherosclerosis

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Progranulin (PGRN) is a multifunctional protein and that mutations in the PGRN gene have been reported to cause frontotemporal dementia. We previously reported that PGRN, which is secreted from human monocyte-derived macrophages, is bound to apolipoprotein A-I, a major component of HDL. Although PGRN is also known to be involved in inflammation, there is no information on the direct effect of PGRN expression on atherosclerosis.
Therefore, we generated PGRN-/-ApoE-/- (double knockout, DKO) mice to explore the role of PGRN in atherogenesis. DKO mice that were fed HFD for 12 weeks developed severe atherosclerosis compared to ApoE KO mice, suggesting that PGRN has an atheroprotective role. The increase in atherosclerotic lesions in DKO mice was in part due to the enhanced expression of adhesion molecules in the aortic lesions. Moreover, lack of PGRN leads to accumulate excessive cholesterol in the macrophages and alter HDL-associated proteins. Although PGRN has been reported to bind directly to TNF receptors and suppress inflammation by disrupting TNF alpha signaling, we examined whether the effect of PGRN is mediated solely by TNF receptors. We checked the PGRN-induced phosphorylation of akt in the macrophages of TNF receptor 1, 2 double knockout mice. Even in the peritoneal macrophages of TNF receptor 1, 2 knockout mice, PGRN phosphorylated akt, suggesting that PGRN has the other pathway but TNF receptors to exert its effects.
Collectively, PGRN has a variety of atheroprotective functions, therefore PGRN can be a promising therapeutic target for atherosclerosis.

P031 Rapid HPLC method for measurement of cholesterol levels in major lipoprotein classes and estimation of lipoprotein profiles in male volunteers without overt diseases

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Objective: Analyzing lipoprotein profile gives very important clinical information for therapy of dyslipidemia which accelerates atherosclerotic diseases, e.g., coronary heart disease (CHD) and stroke. The lipoprotein classes can be isolated from serum by ultracentrifugation. However, the ultracentrifugal method consumes a long time, and needs large amount of serum. We have established a rapid HPLC method for measurement of cholesterol levels in major lipoprotein classes of which the assay time and the injected sample volume are 5.2 min and 1.0 μL, respectively.
Methods: The HPLC method contained a diethylaminoethyl-ligand column, three eluents, and a post-column reactor with a reagent containing cholesterol esterase and cholesterol oxidase. Five lipoprotein classes (HDL, LDL, IDL, VLDL, and Other (chylomicron + lipoprotein(a)) were eluted with step-gradient of perchlorate sodium concentration after injecting serum into the column. These eluted lipoproteins were detected by post-column reaction. We examined the correlation between lipid and lipoprotein profiles, measured by the HPLC method, and the Framingham risk score (FRS) for prediction of 10-year coronary heart disease risk in 171 male volunteers without overt diseases.
Results: The within-day assay and between-day assay coefficients of variation for cholesterol levels in each lipoprotein were in the range of 0.33 - 4.31 % and 2.37 - 9.19 %, respectively. The correlation coefficients between cholesterol values of HDL, LDL, IDL, and VLDL + other by the HPLC method and those by an ultracentrifugation method were 0.97, 0.92, 0.58, and 0.94, respectively. Non-HDL-C, triglyceride, and IDL in sera of male volunteers were significantly correlated with FRS (r=0.454, 0.250, and 0.341, respectively), but VLDL and Other were not significantly correlated.
Conclusion: The present HPLC method could rapidly and accurately determine cholesterol levels in serum major lipoprotein classes. These results suggest that this method may be sufficiently applied to the assay for assessment of therapy of dyslipidemia for prevention of atherosclerotic diseases.

P032 Newly developed apolipoproteinA-I mimetic peptide decreased native and modified high-density lipoprotein-induced aldosterone synthesis in adrenocortical cells

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High-density lipoprotein (HDL) is a source of precursor for steroidogenesis. Native (Nat-), oxidized (Ox-) and glycoxidized (Gly-) HDL may increase aldosterone (Ald) synthesis. Moreover, we recently developed a novel inducible cholesterol efflux peptide (iCE) [24 amino acids of apolipoprotein A-I mimetic peptide without phospholipids (Fukuoka University ApoA-I Mimetic Peptide, FAMP)]. Therefore, we analyzed whether Nat-, Ox- and Gly-HDL increase Ald synthesis, and the synthesis is decreased by FAMP. The incubation of FAMP with HDL generated small HDL particles, and charged ApoA-I-rich particles migrated as pre-β HDL. Next, we evaluated the effects of in vitro Nat-, Ox- and Gly-HDL on adrenal Ald synthesis using angiotensin II (Ang II)-sensitized and -nonsensitized human adrenocortical cell line (NCI-H295R). Nat-HDL was glycoxidized in the presence of glucose and oxidized using sodium hypochloride. We confirmed that Nat-, Ox- and Gly-HDL increased Ald synthesis up to 20 μg/mL in a dose-dependent manner. Finally, Nat-, Ox- and Gly-HDL pretreated with FAMP showed a decrease in Ald synthesis compared to Nat-, Ox- and Gly-HDL pretreated without FAMP. In conclusion, all Nat-, Ox- and Gly-HDL induced Ald synthesis in adrenocortical cells. The synthesis was decreased by FAMP.

P033 Protective effect of Semaphorin 3G on atherosclerosis development

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Objective: Semaphorins are multifunctional proteins involved in axon guidance, angiogenesis and immunity, etc. However the contribution of semaphorins to atherosclerosis progression remains unclear. Here, we analyzed the role of Semaphorin 3G (Sema3G), a recently identified member of secreted semaphorins, in development of atherosclerosis.
Methods and Results: To determine the effect of atherogenic factors on the expression of Sema3G, C57BL/6 mice were fed with high fat diet and examined the Sema3G mRNA level in aorta by real-time PCR. The expression of Sema3G mRNA was reduced in mice fed a high fat diet compared to mice fed normal diet. Next, in order to identify the function of Sema3G in atherosclerosis, the double-target mutation mice was generated with Sema3G knockout mice and ApoE knockout mice. Sema3G/ApoE double knockout mice were maintained with high cholesterol diet from 10 weeks old to 20 weeks old and inducing atherosclerotic lesions in aorta were quantified by oid red O staining. As a result, the relative atherosclerotic lesion area was increased by 50% in Sema3G/ApoE double knockout mice compared to ApoE single knockout mice.
Conclusions: Present findings demonstrated that Sema3G has a protective effect against atherosclerotic formation. Although further studies are needed, Sema3G may be a new therapeutic target.

P034 Long-term effects of VCRESC® (a vitamin micronutrient beverage) on vitamin and homocysteine（Hcy）levels in patients with coronary atherosclerosis

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Aim: Increased blood levels of homocysteine (Hcy) is a risk factor of atherosclerotic cardiovascular diseases. One of possible approach to reduce Hcy levels is a oral supplementation of B-vitamins and folic acid, all of which are known to play a role as a co-factor in Hcy metabolism. Therefore, in the present study, we examined long-term effects of B-vitamins (B6, B12) and folic acid supplementation by means of commercially-available vitamin micronutrient beverage in relation to Hcy level.
Methods: Fifteen patients with angiographically-proven stable coronary artery disease (54.4 ± 3.0 years old) were enoilled. Blood levels of vitamin B6, B12, folic acid and Hcy values were measured before and after over six month-period with consumption of 125 ml/day of VCRESC® (Nutri Co. Ltd, Tokyo).
Results: Levels of vitamin B6 significantly increased（$p<0.01$）, and B12 levels showed modest but significant increase ($p<0.05$). Baseline folic acid levels remained low, and increase significantly after the period with considerable variation ($p<0.01$). In respnses to these changes, Hcy levels significantly decreased from 10.28 to 7.9(nmol/ml) ($p<0.01$).
Conclusion : Levels of B-vitamins and folic acids were significantly increased by six-months consumption of VCRESC® in association with significant reduction of Hcy levels. These results suggested that commercially-available vitamin micronutrient beverage VCRESC® appears to be a novel alternative to reduce blood levels of Hcy.

P035 Effects of eicosapentaenoic acid (EPA) on lipid accumulation in lipoprotein-loaded macrophages

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Objective: To elucidate the antiatherogenic mechanism of eicosapentaenoic acid (EPA), we examined the effects of EPA on lipid accumulation in remnant lipoprotein [remnant-like particles (RLP), cholesterol ester (CE) and triglyceride (TG) rich-lipoproteins], native low-density lipoprotein (LDL, CE rich-lipoproteins) or oxidized LDL (oxLDL, CE rich-lipoproteins)-loaded THP-1 macrophages.
Methods: THP-1 cells were incubated with RLP, LDL, oxLDL, with or without EPA under the various experimental conditions. Cell viability was examined using an MTT cell viability assay kit. We measured cellular accumulation of total cholesterol (TC), CE, and TG using Bligh-Dyer method and the enzymatic assay kits. We also observed the accumulation of lipids in THP-1 cells using Oil red O staining (fat staining), Nile blue (CE staining), or BODIPY 493/503 staining (TG staining). The expression of lipid-associated enzymes [adipose triglyceride lipase (ATGL), hormone sensitive lipase (HSL), and neutral cholesterol ester hydrolase 1(NCEH1)] examined by Western blotting.
Results: TC, CE, and TG contents were significantly increased by RLP, and increased TC, CE, and TG were significantly reduced by RLP with EPA. TC and CE were significantly increased by oxLDL, and increased CE was not significantly reduced by oxLDL with EPA. The degrees of fat, CE, and TG staining were enhanced by RLP. The degrees of fat and CE staining were enhanced by oxLDL.
The expressions of ATGL, HSL, and NCEH1 were significantly elevated by RLP and ATGL, HSL, and NCEH1 elevations were similar to those by RLP+EPA. The expressions of NCEH1 were significantly elevated by oxLDL and NCEH1 elevation was similar to those by oxLDL+EPA. The expressions of ATGL and HSL were not significantly altered by oxLDL and oxLDL+EPA. LDL and LDL+EPA did not significantly alter lipid content, lipid staining, and ATGL, HSL, and NCEH1 expressions.
Conclusion: EPA can reduce cellular CE and TG contents when CE and TG as RLP were loaded in THP-1 cells, but EPA cannot reduce CE contents when CE as oxLDL were loaded.

P036 Normal calorific diet enriched fat and fructose leads to multiple metabolic disorders and enhances atherosclerosis in WHHL rabbits

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Intake of a diet enriched in fat and sugar is detrimental to the metabolism and related to metabolic syndrome, however, it is unknown whether taking normal calorific diet enriched fat and fructose diet has any adverse influence on the lipid metabolism and insulin sensitivity, and the development of atherosclerosis in the setting of hyperlipidemia. To examine this hypothesis, we fed Watanabe heritable hyperlipidemic (WHHL) rabbits, a model of human familial hypercholesterolemia, with a diet supplemented with 10% coconuts oil (saturated fat) and 30% fructose (CF) with restricted normal calories for 8 and 16 weeks and compared with WHHL rabbits fed a normal chow diet in terms of lipid metabolism and insulin response. At the end of the experiments, all rabbits were sacrificed and their aortic and coronary atherosclerosis was compared. We found that CF diet feeding even at normal caloric range led to the elevation of plasma cholesterol and triglycerides and induced insulin resistance. Although the body weight was unchanged, CF diet feeding resulted in adipose accumulation along with hepatic steatosis. Finally, WHHL rabbits fed with a CF diet showed greater aortic and coronary atherosclerosis than control WHHL rabbits.
These results indicate that consumption of normal calorific CF diet leads to multiple metabolic disorders and enhances atherosclerosis in the setting of hyperlipidemia.

P037 Collateral damage: A case of chronic total occlusion of the left main coronary artery

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Background: Occlusion of the left main coronary artery (LMCA) is the most dangerous presentation of arteriosclerotic coronary artery disease (CAD). Total chronic occlusion (CTO) of the left main stem is a rare condition with a reported prevalence of 0.04% to 0.4%. Long-term survival and myocardial function depend on well-developed right to left collateral circulation.
Objective: To present a rare occurrence of a chronic total LMCA occlusion in a 63-year old male patient presenting with recurrent angina and non-ST elevation myocardial infarction.
The Case: A 63-year old male patient with multiple CAD risk factors was admitted due to complaints of recurrent angina. Electrocardiogram showed sinus bradycardia with high lateral wall ischemia. Troponin T was positive and the patient was treated as a case of non-ST elevation myocardial infarction. A two-dimensional echocardiogram showed concentric left ventricular hypertrophy with adequate contractility and normal left ventricular systolic function. The patient underwent coronary angiography which revealed a completely occluded LMCA at its ostium with visualization of the left coronary system via right coronary artery (RCA) injection. The proximal to distal RCA was good-sized and patent, but there was a 70% stenosis at the proximal right posterior descending artery (RPDA) and the proximal right posterolateral (RPL) branch. Revascularization with coronary artery bypass grafting with intra-aortic balloon pump insertion was accomplished. The patient eventually recovered and was discharged improved.
Conclusion: Chronic total occlusion of the left main stem is a rare and dangerous presentation of coronary artery disease. This case underscores the significance of collateral circulation in the survival of patient with total left main stenosis. Revascularization via coronary artery bypass grafting remains the best treatment strategy.

P038 A small-molecule AdipoR agonist ameliorates type 2 diabetes and prolongs the shortened lifespan

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Adiponectin is an anti-diabetic adipokine, which facilitates glucose and lipid oxidation, thereby increasing insulin sensitivity. In liver, activation of AdipoR1 stimulates AMPK pathway thereby decreasing both gluconeogenesis and steatosis and activation of AdipoR2 stimulates PPARalpha pathway thereby increasing fatty acid oxidation and decreasing steatosis. In skeletal muscle, adiponectin stimulates AMPK activity via AdipoR1, thereby activating Sirt1 and PGC-1alpha, leading to increased mitochondrial biogenesis and metabolic fitness.
We next try to characterize one of orally active AdipoR agonists (AdipoRon). AdipoRon activates AMPK and increases PGC-1alpha and mitochondria in C2C12 myotubes and also in skeletal muscle of mice on a high-fat (HF) diet. At the same time, AdipoRon increased fatty-acid combustion and decreased oxidative stress, which are associated with increased insulin sensitivity and exercise endurance. In liver, AdipoRon activates AMPK and suppresses gluconeogenic genes and activates PPARalpha pathways such as increased fatty-acid combustion. In adipose tissues, AdipoRon suppresses pro-inflammatory adipokines such as MCP-1. Importantly, in AdipoR1/R2 double knockout mice, all these effects are almost completely abolished. Interestingly, bone marrow transplantation experiments between wild-type and AdipoR1/R2 double knockout mice revealed that AdipoRs actions not only in metabolic organs but also in hematopoietic cells play pivotal roles in the regulation of insulin sensitivity. Moreover, AdipoRon ameliorated diabetes of genetically obese rodent model db/db mice, and importantly prolonged the shortened lifespan of db/db mice under HF diet.
These data suggest that orally active AdipoR agonists are promising new therapeutic approach for treating HF diet-induced diseases such as type 2 diabetes.

P039 Role of chronic inflammation in diabetic nephropathy through glucolipotoxicity and intraglomerular crosstalk

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Nowadays, inflammatory system could also be involved in the pathogenesis of non-infectious condition including cancer, autoimmune diseases, lifestyle-related diseases and their complications. Such sterile inflammation is referred to as chronic (or homeostatic) inflammation which is caused by interactions between pathogenic receptors and their endogenous ligands. We have identified toll-like receptor 4 (TLR4) and its endogenous ligand, myeloid-related protein 8 (MRP8, also known as S100A8 or calgranulin A), as commonly upregulated genes in two distinct diabetic mouse models using glomerular microarray analysis. Glomerular MRP8/TLR4 genes were remarkably upregulated along with exacerbation of nephropathy in diabetic and hyperlipidemic mouse models, such as streptozotocin (STZ) combined with high-fat diet (HFD)-treated mice and A-ZIP/F-1 lipoatrophic diabetic mice, compared to non-diabetic control mice. We revealed that lack of TLR4 ameliorated the progression of diabetic nephropathy by hyperlipidemia, and also effectively reduced MRP8 upregulation associated with diabetic-hyperlipidemic condition both in vivo (glomeruli) and in vitro (cultured macrophages: Mf). In vitro study suggested that MRP8 could be systemically induced in glucolipotoxic manner in Mf. Furthermore, treatment of STZ mice with HFD enhanced phosphorylation of interferon regulatory factor 3 (IRF3) and inhibitor of kappa B (IkB) in the kidney. This enhancement by HFD was not observed in TLR4-knockout mice. These findings suggest that combination of diabetes and hypterlipidemia activates the TLR4-downstream, TRIF-dependent pathway in the kidney. Enhanced expression of CCAAT element binding protein beta (C/EBPb) and phosphorylation of c-Jun N-terminal kinase (JNK), which were reported in glucolipotoxicity of pancreatic beta cells, were also observed in STZ-HFD-treated kidney. JNK/AP-1 and C/EBPb pathways may also contribute to glucolipotoxicity-induced renal damage through upregulation of MRP8, whose gene promoter region contains AP-1 binding site and C/EBP motif. During these experiments, we unexpectedly observed that glomerular-infiltrated Mf expressed MRP8 much more robustly than tubulointerstitial Mf. Importantly, we and others also confirmed such glomerular-MRP8 dominancy in human diabetic kidney and glomerulonephritis. In vitro study revealed that MRP8 expression in Mf was dramatically induced by co-culture with mesangial cells but not with proximal tubular cells. Its detail molecular mechanism is under investigation. Chronic inflammation associated with MRP8/TLR4 signaling might contribute to the pathogenesis of diabetic nephropathy through Mf-mediated glucolipotoxicity and intraglomerular crosstalk.

P040

Withdrawn

P041 Histone acetyltransferase GCN5 regulates hepatic gluconeogenesis through CITED2-dependent substrate switch

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Hepatic gluconeogenesis is critical to maintain fasting glucose homeostasis; unrestrained activity under hepatic insulin resistance contributes to hyperglycemia in diabetic patients. We recently identified CBP/p300-interacting transactivator with Glu/Asp-rich carboxy-terminal domain 2 (CITED2) as a critical regulator for hepatic gluconeogenesis. CITED2 promotes PGC-1α-dependent gluconeogenesis by inhibiting its acetylation by GCN5. GCN5 is a PGC-1α acetyltransferase (AT) that seems to inhibit gluconeogenesis; however, hepatic GCN5 (not the paralog PCAF) is upregulated in diabetic mice. Therefore, we investigated the role of GCN5 as a histone acetyltransferase (HAT) in the transcriptional regulation of hepatic gluconeogenesis.
GCN5 knockdown in the liver of obese diabetic db/db mice reduced both gluconeogenic gene expression as well as blood glucose concentrations. GCN5 depletion in primary mouse hepatocytes attenuated the induction of gluconeogenic genes by cAMP, PGC-1α or CITED2. Microarray analysis revealed that decreased genes in GCN5-depleted hepatocytes treated with cAMP were similar with fasting response genes targeted by CITED2 or PGC-1α. Neither GCN5 nor its AT-defective mutant (delta AT) enhanced cAMP-triggering gluconeogenic gene induction when overexpressed; co-expression of CITED2 and GCN5, not delta AT, did enhance induction. These data suggest GCN5 induces gluconeogenesis in an AT-dependent manner in concert with CITED2.
We also investigated the regulation of GCN5 activity by AT assays with histone H3 and PGC-1α as substrates. In the absence of CITED2, GCN5 preferentially acetylated PGC-1α. In the presence of CITED2, GCN5 bound CITED2 and acetylated histone H3, not PGC-1α. cAMP treatment in addition to CITED2 overexpression further enhanced HAT activity of GCN5. ChIP analyses revealed that recruitment of, and H3K9 acetylation by, GCN5 on cAMP-induced gluconeogenic gene promoters were abolished by CITED2 depletion.
Our results suggest GCN5 promotes gluconeogenic gene induction through a CITED2-dependent substrate switch from PGC-1α to histone H3. The detailed mechanism underlying this switching is under continued investigation.

P042 The combination of quantity and quality of sleep and the risk of diabetes in Japanese employees with prediabetes

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Objective: This study aimed to investigate whether the combination of the quantity and quality of sleep was associated with the risk of diabetes in Japanese employees with prediabetes.
Methods: A cohort of 1,421 employees, aged 35-67, with prediabetes at a health checkup conducted in 2008 at a company in Japan were followed until they developed diabetes or until 2013. Participants were classified into four groups according to their combination of quantity of sleep (6 hours or more versus less than 6 hours) and quality of sleep (not having sleep disturbance versus having sleep disturbance): normal quantity and normal quality (both normal), poor quantity and normal quality (poor quantity), normal quantity and poor quality (poor quality), and poor quantity and poor quality (both poor). The incidence of diabetes was determined using fasting and random plasma glucose levels, HbA1c levels, or a participant began medical treatment for diabetes. The Cox proportional hazards regression method was used to evaluate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the development of diabetes by sex.
Results: Of 1,421 participants with prediabetes, 378 had both normal quality and quantity of sleep, 545 had poor quantity, 213 had poor quality, and in 285 both were poor. During 5,874 person-years of follow-up, 172 of the participants with prediabetes developed diabetes. In women, the incidence per 1,000 person-years for both normal was 12.6, for poor quantity was 17.9, for poor quality was 24.0, and for both poor was 29.3; in men the rates were 55.6, 56.2, 63.0, and 49.6, respectively. In women (74.0% of participants), after adjusting for age, body mass index, plasma glucose, and other confounding factors, the multivariate-adjusted HRs and 95% CIs for developing diabetes compared with those for both normal were 1.35 (0.71-2.56) for those with poor quantity, 1.80 (0.86-3.79) for those with poor quality, and 1.98 (1.02-3.84) for those with both poor. In men, the multivariate-adjusted HRs and 95% CIs compared with those for both normal were 0.93 (0.53-1.62) for those with poor quantity, 0.79 (0.40-1.57) for those with poor quality, and 0.86 (0.41-1.77) for those with both poor.
Conclusions: Poor quantity and poor quality of sleep were associated with the risk of diabetes in Japanese female employees with prediabetes.

P043 A mouse model of tetrahydrobiopterin deficiency induces progression of diabetes and obesity

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Endothelial nitric oxide synthase (eNOS) dysfunction is known to be involved in glucose intolerance. Tetrahydrobiopterin (BH4) is an essential co-factor of eNOS that regulates eNOS activity. In the diabetic state, BH4 is oxidized to 7, 8-dihydrobiopterin (BH2), which leads to eNOS dysfunction due to eNOS uncoupling. We previously reported that BH4 lowers fasting blood glucose levels by suppression of hepatic gluconeogenesis eNOS-dependently. In the present study, we aimed to examine the effect of BH4 deficiency on glucose metabolism and lipid accumulation using the hph-1 mice in which GTP-cyclohydrolase I (GTPCH I), a rate-limiting enzyme of BH4 syntheses is deficient, and exhibits a marked reduction in BH4 levels. We compared hph-1 mice with control mice of the same background (C57BL/6 CBA mice). Intraperitoneal glucose tolerance test (IPGTT), insulin tolerance test (ITT), and pyruvate tolerance test (PTT) were performed. Hph-1 mice exhibited higher fasting blood glucose levels and fed blood glucose levels. Body weight of the two groups was not statistically different under the normal diet. IPGTT and ITT data indicated that hph-1 mice had glucose intolerance and insulin resistance. PTT data showed that hph-1 mice had higher hepatic glucose production than control mice, and that activation of AMP kinase (AMPK) was decreased in hph-1 mice liver tissues. To assess the correlation between BH4 content and glucose metabolism, hph-1 mice were treated with BH4. BH4 treatment significantly lowered blood glucose levels. AMPK and AKT were activated by administration of BH4 in liver tissues of hph-1 mice. In addition, both mice were fed with control fat diet (CFD) or high fat diet (HFD) for 4 weeks, and body weight, fat, and temperature were measured. Body weight and body fat were increased and body temperature was decreased in hph-1 mice fed with HFD. We conclude that deficiency of BH4 induces progression of diabetes and obesity. BH4 and GTPCH I are possible targets for treatment and prevention of diabetes and obesity.

P044 Long-range transactivation of C/EBPα gene expression by PPARγ through distal enhancers during adipocyte differentiation

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Adipogenesis is controlled by a cascade of transcription factors. Although the regulation of C/EBPα gene expression by PPARγ is crucial, the mechanistic basis of this regulation is poorly understood. Here, we employed ChIP-seq and identified distal PPARγ binding sites (+3, +19, +22, +24, +50, +53kb) in downstream region of the C/EBPα gene in differentiated 3T3-L1 adipocytes. These regions contain DR-1 motifs that bind to the PPARγ/RXRα heterodimer in a gel-shift assay and are functional in a luciferase assay, and exhibit increased histone H3 acetylation and chromatin accessibility (as judged by FAIRE-qPCR) during differentiation. Moreover, we found that the multifunctional insulator protein CTCF, bind to the distal enhancers and the promoter. Chromosome conformation capture (3C) assays showed that these distal enhancers and the C/EBPα promoter organize specific interaction and create a long-range loop structure, which is enhanced upon differentiation. RNA-mediated depletion of either PPARγ or CTCF resulted in decreased loop formation, transcriptional regulation of C/EBPα and differentiation. Our findings indicate that PPARγ and CTCF-dependent DNA loop formation between distal enhancers and the promoter are required for appropriate transactivation of C/EBPα gene expression and adipocyte differentiation

P045 Useful models of pancreatic endocrine progenitor cell line Tec-3p and dual-labeled Ngn3-eGFP/Ins-DsRed2 mice for the identification of the key driving regulators during pancreatic endocrine differentiation

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Development of pancreatic endocrine progenitors is regulated by local factors and physical interactions in microenvironment, associated with combinatory network of transcriptional key drivers. Neurogenin (Ngn)3, which is transiently expressed in endocrine progenitors, is an essential transcription factor in the differentiation of all the endocrine lineages. However, the mechanisms by which the terminal specification from the progenitors into alpha, beta, delta or PP cells, are incompletely understood. To elucidate this, we have established a novel cell line, Tec-3p, from pancreatic neoplasia driven by Simian Virus 40 large T antigen under the control of *Ngn3* gene. As results of the phenotypic feature analysis of Tec-3p cells, we found that Tec-3p cells with spherical in shape expressed critical markers, *ngn3*, *beta2*, *nkx2.2*, *nkx6.1* and *glucokinase but not any hormone genes*, suggesting that, Tec-3p cells resemble immature endocrine progenitors. As an alternative tool, we have developed the lineage-tracing model from endocrine progenitors to beta cells in dual-labeled transgenic mice expressing eGFP and DsRed2 driven by the *Ngn3* and *insulin* promoters. DNA microarray analysis with our unique models showed that key driver(s) might be identified based on the convincing expression profiling in isolated progenitors compared with that in beta cells and Tec-3p cells. Moreover, we found that the treatment of Tec-3p cells with several factors, such as retinoic acid and others, can induce endocrine marker gene expression on individual conditions. Importantly, when treated with the GLP-1 analogue exendin-4, the gene expression of insulin I was induced under high glucose conditions. Together, adherence to extracellular matrix components such as collagen or laminin appears to play an important role in facilitating endocrine lineage differentiation, suggesting that the coordinated interaction with local factors and microenvironment controls the differentiation of early endocrine progenitors to alpha and beta cells, and establishes Tec-3p cells as useful models to study these processes in vitro and screen for agents with regenerative potential in the diabetes. From the above profiling data, we are now focusing on the candidate genes that determine the terminal specification of beta cells

P046 Deletion of Elovl6 ameliorates hyperglycemia in db/db mice

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ELOVL family member 6, elongation of very long chain fatty acids (Elovl6) is a microsomal enzyme, which regulates the elongation of C12-16 saturated and monounsaturated fatty acids (FAs). We have shown previously that Elovl6 is a major target for sterol regulatory element binding proteins and that it plays a critical role in development of obesity-induced insulin resistance by modifying FA composition. To further investigate role of Elovl6 in development of type 2 diabetes (T2D) and its underlying mechanism, we investigated the effects of Elovl6 deletion in leptin receptor-deficient db/db mice, a model of T2D. We analyzed the body weights, serum glucose, insulin and HbA1c levels of db+/m, db/db, and db/db-Elovl6KO mice. We also performed immunohistochemical staining and quantitative RT-PCR analysis of islet. Although the obesity of db/db-Elovl6KO mice was similar to db/db mice, development of hyperglycemia and glucose intolerance was dramatically improved. Histological examination indicated that Elovl6 deletion was associated with increased islet mass in db/db mice, and this correlated with serum hyperinsulinemia and glucose-responsive insulin secretion. The expression of several inflammatory genes such as TNF- α and MCP-1 were reduced, and the expression of genes related to pancreatic β cell function such as PDX-1 and insulin were increased in islets from db/db-Elovl6KO mice compared with db/db mice. These results suggest that Elovl6 is an important factor on both β cell mass and function in type 2 diabetes. Elovl6 inhibition can be a novel therapeutic target for T2D.

P047 Plaque score of ultrasound analysis of carotid arteries is a useful reference index for cerebro-cardiovascular events in patients with type 2 diabetes

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Aims/Introduction: Diabetes mellitus is one of the risk factors for atherosclerosis, and cerebro-cardiovascular disease (CVD) based on atherosclerosis is an important complication affecting the prognosis of diabetic patients. It is suggested that carotid ultrasonography is a useful examination for evaluating the atherosclerosis, and the presence of plaques in carotid arteries is associated with CVD events occurrence. As an indicator of atherosclerosis, mean intima media thickness (IMT) is frequently used, but the sum of the carotid plaque thickness, referred to as plaque score (PS), could be a better indicator of atherosclerosis. Therefore, in this study, we have examined the association between CVD events and carotid plaque findings (mean IMT and PS) in type 2 diabetic patients.
Results: A total of 84 type 2 diabetics with carotid artery plaques were enrolled, and were further observed for approximately 3 years. The demographic values (mean±SD) of enrolled patients (48 males and 36 females) were as follows; age 61.4±10.7 years old, BMI 25.1±5.2, blood pressure 123.5±17.4/73.0±9.7 mmHg, HbA1c 9.3±2.2%, LDL-C 119.8±37.8 mg/dL, HDL-C 52.1±14.3 mg/dL, TG 154.2±88.3 mg/dL, mean IMT 0.796±0.243 mm, and PS 3.055±4.462 mm. As to past history related to CVD, the event numbers of myocardial infarction, angina pectoris and ischemic stroke were 8, 2 and 3, respectively. During the approximately 3-year follow-up period, there were 2 myocardial infarction (including one recurrence) and 4 ischemic strokes (including one recurrence). On multivariate logistic regression analysis using age, sex, BMI, hypertension, HbA1c, dyslipidemia, mean IMT and PS as explanatory variables, PS > or = 5.0 was significantly associated with past history and onset of CVD during the follow-up period (P = 0.046). When the patients were divided into two groups based on PS, patients with higher PS (> or = 5.0) experienced CVD events more frequently than those with lower PS (< 5.0) during the follow-up period (P = 0.011; PS < 5.0: n = 0 *vs* PS > or = 5.0: n = 6), as shown by the Kaplan-Meier plots. On the other hand, no significant association between mean IMT and CVD evvents was observed in the Kaplan-Meier analysis.
Conclusions: In carotid ultrasound evaluations, PS might be a better predictor of CVD events than mean IMT, because it is an index derived by evaluating more extensive regions of carotid arteries.

P048 Loss of Tcf21 in podocytes leads to enhanced diabetic nephropathy

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Background: Tcf21 is a bHLH transcription factor essential for embryonic development. Global Tcf21 knockout (gl-KO) mice die minutes after birth with hypoplastic lungs and tetralogy of Fallot. In kidneys of glo-KO mice, mesenchyme-toepithelial transformation, branching morphogenesis and nephrogenesis are arrested.

Methods: In addition to mesenchymal expression, Tcf21 is expressed in embryonic and adult podocytes. To examine the role of Tcf21 in podocytes, we created a conditional allele for Tcf21 and crossed them to PodocinCre (pod-KO) and Wnt4-Cre mice resulting in deletion of Tcf21 from differentiated and progenitor podocyte populations, respectively.

Results: Pod-KO mice do not exhibit overt defects in podocyte differentiation, but the glomerular structure is greatly simplified with decreased endothelial and mesangial cells. By 4 weeks of age, 30-40% of Pod-KO mice develop FSGS-like lesions and massive proteinuria, while 60% of mice never develop proteinuria. Microarray analysis of glomeruli from Pod-KO mice revealed candidate downstream targets, including Vegf, Pgf and Wif1. Earlier deletion of Tcf21 from podocyte precursors (Wnt4-Cre) leads to columnar shaped podocytes, aberrant distribution of Podocin and defects of mesangial migration, suggesting more profound defect of podocyte differentiation. Strikingly, induction of diabetes in the non-proteinuric Pod-KO mice results in increased proteinuria, suggesting a protective role for Tcf21.

Conclusions: Our results demonstrate a critical role for Tcf21 in the differentiation and maintenance of podocytes in both developing and mature kidneys. Identification of direct targets of this transcription factor may provide new therapeutic targets for proteinuric renal disease including diabetic nephropathy.

P049 Blockade of Kv2.1 channels potentiates GLP-1-induced insulin release in mouse islet β-cells

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Voltage-dependent potassium channels are involved in repolarization of excitable cells. In pancreatic β-cells, activation of delayed rectifier K^+ (Kv) channels possibly repolarizes cells and attenuates glucose-stimulated action potentials to suppress insulin secretion. Among Kv channel families, Kv2.1 is reportedly expressed in islet β-cells as the major component of Kv currents in rodents. It is expected that the inhibition of the β-cell Kv current prolongs action potentials and enhances glucose-induced insulin secretion. It has been reported that gucagon-like peptide 1 (GLP-1) inhibits Kv channels in β-cell. This study aimed to determine whether blockade of Kv2.1 channels could potentiate GLP-1-induced insulin release in mouse islet β-cells. In islets isolated by collagenase digestion, guangxitoxin-1E (GxTx), a Kv2.1 channel blocker, significantly increased glucose (8.3 mM)-induced insulin release without altering basal insulin release at 2.8 mM glucose. Glucose-induced insulin release from isolated islets of $Kv2.1^{+/-}$ mice was significantly greater than that of wild-type mice. Blockade of Kv2.1 channels by GxTx potentiated glucose (8.3 mM)-induced $[Ca^{2+}]_i$ increases in β-cells as monitored by fura-2 microfluorometry, without altering basal $[Ca^{2+}]_i$ levels at 2.8 mM glucose. Furthermore, blockade of Kv2.1 channels by GxTx potentiated the insulin release in response to a GLP-1 receptor agonist, exendin 4, in isolated islets of wild type and type 2 diabetic db/db mice. In in vivo experiments, the treatment with GxTx and a GLP-1 receptor agonist liraglutide in combination enhanced insulin secretion and improved glucose tolerance in a synergistic manner. These results suggest that Kv2.1 channels physiologically restrict glucose-induced Ca^{2+} influx and insulin secretion in β-cells. Blockade of this channel can promote glucose-induced and GLP-1-potentiated insulin release, providing a potential therapeutic tool to treat type 2 diabetes.

P050 Role of N-type calcium channel in diabetic nephropathy

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Objective: Clinical studies have suggested that the blockade of the N-type calcium channel (NCaC) may exert glomerular protective effects in hypertensive and diabetic renal diseases. To explore the role of NCaC in diabetic nephropathy, we investigated renal injury in NCaC-deficient diabetic db/db mice.
Design and Method: Renal expression of NCaC was investigated by *in situ* hybridization. The NCaC α1 subunit (Cacna1b) was deleted by conventional gene knockout technique (C57BL/6J background), and heterozygous NCaC-knockout mice (NCaC HKO) were back-crossed with db/+ mice to gain the BKS background. We prepared 6 mouse groups: db/db wild-type (diabetic WT), db/db NCaC HKO (diabetic HKO), and db/db homozygous NCaC knockout mice (diabetic KO), together with three NCaC genotype groups with db/+ background. Mice were analyzed in BP, blood glucose, urinary catecholamines, and urinary albumin excretion (UAE) through 8 to 16 weeks of age, and glucose and insulin tolerance tests were performed at 15 weeks. Furthermore, diabetic WT mice were administered with cilnidipine or nitrendipine to investigate the effects of pharmacological blockade.
Results: The expression of NCaC was demonstrated in glomeruli, including podocytes. Diabetic KO mice showed significantly lower BP than diabetic WT mice by ~20 mmHg, and exhibited ~50% reduction in urinary catecholamines. Diabetic WT mice showed increased UAE to 600-1200 μg/mgCr throughout the course, but both diabetic HKO and diabetic KO mice revealed significant reduction in UAE by ~70%. Furthermore, there was a significant improvement in glycemic control in diabetic KO mice, along with better ipGTT and ITT results as compared with diabetic WT mice. Enhanced glomerular expression of TGF-β1, CTGF and Col4a3, down-regulation of podocin and nephrin, glomerular mesangial expansion, and glomerular basement membrane thickening observed in diabetic WT mice, were all markedly alleviated in diabetic KO mice. Administration of cilnidipine, but not nitrendipine, in diabetic WT mice resulted in significant reduction of UAE by ~35% and histological improvement.
Conclusions: The inhibition of NCaC may exert renoprotective effects against the progression of diabetic nephropathy, probably by podocyte protection and better glycemic control.

P051 Plasma brain-derived neurotrophic factor, cardiac autonomic function and nocturnal changes in blood pressure: implications in nocturnal hypertension in diabetes

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Background: Basic studies have shown that brain-derived neurotrophic factor (BDNF) has critical roles in the survival, growth, maintenance, and death of central and peripheral neurons, and is involved in the regulation of autonomic nervous system. Recent clinical studies suggest potential role of plasma BDNF in circulatory system.
Method: We investigated the mutual relationships among plasma BDNF, patterns of nocturnal blood pressure changes (dippers, nondippers, extra-dippers, and reverse-dippers), and the cardiac autonomic function as determined by heart rate variability (HRV) in 250 patients with one or more cardiovascular risk factor(s) (obesity, smoking, presence of cardiovascular event history, hypertension, dyslipidemia, diabetes mellitus and chronic kidney disease).
Results: Plasma BDNF levels (natural logarithm transformed) were significantly (p=0.001) lower in patients with the reverse-dippers as compared to the dippers. Multiple logistic regression analysis showed that BDNF (odds ratios: 0.417, 95% confidence interval: 0.228-0.762, P=0.004) was the sole factor significantly and independently associated with the reverse-dippers when compared with the dippers. Furthermore, plasma BDNF level was significantly and positively correlated with time-domain (SDNN, SDANN5, CVRR) and frequency-domain (LF) of HRV parameters. Multiple logistic regression analyses showed that the relationship between plasma BDNF and the reverse-dippers was weakened but still significant or borderline significant even after adjusted for HRV parameters. Finally, the relation between plasma BDNF and nocturnal hypertension was more marked in diabetic as compared with non-diabetic subgroup. In diabetic patients, multiple regression analyses revealed that plasma BDNF was significantly associated with nocturnal blood pressure falls even after adjusted for age, gender, presence of neuropathy or nephropathy, urinary sodium excretion, sleep apnea/hypopnea, and plasma aldosterone concentration.
Conclusions: Low plasma BDNF and an imbalance of cardiac autonomic function can be a predictor for the reverse dipping pattern of nocturnal hypertension, particularly in diabetic patients.

P052 Bone and mineral metabolism and incident diabetes: A prospective study

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Context: Bone and mineral metabolism plays an important role in glucose metabolism, whether markers of bone and mineral metabolism can predict diabetes remains largely unknown
Objective: To evaluate the association of markers of bone and mineral metabolism with incident diabetes.
Design: Prospective cohort study with a median follow-up of 10.2 years
Setting: Community
Participants: 1702 male and 4394 female Southern Chinese aged 20 or above free of diabetes at baseline
Main outcome measures: Incidence of diabetes
Results: In 59130.9 person-years of follow-up, 631 participants developed diabetes. Serum alkaline phosphatase (ALP) (highest quartile, hazard ratio [HR] 1.41; 95% confidence interval [CI] 1.06-1.88; as compared to the lowest quartile) and total calcium (third quartile, HR 1.42; 95% CI 1.12-1.8; highest quartile, HR 1.42; 95% CI 1.11-1.79; as compared to the lowest quartile) were significantly association with incident diabetes. Addition of serum alkaline phosphatase and total calcium to age, sex and BMI significantly improved integrated discrimination and category-less net reclassification index. Significant interactions with BMI and age were observed. Greater total calcium intake was significantly associated with lower incident diabetes (comparing extreme quartile, hazard ratio 0.78; 95% confidence interval 0.61-0.98).
Conclusions: In this prospective study, elevated serum ALP, total calcium, and lower total calcium intake were associated with incident diabetes. Adding serum ALP and total calcium to basic clinical risk factors significantly improved risk prediction. Bone and mineral metabolism may play a role in diabetes development and risk prediction.

P053 MafA is important for maintenance of the mature beta-cell phenotype

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Aims: The plasticity of adult somatic cells allows their conversion to different cell types following extrinsic stimulation or the ectopic expression of transcription factors. However, the mechanisms involved in this process and its relevance to disease remain elusive. The proclivity of committed cells to de-differentiate is inversely correlated with their maturity, suggesting that maturation factors such as MafA, a mature pancreatic beta-cell marker, may be involved in cell plasticity.
Methods: Lineage tracing analysis of beta-cells were performed in MafA knockout (KO) mice and diabetes model mice, in which the expression of MafA was reduced in most beta-cells.
Results: The loss of MafA causes a reduced beta-cell/alpha-cell ratio in pancreatic islets without elevation of blood glucose to diabetic levels. Most cells in MafA KO islets at 12 weeks of age were stained with synaptophysin or chromogranin A, committed endocrine cell markers, but showed reduced or no expression of insulin. Moreover, transmission electron microscopy of MafA KO islets detected many vesicles without insulin granules in beta-cells. A TUNEL assay for the detection of apoptotic beta-cells showed very few positive cells in MafA KO pancreas. Lineage tracing analysis revealed the conversion of beta-cells to glucagon-expressing cells with reduced/lost expression of insulin in MafA KO mice. These islets expressed factors that are normally transiently expressed in endocrine progenitors, such as MafB or Ngn3. Lineage tracing analysis of diabetes model mice also demonstrated similar de-differentiation of the compromised beta-cells with reduced expression of MafA. Analysis of diabetic MafB reporter mice showed MafB promoter was activated in compromised beta-cells in vivo. In beta-cell lines with late-passage numbers, a glucotoxic model, the expression of MafA and insulin was extremely downregulated. In these cells, increased promoter activity and mRNA expression of MafB were observed. Methylation-specific PCR followed by bisulfite sequencing showed that seven CpG sites in the particular CpG island of MafB promoter were demethylated in late-passage beta-cell lines. In vitro methylation of this CpG island in the MafB promoter downregulated its promoter activity in the late-passage beta-cell lines, suggesting that the demethylation of unique CpG island in the MafB promoter has an positive effect on promoter activity in glucotoxic beta-cell cells.
Conclusions: The maturation factor MafA is critical for the homeostasis of mature beta-cells, and regulates cell plasticity. The loss of MafA in beta-cells leads to a deeper loss of cell identity, which is implicated in the pathology of diabetes.

P054 Associations of chemerin and FGF21 with subclinical atherosclerosis and adverse lipid metabolism in type 2 diabetes

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Both adipokines and hepatokines have been implicated in obesity-related disorders such as type 2 diabetes(T2DM) and atherosclerosis. Chemerin, a recently discovered adipokine, is known to function as a chemoattractant for immune cells including macrophages. Emerging evidence supports a role of chemerin in diabetes and inflammation, while the precise role in these pathophysiological states remains unclear. Fibroblast growth factor 21(FGF21) is predominantly produced in liver but also in adipose tissue and skeletal muscle in humans. FGF21 has been shown to exert beneficial effects on glucose and lipid metabolism in animal models. In humans, however, circulating FGF21 levels have been found elevated in insulin resistant states, such as obesity and T2DM, suggesting a possible compensatory elevation of FGF21. Therefore, the true role of FGF21 in insulin resistance still needs to be clarified.
We aimed to explore the relationships of circulating chemerin and FGF21 levels to atherosclerosis and metabolic parameters in Korean T2DM subjects. Circulating chemerin, FGF21, lipid panels, and C-reactive protein levels were measured. We assessed vascular health by measuring aortic pulse-wave velocity(PWV) and carotid intima-media thickness(IMT).
Chemerin was significantly related to age(r=0.18, P<0.05), estimated glomerular filtration rate(GFR; r= -0.35, P<0.01), albumin-to-creatinine ratio(r=0.20, P<0.05), and aortic PWV(r=0.24, P<0.01). Aortic PWV was significantly correlated with age, body mass index, estimated GFR, and chemerin. Multiple regression analysis revealed that chemerin was independently associated with aortic PWV. FGF21 was significantly related to triglyceride(r=0.16, P<0.05), high-density lipoprotein(HDL) cholesterol (r= -0.21, P<0.01), apolipoprotein B100(r=0.22, P<0.05), and estimated GFR(r= -0.23, P<0.01). However, there was no relationship of FGF21 to aortic PWV or carotid IMT. FGF21 is independently related to HDL cholesterol and apolipoprotein B100 in multiple regression analysis.
Circulating chemerin levels are independently related to subclinical atherosclerosis. Elevated levels of FGF21 are associated with adverse lipid profiles in T2DM patients.

P055 The critical role of heat shock protein 72 in diabetic pathophysiology

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Cell stresses, such as ER stress is one of the key factors in pathophysiology of type 2 diabetes. Molecular chaperone, which modulate protein folding and/or assembly and protect cells from several stresses, attracts attentions for diabetic treatment.
Heat shock protein (HSP) 72 is a major inducible heat shock protein against heat, ultraviolet or infection. Induction of HSP72 by pharmacologic agent or mild electrical stimulation with hyperthermia improves glucose tolerance in diabetic model mice. In this study, we investigated glucose metabolism in whole body HSP72 deficient (KO) mice to explore the impacts of HSP72 in diabetes.
Male HSP72 KO mice or their wildtypes were subjected to a high-fat diet (HFD) or high-fat high-sucrose diet (HFHSD) regimen for 16 weeks. Several metabolic parameters, cellular stress markers were evaluated.
KO mice showed significantly higher body weight (BW) after 10 weeks of HFD (KO 36.9 g v.s. control 33.4 g, p=0.04) compared to control. Fasting and Random fed blood glucose were significantly increased after 11 weeks of HFD (KO 143.3 mg/dL v.s. WT 115.5 mg/dL, p=0.024) or after 8 weeks of HFD (KO 185.1 mg/dL v.s. WT 154.9 mg/dL, p=0.013). Food intake was comparable. Upon glucose challenge (1.0 g/kg BW), blood glucose levels at any time points measured were higher in KO mice. Upon insulin tolerance test (0.5 u/kg BW), KO mice exhibited insulin resistant phenotype. Epididymal, mesenteric and retroperitoneal fat mass were all increased in KO. Hepatic steatosis was obvious in KO liver. Upon pyruvate tolerance test (2g/kg BW), KO mice treated with HFHSD exhibited increased hepatic glucose production. Upon insulin stimulation from inferior vena cava, phosphorylation of Akt was decreased by 50% in KO liver extracts, with increased activation of c-jun N-terminal kinase.
In summary, deficiency of HSP72 leads to increased visceral adiposity, insulin resistance, fatty liver and hepatic glucose production. As induction of HSP72 is beneficial to treat diabetes, our observations strongly indicate the abundance of HSP72 is critical in diabetic pathophysiology especially at liver.

P056 Predictors for mild and severe hypoglycemia in Japanese outpatients with insulin-treated diabetes: a 6-month follow-up study

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Aim: The objective of this study was to explore predictors, including social factors, lifestyle factors, and factors relevant to glycemic control and treatment, for mild and severe hypoglycemia in Japanese outpatients with insulin-treated diabetes.
Methods: This 6-month follow-up study included 123 outpatients with insulin-treated diabetes who were referred to an outpatient diabetic clinic between January 2013 and July 2013 at Shiga University of Medical Science Hospital. After a baseline survey examining social factors (education, occupation, and support and checking by family members), lifestyle factors (smoking, drinking, meal regularity, and exercise habits), and factors relevant to glycemic control and treatment (HbA_{1c} levels, total daily insulin, frequency of insulin injection, insulin type, and previous hypoglycemia episode), patients were followed for 6 months. During the follow-up period, patients used a diary to record blood glucose levels using their own portable glucose meter. Mild hypoglycemia was defined as blood glucose level 50-69mg/dl, and severe hypoglycemia was defined as blood glucose level <=49mg/dl. Multinomial logistic regression was used to estimate the age- and sex-adjusted odds ratio (OR) and 95% confidence interval (CI) of each parameter for mild and severe hypoglycemia.
Results: During the 6-month follow-up period, 41 (33.3%) outpatients experienced mild hypoglycemia, and 20 (16.3%) outpatients experienced severe hypoglycemia. Support and checking by family members the patient at the time of the insulin injection [presence/absence, OR (95% CI): 0.37 (0.16-0.88)], drinking [current drinker/non- and ex-drinker, OR (95% CI): 5.07 (1.79-14.37)], higher frequency of insulin injection [3-4 times per day/1-2 times per day, OR (95% CI): 2.61 (1.10-6.20)], and 3-month hypoglycemia episode before the baseline survey [presence/absence, OR (95% CI): 5.83 (2.42-14.08)] affected the mild hypoglycemia. Support and checking by family members at the time of insulin injection [presence/absence, OR (95% CI): 0.18 (0.05-0.69)], higher frequency of insulin injection [3-4 times per day/1-2 times per day, OR (95% CI): 6.63 (1.72-25.52)], insulin type[rapid-acting or short-acting + long-acting or intermediate-acting/other, OR (95% CI): 3.72 (1.15-12.03)], and 3-month hypoglycemia episode before the baseline survey [presence/absence, OR (95% CI): 12.45 (3.48-44.48)] were associated with an increased likelihood of severe hypoglycemia.
Conclusion: This study suggested that not only factors relevant to glycemic control and treatment but also a social factor (support and checking by family members) and a lifestyle factor (current drinking) were predictors for mild or severe hypoglycemia in Japanese outpatients with insulin-treated diabetes.

P057 Effect of sitagliptin and vildagliptin, dipeptidyl peptidase-4 inhibitors, on M1/M2-like phenotypes of peripheral blood monocytes and arterial stiffness in type 2 diabetic patients

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Aims: It has been reported that dipeptidyl peptidase-4 (DPP-4) inhibitors, as well as GLP-1 receptor agonists, exert anti-inflammatory and anti-atherogenic effects in murine atherosclerotic models. Here, we examined the effects of sitagliptin and vildagliptin, DPP-4 inhibitors, on systemic inflammation, pro-inflammatory (M1)/anti-inflammatory (M2)-like phenotypes of peripheral blood monocytes and arterial stiffness in type 2 diabetic patients.
Methods: Twenty-six type 2 diabetic patients treated with sitagliptin (50 mg daily), 6 diabetic patients treated with vildagliptin (100 mg daily) and 24 untreated control subjects were studied for 3months. Measurements were undertaken to assess changes in glucose-lipid metabolism, serum levels of inflammatory cytokines such as serum amyloid A-LDL (SAA-LDL), C-reactive protein (hsCRP), interleukin-6 (IL-6), IL-10 and tumor necrosis factor-α (TNF-α). Furthermore, the effects of each treatment on M1/M2-like phenotypes in peripheral blood monocytes and Cardio-Ankle Vascular Index (CAVI), an index of arterial stiffness, which is less independent of blood pressure, were examined.
Results: Treatment with sitagliptin and vildagliptin significantly decreased fasting plasma glucose, $HbA1_c$. In addition, sitagliptin significantly decreased serum levels of inflammatory markers, such as SAA-LDL, CRP, and TNF-α, and increased serum IL-10, an anti-inflammatory cytokine, as well as plasma GLP-1. Furthermore, sitagliptin increased monocyte IL-10 expression, and both sitagliptin and vildagliptin decreased monocyte TNF-α expression. Multivariate regression analysis revealed that the sitagliptin treatment was the only factor independently associated with an increase in monocyte IL-10 (β = 0.499; R2 = 0.293, P < 0.05). However, other factors including the improvement of glucose metabolism were not associated with the increase. Vildagliptin treatment significantly reduced CAVI, although sitagliptin did not significantly reduce it for 3 months.
Conclusions: This study is the first to show that DPP-4 inhibitors reduces inflammatory cytokines and improves the unfavorable M1/M2-like phenotypes of peripheral blood monocytes, which may lead to anti-atherogenic effect, in Japanese type 2 diabetic patients.

P058 A novel podocyte gene, R3h domain containing-like inhibits non-canonical TGF-β signaling

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[Background and aims] Diabetic nephropathy (DN) is a major microvascular complication of diabetes mellitus and is one of the most common causes of end-stage renal disease. However, the molecular mechanisms underlying DN remain largely unknown. We previously identified >300 glomerulus-enriched transcripts, including R3h domain containing-like (R3hdml), through large-scale sequencing and microarray profiling of the mouse glomerular transcriptome. Therefore, the aim of this study was to analyze both the in vivo and in vitro functions of R3hdml.
[Materials and methods] R3hdml mRNA expression was examined in mice by non-radioactive in situ hybridization, and protein expression was evaluated by immunohistochemistry (IHC) or western blot (WB) analysis. Cultured murine podocytes and human fibroblasts overexpressing R3hdml were used for in vitro analysis. The effects of transforming growth factor-β (TGF-β) on R3hdml expression and function were evaluated by real-time polymerase chain reaction and WB analysis. R3hdml knockout (R3hKO) mice were generated by homologous recombination. Diabetes was induced in mice by intraperitoneal injection of streptozotocin (STZ).
[Results] Both R3hdml mRNA and protein were specifically expressed in glomerular podocytes. TGF-β has been reported to play a major role in DN. Therefore, we evaluated the effects of TGF-β on R3hdml expression and function. TGF-β can activate not only Smad-dependent pathways but also non-Smad pathways, including the non-canonical p38 mitogen-activated protein kinase (p38MAPK) pathway. When human fibroblasts were treated with TGF-β, phosphorylation of p38MAPK (pp38MAPK) increased by 2.26 $\pm$ 0.15-fold (mean $\pm$ SEM). On the other hand, TGF-β-induced pp38MAPK expression was significantly (54%) reduced in human fibroblasts overexpressing R3hdml. Smad phosphorylation was independent of R3hdml, indicating that R3hdml inhibited the non-Smad pathway but not the Smad-dependent pathway. R3hKO mice showed aberrant podocyte structure and partial thickening of the glomerular basement membrane. Furthermore, IHC revealed that pp38MAPK was increased by 2.14 $\pm$ 0.490-fold in R3hKO glomeruli compared with the wild-type (WT) controls. R3hdml mRNA expression in the glomeruli was increased by 2.7 $\pm$ 0.73-fold in the diabetic mice compared with the WT controls. Finally, we induced diabetes in both the WT and R3hKO mice by STZ injection and found that the prevalence of albuminuria was significantly increased in the diabetic and R3hKO mice compared with the diabetic WT controls.
[Conclusions] We identified a novel podocyte-specific gene, R3hdml, which is regulated by TGF-β signaling. This gene product inhibits TGF-β-induced p38MAPK signaling. Our results suggest that podocyte-specific therapy presents a viable option to inhibit DN in the near future.

P059 Diabetes risk score in Bangladesh: A simple non-invasive tool for detecting undiagnosed type 2 diabetes in a Bangladeshi population

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Aims To develop and evaluate a simple non-invasive diabetes risk score for detecting undiagnosed Type 2 diabetes (T2DM) in a Bangladeshi population.

Methods Data from 2,293 randomly selected individuals aged ≥20 years from a cross-sectional study in a rural community of Bangladesh (2009 Chandra Rural Study) was used for model development. The validity of the model was assessed in another rural cross-sectional study (2009 Thakurgaon Rural Study). The logistic regression model used included age, sex, body mass index (BMI), waist hip ratio (WHR) and hypertension (HTN) status to predict high risk individuals who were having T2DM.
Results On applying the developed model to both cohorts, the area under the receiver-operating characteristic (ROC) curve was 0.70 (95% confidence interval (CI) 0.68-0.72) for the Chandra cohort and 0.71 (95% CI 0.68-0.74) for the Thakurgaon cohort. The Risk Score of >9 was shown to have the optimal cut-point to detect diabetes. This score had a sensitivity of 62.4 and 75.7% and specificity of 67.4 and 61.6% in the two cohorts, respectively. This risk score had shown to have improved sensitivity and specificity to detect DM cases compared to the Thai, Indian, Omani, UK, Dutch, Portuguese and Pakistani diabetes risk scores.

Conclusions This simple non-invasive diabetes risk score could detect subjects with undiagnosed T2DM in a Bangladeshi population.

P060 Timing of hypoglycemia is associated with increased mortality and length of stay among patients with diabetes admitted to internal medicine departments

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Background: Hypoglycemia among hospitalized patients with diabetes is associated with poor hospital prognosis. The aim of the study was to examine the effect of hypoglycemia timing on hospital prognosis.
Methods: In this retrospective analysis of electronic medical records, we included all 3941 patients with diabetes (Mean age 71.7+/-12.9 years, 49.3% males) discharged from internal medicine departments during 2009. All glucose measurements were computerized using an institutional glucometer. Patients were categorized into 3 groups according to hypoglycemia timing: Group1, no hypoglycemia, Group 2, hypoglycemia only upon admission and Group 3, hypoglycemia during hospital stay. Included in the analysis were 3413 (86.4%) patients with diabetes who had glucose measurements performed during hospitalization. A total of 157 patients (4.6%) had at least 1 hypoglycemia event during the hospital stay (42 patients upon admission and 115 patients during hospitalization). Patients in Group 3 had significantly increased in-hospital mortality and length of hospital stay (27.0%, 18.4+/-24.7 days), compared to Groups 1 (3.4% mortality, 5.1+/-8.8 hospital days) and Group 2 (4.7% f mortality, , 3.2+/-3.3 hospital days). Mortality rates were associated with the severity and number of hypoglycemia events. Patients in Group 3 had higher creatinine and lower albumin levels compared to Groups 1 and 2.
Conclusions: Hypoglycemia during hospitalization is associated with increased rates of in-hospital mortality and prolonged hospital stay among diabetic patients admitted to internal medicine departments. Poor hospital outcome was associated with timing of hypoglycemia, as well as the number and severity of the events.

P061 Impact of comorbid depression on glycemic control and family functioning in treatment-resistant patients with type 2 diabetes: a 6-month follow-up study

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Background and aims: Depression in patients with diabetes is associated with poorer adherence and worse health outcomes. However, evidence for the efficacy of treating depression in improving glycemic control was mixed. The aim of the study was to investigate the impact of depression on quality of life, family functioning, glycemic control and other related factors among treatment-resistant patients with type 2 diabetes and their family members.
Materials and methods: Ambulatory patients with type 2 diabetes were drawn consecutively from the treatment-resistant inpatient population participated in a two-week educational intervention program at two general hospitals. Those who could have cognitive impairment were cautiously excluded. 123 out of 159 patients, who gave written informed consent, were enrolled in the study. Before and after the intervention program, and also 6 months later, the subjects and their family members completed the Zung Self-rating Depression Scale, the Zung Self-rating Anxiety Scale (SAS), and the subjects also completed the Diabetes Quality of Life (DQOL) and the Problem Areas In Diabetes scale. Family functioning was assessed by the Family Assessment Device (FAD) and the Family Relationships Index (FRI) before the program and 6 months later. This study was approved by the Institutional Review Board and the Ethics Committee of those two hospitals.
Results: The mean value of HbA1c, depression and anxiety as well as diabetes-related emotional distress were significantly improved at the 6-month follow-up both in the Depressed patients (N=69; SDS score at baseline equal to or more than 40) and the Non-depressed (N=54; SDS score at baseline less than 40). Perceived family functioning of Depressed and their caregivers apparently improved over time, though that of Non-depressed and their caregivers was not so much improved. Caregivers of Non-depressed perceived significantly greater conflict over time than those of Depressed, while both Depressed and Non-depressed patients did not show such difference.
Conclusions: It is essential to develop effective intervention that will lead to consistent improvements in depression and to promotion of more affectively open communication and rather healthy conflict among patients with diabetes and their caregivers from the viewpoint of family functioning.

P062 Efficacy of DPP-4 inhibitors on serum lipid profile according to glycemic control in Japanese patients with type 2 diabetes

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Although it has been reported that the extra-pancreatic effects of DPP-4 inhibitors on serum lipid profile, the effects by degree of glycemic control have not been investigated yet. In the present study, we retrospectively analyzed serum lipid profile in Japanese patients with type 2 diabetes treated with DPP-4 inhibitors. The subjects were 254 patients with type 2 diabetes, consisting of 182 men and 72 women who were treated with any one of six DPP-4 inhibitors (sitagliptin 100 mg qd [SITA], vildagliptin 50 mg bid [VILDA], alogliptin 25 mg qd [ALO], linagliptin 5 mg qd [LINA], teneligliptin 20 mg qd [TENELI], and anagliptin 200 mg bid [ANA]) for 3-12 months. The patients were classified according to HbA_{1c} level in baseline based on the guideline launched by the Japan Diabetes Society in 2010 (poor-controlled: >8.3% [SITA: n=17, VILDA: n=10, ALO: n=14, LINA: n=7, TENELI: no data, ANA: n=6]; fair-controlled: 6.9-8.3% [SITA: n=29, VILDA: n=6, ALO: n=21, LINA: n=6, TENELI: no data, ANA: n=4]; good- or excellent-controlled: <6.9% [SITA: n=20, VILDA: n=6, ALO: n=76, LINA: n=21, TENELI: n=6, ANA: n=5]), and were investigated changes of serum lipid profile before and after treatment of DPP-4 inhibitors. As a result of treatment of drugs, in poor-controlled group, SITA, VILDA, ALO, and LINA reduced total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) levels, and ALO and LINA also reduced triglyceride (TG). Furthermore, SITA, VILDA, ALO, and ANA tended to increase high density lipoprotein cholesterol (HDL-C). In fair-controlled group, SITA tended to improve TC, HDL-C, LDL-C, and TG. ALO and LINA tended to lower TC and LDL-C, and LINA also raised HDL-C. VILDA reduced TG level. In good- or excellent-controlled group, TENELI tended to improve TC, HDL-C, and TG levels. Besides, SITA and VILDA tended to raise HDL-C level. In conclusion, DPP-4 inhibitors improved serum lipid profile in patients with type 2 diabetes. Recently, it is reported that DPP-4 inhibition prevents inflammation of adipose tissue, and that lipid-improving-effects may be class effects of DPP-4 inhibitors. However, the results obtained from the present study suggest that each DPP-4 inhibitor may have unique features on serum lipid profile, and that the lipid-improving-effects are observed under relatively poor-controlled glycemic condition.

P063 Statins improve glucose tolerance in high fat-fed mice possible through PPAR γ activation in adipocytes

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Background and aims:Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (statins) are generally used for the treatment of hyperlipidemia. Recent studies have suggested that the beneficial effects of statins may extend to mechanisms beyond cholesterol reduction. We have revealed in macrophages that 3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitors (statins) had anti-atherogenic effects through the activation of peroxisome proliferator-activated receptor- γ (PPAR γ). However, there is no evidence whether statins can activate PPAR γ in adipocytes and improve glucose tolerance in insulin resistance model mice. The aim of the study was to investigate the effect of statins on PPAR γ activation and adipocyte differentiation in 3T3-L1 adipocytes, and on insulin resistance in high-fat diet (HFD)-fed mice.
Materials and methods: Fluvastatin, pitavastatin and atorvastatin were used in this study. Mouse 3T3-L1 adipocytes were used in in vitro assay. PPAR γ activity was measured by luciferase assay system. C57BL/6 male mice were fed with high-fat diet (HFD) plus each statin (5 mg/day) for 6 weeks.
Results: PPAR γ was activated by fluvastatin and pitavastatin, but not by atorvastatin in 3T3-L1 adipocytes. Fluvastatin and pitavastatin induced cyclooxygenase-2 (COX-2) expression, and COX-2 siRNA abrogated the statin-mediated PPAR γ activation, suggesting that over-expression of COX-2 is involved in statin-induced PPAR γ activation in 3T3-L1 adipocytes. Oil red O staining indicated that fluvastatin and pitavastatin enhanced the lipid accumulation into adipocytes. Moreover, these statins significantly enhanced the mRNA expression of aP2, CD36 and adiponectin. Fluvastatin and pitavastatin significantly increased basal glucose transport by 2-fold, whereas the ratio of insulin-stimulated uptake was unaffected in 3T3-L1 adipocytes. Treatment with fluvastatin and pitavastatin improved hyperglycemia and insulin intolerance, and decreased adipocyte cell size in HFD-fed mice. However, atorvastatin had no effect. Euglycemic-hyperinsulimenic clamp assay revealed that glucose infusion rate was increased in HFD-fed mice treated with fluvastatin and pitavastatin, but not those with atorvastatin.
Conclusion: Fluvastatin and pitavastatin but not atorvastatin induced PPAR γ activation in 3T3-L1 adipocytes, thereby improving glucose intorelance. These unique action may contribute beneficial effects for the patient with obesity, metabolic syndrome or type 2 diabetes.

P064 Sitagliptin add on therapy rapidly improved daily glycaemic excursion within 24 hours in the type 2 diabetic patients with secondary failure to sulfonylureas. SUNSHINE Study

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Background and aims:
Inhibitors of dipeptidyl peptidase (DPP) 4 have been widely used for the patients with type 2 diabetes mellitus (T2DM). Furthermore, add on therapy with these agents will be expected to avoid or delay to start with insulin therapy in T2DM patients with secondary failure to sulfonylureas. However, it is unclear how fast and strong DPP4 inhibitors could ameliorate hyperglycemia in these patients. In the current study, we assessed the daily glucose excursion in the patients by continuous glucose monitoring (CGM) when sitagliptin were added on.
Materials and methods:
Twenty poorly controlled T2DM patients receiving sulfonylureas (62 ± 11 years old, M/F 11/9, HbA1c 8.5 ± 1.1 %) were enrolled. After the three day hospitalized life-style intervention (28 kcal/kg/day), their daily glucose profile was assessed by CGM for 48 hours before and after sitagliptin (50 mg/day) administration.
Results:
Rapid decrease in the postprandial glucose levels after dinner was observed on the same day of firstly receiving sitagliptin. The average glucose levels at 6 PM to 0 AM on the day before and the first day were 190.8 and 160.6 mg/dl ($p<0.001$). Notably, the mean glucose levels during the night time (6 PM to 0 AM) were decreased and flattened (138.3 mg/dl to 124.0 mg/dl, $p<0.001$). One out of 20 patients dropped out the protocol due to a symptomatic hypoglycemia. One started insulin therapy because of the positive for anti-GAD antibody. Eighteen patients successfully avoided to start insulin therapy over 6 months. The average HbA1c level decreased to 7.0 ± 0.9 % after 6 month.
Conclusion:
Sitagliptin add-on therapy to T2DM patients with secondary failure to sulfonylureas ameliorated the postprandial glucose levels from the first evening and flattened them during the night time. Ninety percent of the patients could avoid starting insulin therapy over 6 months. These results suggest that sitagliptin add-on therapy should be considered before starting insulin therapy for these patients.

P065 Change of urinary angiotensinogen predicts progression of diabetic nephropathy

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Background and aims: The intrarenal renin-angiotension system (RAS) plays an important role in the pathogenesis of diabetic nephropathy and urinary angiotensinogen (AGT) might reflect intrarenal RAS activity. The aim of this study was to evaluate that the change of urinary AGT reflects the efficacy of RAS blockages and predict the progression of diabetic nephropathy.
Materials and methods: This was a prospective observational study to assess early biomarkers for diabetic nephropathy (Diabetic Kidney Disease Study [DKDS]) at Pusan National University Hospital. Type 2 diabetic patients with estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m2 were enrolled. All patients had no history of RAS blockades or washout period for 2 months before enrollment. Urinary AGT were measured by ELISA kit at baseline and first year. A total 93 patients were followed up for 33 months (10-49 months).
Results: Both urinary AGT at baseline (AGT0) and first year (AGT1) were significantly correlated with the annual decline in eGFR in univariate analysis (r = 0.208, P = 0.046; r = 0.209, P = 0.044). After adjusting for several clinical parameters, AGT1, but not AGT0, remained significant association with the decline of eGFR in multivariate analysis. The change of urinary AGT (AGT1-AGT0) was also significantly correlated with the annual decline rate of eGFR after several clinical factors including baseline eGFR and albuminuria (r = 0.239, P = 0.016). There was no significant difference of the changes of urinary AGT between the patients with or without use of RAS blockades after enrollment. In analysis with the patients without use of RAS blockades, the change of urinary AGT was significantly correlated with the decline of eGFR in multivariate analysis. However, the change of urinary AGT was not correlated with the decline of eGFR in analysis with the patients with use of RAS inhibitors.
Conclusion: The change of urinary AGT might predict the progression of type 2 diabetic nephropathy but not reflect the efficacy of RAS blockade in these patients.

P066 Association between serum fatty acid compositions and clinical and nutritional factors in Japanese patients with type 2 diabetes

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Objective
The aim of our study was to investigate clinical and nutritional factors associated with the serum fatty acids in patients with type 2 diabetes.
Methods
Forty three patients with type 2 diabetes who had received nutritional guidance at our hospital from May 2013 to December 2014 were enrolled in this study. We performed a cross-sectional study of 39 patients. (We excluded 4 patients who had taken eicosapentaenoic acid (EPA) preparations at the time of the enrolement). We examined the relationship between the clinical factors, body compositions, physical activity levels (PAL) and nutrient intake, and the serum levels of dihomo-gamma linolenic acid (DHLA), arachidonic acid (AA), EPA, dochosahexaenic acid (DHA) and EPA/AA ratio.
Results
Of 39 patients, 20 were males sex. The mean values for age, BMI, fat mass, PAL, HbA1c, Cr, total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol were 64 years, 25 kg/m^2, 18.7kg, 1.6 Activity factor, 6.9 %, 0.78 mg/dl, 183 mg/dl, 113 mg/dl, 53 mg/dl and 98 mg/dl, respectively. The intake of total energy, carbohydrate, protein and fat were 33 kcal/kg ideal body weight (IBW), 4.5 g/kg IBW, 1.1 g/ kg IBW, and 0.87 g/ kg IBW, respectively. The EPA/AA ratio had a significant negative correlation with the BMI, fat mass, the intake of fat, saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), meats or oils, whereas it had a significant positive correlation with PAL, the intake of beans or fish and shellfish. The DHLA was significantly correlated with the BMI, the intake of fat, eggs or oils. The AA showed a significant positive correlation with the intake of fat, eggs, milks or oils, whereas it showed a significant negative correlation with the pulse wave velocity. The EPA was negatively correlated with the BMI, the intake of fat, MUFAs or meats, whereas it was positively correlated with PAL, the intake of beans or fish and shellfish. The DHA was positively correlated with the age and the intake of beans, whereas it was negatively correlated with the intake of fat, SFA, MUFAs, meats or oils.
Conclusions
Our data demonstrate that a high EPA/AA ratio is associated with high PAL, low fat intake, and low BMI/fat mass in patients with type 2 diabetes. It was suggested that the increase in intake of beans or fish and shellfish, and the decrease in that of meats or oils are important to achieve a high ratio of EPA/AA.

P067 Clinical factors that influence the long term efficacy of sitagliptin in patients with type 2 diabetes

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Objective: The aim of the present study is to assess the long-term efficacy of sitagliptin.
Methods: Subjects consisted of 151 Japanese patients with type 2 diabetes who received sitagliptin more than 96 weeks.
Results: After 96 weeks, the administration of sitagliptin led to significant reductions of the average HbA1c levels (7.4 ±0.9 %) relative to baseline (7.9 ±1.0 %) ($p < 0.01$).
However, we observed that HbA1c levels had initially decreased until 24 weeks (7.1 ±0.8 %) and then relapsed until 96 weeks (7.4 ±0.9 %) ($p < 0.01$).
Patients were classified into groups by clinical factors and reductions in HbA1c levels were compared between groups.
There was no significant difference in HbA1c reduction between groups classified by age, duration of diabetes, body mass index (BMI), body weight change after administration of sitagliptin, seasons in which sitagliptin were administered, and concomitant oral hypoglycemic agent (n.s. respectively).
Patients were also classified into two groups with or without relapse in HbA1c during observation period from 48 to 96 weeks (Relapse group and non-Relapse group).
There was significant difference in HbA1c reduction during period from 24 to 48 weeks between two groups. Relapse group significantly showed prior improvement in HbA1c during period from 24 to 48 weeks (-0.1 ±0.9 % vs +0.2 ±0.7 %, $p < 0.05$).
Mean BMI of Relapse group is significantly higher than that of non-Relapse group (27.1 ±5.6 % vs 25.0 ±4.7 %, $p < 0.05$).
Body weight gain of Relapse group is much more than that of non-Relapse group (+1.1 ±2.0 %vs -0.7 ±3.5 %, $p < 0.05$).
Conclusion: The administration of sitagliptin showed significant reductions of the HbA1c levels relative to baseline over 96 weeks.
However, HbA1c levels of some patients had initially decreased and relapsed thereafter.
It is possible that the great hypoglycemic effect of sitagliptin would be followed by relapse in glycemic control, which accompanies increase in body weight.

P068 A critical role of hormone-sensitive lipase in streptozotocin-induced diabetic hypertriglyceridemia

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[Background] The molecular mechanism of diabetic lipemia in the setting of insulin deficiency is not fully understood. We have previously found that the plasma level of triglycerides is lower in hormone-sensitive lipase (HSL) deficient mice (*Hsl*$^{-/-}$) than in wild-type mice (*WT*) when they are challenged with streptozotocin (STZ). HSL may play a critical role in chylomicron (CM) production, VLDL production, or CM/VLDL clearance. [Aim] The current study was aimed at elucidating the molecular mechanism of diabetic lipemia by understanding the markedly reduced levels of plasma triglycerides in *Hsl*$^{-/-}$ compared with *WT* in the insulin-deficient status. [Methods] *WT* and *Hsl*$^{-/-}$ male littermates at 10-13 weeks old were injected with 100 mg/body weight (g) of STZ twice every other day using a standard protocol. Plasma levels of triglycerides were measured after challenging these mice with fat-free high sucrose diet to maintain VLDL production, olive oil gavage to increase chylomicron production, or Triton WR-1339 to block VLDL/CM clearance. The mRNA expression levels of lipoprotein lipase (LPL) and LPL-related genes (Angptl3, Angptl4, Gpihbp1, Lmf1, and so on) in various tissues (white adipose tissue, liver, and muscle) were evaluated by quantitative polymerase chain reaction. Plasma LPL activity was measured using ^{3}H-triolein in post-heparin plasma obtained from *WT* or *Hsl*$^{-/-}$. [Results/Conclusion] *WT* and *Hsl*$^{-/-}$ equally became diabetic and insulin-deficient after STZ treatment. In *WT*, the plasma level of triglycerides was not increased after feeding fat-free diet, but increased dramatically after olive oil gavage, suggesting the major contribution of CM accumulation in this type of diabetic hypertriglyceridemia. Compared to *WT*, the increase in plasma triglycerides after olive oil gavage is substantially lowered in *Hsl*$^{-/-}$, suggesting that HSL may reduce CM production or increase CM clearance. We found no difference in plasma LPL activity and mRNA levels of LPL and other LPL related genes between *WT* and *Hsl*$^{-/-}$ in the insulin-deficient status. Regulation of intestinal lipid absorption or other yet-to-be-determined factors that regulate LPL activity in vivo by HSL may explain the phenotypic difference, which are currently under investigation.

P069 Reconstituting pancreas development from purified progenitor cells reveals genes essential for islet differentiation

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Pancreas biology is challenged to reveal the function of prodigious numbers of candidate genes implicated by recent genome-scale studies as regulators of organ development and diseases. Recapitulating organogenesis from purified progenitor cells that can be genetically manipulated would provide powerful opportunities to dissect such gene functions. Here we describe systems for reconstructing pancreas development from purified single fetal progenitor cells. Differentiation of pancreatic endocrine cells, including glucose-responsive β-cell, α-cell and exocrine cells in monoclonal spheres derived from a single cell provides unique evidence that pancreatic progenitor cells are multipotent. A strict requirement for native genetic regulators of in vivo pancreas development, like Ngn3, Arx and Pax4 revealed the authenticity of differentiation programs in vitro. This system allowed unprecedented genetic complementation testing and functional assessment of human disease alleles associated with congenital pancreatic islet hypoplasia and diabetes. Sphere cultures also permitted screening and identification of molecules that promote progenitor cell propagation and β-cell differentiation. Efficient genetic screens permitted by this system revealed novel transcriptional factors that are required for pancreatic islet development in vivo. Discovering the function of genes regulating pancreas development, and the ability to study a purified native pancreatic progenitor cell with our system should enrich strategies to regenerate islets for treating diabetes mellitus.

P070 Metabolic status in lean and overweight type 2 diabetes mellitus

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Introduction: Type 2 Diabetes Mellitus (T2DM) individuals in India are nonobese compared to Western population. As per Body Mass Index (BMI) more than 60% subjects are lean or normal weight. We hypothesized that lean and obese T2DM subjects have different metabolic status and so compared anthropometric parameters and metabolic profile among them. Nonestrified fatty acid (NEFA) is an important link between obesity, insulin resistance and T2DM. Sustained elevation of NEFA is a major cardiovascular risk factor in T2DM patients.
Aims and objectives: To evaluate clinical and biochemical profile in lean and overweight T2DM subjects.
Materials & methods: Cross sectional study carried out in 62 patients of T2DM referred to Diabetic O.P.D. According to BMI patients were categorized into lean (n= 33) and overweight (n=29). Detailed clinical history of T2DM duration and complications, demographic data obtained. Anthropometric measures BMI, waist circumference, and waist: hip and blood pressure recorded. After overnight fast blood samples collected and assayed for blood glucose, serum total Cholesterol (TC), Triglycerides (TG), LDL, HDL and plasma NEFA by standard methods.
Results and observations: Lean diabetics had significant hyperglycemic status (mean FPG183 +/-26 Vs 129+/-17 p<0.05) compared to overweight. TC and LDL were significantly raised in overweight T2DM (mean 254+/-15 vs 219+/-19, mean 132+/-14Vs 112+/-13p<0.05). Hypertriglyceredemia observed in both groups but highly significant in overweight diabetics (mean 283+/-43vs 215+/-24 p<0.001). HDL was decreased significantly in lean compared to overweight group (mean 32+/-7 Vs 27+/-6). NEFA were significantly raised in overweight compared to lean T2DM (mean 2.4mmol/l+/-0.4 Vs 1.2mmol/l+/-0.3 p<0.001)
Discussion: We observed altered metabolic profile in both groups. Lean T2DM had hyperglycemia but less derangement in lipid profile whereas overweight group had normal glycemic status with significantly deranged lipid profile with raised FFA levels. So lean individuals are more prone to microvascular complications and obese have multiple cardiovascular risk factors.

P071 Voluntary exercise under a food restriction condition decreases blood branched-chain amino acids levels, in addition to improvement of glucose and lipid metabolism, in *db* mice, type 2 diabetes animal model

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Objectives: Exercise is effective for preventing the onset and development of type 2 diabetes mellitus (T2DM) in human cases; however, an animal model of T2DM evaluating the effect of exercise on the pathophysiology has not been fully established.
Methods: We applied voluntary exercise under pair-fed (P) conditions in *db* mice, T2DM animal model. Exercising (Ex) and sedentary (Se) mice were placed in a cage, equipped with a free or locked running wheel, for 4 weeks, respectively. The amount of food consumed by *ad libitum*-fed wild-type mice under the Se condition (ad-WT) was supplied to all mice, except *ad libitum db* mice (ad-*db*). Blood parameters and expression of the genes involved in nutrient metabolism were analyzed.
Results: PEx-*db* (pair-fed and exercising) mice showed significantly lower HbA1c, body weight and liver weight than PSe-*db* and ad-*db* mice. Decreased hepatic triglycerides in PEx-*db* mice corresponded to a lower expression of lipogenic enzyme genes in the liver. Moreover, PEx-*db* mice showed significantly lower plasma branched-chain amino acids (BCAA), arginine, proline and tyrosine, in addition to increased skeletal muscle (SM) weight, than PSe-*db* and ad-*db* mice, in spite of little influence on the expression of the BCAA transaminase gene, in SM and WAT.
Conclusion: We found that exercise under a food restriction condition decreases several amino acids, including BCAA, and improves insulin sensitivity more than mere food restriction. We propose that the decreased concentration of blood amino acids may be a valuable marker evaluating the effects of exercise on diabetic conditions.

P072 Use second trimester prenatal screening markers for down syndrome to predicting gestational diabetes mellitus

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Gestational diabetes mellitus (GDM) is a common complication that may occur during pregnancy. Continuously rising and poorly controlled hyperglycemia can endanger both mother and fetus because of adverse pregnancy outcome. Particularly, women who have had GDM are more likely to develop type 2 diabetes than women who have not had GDM in pregnancy. However, GDM cannot be diagnosed until 24-28 weeks of gestation. The purpose of this study was used Down syndrome quadruple test (AFP, total hCG, uE3, and inhibin A) in the second trimester to predicting GDM. The participants were selected from 4293 pregnant women who received prenatal examinations in Chi Mei Medical Center between August 2009 and July 2012. In this study, 117 healthy pregnant women were included into the control group; 110 participants were within all normal glucose range on the oral glucose tolerance test (OGTT); 38 women received one abnormal result on the OGTT; and 60 were confirmed to have GDM. This study explores the correlation of the quad markers to varying glucose intolerance levels and the development of GDM. GDM was confirmed based on the diagnostic criteria for the 100g OGTT established by the American Diabetes Association (ADA, 2009). The statistical results showed that the prevalence of GDM was 4.05%. The group with GDM all demonstrated heavier weights and older ages compared to other groups (weight: p= 0.000; age: p= 0.036). Pregnant women at high risk of Down syndrome had a higher GDM incidence rate compared to healthy pregnant women (5.9%:2.4%; p= 0.005). Only uE3 among the quad markers presented statistically significant differences (uE3: 0.93 MoM, 95% CI: 0.87-0.99; control: 1.02 MoM, 95% CI: 0.97-1.0; p= 0.022). The area under the receiver operating characteristic (ROC) curve was 0.612 (p= 0.015). The results indicated that pregnant women at high risk for Down syndrome tended to have a higher incidence rate of GDM compared to pregnant women with normal risks. In the second trimester screening for Down syndrome using the quad markers, uE3 in a low concentration can to prediction the development of GDM.

P073 Relation of an elderly diabetes and frailty -Classification by the Kihon Checklist-

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Background
In order to discover a frailty state at an early stage, the Kihon Checklist (KCL) is used as a preventive measure for the healthy. We have reported as to whether it corresponds to the frailty standard used widely overseas in general when a KCL synthesis score is eight or more points. In previous study, there has been much research on the sarcopenia of community-dwelling healthy subjects and the ambulatory elderly. Not many studies of diabetes and frailty, and sarcopenia have been carried out. Since in diabetes self -control in daily life is needed verification of problem with frailty is crucial for an elderly diabetes patient.
Purpose
The classification of frailty examines the kind of measured value and pertinent details of diabetes which are related in elderly diabetics.
Method
For the diabetes outpatient aged 65 and over, a frailty classification (healthy: 0-3, pre-frailty: 4-7, frailty: over 8) based on the Kihon Checklist (KCL) total score was performed. The difference among 3 groups was analyzed by the Kruskal-Wallis test, and logistic regression analysis was conducted to examine the relation of a frailty classification and relevant details on diabetes.
Result
Among 370 participants, the number of patients with frailty was 133 (35%), those with pre-frailty were 106 (29%), and healthy patients numbered 131 (36%). The items which had a significant difference among 3 groups were age, sex, BMI, HbA1c, MMSE, MNA, nephropathy, retinopathy, neuropathy, cerebrovascular disorder, depression, osteoporosis, hump back, grip strength, lower thigh boundary length, walking speed, and history of falls. In addition, in order to clarify the diabetes items related with the classification of frailty, as a control group a healthy group was subjected to evaluation by logistic regression analysis.
HbA1c, grip strength and walking speed were identified as significant independent variables that were correlated with frailty.
Conclusion
Elderly diabetics with frailty had poor glycemic control, and walking speed and grip strength reached a significantly low level. Compared to such features, blood glucose management is critical for elderly diabetics classified to have frailty in terms of recuperation. Due consideration of the decrease in muscle strength and walking rate is required. Moreover, for an elderly diabetic with frailty and a history of frequent falling; intervention for fall prevention in outpatients is also important.

P074 Type 2 diabetes, obesity and malnutrition risk in adults hospitalized in internal medicine departments

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Background: Malnutrition risk is an overlooked comorbidity among patients with type 2 diabetes (T2DM), perhaps due to its association with overweight and obesity. The present study was designed to estimate malnutrition risk among newly hospitalized patients with T2DM, and to assess the effect of T2DM, body mass index (BMI) and malnutrition risk on duration of hospitalization and risk of in-hospital death.
Methods: In this survey, all adults newly admitted to internal medicine departments at a large tertiary medical center, during the 5-week data acquisition period in 2010, were screened for malnutrition risk using the Nutrition Risk Screen (NRS 2002). Increased malnutrition risk was defined as an age-adjusted NRS 2002 score >/= 3. Malnutrition risk was compared by T2DM status and across body weight categories. In addition, T2DM patients were compared by malnutrition risk category.
Results: Of the 306 individuals screened 100 (32.7%) were T2DM patients, 85 of whom had anthropometric data recorded. Mean age of T2DM patients was 71.9+/-14.4 years vs. 70.8+/-17.1 years, p=0.6. BMI was similar between T2DM patients (26.9+/-6 kg/m2) and patients without T2DM: (25.7+/-6 kg/m2, p=0. Elevated malnutrition risk was observed in 37% T2DM patents and in 39.3% patients without T2DM, p=0.69. Duration of hospitalization did not differ significantly between patients with vs. without T2DM: 4 (1-86) vs. 4 (1-123) days, p=0.3. Elevated risk for malnutrition prolonged hospitalization from 4 (1-50) to 5 (1-86) days, p=0.04 in T2DM and from 3 (1-26) to 5 (1-123) days in patients without T2DM, p<0.0001. In a general linear model of length of hospital stay, malnutrition risk remained a significant predictor (p=0.01) even after controlling for age, smoking and BMI. No DM-malnutrition risk interaction was observed. Malnutrition risk significantly increased odds of in-hospital death: odds ratio (OR) 3.6, 95% confidence interval (CI) 1.8-7.2, P<0.0001, even after controlling for age, sex, smoking status, T2DM and BMI.
Conclusions: Increased malnutrition risk is a frequent finding in patients newly hospitalized in internal medicine departments, regardless of diabetes status. Malnutrition risk prolongs length of hospital stay and increases risk of in-hospital mortality in patients with and without T2DM.

P075 Blend of sesame and rice bran oils as cooking oil improves glucose and lipid metabolism in type 2 diabetes mellitus- An open label dietary approach study

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By considering the substantial interest in the nutritional benefits of sesame and rice bran oils, the current study was to examine the extent to which the daily incorporation of the blend of unrefined sesame and physically refined oryzanol rich rice bran oils (20:80 ratio) as cooking oil beneficial in type 2 diabetes mellitus (T2DM). This open label study comprised of 300 T2DM and 100 normoglycemic subjects. Blend of sesame and rice bran oils (VivoTM) was supplied to T2DM (n=100) and normoglycemic subjects. Hundred T2DM were treated with glibenclamide (5mg/d) only and 100 T2DM were supplied with the oils blend in addition to glibenclamide (5mg/d). The groups supplied with the oils blend were instructed to use it as the only cooking oil for 60 days. Fasting and postprandial blood glucose was measured at 0, 30 and 60 days. Glycated hemoglobin (HbA1C) and lipid profile (TC, TG, LDL-C and HDL-C) were measured at 0 and 60 days. Fasting and postprandial blood glucose was significantly lowered (< 0.001) from 30 days, and HbA1C and lipid profile were improved significantly (< 0.001) at 60 days in T2DM subjects substituted with the oils blend only while no significant changes were noted in normoglycemic subjects substituted with the oils blend. Glibenclamide alone treatment showed a significant reduction in both fasting and postprandial blood glucose (< 0.001) from 30 days and HbA1C at 60 days except lipid profile where as glibenclamide plus oils blend group showed a remarkable reduction in both fasting and postprandial blood glucose (< 0.001) from 30 days, and a significant changes observed in HbA1C and lipid profile (< 0.001) at the end of 60 days in T2DM subjects. These results suggest that the blend of sesame and rice bran oils exhibits anti-diabetic and lipid lowering efficacies, only in the subjects with T2DM, providing the evidence that these oils blend as cooking oil could be functional for the management of T2DM.

P076 Anagliptin affects lipid metabolism in patients with Type 2 diabetes mellitus and dyslipidemia

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Introduction : The aim of present study is to determine the effect of anagliptin on lipid metabolism in patients with type 2 diabetes mellitus (DM). Materials and methods : Twenty five patients with type 2 DM (male :female 17 :8, age : 69.6 ± 8.6 years old, BMI : 26.01 ± 2.95kg/m^2, HbA1c : 6.40 ± 0.44%, low-density lipoprotein cholesterol (LDL-chol) : 111.0 ± 26.0mg/dl, high-density lipoprotein cholesterol (HDL-chol) : 54.4 ± 13.3 mg/dl, triglycerides(TG) : 122.7 ± 53.8mg/dl, data are mean ± SD) were treated with 100mg of anagliptin in substitution of other oral glucose-lowering agents such as sulfoniyl urea (2 cases), pioglitazone (5 cases), DPP-4 inhibitor (14 cases), alpha-glucosidase inhibitor (4 cases). The following parameters were evaluated at 0, 6 and 12 weeks after anagliptin treatment : body weight, blood pressure, HbA1c, fasting plasma glucose, 1,5-AG, TG, LDL-chol, HDL-chol. Results : Serum LDL-chol levels at 12 week were significantly decreased compared to levels at 0 week in 5 patients with LDL-chol > 140mg/dl (150.2 ± 6.0mg/dl at 0 week, 130.6 ± 15.3mg/dl at 12week, p < 0.05) with no significant difference in HbA1c levels(6.40 ± 0.35% at 0 week, 6.16 ± 0.29% at 12 week). There was a positive correlation (r=0.56, p < 0.01) between the baseline (0 week) LDL-chol level and the delta-LDL-chol (baseline LDL chol levels- 12 weeks LDL chol levels). There were no significant differences in LDL chol levels between 0 week and 12 weeks in patients with LDL-chol < 140mg/d (101.2 ± 18.4mg/dl at 0 week, 102.8 ± 22.0mg/dl at 12week). Moreover, there were no significant differences in other parameters between 0 week and 12 weeks. Conclusion : These results show that anagliptin ameliorates LDL-chol levels independently of HbA1c levels after substitution from other oral hypoglycemic agents including DPP-4 inhibitor. These novel findings suggest that anagliptin may affect lipid metabolism leading to reduction of serum LDL-chol levels. Anagliptin may have a different mechanism of action on lipid metabolism compared to other oral hypoglycemic agents.

P077 Differences in the clinical characteristics between young onset adult type 1 and type 2 diabetes mellitus under insulin treatment

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[Introduction] Recently, there is an increase in the number of diabetic patients of young onset. Previous reports have shown that the prognosis of young onset type 2 diabetic patients is worse than that of young onset type 1 diabetic patients because of vascular complications caused by uncontrolled obesity, dyslipidemia and hypertension. However, differences in the clinical characteristics of young onset diabetes among Japanese diabetic patients under insulin treatment remain unclear. The aim of present study was to investigate the differences in the clinical characteristics between type 1 and type 2 diabetes mellitus (DM) under insulin treatment that occur in patients less than 35 years old. [Materials and methods] The clinical characteristics of 24 patients with type 1 (male : female 10 :14, age: 32.3 ± 4.3 years old, mean ± SD) and 18 with type 2 DM (3 :15, 34.3 ± 4.4 years old) were as follows: BMI: 21.9 ± 3.5 vs 28.9 ± 4.6 kg/m^2 ($p<0.05$), duration: 14.3 ± 8.6 vs 8.9 ± 5.7 years, systolic blood pressure: 117.0 ± 13.4 vs 132.5 ± 15.4 mmHg ($p<0.05$), diastolic blood pressure: 68.2 ± 9.3 vs 78.4 ± 11.3 mmHg, HbA1c: 7.6 ± 1.0 vs 8.7 ± 2.0 % ($p<0.05$), total cholesterol(Chol): 191.2 ± 27.7 vs 217.1 ± 49.0 mg/dl, LDL-Chol: 103.2 ± 19.0 vs 130.8 ± 44.3 mg/dl ($p<0.05$), HDL-Chol: 71.0 ±17.6 vs 47.6 ± 9.3 mg/dl ($p<0.01$), eGFR: 89.0 ± 22.5 vs 97.0 ± 28.0 ml/min/1.73m^2, total insulin dose: 46.7 ± 26.7 vs 43.5 ± 22.7 Unit/day. Frequency of HbA1c< 7.0%: 12.5 vs 33.3%, 7.0< HbA1c<10.0%: 87.5 vs 38.9%, 10.0< HbA1c: 0 vs 27.8%. Moreover, the frequency of diabetic microvascular complications was as follows: Diabetic nephropathy stage I: 87.5 vs 77.8 %, stage II-V: 12.5 vs 22.2%. Diabetic retinopathy: none 80 vs 72.2%, simple or proliferative changes 20 vs 27.8%. [Conclusion] These results indicate that the control of blood glucose, lipid profile and blood pressure were worse in patients with young onset type 2 DM than in type 1 DM patients under insulin treatment. Increased BMI without difference in the insulin dose may be associated with the lipid profile and blood pressure. Overall, these observations suggest that the control of both blood glucose and BMI in type 2 DM patients is important to prevent progressive vascular complications.

P078 The relationship between medial temporal lobe atrophy and diabetes mellitus

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Introduction: Recent studies suggest that Alzheimer's disease (AD) is related with diabetes mellitus (DM). The number of patient of both AD and DM is increasing in Japan, and many patients in early stage of AD are considered not to receive medical and social support. AD is a type of dementia characterized with medial temporal lobe atrophy of the brain. Voxel-based Specific Regional Analysis for Alzheimer's Disease (VSRAD®) is the program to asses medial temporal lobe atrophy on brain MRI. This program assists to diagnose AD by offering severity of medial temporal lobe atrophy as Z-scores (VSRAD), and VSRAD>2 suggest that the levels of atrophy of this area is significant. It is especially useful for detect early stage of AD. Recently many hospitals in japan have become to use VSRAD with brain MRI.
Methods: We obtained results of VSRAD from outpatients who were taken brain MRI with complaints about cognitive dysfunction. We checked their cognitive impairment levels by using Mini-Mental State Examination (MMSE). We also measured HbA1c or obtained information of having or not having DM by self-report of those patients. We surveyed relationship between VSRAD and MMSE, age, HbA1c, and having or not having DM.
Results: There was a negative correlation between the levels of VSRAD and the points of MMSE, though it was not so strong (r=-0.35). When patients were divided in two groups by using cut-off line with VSRAD=2, the prevalence rate of DM was higher in VSRAD>2 group than another one (24.3% vs. 12.6%). We could not find any correlation between the level of VSRAD and age (r=0.11), and HbA1c (r=-0.05). Mean VSRAD of patients with DM was higher than that of patients without DM (1.83 vs. 1.61), but it was not significant (P=0.11).
Conclusions: As some studies have reported, the levels of VSRAD might be associated with the levels of cognitive impairment. These also were not influenced by patients' age. In this study we concluded that DM has a possibility to relate medial temporal lobe atrophy. It seems that DM itself might be a risk of atrophy of this area, not depending on the levels of glycemic control. As we have not checked ill period of DM and other risks such as hypertension and lipid profiles, farther studies will be needed.

P079 Ultra-long-acting insulin degludec improved the nadir of the nocturnal plasma glucose by fitting to basal insulin secretion in type 2 diabetes

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Background and aims:
Conventional long acting insulin Glargine and Detemir have been used as a basal insulin. However, some diabetic patients encountered by nocturnal hypoglycemia by this conventional long acting insulin therapy.
We observed the effects of ultra-long-acting insulin Degludec on insulin peak effect after converting from Glargine or Detemir.
To investigate whether the improvement of peak of insulin effect by Degludec or not, all patients were investigated by continuous glucose monitoring (cgm) method before and after switching to Degludec.
Materials and methods:
In total, 32 type 2 diabetic patients were observed in this study. Diabetic subjects consisted of 19 males and 13 females. The average age was 66.9+9.8yo, the average eGFR was 65.7ml/min/1.73m2.
Before and after switching of Insulin Glargine or Detemir to Degludec, fluctuation of plasma glucose were estimated by cgm. Measuring points of night time were devided by quartile method.
Nocturnal nadir of plasma glucose were calculated by average value of second quartile and third quartile.
Results:
At the begin of the night plasma glucose 107.7+31.1mg/dl(M+SD) before switching and the value of plasma glucose showed 107.6+39.9mg/dl after switching.
Nadir of nocturnal plasma glucose in the midnight showed 100.0+22.8mg/dl and 103.8+30.8mg/dl before and after switching, respectively. Degludec lift the nadir of nocturnal plasma glucose by 3.8mg/dl significantly ($p<0.05$, SPSS, general lineal model analysis).
Conclusion:
Ultra-long-acting insulin Degludec improved by lifting up the nadir of nocturnal plasma glucose. Degludec contributed on the improvement of nocturnal insulin peak problem.

P080 Preclinical study of cytopiloyne as an anti-diabetic novel phytocompound

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Cytopiloyne was identified as a novel polyacetylenic compound. However, its anti-diabetic properties are poorly understood. The aim of the present study was to investigate the anti-diabetic effect and mode of action of cytopiloyne on type 2 diabetes (T2D). We first evaluated the therapeutic effect of cytopiloyne on T2D in db/db mice. We found that one dose of cytopiloyne reduced postprandial glucose levels while increasing blood insulin levels. Accordingly, long-term treatment with cytopiloyne reduced postprandial blood glucose levels, increased blood insulin, improved glucose tolerance, suppressed the level of glycosylated hemoglobin A1c (HbA1c) and protected pancreatic islets in db/db mice. Next, we studied the anti-diabetic mechanism of action of cytopiloyne. We showed that cytopiloyne failed to decrease blood glucose in streptozocin (STZ)-treated mice whose beta cells were already destroyed. Additionally, cytopiloyne dose-dependently increased insulin secretion and expression in beta cells. The increase of insulin secretion/expression of cytopiloyne was regulated by protein kinase C alpha (PKC alpha) and its activators, calcium and diacylglycerol (DAG). Overall, our data suggest that cytopiloyne treats T2D via regulation of insulin production involving the calcium/DAG/PKC alpha cascade in beta cells. These data thus identify the molecular mechanism of action of cytopiloyne and prove its therapeutic potential in T2D.

P081 The role of survivin and Raf-1 kinase against enhancement of pancreatic beta cell apoptosis in patients with type 2 diabetes mellitus

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Introduction:This study aimed to reveal differences in levels of survivin and Raf-1 kinase in prediabetes, T2DM controlled, uncontrolled T2DM and their relationship with HbA1c levels and serum triglyceride levels.
Methodology: This study was an observational study with cross-sectional design. The study involved sixty people with T2DM who visited the endocrine and metabolic clinic and thirty people with prediabetes. The variables studied were the control of blood sugar as reflected by HbA1c values measured by enzymatic method, triglyceride levels and levels of survivin and raf-1 kinase which reflected pancreatic beta cell apoptosis.
Result: Average level of serum Raf-1 kinase in prediabetes group (11.6 (1.4) pg / mL) were significantly higher in the prediabetes group to be compared with controlled T2DM (9.9(1.1) pg / mL) and uncontrolled T2DM (9.1(1.5) pg/mL) with $p < 0.05$. Average level of serum Survivin were significantly higher in the prediabetes group (5.4 (0.4) pg / mL) to be compared with controlled T2DM group (5.0 (0.2) pg/mL) and uncontrolled T2DM group (4.7 (0.1) pg/mL) wih $p < 0.05$. There was no correlation between HbA1c with Raf-1 kinase level ($R = - 0.215$, $p = 0.250$), but there was a negative correlation between HbA1c with serum Survivin level ($R = - 0.6$, $p < 0,05$). There was a negative correlation between the levels of triglycerides with Survivin ($R = - 0.267$, $p < 0.05$) but not with Raf-1 kinase.
Conclusions: Levels of survivin and raf-1 kinase are significantly higher in the group of prediabetes, controlled T2DM and uncontrolled T2DM. There is a negative correlation between survivin with HbA1 C and triglyceride levels, whereas no correlation between the raf-1 kinase either with HbA1C and with serum triglycerides
Keywords: Survivin, Raf-1 kinase, Pancreatic Beta Cell, Apoptosis

P082 Clinical results of hospitalization according to a two-week clinical path in diabetic patients with visceral fat accumulation

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Aim: To evaluate clinical results of hospitalization according to a two-week clinical path (CP-hosp.) in diabetic patients with visceral fat accumulation.
Patients and Methods: In CP-hospitalized patients discharged at from November 2010 to October 2013, being CP-hosp. a patient twice or more during a year from November to October, the last was, and being two or more data of CP-hosp. available during three years, the first was selected. Patients were divided from whether visceral fat area, calculated from umbilical section of abdominal CT, was more than 100 cm^2; (V) or less (C), and further from being followed for longer than six months after discharge(F1) or not (F0). Fatty liver was evaluated from abdominal CT. Clinical results were compared between the groups (v1: V/F1, n=59, c1: C/F1, n=49, v0: V/F0, n=36, c0: C/F0, n=48) or between on CP-hosp. and after followed. χ^2; test was used, and $p<0.05$ was determined as statistically significant.
Results: On CP-hosp., more frequent in the group V were BMI>=25 (70 vs. 18), serum TG>=150mg/dl (36 vs. 17), HDL-cholesterol<40mg/dl (24 vs. 12), and fatty liver (44 vs. 14) than in the group C. As for vascular complications or other coexisting diseases, only renal imparement (GFR<30ml/min/1.73m^2;) was more frequent in group C (1 vs. 7). In group F1, more patients had durations of diabetes>=10 years (59 vs. 29), and had history of hospitalization (32 vs. 14) than in group F0. In group v0/c0, more have been followed by primary-care physicians for attaining good glycemic control than in group v1/c1 (26/36 vs. 19/16). In the patients followed after discharge (v1:59, c1:49, v0:24, c0:27), increased was the frequency of A1C<7% (4»35, 3»34, 3»16, 7»22), and the use of insulin (29»41, 18»42, 10»10, 11»14) and GLP-1 analog (0»14, 0»8, 0»7, 0»12). In the group v1, the frequency of BMI>=25 (47»37), BP>=130/80mmHg (42»31), TG>=150mg/dl (22»14) , visceral fat area>=100 cm^2; (59/59»30/45), and fatty liver (29/59»12/47) were decreased, and the dose of insulin >=0.5units/kg ideal body weight/day was more frequent than in the group c1 (23/41 vs. 12/42).
Discussions: Metabolic conditions of diabetic patients with visceral fat accumulation have improved owing to the organized hospitalization with clinical path. The sooner hospitalization could promise the faster outcome.

P083 Serum insulin-like growth factor-I is related to lipoprotein(a) level in patients with type 2 diabetes mellitus

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Insulin-like growth factor-I (IGF-I) is considered as a candidate factor responsible for the pathogenesis of diabetic microvascular complications. Short-term and long-term administration of human growth hormone (GH) in GH-deficient patients showed the increase in serum lipoprotein(a) concentration, but IGF-I treatment resulted in the decrease of Lp(a) level. And the increase in serum Lp(a) concentration was noted in patients with diabetic retinopathy and nephropathy. So we studied to evaluate the relationship between serum IGF-I and lipoprotein(a) in patients with type 2 diabetes mellitus.
116 type 2 diabetic patients were studied. Serum IGF-I by IRMA (Diagnostic Systems Laboratories Inc.) and Lp(a) using nepherometry method were measured.
Serum Lp(a) concentration was increased in patients with proteinuria, but not in patients with microalbuminuria compared to normoalbuminuria. There was no significant linear correlation between serum IGF-I and LP(a), but significant correlation was noted between serum IGF-I and Lp(a) in high IGF-I (IGF-I > median value, 191.4 ng/mL). So we divided study group as quartile by Lp(a) concentration. 3rd and 4th quartile showed elevated serum IGF-I level compared to lowest (1st) quartile.
In conclusion, serum lipoprotein(a) concentration is related to insulin-like growth factor-I level in patients with type 2 diabetes mellitus. But underlying mechanism and its clinical implications should be determined.

P084 Study on the expansion of a Japanese-style medical diabetes service in China

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Objective: In Japan there are many excellent medical technologies including team-based diabetes care, but the number of people in need of medical treatment is decreasing; on the other hand, it is a fact that many foreigners are interested in receiving superior Japanese medical care. Thus, we believe that internationalization of medical activities is a necessary move and future directions with the aim of improving the quality of the health care in Japan while maintaining the domestic medical social insurance system and effectively using of limited medical resources. We carried out the research on the usefulness of a Japanese-style team-based medical diabetes service in China.
Methods: A medical team composed of Japanese physicians, nurses, dietitians and pharmacists formed a consortium with companies and created a Japanese-style diabetes outpatient clinic in the hospital of Shanghai and Hangzhou, China. Outpatient service was provided once a month, for 1-2 days, and the usefulness of services including nutritional guidance by dietitians, education for diabetes and foot care by nurses, and guidance on the use of drugs and insulin by pharmacists was investigated.
Results: 1) 30% of the patients were obesity at the first visit and 70% of the patients were obesity in the past. 2) 60% of the patients had abnormal in eating behavior, 3) more than 60% of the patients had never received education on diabetes, including nutritional guidance. 4) In many cases how to adjust the diet, exercise, medication / insulin dose was by self-taught. 5) Treatment of diabetes in China was based on drug therapy including mainly sulfonylurea and glinide. 6) More than half of the patients were poor control, 7) foot drying and ringworm infection was higher. 8) All services provided by the Japanese medical team were very well-received by the Chinese diabetes patients. 9) All items investigated including body weight, blood glucose, blood pressure and lipids were improved significantly, and the Japanese-style diabetes care was confirmed to be very effective.
Conclusion: We confirmed that the need in China for the Japanese-style team-based medical diabetes service was very high.

P085 The importance of appropriate insulin treatment in aging society -from the standpoint of hypoglycemia-

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Background and aims: Hypoglycemia is a constant threat for patients with diabetes. Many diabetic patients treated with insulin have experienced hypoglycemia. The aim of the present study is to investigate the background of insulin-induced hypoglycemia.
Materials and methods: Subjects consisted of 63 diabetic patients treated with insulin were admitted to our hospital for hypoglycemia between April 2011 and July 2013. We retrospectively analyzed these cases based on the patients' clinical records.
Results: Characteristics of 63 patients are as below: mean age: 69±14 years, mean HbA1c level: 7.76±1.55%, mean eGFR: 58.9±33.2ml/min/1.73m^2, and severe hypoglycemia (JCS-II≦consciousness disorder): 34 subjects. Type 1 and type 2 diabetes account for 22% and 78% respectively. 50patients were treated with only insulin injection. The breakdown is as follows: Five times daily insulin injection (10%), four times daily (50%), three times daily (14%), twice daily (24%), once daily (2%). The breakdown of daily total insulin dose is as follows: over 40units (26%), 32~39units (20%), 24~31units (38%), lower than 23units (16%).Thirteen patients were treated with insulin with oral hypoglycemic agent (OHA). The breakdown of OHA is as follows: α-glucosidase inhibitors: (38%), sulfonylureas: (31%), DPP-IV inhibitors: (7.7%), thiazolidinediones: (7.7%), biguanides: (7.7%), glinides: (7.7%). In addition, we detected patient factors such as insulin overdose injection, meal skip, etc.
Conclusion: 64% of diabetic patients who admitted to our hospital for hypoglycemia were received insulin. It is important to reduce the human error in insulin injection and to inject appropriate units of insulin from the viewpoint of aging society.

P086 Effect of acupuncture for appetite control in type 2 diabetes with obesity- a pilot study

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Background: The treatment of Type 2 diabetes with obesity has incomplete efficacy and side-effects when given as combination therapy. In this pilot study, we evaluated the effect of acupuncture for appetite in type 2 diabetes with obesity.
Methods: A total of 14 patients were completed this study. Subjects were defined as having type 2 diabetes and body mass index(BMI) ≥ 23kg/m^2. Acupuncture was delivered two times a week for 6weeks. The previous medicine was continued in the subjects. At initial and follow-up after 6weeks, all subjects underwent Hunger visual analogue scale (VAS), BMI, and laboratory test such as hemoglobin A1c, fructosamine, insulin, c-peptide and lipid profiles.
Results: 7 subjects with acupuncture treatment and 7 subjects without it were included in the study. After initial (0week) and follow up (10weeks), Hunger VAS and BMI were not significantly different with two groups (respectively, p=0.663, p=0.531). The factors related with glucose such as insulin, c-peptide, hemoglobin A1c, and fasting blood glucose were not significantly different with two groups(respectively, p=0.808, p=0.932, p=0.514, and p=0.529). Fructosamine were decreased after acupuncture intervention, However, there was not significantly different with two groups (p=0.237).
Conclusion: These data suggest that acupuncture may not be the effects of appetite for type 2 diabetes with obesity. Further investigations are required to elucidate the role of acupuncture for appetite control of type 2 diabetes with obesity.

P087

Withdrawn

P088 The transcriptional coregulator CITED2 regulates adipocyte differentiation by interacting with retinoblastoma protein

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During the progression to obesity, adipocyte hypertrophy and hyperplasia are critical for adipose tissue expansion. Increased adipocyte number is accounted for by enhanced proliferation and differentiation of preadipocytes. Adipocyte differentiation is critically regulated by the coordination of reentry into the cell cycle (mitotic clonal expansion: MCE) and activation of the adipogenic transcriptional program encompassing C/EBPs and PPARγ and histone acetyltransferases such as CBP and GCN5. The transcriptional regulator CBP/p300-interacting transactivator with Glu/Asp-rich carboxy-terminal domain 2 (CITED2) interacts with many of these molecules. However, the role of this protein in adipogenesis regulation is unknown. In this study, we investigated the role of CITED2 in adipocyte differentiation using 3T3-L1 cells. CITED2 knockdown in 3T3-L1 preadipocytes impaired lipid accumulation with decreased induction of PPARγ and C/EBPα but not of C/EBPβ/δ, suggesting impaired adipogenesis. Defective adipogenesis induced by CITED2 knockdown was rescued, at least in part, by treatment with PPARγ agonist rosiglitazone, indicating that CITED2 promotes adipogenesis by PPARγ induction. CITED2 knockdown also impaired transient cell proliferation 48 h after adipogenic induction, with a concomitant decrease in retinoblastoma protein (Rb) phosphorylation and cyclin A induction, suggesting impairment in MCE, a critical step for PPARγ induction. Co-immunoprecipitation analysis revealed that CITED2 interacted with Rb and enhanced its phosphorylation by CDK-cyclin complex. Thus, CITED2 regulates adipocyte differentiation via MCE induction by promoting the CDK-dependent phosphorylation of Rb.

P089 Differences in vasodilation via protease-activated receptor-2 in various arteries from SHRSP.Z-*Lepr*^{fa}/IzmDmcr rats with metabolic syndrome

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Protease-activated receptor-2 (PAR2) activation causes vascular inflammation and vasodilation, but its role in metabolic syndrome remains uncertain. We reported PAR2-induced vasodilation of thoracic aorta was preserved in SHRSP.Z-*Lepr*^{fa}/IzmDmcr rats (SHRSP.ZF) with metabolic syndrome, which were less responsive to nitric oxide (NO)-mediated vasodilation. In this study, we aimed to determine whether PAR2-induced vasodilation remains unchanged in other large caliber arteries, and whether ageing affects these responses in rats with metabolic syndrome. Specifically we compared the vasodilations elicited by PAR2-activating peptide, 2-furoyl-LIGRLO-amide (2fly), and nitrovasodilator, nitroprusside, in superior mesenteric and renal arteries of SHRSP.ZF and Wistar-Kyoto (WKY, controls) rats at 13 and 18 weeks of age.
Superior mesenteric and renal arteries were removed from each animal under sodium pentobarbital anesthesia and immediately placed in Krebs-Henseleit solution. The vessels were cleaned of their adherent tissue and cut into approximately 3-mm wide ring, taking care not to damage the endothelial cells. The rings were mounted isometrically at an optimal resting tension in an organ bath filled with the solution. The arterial rings were contracted by phenylephrine, and exposed to cumulative concentrations 2fly or nitroprusside.
Body weight, waist-length ratio, serum levels of lipids, glucose and insulin, and systolic blood pressure of 13 and 18 weeks of age SHRSP.ZF increased more at than in age-matched WKY. At 13 weeks of age, vasodilations in response to 2fly remained unchanged in both mesenteric and renal arteries of SHRSP.ZF. Nitroprusside-induced vasodilations were decreased compared with those of WKY. At 18 weeks of age, vasodilations in response to both 2fly and nitroprusside were decreased in superior mesenteric and renal arteries of SHRSP.ZF.
Our results demonstrate that at an early stage of metabolic syndrome, vasodilation via PAR2 activation was preserved in superior mesenteric and renal arteries under conditions, in which NO-mediated responses were impaired. We have previously reported that 2fly-induced vasodilation remains unchanged in the thoracic aorta of SHRSP.ZF at not only 13, but also 18 weeks of age. Taken together, these findings suggest that deterioration of PAR2-mediated vasodilation occurs in small caliber arteries earlier than that in large conduit vessels in metabolic syndrome.

P090 Phenotypic shift of bone marrow monocytes into a pro-inflammatory subset in obese diabetes and established obesity

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Background: Adipose tissue (AT) inflammation in obesity causes insulin resistance, leading to type 2 diabetes and multiple organ damage. Although macrophage is emerged as an important initiator, the mechanism underlying its accumulation and activation in AT is not fully understood. Especially, its precursor cell monocyte contribution is little known.
Aim: To investigate whether monocytes is affected in obesity and explore its role in adipose tissue inflammation
Method: In db/db mice and high fat diet (HFD)-fed mice, bone marrow and circulating monocytes were isolated using EasySep monocyte isolation kit and its subpopulations were analyzed by flowcytometry. Tracking experiments were performed by sorting out bone marrow Ly6C-high and Ly6C-low monocytes, labeling with red (PKH26) and green (PKH67) dyes respectively and transplanting into the same strain mice. Additionally, microarray analysis was performed.
Results: We found that bone marrow monocytes were phenotypically shifted into a pro-inflammatory Ly6C-high subset in obese diabetic db/db mice. Compatibly, Ly6C-high monocyte was significantly increased in peripheral blood. For HFD-induced obesity, flow cytometry analysis showed that AT macrophages were polarized into M1 macrophage, whereas there was no significant change observed in neither bone marrow nor circulating monocyte at 10 weeks of HFD. However, we found a significant increase in the number of Ly6C-high monocytes obtained from both bone marrow and peripheral blood at 18 weeks of HFD. The tracking experiments of bone marrow Ly6C-high and Ly6C-low monocytes in vivo revealed that transplanted Ly6C-high monocytes were selectively recruited into AT and differentiated into pro-inflammatory M1 macrophages in obese diabetes. In addition, they also migrated into the liver, kidney and heart. Total RNA microarray analysis revealed distinct patterns of gene expression in bone marrow Ly6C-high monocytes, which exhibited increased expression of inflammation-related gene and toll like receptors.
Conclusion: Our findings showed for the first time that obese diabetes and established obesity induce phenotypic shift of bone marrow monocytes into a pro-inflammatory subset, and this phenomenon may at least in part contribute to the increased recruitment and M1 polarization of macrophages in AT, and possibly lead to systemic inflammation and multiple organ damage.

P091 FABP5 is an essential modulator of fatty acid-induced GIP secretion in enteroendocrine K cells

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Background and aims: Fatty acid-binding protein 5 (FABP5) is a 15-kDa cytosolic-protein with high affinity to long chain fatty acids (LCFA), which has been known as an intracellular chaperon transporting LCFA into various organelles. Using microarray analysis, we demonstrated FABP5 is expressed in murine enteroendocrine GIP-producing K-cells. We investigated the physiological function of FABP5 in K-cells.
Materials and methods: Immunostaining for FABP5 and GIP was performed in murine small intestine for confirmation of specific expression of FABP5 in K-cells. To evaluate the acute GIP secretory response in FABP5-/- mice, lard (10ml/kg) and glucose were injected orally and plasma glucose and serum levels of GIP, GLP-1 and insulin were measured. Using K-cells isolated from newly-generated GIP-GFP knock-in hetero (GIPgfp/+)-FABP5+/+ and GIPgfp/+-FABP5-/- mice, quantitative real-time PCR (qPCR) for GIP expression and measurement of GIP content were performed to determine whether or not FABP5 is involved in GIP biosynthesis. To assess potential effects of FABP5-deficiency on body weight and composition, mice were fed a high fat diet (HFD) for 10 weeks. Whole body CT scans of HFD-fed wild-type (WT), FABP5-/-, GIPgfp/gfp-FABP5+/+ and GIPgfp/gfp-FABP5-/- mice were compared.
Results: Immunostaining of intestinal mucosa showed that GIP-positive cells were totally merged with FABP5-positive cells and 90% of FABP5-positive cells were merged with GIP-positive cells. Plasma GIP levels after lard injection were significantly lower in FABP5-/-mice compared to those in WT mice, whereas there were no significant differences in the results of OGTT. Plasma glucose, insulin and GLP-1 levels after both glucose and lard administration were similar in WT mice and FABP5-/- mice. There was no significant difference in GIP mRNA expression or GIP content in K-cells from GIPgfp/+-FABP5+/+ and GIPgfp/+-FABP5-/-mice. Under HFD feeding conditions, FABP5-/- mice exhibited significantly decreased body weight gain compared to WT control, but there was no significant difference in body weight between GIPgfp/gfp-FABP5+/+ and GIPgfp/gfp -FABP5-/- mice, in which GIP expression is genetically deleted. Whole body CT scan showed that body fat mass was significantly reduced in FABP5-/- mice compared to that in WT mice and that body fat mass in GIPgfp/gfp -FABP5+/+ and GIPgfp/gfp -FABP5-/- mice was comparable.
Conclusion: Our results show that FABP5 is involved in fatty acid-induced acute GIP secretion and that it contributes to the development of HFD-induced obesity in a GIP-dependent manner.

P092 Butyrate suppresses inflammatory responses generated by the interaction of adipocytes and macrophages

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Aim: Recent studies demonstrated a strong relationship between obesity and the development of cardiovascular diseases. Paracrine interaction between macrophages and adipocytes in obese visceral fat tissues may be a key factor in the underlying mechanisms. Since the short chain fatty acid, butyric acid, has the immunomodulatory effect in the inflammatory bowel diseases, we hypothesize that sodium butyrate (butyrate) attenuates inflammatory responses and lipolysis generated by the interaction of macrophages and adipocytes.

Methods: Using contact or transwell co-culture methods with differentiated 3T3-L1 adipocytes and RAW264.7 macrophages, we investigated the effects of butyrate on the production of tumor necrosis factor alpha (TNF-alpha), monocyte chemoattractant protein 1 (MCP-1) and interleukin 6 (IL-6), and the release of free glycerol and free fatty acids (FFAs) into the medium. We also examined the activity of nuclear factor-kappaB (NF-kappaB) and the phosphorylation of mitogen-activated protein kinases (MAPKs) in co-cultured macrophages, as well as lipase activity and expression in co-cultured adipocytes.

Results: We confirmed that butyrate below 2.0 mmol/L was available without cellular toxicity. We found the great increase of the production of TNF-alpha, MCP-1, and IL-6 and the release of glycerol and FFAs in the co-culture medium compared to those of separated culture cells, and butyrate significantly and dose-dependently reduced them. Butyrate inhibited the phosphorylation of MAPKs, the activity of NF-kappaB in co-cultured macrophages, and suppressed lipase activity in co-cultured adipocytes. Lipase inhibitors significantly attenuated the production of TNF-alpha, MCP-1 and IL-6 in the co-culture medium as effectively as butyrate. Butyrate suppressed the protein production of adipose triglyceride lipase, hormone sensitive lipase, and fatty acid-binding protein 4 in co-cultured adipocytes. Pertussis toxin, which is known to block GPR41, completely inhibited the anti-lipolysis effect of butyrate.

Conclusion: Butyrate suppresses inflammatory responses generated by the interaction of adipocytes and macrophages through reduced lipolysis and inhibition of inflammatory signaling.

P093 Sarcopenia is associated with non-alcoholic fatty liver disease regardless of obesity and metabolic syndrome: Nationwide surveys (KNHANES 2008-2011)

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Although sarcopenia is associated with obesity-related comorbidities, their influence on non-alcoholic fatty liver disease (NAFLD) has not been fully determined. The aim of this study was to investigate the relationship between sarcopenia and NAFLD in the general population in Korea.
We conducted a cross-sectional study with nationally representative samples of 13,199 subjects from the Korea National Health and Nutrition Examination Surveys (KNHANES) between 2008 and 2011. Subjects with heavy alcoholics or positive results for serology tests of hepatitis B or C were excluded. NAFLD was defined by applying previously established models for NAFLD prediction such as Fatty Liver Index, Hepatic steatosis index and NAFLD liver fat score. Sarcopenic index (appendicular skeletal muscle mass as a percentage of body weight or ASM/Wt) measured by dual-energy X-ray absorptiometry was used to define sarcopenia.
Sarcopenic index (ASM/Wt) was inversely correlated with all NAFLD predicting indices. After stratification with obesity (BMI≥25 kg/m2) or metabolic syndrome, sarcopenic subjects had significantly higher proportion of NAFLD regardless of the presence of obesity or metabolic syndrome. Multiple logistic regression analysis showed that sarcopenia, BMI, HOMA-IR, triglycerides, diabetes and smoking were significantly associated with the increased odds ratios (ORs) for the risk of NAFLD, whereas exercise and moderate drinking had decreased ORs for the risk of NAFLD. Furthermore, among subjects with NAFLD, sarcopenic subjects had higher proportion of severe liver fibrosis, assessed by using BARD score regardless of the presence of obesity or metabolic syndrome. In subgroup analysis, only obese subjects with preserved skeletal muscle mass who exercise regularly had a lower proportion of NAFLD compared to those who do not exercise.
In conclusion, this study can provide a strong evidence that sarcopenia is associated with liver fibrosis as well as NAFLD, regardless of obesity or metabolic syndrome.

P094 Genome-wide profiling of brown fat-specific open regulatory regions identifies NFIA as a transcriptional regulator of brown fat muscle cell lineage specification

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Brown fat of human and rodents dissipate energy as heat and an important target of treatment for obesity. We performed genome-wide FAIRE-seq on murine brown and white fat tissues to map open chromatin regions that control cell-type specific gene expression. We identified multiple brown fat-specific open chromatin regions near genes, such as Ucp1, Cidea, Ppargc1a and Prdm16. Globally, about half of those regions are binding sites for PPARγ, while the rest was not bound by PPARγ. One of the most enriched binding motifs in nucleotide sequence of the brown fat-specific open chromatin regions--besides those for C/EBP and EBFs--was that for a transcription factor NFIA. NFIA is expressed abundantly in both brown and white fat cells but expressed at low levels in muscle cells. Retroviral expression of NFIA in C2C12 muscle cells results in loss of muscle phenotype and induction of brown fat phenotype characterized by formation of lipid droplets and induction of brown fat-specific genes such as Ucp1 and Pparg1a in response to cAMP stimulus. Co-expression studies of NFIA and PPARγ in C2C12 cells indicated that NFIA not only stimulates brown fat-specific genes but also represses white fat-specific genes independently of its adipogenic effect. Finally, expression levels of brown fat-specific genes were decreased in primary brown adipocyte cell line by RNAi-mediated knock-down of NFIA or in brown fat of NFIA-/- mice when compared to their controls. Together, global profiling of brown fat-specific regulatory regions by FAIRE-seq is useful in identifying the essential role of NFIA in brown fat and muscle cell lineage specification.

P095 Anthropometric indices of obesity and type 2 diabetes in a rural Bangladeshi population

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Objective: To identify markers for diabetes (DM) through body mass index (BMI), waist circumference (WC), waist hip ratio (WHR) and waist height ratio (WHtR) and identify the optimal cut-off values to be suitable for adult Bangladeshi population.
Methods: A total of 2293 subjects aged ≥20 years from rural Bangladesh were randomly recruited to participate in a population-based, cross sectional survey. Age adjusted data for anthropometric indices and diabetes risk were assessed and their relationships were examined.
Results: Age adjusted prevalence of DM in men and women were 9.5% and 7.0%, respectively. Both men and women with DM had a higher rate of general obesity (defined by BMI) and central obesity (defined by WC, WHR and WHtR) than non-diabetic subjects. The most sensitive indice was WHR for predicting DM for both men and women. The appropriate cut-offs values for WHR to predict DM in men and women were 0.93 and 0.87, respectively. WC of 82 cm for both sexes was appropriate to predict DM. Those of BMI and WHtR were 21.2 kg/m2 and 21.8 kg/m2, 0.53 and 0.54 in men and women, respectively.
Conclusions: Compared with BMI, measures of central obesity, WHR, WC, WHtR showed a better association with the risk of DM for both sexes. Future studies needed validify these cut-offs in a follow-up study, essential both for prevention and treatment.

P096 The change of the prevalence of metabolic syndrome this ten years in Okinawa

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Metabolic syndrome (Mets) is now widely known as an independent risk-factor of a blood vessel event. In Okinawa Prefecture, compared with the national average, the prevalence rate of Mets is high, and it is apprehensive about the increase of a blood vessel event. As a result of guessing the prevalence rate of Mets in Okinawa prefecture by a cross-sectional research of the result of an annual physical checkup between May 2003 and March 2004 in Tomishiro Chuo hospital by Tanaka, et al, it is mentioned the prevalence rate of Mets in Men was 30.2% and 10.3% in women. It was higher than that of national average.
This time We studied 7938 men and 8949 women a total of 16887 people aged from 30 years old to 79 years old who came to our clinic (Chibana clinic health-care-administration center) for an annual checkup between January 2013 and December 2013 to check the latest prevalence rate of Mets. We used the same criteria of Mets as Tanaka, et al to compare with them(Hypertriglyceridemia(triglyceride>149mg/dl),low high-density lipoprotein(HDL)cholesterol(HDL cholesterol<40mg/dl for men and <50mg/dl for women), hypertension(systolic blood presser>129mmHg and/or diastolic blood pressure>84mmHg), and impaired fasting glucose(fasting blood glucose>109mg/dl), abdominal circumference(abdominal circumference>84cm in men,>89cm in women)Those who met 3 or more of the 5 risk factors listed above were diagnosed Mets.).
As a result, the prevalence rate of Mets was 31.9% in men, and 16.7% in women. In men the people who were 60 to 69-year-old, In women who were 70 to 79-year-old had highest prevalence rates of Mets. In the positive rate of the 5risk factors of the criteria, the abdominal circumference was highest, hypertension was second, hypertriglyceridemia was third in men. In women hypertension was highest, low HDL cholesterol was second, abdominal circumference was third.
The rate of over abdominal circumference and low HDL cholesterol was increased in men, In women, that of over abdominal circumference, hypertriglyceridemia and low HDL cholesterol was increased compared with the data of Tanaka H, et al ten years ago. In both sex the prevalence rate of Mets was increased, especially, In women it was remarkable.

P097

Withdrawn

P98 Visceral fat area is significantly related with hepatic steatosis assessed by controlled attenuation parameter

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Controlled attenuation parameter (CAP) is noninvasive method of measuring hepatic steatosis with high accuracy. The aim of this study is to investigate the relationship between hepatic steatosis assessed by CAP and clinical factors including regional fat distribution measured by computed tomography (CT).
Clinical and metabolic measurement, laboratory data, regional fat distribution, and CAP value were evaluated in 304 patients (165 male, 139 female) who underwent CAP and abdominal fat CT. In this study, significant steatosis is defined when CAP value
Figure 1 showed visceral fat area (VFA) was significantly related with CAP value, together with triglycerides (TG), and alanine aminotransferase. Figure 2 showed severity of NAFLD according to the glucose tolerance status. In the multiple logistic regression analysis, VFA (odd ratio [OR], 1.010; 95% confidence interval [CI], 1.001-1.019; P=0.028) and TG (OR, 1.006; 95% CI, 1.001-1.011; P=0.022) were selected as independent risk factor for significant hepatic steatosis. In sub analysis of 110 patients with BMI <23 kg/m^2, only VFA was significantly related with hepatic steatosis (OR, 1.006; 95% CI, 1.001-1.011; P=0.022).
Our data demonstrated that VFA was significantly related with significant hepatic steatosis assessed by CAP.even in non-obese patients.

P99 Comparison of changes in metabolic markers after Roux-en-Y gastric bypass between non-obese and obese patients

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Background: This study was aimed to investigate the effects of bariatric surgery in non-obese patients through the comparison of the changes in body weight (BW) and serum lipid profile between non-obese and obese patients after Roux-en-Y gastric bypass.
Methods: In this study, 116 patients, who had to undergo laparoscopic Roux-en-Y gastric bypass for early gastric cancer, were included. Patients were divided into two groups, non-obese group (N = 76), including patients with body mass index (BMI) < 25 kg/m^2, and obese group (N = 40), including patients with BMI ≥ 25 kg/m^2. BW and serum lipid profile before surgery and at 3, 6, 9, and 12 months after surgery were examined.
Results: The mean age of 116 study patients was 59.57 ± 13.27 years, and the mean BMI was 23.47 ± 3.42 kg/m^2. The majority was male (72.4%). When comparing two groups, there were significantly statistical differences in sex, BMI, and low-density lipoprotein cholesterol (LDL-C). In all groups, according to sex, there was no difference except height and BW. In all groups, BW and triglyceride (TG) showed significant ($p < 0.05$) decrease after surgery, and high-density lipoprotein cholesterol (HDL-C) showed significant increase except at 3 months after surgery in obese group. Total cholesterol and LDL-C showed decrease. However, some time periods after surgery only had statistical significance. When comparing two groups, mean percentages of BW loss and TG decrease after surgery in obese group were greater. However, some time periods after surgery only had statistical significance. Mean percentage of HLD-C increase in non-obese group was greater without significance. There were no differences in mean percentages of total cholesterol and LDL-C decrease between two groups.
Conclusion: At 12 months after surgery, all groups showed significant improvement in BW and serum lipid profile. However, mean percentages in BW loss, TG decrease, and HDL-C increase between two groups were different.

P100 The serine protease prostasin regulates hepatic insulin sensitivity by modulating TLR4 signaling

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Although the effects of a high fat diet (HFD) and postprandial endotoxemia on the development of type 2 diabetes have been extensively studied, the precise mechanisms are not fully understood. Here we show that a serine protease prostasin (PRSS8) regulates hepatic insulin sensitivity by modulating Toll-like receptor 4 (TLR4)-mediated signaling. We demonstrate that HFD triggers the suppression of PRSS8 expression by inducing endoplasmic reticulum (ER) stress and increases TLR4 levels in the liver. PRSS8 released the ectodomain of TLR4 by cleaving it at the Lys560/Lys561 residues, which resulted in a reduction in the full-length form at the plasma membrane and reduced activation of TLR4 by its ligands. Liver-specific PRSS8 knockout (LKO) mice developed hepatic insulin resistance associated with an increase in hepatic TLR4. Restoration of PRSS8 expression in the liver of HFD, LKO, and db/db mice decreased TLR4 levels and ameliorated hepatic insulin resistance. Furthermore, we demonstrated that a major component of serum PRSS8 may originate from the liver and that the serum PRSS8 levels were negatively correlated with body mass index (BMI) and homeostasis model assessment-insulin resistance (HOMA-IR) in healthy human subjects. Our results identify a novel role for PRSS8 and provide a new insight into the development of diabetes resulting from HFD or metabolic endotoxemia.

P101 Sexually dimorphic, fat depot-dependent expression of a fibrogenic adipokine, thrombospondin 1 (THBS1) in human obesity

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OBJECTIVE: Thrombospondin 1 (THBS1 or TSP-1) is a multifunctional glycoprotein released from various types of cells including platelets, macrophages and adipocytes. THBS1 may activate latent transforming growth factor-β, which contributes to wound healing, fibrotic tissue remodeling, and inflammatory response. Our findings and others suggest the causal role of adipose-derived THBS1 in the pathogenesis of insulin resistance and tissue fibrosis in obesity (Inoue et al., Endocrinology 2013). In this study, we aimed to determine fat depot-dependent *THBS1* expression and circulating THBS1 levels in Japanese obese subjects.
METHODS & RESULTS: The expression level of *THBS1* was quantified in paired samples of subcutaneous (SAT) and visceral adipose tissue (VAT) obtained from 16 surgical patients (average BMI, 22.8). *THBS1* mRNA expression was 2.5-fold higher in VAT than SAT ($p < 0.01$). The visceral *THBS1* mRNA expression was associated positively with BMI ($r = 0.56$, $p < 0.05$) and negatively with high-density lipoprotein cholesterol (HDL-C) ($r = -0.63$, $p < 0.01$). To define the association between serum THBS1 levels and body fat distribution, we assessed circulating THBS1 levels and fat distributions in 69 obese subjects (average BMI, 31.2). Serum THBS1 levels displayed a positive trend with visceral fat mass but not with subcutaneous fat mass in 32 male subjects ($r = 0.21$ and -0.03, respectively). The THBS1 level in premenopausal female subjects ($n = 11$) showed a positive relationship with both visceral and subcutaneous fat mass ($r = 0.46$ and $r = 0.22$, respectively); however, no correlation with adiposity was observed in postmenopausal female subjects ($n = 26$).
CONCLUSIONS: Our results suggest that *THBS1* expression in visceral adipose tissues serves as the direct marker of visceral adiposity and metabolic syndrome, whereas circulating THBS1 levels are modified by gender and sex hormones in human obesity.

P102 Enriched environment reverses food preference for fat over carbohydrate involving leptin signaling

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Feeding behavior, including meal size, meal frequency and food preferences, is affected by various kinds of stress, such as psychological distress and traumatic stress in both animals and humans. Such aversive stimuli often shift preferences toward palatable food,e.g. a high fat diet. However, it remains to be elucidated whether desirable environment,e.g.housing conditions making animals less anxious and curious, affects food preferences. Therefore, we investigated the effect of an enriched environment (EE).Exposure to EE, such as larger cages with running wheels, tunnels and shelters, is a well-established approach to investigating brain functions in animals. Living in an EE provides optimal conditions for enhanced exploration, cognitive activity and physical exercise.There are many reports showing the beneficial effects of EE on neurodegenerative diseases, Alzheimer's disease and depression in animal models. After one-week acclimatization to the control cage with food jars, the C57BL/6 mice were allowed to select from a two-choice, high fat/high carbohydrate, diet protocol for one week. Both diets contained in jars were supplied ad libitum. Mice were able to freely access both jars. During the first week, mice showed a high preference for fat. Since the second week, half of the mice (EE mice) were introduced to the EE with larger cages, tunnels, running wheels and shelters, while the other half were moved to the control cages. During the two weeks after EE introduction, the preference for fat gradually diminished and fat-to-carbohydrate ratios were ultimately completely reversed. To clarify the molecular mechanism, we next focused on leptin signaling, because leptin has many targets in the brain, in areas which are responsible for not only feeding but also emotional and cognitive behaviors. Therefore, to examine the involvement of leptin in the mechanism altering food preference, we placed leptin-deficient *ob/ob* mice in the EE. The baseline fat preference of *ob/ob* mice is almost the same as the wild-type controls. However, in contrast to the wild-type controls, EE introduction did not alter fat-to-carbohydrate ratios in *ob/ob* mice. How leptin is involved in this mechanism is unknown, but these findings demonstrate that leptin is required for shifting food preference in the desirable environment. Thus, improving the quality of the environment may dramatically decrease food preference for fat. In addition, these results provide new insights into our understanding of feeding behaviors: leptin signaling may play an important role in modulating feeding behaviors controlled by a complex environment-dependent system.

P103 A prospective study of serum leptin and incident metabolic syndrome: The ARIRANG Study

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Objective: Increased leptin levels may play a role in the development of metabolic abnormalities, but prospective studies of the predictive value of serum leptin to identify individuals at high risk of new-onset metabolic syndrome are lacking. We investigated whether serum leptin predicts incident cases of the metabolic syndrome in a population-based longitudinal study.
Research design and methods: Prospective cohort study of 1,590 adults (661 men and 929 women) aged 40 to 70 years without metabolic syndrome examined in 2005 -2008 (baseline) and 2008 -2011 (follow-up). Baseline serum leptin concentrations were measured by radioimmunoassay.
Results: During an average of 2.8 years of follow-up, 113 men (17.1%) and 148 women (15.9%) developed metabolic syndrome. In multivariable adjusted models, the odds ratio (95% confidence interval) for incident metabolic syndrome comparing the lowest to the highest quartiles of leptin levels was 3.87 (1.88-7.96) in men and 2.80 (1.53-5.14) in women. While serum leptin did not improve the area under the ROC curve for predicting new-onset metabolic syndrome based on information from metabolic syndrome components, the net reclassification improvement and the integrated discrimination improvement of prediction models including leptin were significantly higher compared to those of models not including leptin among men.
Conclusions: Increased leptin is an independent risk factor for incident metabolic syndrome in men and women, and it may have a clinical role in predicting new onset metabolic syndrome among men.

P104 EP4 receptor regulates obesity-related inflammation and insulin sensitivity

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In both humans and rodents, macrophages accumulate in adipose tissue with increasing body weight. Activated adipose tissue macrophages (ATMs) secrete numerous proinflammatory cytokines and chemokines, such as TNF-α and MCP-1, giving rise to chronic, low-grade inflammation that are known to cause insulin resistance. Therefore, inhibiting ATM activation is expected as a new therapeutic target against obesity and type 2 diabetes mellitus (T2DM). We previously reported that prostaglandin E_2 suppressed macrophages activation via EP4 receptor; however, the role of EP4 receptor signaling in insulin resistance or T2DM in vivo remains unknown. In this study, we treated db/db mice, animal models of obesity and T2DM, with EP4 selective agonist, ONO-AE1-329, or vehicle for 4 weeks to analyze the role of EP4 signaling in obesity-related chronic inflammation in vivo. Administration of EP4 agonist did not affect body weight gain or food intake; however, in EP4 agonist-treated group, glucose tolerance and insulin resistance significantly improved compared to vehicle-treated group. In addition, the number of F4/80 positive macrophages in white adipose tissue (WAT) and the size of each adipocyte were significantly smaller in EP4 agonist-treated group. Regarding the phenotype of ATMs, EP4 agonist treatment remarkably increased the accumulation of anti-inflammatory M2-type macrophages. In addition, in stromal vascular fraction, which includes macrophages in WAT, the levels of inflammatory cytokines and chemokines were markedly decreased in EP4 agonist-treated group. Thus, our results suggest that EP4 signaling plays a critical role in obesity-induced adipose tissue inflammation and insulin resistance by regulating both macrophage recruitment and M1/M2 status. EP4 signaling could be a therapeutic target against obesity and T2DM.

P105

Withdrawn

P106 An eight-week high complex carbohydrate, energy restricted dietary intervention is associated with weight loss and a reduction of inflammation markers

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Background: Sub-clinical systemic inflammation has been implicated in the pathophysiology of obesity. In addition to impacting body weight, dietary modification may modulate markers of inflammation.
Methods: Overweight/obese adults were recruited to an eight-week dietary intervention characterized by energy restriction and increased complex carbohydrate intake. Blood samples for inflammatory and metabolic markers as well as anthropometric measurements were taken before and following the intervention.
Results: The study included 72 overweight or obese participants (BMI 31.8+/-5.8 kg/m^2). Significant reductions from baseline weight, BMI, waist and hip circumference were observed following dietary intervention. Levels of inflammatory markers hs CRP, ESR, WBC, and ICAM decreased significantly from baseline following the 8-week intervention. Metabolic measures including serum triglycerides, total and low density lipoprotein cholesterol significantly declined from baseline. Insulin and HOMA-IR declined in the subgroup of hyperinsulinemic participants.
Conclusion: An energy-restricted diet rich in complex carbohydrates is associated with weight loss, reduction of inflammatory markers and improved metabolic profile.

P107 Lycopene attenuates high fat diet-induced adipose tissue inflammation and insulin resistance by regulating both macrophage recruitment and M1/M2 status

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Aims: Adipose tissue macrophages (ATM) recruitment and polarization are considered pivotal in the development of insulin resistance. However, promising treatment modalities targeting ATM for insulin resistance and type 2 diabetes remain limited. In this study, we show that lycopene, an antioxidant carotenoid compound, ameliorates adipose tissue inflammation and whole-body insulin resistance in high-fat diet (HFD)-induced obese (DIO) mice by regulating both macrophage recruitment and M1/M2 status.
Methods: Eight-week-old C57BL/6J male mice were fed normal chow (NC; 10% calories from fat), NC containing lycopene (NC+LY; 12 mg/kg/day), HFD (60% calories from fat), or HFD containing lycopene (HFD+LY; 12 mg/kg/day). After 8 weeks of feeding, the histology of epididymal white adipose tissue (eWAT) and insulin were evaluated.
Results: Lycopene improved HFD-induced glucose intolerance, hyperinsulinemia (DIO 4.0+/-0.2 vs HFD+LY 2.0+/-0.1 ng/mL, $p < 0.01$; fed state), and fatty liver without changing body weight and adiposity. HFD+LY mice exhibited decreased macrophage number and crown-like structure formation in epididymal white adipose tissue (eWAT) compared with those of DIO mice. To further assess the impact of lycopene on adipose tissue inflammation, flow cytometry analysis was performed on stromal vascular cells isolated from eWAT. ATMs identified as CD45+CD11b+F4/80+ cells were increased in DIO mice by 11.4-fold compared with WT mice. In addition to the reduction of total ATM content, HFD+LY mice had 35% fewer CD11c+CD206- (classically activated or M1) ATMs whereas 60% more CD11c-CD206+ (alternatively activated or M2) ATMs than DIO mice, resulting in the predominance of M2 over M1 ATM population. However, the predominance of the Ly6Clow over Ly6Chigh monocyte population was not observed in both peripheral blood and bone marrow of HFD+LY mice. In parallel, lycopene (10-50 nM) suppressed LPS-induced M1 markers mRNA expression (TNFalpha, MCP-1, and RANTES) in peritoneal macrophages isolated from C57BL/6J mice, whereas it augmented IL-4-induced M2 markers mRNA expression (IL-10 and Arg1) in a dose-dependent manner.
Conclusion: Lycopene causes dynamic M2 dominant phenotypic shift of ATM and thereby attenuates obesity-induced inflammation and insulin resistance in mice. Reduction of oxidative stress might be a relevant strategy to limit inflammatory adipose tissue response and subsequent development of insulin resistance.

P108 Hepatic CREB3L3 controls whole-body energy homeostasis and improves obesity and insulin resistance

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Transcriptional regulation of metabolic genes in the liver is the key to maintaining systemic energy homeostasis during starvation. The membrane-bound transcription factor cAMP responsive element-binding protein 3-like 3 (CREB3L3) has been reported to be activated during fasting and to regulate triglyceride metabolism. Here we show that CREB3L3 confers a wide spectrum of metabolic responses to starvation in vivo. Adenoviral and transgenic overexpression of nuclear CREB3L3 induced systemic lipolysis, hepatic ketogenesis, and insulin sensitivity with increased energy expenditure, leading to marked reduction in body weight, plasma lipid levels, and glucose levels. CREB3L3 overexpression activated gene expression levels and plasma levels of antidiabetic hormones, including fibroblast growth factor 21 (FGF21) and insulin-like growth factor-binding protein 2 (IGFBP2). Amelioration of diabetes by hepatic activation of CREB3L3 was also observed in several types of diabetic obese mice. Nuclear CREB3L3 mutually activates the peroxisome proliferator-activated receptor α (PPAR α) promoter in an autoloop fashion and is crucial for the ligand transactivation of PPAR α by interacting with its transcriptional regulators. CREB3L3 directly and indirectly controls FGF21 expression and its plasma level, which contributes at least partially to the catabolic effects of CREB3L3 on systemic energy homeostasis in the entire body. Therefore, CREB3L3 is a therapeutic target for obesity and diabetes.

P109 Relationship between body fat distribution and cardiometabolic risk factors in nonobese Japanese subjects

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Background: It is well known that Asian populations have higher risk of cardiometabolic risk factors, such as diabetes, compared with Caucasians, even though the number of obese Asians is limited. Epidemiology studies have revealed positive associations between cardiometabolic risk factors and trunk fat mass, and negative associations between cardiometabolic risk factors and leg fat mass; however, only a limited number of studies have examined the relationship between body fat distribution and cardiometabolic risk factors in nonobese subjects. Purpose: To examine the relationship between cardiometabolic risks factors and body fat distribution in nonobese Japanese subjects. Methods: The subjects of this study were 1,353 nonobese (BMI <25 kg/m2) subjects (469 males and 884 females, average age: 65.6 years old) in the Hiroshima Adult Health Study cohort, consisting of atomic bomb survivors and their controls, whose body composition was measured using whole-body dual-energy X-ray absorptiometry during the period 1994-1996. To determine body fat distribution, fat-mass percentages for the trunk, arms and legs were calculated by dividing each site specific fat mass by total fat mass, which were divided into tertiles. The relationship between body fat distribution and cardiometabolic risks diagnosed with the AHA/NHLBI metabolic syndrome criteria was examined. Further we defined metabolically unhealthy as having two or more of component factors other than abdominal obesity, and divided the subjects into metabolically healthy nonobese (MHNO) and metabolically unhealthy nonobese (MUNO) in order to examine the relationship between body fat distribution and MUNO prevalence. Results: After adjusting for age, sex, smoking and alcohol consumption status, and radiation dose, leg fat percentage was negatively associated with cardiometabolic risk factors and trunk fat percentage was positively associated with cardiometabolic risk factors. No significant relationship was observed between arm fat percentage and cardiometabolic risks. Further, in the analysis of the relationship between body fat distribution and MUNO prevalence, the odds ratios (ORs) (95% CI) of the intermediate (2nd tertile) and highest (3rd tertile) groups of leg fat percentage as compared to the lowest group (1st tertile) were 0.50 (0.38-0.66) and 0.17 (0.12-0.23), respectively. The ORs (95% CI) of the intermediate and highest groups of trunk fat percentage as compared to the lowest group were 2.75 (2.02-3.76) and 6.15 (4.50-8.40), respectively. Conclusion: Among nonobese subjects, cardiometabolic risk factors were also positively associated with trunk fat percentage and negatively associated with leg fat percentage.

P110 Can children intervene on reducing tobacco in the community where they live? Health promotion tool to reduce tobacco consumption in low socioeconomic communities in Sri Lanka

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Introduction - Tobacco smoking is one of leading cause of premature deaths and disability in worldwide, and over 80% of the world's smokers live in low and middle income countries. In Sri Lanka, it is estimated that annual mortality from tobacco-related deaths is about 20 000.

Objective - To determine the effectiveness of a health promotion tool in reducing cigarettes consumption among men in low socioeconomic communities through the participation of their children

Method- This community based intervention was conducted through two children' s group as "intervention" (n=76) and "Control" (n=69) in four settings including two tea estates. Socioeconomic characteristics were similar in both groups. Intervention groups was given a health promotion tool to facilitate the reduction of tobacco consumption among smokers. Smokers were encouraged by their children, to reduce "one cigarette " out of their daily consumption ad save that money utilizing on children's necessaries. Children were given a training to use the tool through role play model. regular follow-ups were carried out to strength the programme. pre-data and post data were collected through using a specific format.

Results - After six months, 85% of intervention group (n=65) and 79% of children (n=55) in control group have successfully completed the study. There was no significant difference (p=0.081 95% CI) for the mean number of cigarettes consumed by both groups before intervention; cigarettes per day by intervention and control were 9.22 (SD=3.61) and 9.07 (SD=3.61) respectively. After the intervention, international group was significantly able to reduce their daily cigarettes consumption (mean - 7.12 cigarettes) with compared to control group (mean - 8.36 cigarettes) (P<0.025, 95% CI). Independent samples t test showed that the health promotion tool was an effective method to lower the tobacco use among smokers.

Conclusion - Children based intervention through health promotion approach and proposed tool can be used to reduce the tobacco consumption among smokers in low socioeconomic communities.

P111 Treatment of familial LCAT deficiency syndrome by self-transplantation of therapeutic-enzyme secreting adipocytes

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Familial lecithin:cholesterol acyltransferase (LCAT) deficiency syndrome is an autosomal recessive disease characterized by severe dysfunction of HDL with subsequent generation of abnormal LDL. Patients often develop life-threatening complications such as renal failure and corneal opacity. Long-lasting LCAT protein replacement is one of the therapeutic approaches to prevent the LCAT-deficient patients from progressive tissue damages. However, such treatment has not been developed since it is difficult to provide stable recombinant enzyme due to the cost problems and the rareness of disease. Our previous basic experimental data together with clinical experience in transplantation therapy strongly suggested that autologous adipocyte transplantation is an effective maneuver to perform ex vivo gene therapy enabling sustained secretion of therapeutic enzymes. We have recently reported that ceiling culture-derived proliferative adipocytes (ccdPAs) are useful for an effective LCAT production using the retroviral gene transfection. The lcat gene-transduced ccdPAs secreted functional LCAT protein, which caused maturation of HDL derived from LCAT-deficiency patients and reduced renal-damaging LDL poor in esterified-cholesterol, in vitro. Furthermore, subcutaneous transplantation of the ccdPAs ameliorated the circulating abnormal lipoproteins in lcat-deficient mice. Thus, ccdPAs would provide an excellent platform for developing a protein replacement therapy not only for LCAT deficiency but also other disorders caused by deficiency in serum protein requiring long-term therapeutic protein supplementation. In addition, fibrin glue, which is clinically available scaffold, increased the survival of transplanted lcat-gene transduced ccdPAs in mice. Based on the accumulated data in animal models, the ex vivo gene and cell therapy protocol has now been approved by Ministry of Health, Labour and Welfare in Japan followed by initiation of patient enrollment.

P112 MicroRNA-451 is involved in diabetic cardiomyopathy through suppression of the LKB1/AMPK pathway

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[Rationale]: In some obese and type 2 diabetes mellitus (DM) patients without hypertension, cardiac hypertrophy and attenuated cardiac function are observed, and this insult is termed "diabetic cardiomyopathy." microRNAs are endogenous small non-coding RNAs and play pivotal role in cardiovascular diseases. However, microRNA functions in diabetic cardiomyopathy remain to be elucidated.
[Objective]: To clarify the functions of microRNAs involved in diabetic cardiomyopathy caused by type 2 DM.
[Methods and Results]: C57BL/6 mice were fed a high-fat diet (HFD) for 20 weeks, which induced obesity and type 2 DM. MicroRNA microarray analyses and real-time PCR revealed that miR-451 levels were significantly increased in the HFD-fed obese mouse hearts (n = 4-5, p<0.05). To examine whether miR-451 exists in cardiomyocytes, we isolated cardiomyocytes and cardiac fibroblasts from neonatal mouse hearts using FACS. We confirmed that miR-451 level in cardiomyocytes was significantly higher compared with that in fibroblasts by 30-fold (n = 4, p<0.05). Because excess supply of saturated fatty acids is a cause of diabetic cardiomyopathy, we stimulated neonatal rat cardiomyocytes (NRCMs) with palmitic acid and confirmed that miR-451 expression was increased in a dose- and time-dependent manner (n = 3-6, p<0.05). Loss of miR-451 function ameliorated palmitic acid-induced cell toxicity in NRCMs (n = 3-4, p<0.01). Calcium-binding protein 39 (Cab39) is a scaffold protein of liver kinase B1 (LKB1), a major upstream kinase of AMP-activated protein kinase (AMPK). We showed that Cab39 was a direct target of miR-451 in NRCMs and Cab39 overexpression rescued the lipotoxicity caused by palmitic acid stimulation (n = 3-5, p<0.01). To clarify miR-451 functions in vivo, we crossed the α MHC-Cre transgenic mice and floxed miR-451 mice to generate cardiomyocyte-specific miR-451 knockout (miR-451 cKO) mice. HFD-induced cardiac hypertrophy was ameliorated in miR-451 cKO mice compared with control mice (n = 3-4, p<0.05). We performed western blotting analysis to evaluate the signaling pathways. Protein levels of Cab39 and phosphorylated AMPK were increased and phosphorylated mammalian target of rapamycin (mTOR) was reduced in miR-451 cKO mouse hearts compared with control mouse hearts on HFD (n = 10-12, p<0.05). Finally, cardiac stress was induced by dobutamine infusion and was monitored by cardiac catheterization. We found that contractile reserve was reduced in HFD-fed control mouse heart compared with NC-fed control mouse heart, but not in HFD-fed cKO mouse heart (n = 5-7, p<0.05).
[Conclusions]: Our results demonstrate that miR-451 is involved in diabetic cardiomyopathy through suppression of the LKB1/AMPK signaling pathway.

P113 MicroRNA-33, embedded in *Srebf2* intron, regulate fatty acid synthesis through targeting SREBP-1 *in vivo*

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Introduction: MicroRNAs (miRs) are small non-protein-coding RNAs that bind to specific mRNAs and inhibit translation or promote degradation. Recent reports, including ours, indicated that miR-33 located within the intron of sterol regulatory element binding protein (SREBP) 2 controls cholesterol homeostasis and can be a possible therapeutic target for treating atherosclerosis. Unexpectedly, miR-33 deficient (miR-33$^{-/-}$) mice fed high fat diet (HFD) developed severe fatty liver and the mechanisms were investigated.
Methods and Results: The liver weight of miR-33$^{-/-}$ mice were about 1.5 times heavier than that of miR-33$^{+/+}$ mice and histological examination revealed that miR-33$^{-/-}$ mice developed severe hepatosteatosis under HFD feeding. We analysed the gene expression profiles by microarray analysis using the liver of miR-33$^{+/+}$ and miR-33$^{-/-}$ mice fed normal chow at the age of 16 weeks when they did not show fatty liver. As a result, genes involved in fatty acid metabolism were upregulated in miR-33$^{-/-}$ mice. Among them we found SREBP-1 as a new potential target gene of miR-33 *in silico* and confirmed that miR-33 targets the 3'UTR of SREBP-1 *in vitro*. The expression of SREBP-1 and de novo fatty acid production were significantly increased in the liver of miR-33$^{-/-}$ mice. We further intercrossed miR-33$^{-/-}$ mice with *Srebf1*$^{+/-}$ mice and fed them HFD. Hepatic steatosis was reversed in miR-33$^{-/-}$*Srebf1*$^{+/-}$ mice compared with miR-33$^{-/-}$*Srebf1*$^{+/+}$ mice by histological analysis and measurement of triglyceride levels. The expression levels of genes involved in fatty acid synthesis, including *Scd1*, *Fasn*, *Acc1*, and *Pparg* were increased in miR-33$^{-/-}$*Srebf1*$^{+/+}$ mice compared with miR-33$^{+/+}$*Srebf1*$^{+/+}$ mice, and those increase were reversed in miR-33$^{-/-}$*Srebf1*$^{+/-}$ mice.
Conclusions: These results demonstrate that miR-33 deficiency showed severe hepatic steatosis under HFD and miR-33 regulates lipogenic pathway through regulating SREBP-1 as a novel target. In sterol-depleted conditions, acetyl-CoA might be preferred as a substrate for cholesterol production and not for fatty acid production by the downregulation of SREBP-1 through the upregulation of miR-33. Conversely, in cholesterol-rich condition, acetyl-CoA might be preferred as a substrate for fatty acid production through the downregulation of miR-33.

P114 Targeted next-generation sequencing and fine linkage disequilibrium mapping reveals association of *PNPLA3* and *PARVB* with the severity of nonalcoholic fatty liver disease

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Aim: The genomic regions containing *PNPLA3*, *SAMM50*, and *PARVB* are susceptibility loci for the development and progression of nonalcoholic fatty liver disease (NAFLD). Our purpose of this study is to search for all common variations in this region and to examine association of those variations with NAFLD. **Method:** We amplified the genomic DNA of 28 NAFLD patients by long-range PCR, covering the entire susceptibility region and sequenced the DNA using indexed multiplex next-generation sequencing. We genotyped 540 NAFLD patients (488 with nonalcoholic steatohepatitis (NASH) and 52 with simple steatosis) and 1012 control subjects. The multiple regression analysis Odds ratios (ORs) and *P*-values, adjusted for age, sex, (BMI, and the presence of type 2 diabetes mellitus, were calculated using multiple logistic regression analysis. Multiple linear regression analyses were performed to test the independent effect per allele of each SNP on biochemical traits and histological parameters, accounting for effects of the other variables (i.e., age, sex, BMI and the presence of type 2 diabetes mellitus). **Results:** We found 329 variations, including 4 novel variations. Fine mapping of variations including insertion/deletions was performed for HaploView analysis showed that linkage disequilibrium (LD) block 1 and 2 occurred in *PNPLA3*, block 3 in *SAMM50*, and block 4 in *PARVB*. Variations in LD blocks 1 to 4 were significantly associated with NAFLD as compared to control subjects ($P < 1 \times 10^{-8}$). Variations in LD block 2 were significantly associated with the NAFLD activity score (NAS, ($P < 1 \times 10^{-5}$)), aspartate aminotransferase, and alanine aminotransferase ($P < 1 \times 10^{-7}$). Variations in LD block 1 were significantly associated with the fibrosis stage. The strongest associations were observed for variations in LD block 4, with NASH as compared to simple steatosis ($P = 7.1 \times 10^{-6}$) and NAS ($P = 3.4 \times 10^{-6}$). **Conclusion:** Our results suggested that variations, including insertion/deletions, in *PARVB*, as well as those in *PNPLA3*, are important in the progression of NAFLD.

P115 Lipoprotein subfractions highly associated with renal damage in familial LCAT deficiency

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Lecithin:cholesterol acyltransferase (LCAT) deficiency syndromes are rare autosomal recessive diseases caused by mutations in lcat gene, characterized by severe dysfunction of HDL and corneal opacity. These syndromes are essentially classified into two forms: familial LCAT deficiency (FLD) and fish-eye disease (FED). The molecular difference of lcat mutations is causal to the major clinical difference between FLD and FED: FLD patients develop renal failure, whilst FED patients do not. This study was performed to identify the lipoproteins important for the development of renal failure in FLD in comparison to FED, using high-performance liquid chromatography with a gel filtration column (HPLC-GFC). Four lipoprotein fractions specific to LCAT deficiency were identified: 1) large lipoproteins (>80 nm), lipoproteins corresponding to 2) large LDL, 3) very small LDL to large HDL, and 4) small HDL. Contents of esterified cholesterol and triglyceride of the large LDL in FLD are significantly different from those in FED. Upon in vitro incubation with recombinant LCAT (rLCAT), content of esterified cholesterol in the large LDL in FLD, but not in FED, was significantly increased, whilst dysfunctional HDL was diminished in both FLD and FED. The lipid contents of the large LDL in FLD were different from those in lipoprotein-X. In conclusion, our analytical approach using HPLC-GFC identified large LDL only in patients with FLD, and not those in FED. The novel abnormal lipoproteins were diminished by treatment with rLCAT, suggesting that they were primarily caused by dysfunctional LCAT, and thus may play a causal role in the renal pathology of FLD.

P116 Apolipoprotein A-V Gly185Cys is a possible risk factor for severe hypertriglyceridemia in patients with normal circulating lipoprotein lipase protein concentrations

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Aim:
Lipoprotein lipase (LPL) plays an important role in determining plasma triglyceride concentration. Recently, single nucleotide polymorphisms (SNPs) in the apolipoprotein A-V (apoA-V) gene have been reported to relate to hypertriglyceridemia in various study populations. However, the clinical significance of the apoA-V SNPs has not been clarified in association with the LPL function. We have studied the clinical significance of 553G-T, one of the apoA-V SNPs which cause amino acid substitution Gly185-Cys (G185C), in patients with severe hypertriglyceridemia in association with circulating LPL protein concentrations and activities.
Methods:
Study subjects were 104 patients with serum triglyceride concentrations over 1000 mg/dl in our hospital. LPL protein concentration and activity were measured 10 minutes after 30 units/kg heparin injection. The apo A-V G185C polymorphism was analyzed by PCR-RFLP.
Results:
The frequencies of apoA-V G185C in hypertriglyceridemic patients and normolipidemic controls were 58.7 % and 2.3%, respectively. The frequency of apoA-V 185C homozygote and heterozygote was significantly increased in patients with normal level of circulating LPL protein concentrations and activity, compared with those with decreased levels of LPL. Circulating LPL protein levels in the patients with apoA-V 185C homozygote were significantly higher than those in the patients with the apoA-V 185G homozygote.
Conclusion:
An amino acid substitution, G185C in apoA-V possibly causes severe hypertriglyceridemia as a risk factor independent from LPL abnormality. The mutation may accelerate the release of LPL after heparin injection.

P117 Autoimmune severe hypertriglyceridemia induced by anti-apolipoprotein C-II antibody

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CONTEXT:
Among type V hyperlipoproteinemias, only one-fourth of the patients have genetic defects in lipoprotein lipase (LPL) or in its associated molecules; the exact mechanism in other patients is usually unknown.
OBJECTIVE:
The aim of the study was to report a case of severe hypertriglyceridemia induced by anti-apolipoprotein (apo) C-II autoantibody and to clarify its pathogenesis.
SUBJECT AND METHODS:
A 29-year-old Japanese woman presented with severe persistent hypertriglyceridemia since the age of 20 years. The past history was negative for acute pancreatitis, eruptive xanthomas, or lipemia retinalis. LPL mass and activities were normal. Plasma apo C-II levels were extremely low, but no mutation was observed in APOC2.
RESULTS:
Apo C-II protein was detected in the serum by immunoprecipitation and Western blotting. Large amounts of IgG and IgM were incorporated with apo C-II protein coimmunoprecipitated by anti-apo C-II antibody. IgG, but not IgM, purified from the serum prevented interaction of apo C-II with lipid substrate and diminished LPL hydrolysis activity.
CONCLUSION:
We identified anti-apo C-II antibody in a myeloma-unrelated severe hypertriglyceridemic patient. In vitro analysis confirmed that the autoantibody disrupted the interaction between apo C-II and lipid substrate, suggesting the etiological role of anti-apo C-II antibody in severe hypertriglyceridemia in this patient.

P118 Plasma fetuin-A levels are associated with insulin resistance in a general population in Uku-town

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Background: Fetuin-A, a protein exclusive secreted by the liver, induces insulin resistance and subclinical inflammation in rodents. It is suggested that higher fetuin-A levels are associated with metabolic syndrome (Mets). However, little is known whether higher fetuin-A levels are associated with Mets in a general population. We investigated whether high levels of fetuin-A are associated with Mets.Methods: We performed an epidemiological survey in Uku town from 2009 through 2012. The participants consisted of 659 subjects (253 males and 406 females). Fetuin-A levels were determined by an immunoturbidimetric method.Results: Mean plasma fetuin-A levels are 249.7 plusminus 45.1microg/ml in males and 262.7 plusminus 55.8microg/ml in females,which are associated with female gender, insulin, HOMA-IR, total-cholesterol, LDL-cholesterol, teststeron, and habitual drinking. We performed univariate analysis stratified by gender. Fetuin-A in males are associated with BMI, waist circumference, systolic and diastolic BPs, insulin, HOMA-IR, total-cholesterol, LDL-cholesterol, triglycerides and the high prevalence of Mets. In contrast, fetuin-A in females are associated with uric acid only. When we analyzed data using multiple stepwise regression analyses in males, Mets was still remained. Furthermore, we demonstrated an upward trend of serum fetuin-A levels as the large number of components of Mets increased after adjustments for confounders. Conclusion:The present study indicated that fetuin-A is associated with Mets, especially in a positive relationship between fetuin-A and Mets in male population.

P119 Urinary liver-type fatty acid binding protein is associated with microalbuminuria as well as insulin resistance in a general population

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Background: Liver-type fatty acid binding protein (L-FABP) is expressed in the proximal tubules of the human kidney and participates in fatty acid metabolism. It has been demonstrated to be a marker of tubular damage. Recent reports showed that urinary L-FABP was increased in diabetic patients even before they develop signs of glomerular damage. It is still unclear whether urinary L-FABP is associated with insulin resistances.
Methods: A total of 239 residents (104 men and 135 women, mean age 67.2 ± 9.7 years) underwent a physical examination. They received data for fasting blood samples and urine test including urinary levels of liver-type fatty acid binding protein (L-FABP) and microalbuminuria.
Results: The mean levels of urinary L-FABP were increased with age. The mean levels of urinary L-FABP were significantly associated with age ($p<0.0001$), hsCRP ($p<0.05$), insulin ($p=0.01$), HOMA-R ($p<0.01$) and microalbuminuria ($p=0.0001$) using by analysis of co-variance adjusted age and sex. In the group of high urinary L-FABP, odds ratio for the existence of microalbuminuria and insulin resistance was higher after adjustment for confounding factors (Odds ratio, 4.6; 95% confidence interval, 1.5-14.0; $p<0.05$, Odds ratio, 3.5; 95% confidence interval, 1.5-8.6; $p<0.05$, respectively).
Conclusion: The present study demonstrated urinary L-FABP levels were strongly associated with microalbuminuria as well as insulin resistance in a general population.

P120 Association between lifestyle and the prevalence of chronic kidney disease: the Saku study

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Aim: The objective was to investigate the association between lifestyle and the prevalence of chronic kidney disease (CKD) in a Japanese population.
Methods: This cohort study involved 4906 participants (2868 men and 2038 Women) aged 30-79 years who underwent a comprehensive medical check-up at Saku Central Hospital in 2008. Participants were given lifestyle scores on a scale of zero to five. Recommended lifestyles were 1) body mass index <25.0kg/m^2, 2) alcohol consumption <120g/week, 3) never smoked cigarettes, 4) having physical activity ≥once/week, 5) not often eat salty food. Participants scored one point for each recommendation. CKD was determined by proteinuria ≥+1 and/or estimated glomerular filtration rate (eGFR) <60ml/min/1.73m^2. Because of small number of participants, men were categorized by lifestyle scores into five groups (0-1, 2, 3, 4 and 5 points), and women were categorized into three groups (0-3, 4, and 5 points). Adjusted logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for four groups of men (from 2 to 5 points) and two groups of women (4 and 5 points) compared with men with 0-1 points and women with 0-3 points, respectively.
Results: Of 4906 participants, 193 men (0-1 points: 37, 2 points: 69, 3points: 46, 4 points: 31 and 5 points: 10) and 72 women (0-3 points: 24, 4 points: 22 and 5 points: 26) had proteinuria, and 464 men (0-1 points: 35, 2 points: 117, 3points: 156, 4 points: 121, 5 points: 35) and 312 women (0-3 points: 71, 4 points: 125 and 5 points: 116) had eGFR <60ml/min/1.73m2. The ORs for proteinuria significantly decreased among men with 2, 3, 4 and 5 points compared with men with 0-1 points; the ORs (95%CIs) were 0.86 (0.57-1.31), 0.52 (0.33-0.82), 0.57 (0.34-0.94) and 0.66 (0.32-1.39), respectively (P for trend=0.007). However, the ORs for proteinuria did not significantly decrease among women with 4 and 5 points compared with women with 0-3 points; the ORs (95%CIs) were 0.62 (0.34-1.12) and 0.99 (0.55-1.70), respectively. The ORs for eGFR <60ml/min/1.73m^2 did not decrease among men and women with high lifestyle scores.
Conclusion: Healthy lifestyle was inversely associated with the prevalence of proteinuria among men.

P121 Serum ferritin and oxidative stress biomarkers in Japanese with and without metabolic syndrome

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Background:
Metabolic syndrome (MS) is a condition related to life-style and characterized by central obesity leading to pathological conditions such as diabetes mellitus or atherosclerosis. The increased level of oxidative stress, which overwhelms the antioxidative defense capacity, induces oxidative damage to lipids, DNA and proteins. However, the relation between MS and oxidative stress still remains to be investigated in public health for clinical intervention. Then, we have investigated several oxidative stress biomarkers and serum ferritin in Japanese workers with and without MS.
Methods:
Data were obtained from a worksite lifestyle intervention study in six offices in a city in Japan (293 men and 392 women). Fasting blood and urine samples were collected for determination of above mentioned biomarkers. Blood pressure and life-style were also recorded. MS was defined on the basis of the Japanese criterion.
Biomarkers of oxidative stress, including urinary 8-hydroxy-2-deoxyguanosine (8-OHdG), 8-isoprostane, hydrogen peroxide (H2O2), high-sensitivity C-reactive protein (hs-CRP), and serum ferritin were determined. Health parameters and oxidative stress markers were compared between subjects with and without MS.
Results:
Most of the health parameters such as LDL-C, HbA1c, HOMA-R, AST, ALT or others were significantly higher in subjects with MS as compared with those without MS, except for Fe, TIBC and smoking habits. According to the metabolic parameters related to oxidative stress, hs-CRP, ferritin and H2O2 were significantly higher in subjects with MS than those in subjects without MS, except for 8-OHdG and 8-isoprostane. Among iron related markers, only serum ferritin was high in subjects with MS but serum iron was not.
Serum ferritin and urinary H2O2 levels were significantly higher in subjects with MS than those without. There was a significant positive correlation between ferritin and HOMA-R. In addition, serum ferritin was positively correlated with 8-OHdG in all subjects and it was negatively correlated with 8-isoprostane and H2O2 in men. By using multiple regression analysis, serum ferritin was closely correlated with HOMA-R, r-GT, 8-OHdG, smoking value and amount of alcohol ingestion in men, and it was correlated with 8-OHdG, r-GT, HOMA-R in women under 50 years old.
Conclusions:
Serum ferritin is related to HOMA-R as well as hs-CRP in Japanese with MS, suggesting the importance of oxidative stress, especially men.
Therefore, serum ferritin might be an important risk marker of MS, reflecting the importance of oxidative stress in Japanese with MS.

P122 Intervention to reduce childrens television time and get their participation to improve the knowledge on NCDs in a middle income community, Sri Lanka

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Introduction - NCDs are in fact a worldwide pandemic of devastating proportion. It is estimated that 35 million deaths from heart disease, stroke, cancer and chronic respiratory diseases. Of these, 80% occurred in low and middle income community in the long term.

Objective- To improve the knowledge on NCDs among adult with the participation of children and to reduce childrens TV time through health pr motion approach.

Method- This community based intervention was carried in middle income community in Colombo district Sri Lanka. Intervention was delivered through children. Children were trained to measure height, weight and trained to calculate BMI. Children made home visits (32 homes) regularly and measured BMI of householders and delivered the knowledge on NCDs risk factors. Blood pressure of households was measured by researcher. Each house was visited once a month by children. Pre and post level of knowledge were measured using a specific format. Especial activities were carried out to improve the skills of children. Children were encouraged to invest their TV time for outdoor activities. Pre and post average time which invest on TV was assessed.

Results- Before the intervention, 33.6 % of adults (n=18) have not measured their height. 69.2 % adults (n=36) have not measured their weight previously. 42.3% adults (n=22) have not measured BMI while only 19.2% knew their BMI level. Only 48% adults (n=25) have measured BP in their life. 34.6% could range the healthy systolic and diastolic BP values. Following six months intervention, it was found that 61% (n=28) knew their BMI levels. 58.7 % adults (n=27) could remember their BMI levels while 82.6% adults (n=38) could range the healthy BP range accurately.

Before the intervention average time on TV among children group were 4.5 hours per day. after six months of the intervention, it was found that the average time spend on TV were 2.5 hours.

Conclusion- Children participation can significantly effect on improving knowledge on NCDs in a middle income communities. Also this would useful to improve the various skills of children. Health promotion approach was an effective to reduce TV time among children in an effective manner.

Recommendation - Even though this study did not measure the improvement of academic skills of children, future study should design in order to assess the children academic performance as well.

P123 Relationship between cognitive function and oxidative stress

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Background It is rather difficult to recognize an impairment of cognitive function, and the cognitive function tends to decrease sub-clinically. Urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) has been reported to accept as a sensitive biomarker of oxidative stress. Oxidative stress is thought to be involved in the pathogenesis of Alzheimer's disease. Therefore, in this study, we aimed to elucidate the impact of decreased cognitive function on oxidative stress.
Methods A total of 240 subjects aged 67.3±9.7 years (104 men and 136 women) underwent a physical examination in 2012. All of them were assessed cognitive function with mini-mental state examination (MMSE). We also measured urinary 8-OHdG by high-performance liquid chromatography (HPLC) as a marker of oxidative stress.
Results The mean levels of urinary 8-OHdG were 3.5 (range 2.0-12.9) ng/ml in men, and 2.8 (range 2.0-12.8) ng/ml in women. The means of MMSE score were 27.5±2.2. Univariate regression analyses revealed that age ($p<0.0001$, inversely), male gender ($p<0.05$), MMSE ($p<0.05$, inversely), triglycerides ($p<0.001$, inversely), and habitual smoking ($p<0.05$) were significantly associated with urinary 8-OHdG. In multiple regression analyses adjusted for age and gender, the significance of inverse relationship between MMSE and urinary 8-OHdG was still remained ($p<0.05$).
Conclusion We demonstrated for the first time that cognitive function was significantly and inversely associated with urinary 8-OHdG in a general population.

Author Index

A

Abe, Yoshimi....P025
Abudukadier, Abulizi....P043
Aburatani, Hiroyuki....P044, P094
Accili, Domenico....SY2-2
Adachi, Hisashi....P118, P119, P123
Adachi, Yasuhiro....P091
Aghade, Sunita....P070
Ahn, Kyu Jeung....P093
Ahn, Song Vogue....P103
Akamizu, Takashi....P082
Akesaka, Kazuyuki....P002
Akimoto, Yoshiro....P058
Akiyama, Yoshitaka....P025
Aoyagi, Yasuyuki....P111, P115
Aoyama, Tomohisa....P044
Aoyama-Sasabe, Sae....SY2-3
Arai, Hidenori....P021
Araki, Eiichi....P010, P055, P063, P100
Araki, Rika....P077
Arimura, Emi....P071
Arisawa, Kokichi....P029
Ariyoshi, Kyoko....P047
Asada, Sakiyo....P111, P115
Asegaonkar, Shilpa B....P070
Ashida, Noboru....P021
Aso, Masayuki....P111
Atsumi, Yoshihiro....P011

B

Baba, Osamu....P001, P005, P112, P113
Baik, Seihyun....P099
Bar Dayan, Yosefa....P060, P074
Batchuluun, Baigalmaa....P090
Batchuluun, Battsetseg....P090
Bavikar, Jayshree S.....P070
Benner, Chris....SY8-2
Berliner, Shlomo....P106
Betsholtz, Chirster....P058
Bhowmik, Bishwajit....P059
Bo Hyun, Kim....P065
Boaz, Mona....P060, P074, P106
Borkar, Mangala....P070
Bujo, Hideaki....P111, P115, P116
Byun, Dongwon....P054

C

Cha, Bong Soo....P093
Chang, Cicero L. T.....P080
Chapman, John M....SY5-4
Chatterjee, Biprabuddha....P075
Chayama, Kazuaki....P114
Chen, Sheng Hsien....P072
Chen, Tana....P062
Cheung, Bernard MY....P052
Cheung, ChingLung....P052
Chinju, Sayaka....P067
Choi, Han Seok....P098
Chun, Tae Hwa....P101
Cohen, Jonathan C....SY8-4

D

Da Hong, Wang....P121
Decroli, Eva....P081
Després, Jean-Pierre....SY3-3
Deura, Kijyo....P120
Devarajan, Sankar....P075
Dezaki, Katsuya....P049
Dhanapala, Nayana....P122
Dhanapala, Nayana D....P110

E

Ebisui, Osamu....P002
Egawa, Katsuya....P064
Enomoto, Mika....P118, P119, P123
Eonju, Jeon....P086

F

Fan, Jianglin....P036
Faraj, May....SY6-4
Fermin, Carolyn K....P037
Fernando, Manoj....P110
Fonseca, Greg....SY8-2
Fruchart, Jean-Charles....SY5-1
Fu, Jian....P084
Fujikawa, Tatsuya....P067, P085
Fujioka, Yoshio....P003, P035, P092
Fujita, Hayato....P024
Fujita, Yoshihito....P043
Fukami, Ako....P118, P119, P123
Fukuda, Kazuki....P063, P100
Fukumoto, Yoshihiro....P118, P119, P123
Fukushima, Makoto....P006
Fukushima, Mitsuo....SY2-3
Fukushima, Toru....P043
Fumio, Nikami....P027
Funahashi, Nobuaki....P053
Funahashi, Tohru....SY4-1, P117
Furusawa, Rie....P066
Furuta, Noriko....P077
Furuuchi, Megumi....P066
Furuya, Futoshi....P043

G

Galton, Virginia....SY6-3
Ginsberg, Henry N.....SY6-3
Giyres, Sami....P074
Glass, Christopher K....SY8-2
Godai, Kayo....P042, P056
Goto, Rieko....P055
Giral, P....SY5-4

H

Hamasaki, Akihiro....P091

Author Index

Hamaue, Akiko....P022
HAN, KI HOON....P026
Han, Seung H....P020
Hanada, Hiroyuki....P012
Hara, Kazuo....P024
HARADA, Aushi....P073
Harada, Izumi....P079
Harada, Norio....SY7-3, P091
Harada, Takanari....P091
Hasegawa, Hiroyuki....P043
Hasegawa, Koji....P005
Hashimoto, Ari....P021
Hashimoto, Rei....P077
Hata, Hiroaki....P101
Hatano, Takafumi....P035
Hatayama, Miki....P051
Hattori, Akiko....P033
Hayakawa, Tomoko....P088
Hayata, Manabu....P100
He, Peng....P033, P058
Heinz, Sven....SY8-2
Hermans, Michel P....SY6-2
Hernandez-Ono, Antonio....SY6-3
Hiraike, Yuta....P094
Hirao, Tomohiro....P121
Hirasaki, Masataka....P045
Hirata, Ken-ichi....SY7-2
Hiromine, Yoshihisa....P082
Hironaka, Asako....P007
Hirota, Yusuke....P069
Hirowatari, Yuji....P031
Hisai, Yoshiyuki....P084
Holleboom, Adriaan G....P115
Horie, Takahiro....P001, P005, P112, P113
Horiguchi, Masaki....P067, P085
Horiuchi, Masahisa....P071
Horton, Jay D....SY4-4
Hotta, Kikuko....P114
Hotta, Yasuhiro....P076, P077
Hounslow, N....SY5-4
Hsieh, Joanne....P009
Hui, Zhao....P046
Hung, Ting Chun....P072
Hussain, Mahmood....P009
Hyogo, Hideyuki....P114

I

Ichikawa, Takehiko....P076
Igata, Motoyuki....P055
Iizuka, Yoko....P004, P068, P084
Ikai, Iwao....P101
Imaizumi, Tsutomu....P118
In Joo, Kim....P065
Inaba, Masaaki....P013
Inagaki, Nobuya....SY7-3, P043, P091
Inoguchi, Toyoshi....P090
Inoue, Kentaro....P067, P085
Inoue, Kyoko....P084
Inoue, Mariko....P028
Inoue, Mayumi....P101
Inoue, Tsuyoshi....P044
Iqbal, Jahangir....P009
Ishibashi, Ryoichi....P033, P058
Ishibashi, Shun....SY5-2, P024, P066, P068, P115
Ishida, Kazufumi....P061
Ishii, Norio....P063
Ishii, So....P006
Ishikado, Atsushi....P027
Ishikawa, Takahiro....P033, P058
Ishiura, Hiroyuki....P024
Ito, Miki....P003, P035, P092
Itoh, Hiroshi....SY3-1
Iwabu, Masato....P008, P038, P069
Iwabu, Miki O....P008, P038
Iwanaga, Suketaka....P121
IWASAKI, Hitoshi....P108
Iwasaki, Kanako....P091
Izuhara, Masayasu....P001, P112

J

Jia, Weiping....P084
Jiang, Meizi....P015
Jo, Rie....SY3-1
Jong Ho, Kim....P065
Joo, Erina....P091
Jung, Euidal....P086

K

Kabeya, Yusuke....P011
Kadowaki, Takashi....P004, P008, P024, P028, P038, P044, P068, P069, P084, P094
Kadoya, Manabu....P051
Kagaya, Hiroki....P018
Kagota, Satomi....P089
Kaikkonen, Minna....SY8-2
Kaji, Hidesuke....P022
Kajinami, Kouji....P034
Kakizoe, Yutaka....P100
Kaku, Kohei....SY1-4
Kamano, Sakurako....P029
Kamata, Kouju....P115
Kamei, Kaeko....P021
Kamiya, Norihumi....P096
Kanai, Yoshikatsu....SY1-1
Kanamoto, Junko....P082
Kanbara, Sakiko....P121
Kaneko, Keizo....P102
Kaneko, Shuichi....P107
Kang Hee, Ahn....P065
Kang, Eun Seok....P093
Kang, Seokbong....P086
Kareem, Ishrat....P070
Kasahara, Masato....P050

Author Index

Kasuga, Masato P041, P088
Katagiri, Hideki P102
Katamine, Youko P079
Kato, Kiyoe P011
Katsukawa, Fuminori P078
Katsuki, Takeshi P011
Katsumata, Harumi P006
Katulanda, Prasad P110, P122
Kawabata, Nao P066
Kawaguchi, Miho P053
Kawamura, Harukiyo P033
Kawase, Ryota P030
Kawashima, Junji P055
KAWASHIMA, Syuji P073
Kawatsu, Yuichiro P042
Kida, Yasuo P064
Kihara, Shinji P117
Kim, Dongsun P099
Kim, Dooman P083
Kim, Hyejung P054
Kim, Jang Young P103
Kim, K Seung P069
Kim, Kwang Joon P098
Kim, Myeong gun P020
Kim, Seung K P069
Kim, Yoonjung P083
Kim, Yuna P026
Kimura, Hiroshi P007
Kimura, Takeshi P001, P005, P021, P112, P113
Kingwell, BA SY5-4
Kinoshita, Hiroyuki P063
Kish, Akio P064
Kishitani, Yuzuru P082
Kita, Toru P005, P021, P112, P113
Kitamoto, Aya P114
Kitamoto, Takuya P114
Kitamura, Kenichiro P100
Kitamura, Tadahiro MS2
Kitano, Sayaka P055
Kobayashi, Kazuki P033
KOBAYASHI, Kazuto P108
Kobayashi, Takuya P012
Kodama, Tatsuhiko P044
Koh, Kwang K P020
Koh, Sang Baek P103
Komo, Tomoyuki P061
Kondo, Keiko P027
Kondo, Tatsuya P055, P063, P100
Kono, Shigeo P057
Koseki, Masahiro P009, P012, P030
Koyama, Hidenori P013, P051
Kubota, Naoto P008, P028
Kubota, Tetsuya P008, P028
Kudo, Kana P090
Kumagai, Eita P119, P123
Kume, Noriaki P005
Kung, Annie WC P052
Kurajoh, Masafumi P051
Kurano, Makoto P023
Kurihara, Isao SY3-1
Kuroda, Masayuki P111, P115
Kusunoki, Masataka P062
Kuwabara, Takashige P039
Kuwabara, Yasuhide P001, P005, P112, P113
Kuwahara, Koichiro P050
Kwak, Mina P086
Kyotani, Yoji P007

L

Lam, Michael SY8-2
Landau, Zohar P060, P074
Lee, Byung Wan P093
Lee, Gendai P079
Lee, Hyun Chul P093
Lee, Jae Hyuk P098
Lee, See Hoon P098
Lee, Seungik P020
Lee, Yong ho P093
Leibovitz, Eyal P060, P074
Li, Guoping SY6-3
Liang, Guosheng P004
Libby, Peter SY7-1
Link, Verena SY8-2
Liu, Jing SY6-3

M

Maegawa, Hiroshi SY3-2, P027, P056, P064
Maekawa, Yoko P096
Maezawa, Yoshiro P048, P058
Maimun, Arthamin Zulhaidah P019
Makino, Taketoshi P027
Malalgoda, Shanika P110
Mamoto, Rie P003, P035, P092
Manabe, Ichiro SY8-1
Manaf, Asman P081
Manita, Daisuke P031
Marchianti, Ancah C.N. P071
Maruyama, Kana P089
Masuda, Daisaku P012, P030
Masuzaki, Hiroaki MS1
Matsuda, Masafumi P025
Matsui, Natsumi P079
MATSUI, Yasumoto P073
Matsumoto, Masahito P045
Matsumoto, Michihiro P041, P088
Matsumoto, Motonobu P027
Matsumura, Takeshi P010, P055, P063, P100
Matsunaga, Kimie P047
Matsuo, Yoshino P032
Matsuo, Yoshiyuki P016, P057, P101
Matsuyama, Akifumi P030

Author Index

Matsuyama, Rina P055
Matsuzaka, Takashi P046, P108
McGuire, John J P089
Meikle, PJ SY5-4
Millán Núñez-Cortés, Jesús SY4-2
Minami, Shiro P006
Mitsushima, Masaru P088
Mitusi, Jun P024
Miura, Katsuyuki SY3-2
Miura, Shinichiro P014, P032
Miyagi, Ren P003
Miyahara, Mayako P066
Miyake, Kana P094
Miyamatsu, Naomi P042, P056, P120
Miyasato, Yoshikazu P100
Miyase, Yuiko P014, P032
Miyata, Tetsuro P062
Miyatake, Nobuyuki P121
Mizumoto, Teruhiko P100
Monden, Masayo P013
Mori, Kiyoshi P039, P050
Mori, Yasuo P050
Morimoto, Akiko P042, P056, P120
Morino, Katsutaro P027, P056, P064
Morisawa, Chieko P025
Morita, Tomoko P025
Moriwaki, Yuji P051
Motoshima, Hiroyuki P055, P063
Mukoyama, Masashi P039, P050, P100
Murakami, Saiko P063
Muranaka, Kazuya P016, P057, P101
Murano, Takeyoshi P116

N

Nagai, Masami P022
Nagao, Yuko P047
Nagashimada, Mayumi P107
Nagata, Daisuke P017, P066
Nagata, Naoto P107
Nagayama, Daiji P116
Nagayama, Kosuke P007
Nakagawa, Akihiko P034
Nakagawa, Fumiyuki P027
Nakagawa, Yoshimi P046, P108
Nakajima, Atsushi P114
Nakamura, Ayumi P014, P032
Nakamura, Kazuki P089
Nakamura, Masahiro P044, P094
Nakamura, Sachiko P118, P119, P123
Nakamura, Takaaki P064
Nakamura, Takao P062
Nakano, Yuta P046
Nakao, Erika P118, P119, P123
Nakao, Kazuwa P039, P050
Nakao, Tetsushi P001, P112
Nakatani, Kazuhiro P012, P030
Nakayama, Asuka P014, P032
Namba, Mitsuyoshi P013, P051
Nammo, Takao P053
Nanjo, Kishio P082
Nasteska, Daniela P091
Natsume, Yukie P062
Negita, Emi P010
Nemoto, Ken-ichi P056
Nguyen, Dat Tien P021
Ni, Yinhua P107
Nie, Tang P046
Ning, Bo P036
Nishida, Makoto P012, P030
Nishida, Masako P003, P035, P092
Nishiga, Masataka P001, P112
Nishikawa, Takeshi P010, P063
Nishimura, Masataka P064
Nishimura, Wataru P053
Nishino, Tomohiro P001, P112, P113
Nishio, Yoshihiko P027, P064
Nishiura, Mina P079
Niwano, Fumimaru P082
Noda, Akari P004, P068
Nohara, Yume P118, P123
Nomiyama, Ryuta P047
Norimatsu, Kenji P014
Numata, Tomohiro P050

O

Obara, Akio P043
Obata, Akiko P079
Obuchi, Aya P118, P119, P123
Ochi, Hidenori P114
Odawara, Masato ..... ES
Odori, Shinji P057
Oe, Makoto P084
Ogawa, Kenichi P082
Ogino, Keiki P121
Ogura, Masahito P043
Oguri, Yasuo P043
Oh, Pyung C P020
Ohama, Tohru P012, P030
Ohashi, Akiko P043
Ohashi, Koji P006
Ohashi, Yumiko P084
Ohbu, Kyoko P118
Ohira, Hideo P003, P035, P092
Ohishi, Waka P109
Ohno, Keizo P002
Ohno, Shoko P050
Ohno, Yuko P120
Ohoshi, Takashi P082
Ohyama, Takako SY3-1
Oikawa, Yoichi P011
Okada Iwabu, Miki P069
Okada, Mio P022

Author Index

Okada, Takeshi P030
Okamoto, Masaaki P006
Okamoto, Motozumi SY3-2
Okamoto, Yoshihisa P006
Okano, Yuko P077
Okazaki, Hiroaki P004, P024, P068
Okazaki, Hirokazu P051
Okazaki, Sachiko P004, P068
Okazaki, Yasushi P045
Okisugi, Mari P011
Okubo, Manabu P012
Okubo, Setsuya P076
Okuya, Shigeru P047
Omura, Yasushi P064
Onay, Tuncer P048
Onishi, Atsuo SY3-2
Onishi, Yuki P077
Ono, Kaoru P055
Ono, Koh P001, P005, P112, P113
Onoguchi, Atsuko P066
Orsoni, A SY5-4
Osawa, Masaya P011
Oshida, Yoshiharu P062
Osuga, Junichi P024, P068
Ota, Hiroyo P007
Ota, Tsuguhito P107
Ouchi, Noriyuki P006
Owada, Yuji P091
Ozawa, Kentaro P007
Ozcan, Lale SY2-1

P

Pagdhune, Avinash P070
Park, Chulyun P086
Park, Hyeongkyu P054
Park, Junghwan P099
Park, Juri P083
Putu, Arsana Moda P019

Q

Quaggin, Susan E. P048

R

Rader, Daniel J. P009
Raz, Olga P106
Rifqi, Destiansyah Aulia P019
Rita, Rauza S. P049
Rosenzweig, Tovit P106

S

Sabe, Hisataka P021
SABLE MORITA, Sayuri P073
Saeki, Toshinari P061
Saiki, Atsuhito P116
Saito, Yasushi P111, P115
Sakai, Juro P044
Sakai, Mashito P041, P088
Sakaki, Yuka P090
Sakamoto, Kenichi P033, P058
Sakano, Noriko P121
Sakashita, Anna P025
Sakata, Yasushi P009, P012, P030
Saku, Keijiro P014, P032
Salces, Neil Wayne C. P037
Sang Heon, Song P065
Sang Soo, Kim P065
Sasagawa, Michiyo P034
Sasaki, Naoto SY7-2
Sasaki, Yousuke P016, P057, P101
SATAKE, Syosuke P073
SATHO, Aoi P108
Sato, Daisuke P062
Sato, Toshiko P066
Satoh Asahara, Noriko P016, P057, P101
Scott, Rizaldy P048
Seidah, Nabil G. PL2
Seino, Yutaka SY2-3, LS2
Sekikawa, Akira SY3-2
Sekine, Osamu P056
Senevirathne, Chamil P P110, P122
Senokuchi, Takafumi P010, P063
Shapira, Itzhak P106
Shen, Hui Chuan P072
Shibata, Hirotaka SY3-1
Shibue, Kimitaka P091
Shiga, Yuhei P014, P032
Shima, Azusa P042
Shimada, Akira P011
Shimano, Hitoshi SY8-3, P046, P108
Shimatsu, Akira P016, P101
Shimazu, Akira P057
Shimojima, Kazuya P078
Shimomura, Iichiro P117
Shin, Dong Yeob P098
Shin, Imhee P086
Shinozuka, Kazumasa P089
Shiomi, Masashi P036
Shionoiri, Futoshi P068
Shirai, Kohji P116
Shirakawa, Shinobu P084
Shiroma, Isao P096
Shoji, Takuhito P013, P051
Shon, Hosang P086
Siddiquee, Tasnima P095
Sing, ChorWing P052
Singh, Ravinder P075
Son, Hoyoung P083
Sonoda, Nao P042, P056
Sonoda, Noriyuki P090
Soo Bin, Park P065
Sowa, Naoya P005
Spann, Nathan SY8-2
Steinvil, Arie P106

Author Index

Stroes, Erik S.G. P115
Suematsu, Yasunori P032
Sugawara, Akira P050
Sugawara-Yamashita, Yzumi P045
Sugiyama, Takuya P069
Sugiyama, Teruaki P011
Suh, Kyoil P054
Suwa, Makoto P027
SUZUKI, Hiroaki P108
Suzuki, Kazuyo P091
Suzuki, Ken P094
Suzuki, Marii P046
Suzuki, Satomi P045
Suzuki, Toshinari P077
Syafril, Syahbuddin P081

T

Tabas, Ira SY2-1
Tada, Norio P031
Taira, Yoshino P068
Takahara, Noriko P064
Takaishi, Miki P061
Takamoto, Iseki P028
Takanashi, Mikio P004, P024, P068
Takasawa, Shin P007
Takase, Satoru P004, P024, P068
Takayanagi, Ryoichi P090, P091
Takeda, Komei P047
Takei, Yoshiyuki P077
Takemoto, Minoru P033, P048, P058
Taketa, Kazuhisa P121
Takiguchi, Shunichi P009
Tall, Alan R P009
Tamaki, Mizune P002
Tan, Kathryn CB P052
Tan, R SY5-4
Tanaka, Masashi P016, P057, P101
Tanaka, Minoru P117
Taniguchi, Ataru SY2-3
TANIKAWA, Takahisa P073
Tanizawa, Yukio P047
Tatsukawa, Yoshimi P109
Tatsumi, Yukako P042, P120
Tatsuno, Ichiro SY3-4, P116
Tazuma, Susumu P061
Terauchi, Yasuo SY1-3
Thennakoon, Shalika P110
Thor, Hongwooi P084
Thorat, Anand P. P070
TOKUDA, Haruhiko P073
Tokumoto, Emi P079
Tokunaga, Hitto P002
Tokuyama, Hirotake P033
Tomita, Masuomi P011
Tomita, Sayo P014, P032
Tryggvason, Karl P058
Tsuchida, Sumiyo P007
Tsuji, Shoji P024
Tsukahara, Tetsuya P016
Tsutsui, Hideyo P062
Tsutsui, Wao P003, P035, P092
Tsutsumi, Shuichi P094

U

Uchimura, Kohei P100
Udagawa, Haruhide P053
Ueda, Teruhisa P002
Ueki, Kohjiro LS1, P028, P094
Uemura, Hirokazu P029
Uemura, Mei P077
Ueno, Takato P114
Ueshima, Hirotsugu SY3-2
Ugi, Satoshi SY3-2, P027, P056, P064
Uni, Asahi P004
Usami, Shunsuke P001, P112
Ushikai, Miharu P071

V

Vale, Wylie P045

W

Wada, Youichiro P044
Wainstein, Julio P060, P074
Wakabayashi, Kenichi P044
Waki, Hironori P044, P069, P094
Wakuda, Hirokazu P089
Wakuta, Kenichiro P096
Wang, Chieh Tien P072
Wang, Xiaoyan P036
Wang, Yiwen P084
Waqar, Bilal P036
Watada, Hirotaka SY7-4
Watanabe, Kurando P096
Welch, Carrie P009
Won Jin, Kim P065
Wong, G SY5-4
Wong, Ian CK P052
Wu, Li Ching P072

X

Xu, Liang P107
Xu, Pengfei P004

Y

Yada, Toshihiko P049
Yagi, Takashi P088
Yahagi, Naoya P046, P108
Yakushiji, Emi P009
Yamada, Michiko P109
Yamada, Nobuhiro P046, P108
Yamada, Sarie P010, P063
Yamaga, Masaya P033
Yamaguchi, Miwa P029
Yamaguchi, Sayaka P003, P035, P092

Author Index

Yamaji, Daisuke P088
Yamakage, Hajime P016, P057, P101
Yamamoto, Hiroshi P013
Yamamoto, Hiroyasu P117
Yamamoto, Kayo P034
Yamamoto, Tetsuya P051
Yamamoto, Yasuhiko P013
Yamanaka, Shinya PL1
Yamane, Shunsuke SY7-3, P043, P091
Yamashita, Shizuya P009, P012, P030, P115
Yamashita, Tomoya SY7-2
Yamauchi, Akiyo P007
Yamauchi, Toshimasa SY4-3, P008, P028, P038, P044, P069, P094
Yamawaki, Shigeto P061
Yan, Kunimasa P058
Yanagita, Motoko P039, P050
Yang, WenChin P080
Yano, Hiroyuki P088
Yano, Yutaka P076, P077
Yara, Tomohiro P096
Yasuda, Kazuki P053
Yasui, Mika P104
Yasuma, Taro P077
Yasunami, Yoichi P045
YATOH, Shigeru P108
Yatsuka, Yukiko P045
Yokode, Masayuki P005, P021, P113
Yokoi, Hideki P039, P050
Yokote, Koutaro SY5-3, P033, P048, P058, P111
Yoneda, Masato P114
Yoneda, Masayasu P109
Yonei, Taiji P067, P085
Yoo, Myunghi P054
Yoon Jeong, Nam P065
Yoon, Hye Jin P093
Yoshida, Aya P079
Yoshida, Hiroki P004
Yoshida, Hiroshi P031
Yoshida, Yasunari P067, P085
Yoshiga, Satomi P117
Yoshikawa, Ayumu P021
Yoshikawa, Noriko P089
Yoshimura, Ayako P118, P119, P123
Yoshinaga, Reie P025
Yoshizumi, Masanori P007
Ypil, Wilfredo M. P037
Yu, Jing P094
Yu, Ying P036
Yun Kyung, Jeon P065

Z

Zambon, Alberto SY6-1
Zhang, Bo P075
Zhao, Jing P007
Zhao, Liping SY2-4
Zhu, Yinghong P030
Zhuge, Fen P107

【禁忌】(次の患者には投与しないこと)
1.本剤の成分に対し過敏症の既往歴のある患者
2.妊婦又は妊娠している可能性のある婦人(「妊婦、産婦、授乳婦等への投与」の項参照)
3.アリスキレンフマル酸塩を投与中の糖尿病患者(ただし、他の降圧治療を行ってもなお血圧のコントロールが著しく不良の患者を除く)[非致死性脳卒中、腎機能障害、高カリウム血症及び低血圧のリスク増加が報告されている。](「重要な基本的注意」の項参照)

効能・効果 高血圧症
用法・用量 通常、成人にはオルメサルタン メドキソミルとして10～20mgを1日1回経口投与する。なお、1日5～10mgから投与を開始し、年齢、症状により適宜増減するが、1日最大投与量は40mgまでとする。
使用上の注意
1.慎重投与(次の患者には慎重に投与すること)(1)両側性腎動脈狭窄のある患者又は片腎で腎動脈狭窄のある患者(「重要な基本的注意」の項参照)(2)高カリウム血症の患者(「重要な基本的注意」の項参照)(3)重篤な腎機能障害のある患者[腎機能を悪化させるおそれがある。血清クレアチニン値が3.0mg/dL以上の患者での十分な使用経験はないので、このような患者に対しては状態を観察しながら慎重に投与すること。](4)肝機能障害のある患者[外国において、軽度又は中等度の肝機能障害患者でオルメサルタンの血漿中濃度(AUC)が、健康な成人と比較してそれぞれ1.1倍と1.7倍に上昇することが報告されている。](5)脳血管障害のある患者[過度の降圧が脳血流不全を惹起し、病態を悪化させるおそれがある。](6)高齢者(「高齢者への投与」の項参照)
2.重要な基本的注意(1)両側性腎動脈狭窄のある患者又は片腎で腎動脈狭窄のある患者においては、腎血流量の減少や糸球体ろ過圧の低下により急速に腎機能を悪化させるおそれがあるので、治療上やむを得ないと判断される場合を除き、使用は避けること。(2)高カリウム血症の患者においては、高カリウム血症を増悪させるおそれがあるので、治療上やむを得ないと判断される場合を除き、使用は避けること。また、腎機能障害、コントロール不良の糖尿病等により血清カリウム値が高くなりやすい患者では、高カリウム血症が発現するおそれがあるので、血清カリウム値に注意すること。(3)本剤の投与によって、**一過性の急激な血圧低下を起こすおそれがあるので、そのような場合には投与を中止し、適切な処置を行うこと。また、特に次の患者では低用量から投与を開始し、増量する場合は患者の状態を十分に観察しながら徐々に行うこと。**1)血液透析中の患者 2)利尿降圧剤投与中の患者 3)厳重な減塩療法中の患者 (4)アリスキレンフマル酸塩を併用する場合、腎機能障害、高カリウム血症及び低血圧を起こすおそれがあるため、患者の状態を観察しながら慎重に投与すること。なお、eGFRが60mL/min/1.73m²未満の腎機能障害のある患者へのアリスキレンフマル酸塩との併用については、治療上やむを得ないと判断される場合を除き避けること。(5)本剤を含むアンジオテンシンII受容体拮抗剤投与中に重篤な肝機能障害があらわれたとの報告がある。肝機能検査を実施するなど観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。(6)手術前24時間は投与しないことが望ましい。(7)降圧作用に基づくめまい、ふらつきがあらわれることがあるので、高所作業、自動車の運転等危険を伴う機械を操作する際には注意させること。
3.相互作用 併用注意(併用に注意すること) **●カリウム保持性利尿剤:**スピロノラクトン、トリアムテレン等 **●カリウム補給剤:**塩化カリウム等 **●リチウム製剤:**炭酸リチウム **●アリスキレンフマル酸塩 ●アンジオテンシン変換酵素阻害剤 ●非ステロイド性消炎鎮痛剤**
4.副作用 総症例569例中65例(11.4%)に自他覚症状の副作用が認められた。臨床検査値異常変動の副作用は15.5%(87/563例)に認められた。〔承認時〕 使用成績調査6,327例中244例(3.9%)に副作用(臨床検査値異常を含む)が認められた。〔再審査終了時〕
(1)**重大な副作用** 1)**血管浮腫**(頻度不明[注1)]):顔面、口唇、咽頭、舌の腫脹等が症状としてあらわれることがあるので観察を十分に行うこと。2)**腎不全**(0.1%未満):腎不全があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。3)**高カリウム血症**(頻度不明[注1)]):重篤な高カリウム血症があらわれることがあるので、観察を十分に行い、異常が認められた場合には、直ちに適切な処置を行うこと。 4)**ショック**(頻度不明[注1)])、**失神**(頻度不明[注1)])、**意識消失**(頻度不明[注1)]):ショック、血圧低下に伴う失神、意識消失があらわれることがあるので、観察を十分に行い、冷感、嘔吐、意識消失等があらわれた場合には、直ちに適切な処置を行うこと。特に血液透析中、厳重な減塩療法中、利尿降圧剤投与中の患者では低用量から投与を開始し、増量する場合は患者の状態を十分に観察しながら徐々に行うこと。 5)**肝機能障害**(0.1%未満)、**黄疸**(頻度不明[注1)]):AST(GOT)、ALT(GPT)、γ-GTPの上昇等の肝機能障害、黄疸があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。 6)**血小板減少**(頻度不明[注1)]):血小板減少があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。 7)**低血糖**(頻度不明[注1)]):低血糖があらわれることがある(糖尿病治療中の患者であらわれやすい)ので、観察を十分に行い、脱力感、空腹感、冷汗、手の震え、集中力低下、痙攣、意識障害等があらわれた場合には投与を中止し、適切な処置を行うこと。 8)**横紋筋融解症**(頻度不明[注1)]):筋肉痛、脱力感、CK(CPK)上昇、血中及び尿中ミオグロビン上昇を特徴とする横紋筋融解症があらわれることがあるので、観察を十分に行い、このような場合には直ちに投与を中止し、適切な処置を行うこと。 9)**アナフィラキシー**(頻度不明[注1)]):そう痒感、全身発赤、血圧低下、呼吸困難等が症状としてあらわれることがあり、またアナフィラキシーショックを起こしたとの報告もあるので、観察を十分に行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。 10)**重度の下痢**(頻度不明[注1)]):長期投与により、体重減少を伴う重度の下痢があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。なお、生検により腸絨毛萎縮等が認められたとの報告がある。
注1)自発報告又は海外のみで認められている副作用については頻度不明とした。

●上記以外の使用上の注意等は製品添付文書をご覧ください。

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* International Diabetes Federation. *IDF Diabetes Atlas*, sixth edition, 2013:11. Calculation based on the IDF's estimate that 8.3% of adults have diabetes.

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【禁忌(次の患者には投与しないこと)】
1.本剤の成分に対し過敏症の既往歴のある患者
2.重症ケトーシス、糖尿病性昏睡又は前昏睡の患者[輸液、インスリンによる速やかな高血糖の是正が必須となるので本剤の投与は適さない。]
3.重症感染症、手術前後、重篤な外傷のある患者[インスリン注射による血糖管理が望まれるので本剤の投与は適さない。]

効能又は効果

2型糖尿病

〈効能又は効果に関連する使用上の注意〉
(1)本剤は2型糖尿病と診断された患者に対してのみ使用し、1型糖尿病の患者には投与をしないこと。 (2)重度の腎機能障害のある患者又は透析中の末期腎不全患者では本剤の効果が期待できないため、投与しないこと。[「**2.重要な基本的注意**」の項(6)、**【薬物動態】**及び**【臨床成績】**の項参照] (3)中等度の腎機能障害のある患者では本剤の効果が十分に得られない可能性があるので投与の必要性を慎重に判断すること。[「**2.重要な基本的注意**」の項(6)、**【薬物動態】**及び**【臨床成績】**の項参照]

用法及び用量

通常、成人にはトホグリフロジンとして20mgを1日1回朝食前又は朝食後に経口投与する。

使用上の注意(抜粋)

1.慎重投与(次の患者には慎重に投与すること)
(1)次に掲げる患者又は状態[低血糖を起こすおそれがある。] 1)脳下垂体機能不全又は副腎機能不全 2)栄養不良状態、飢餓状態、不規則な食事摂取、食事摂取量の不足又は衰弱状態 3)激しい筋肉運動 4)過度のアルコール摂取者 (2)他の糖尿病用薬(特に、スルホニルウレア剤又はインスリン製剤)を投与中の患者[併用により低血糖を起こすおそれがある。「**2.重要な基本的注意**」、「**3.相互作用**」、「**4.副作用**」及び**【臨床成績】**の項参照] (3)尿路感染、性器感染のある患者[症状を悪化させるおそれがあるので、本剤投与開始前に適切な処置を行うこと。] (4)重度の肝機能障害のある患者[使用経験がなく安全性が確立していない。**【薬物動態】**の項参照]

2.重要な基本的注意
(1)本剤の使用にあたっては、患者に対し低血糖症状及びその対処方法について十分説明すること。特に、スルホニルウレア剤又はインスリン製剤と併用する場合、低血糖のリスクが増加するおそれがある。スルホニルウレア剤又はインスリン製剤による低血糖のリスクを軽減するため、これらの薬剤と併用する場合には、スルホニルウレア剤又はインスリン製剤の減量を検討すること。[「**1.慎重投与**」、「**3.相互作用**」、「**4.副作用**」及び**【臨床成績】**の項参照] (2)糖尿病の診断が確立した患者に対してのみ適用を考慮すること。糖尿病以外にも耐糖能異常・尿糖陽性等、糖尿病類似の症状(腎性糖尿、甲状腺機能異常等)を有する疾患があることに留意すること。 (3)本剤の適用はあらかじめ糖尿病治療の基本である食事療法、運動療法を十分に行った上で効果が不十分な場合に限り考慮すること。 (4)本剤投与中は、血糖値等を定期的に検査し、薬剤の効果を確かめ、3ヵ月投与しても効果が不十分な場合には、より適切な治療法への変更を考慮すること。 (5)投与の継続中に、投与の必要がなくなる場合があり、また、患者の不養生、感染症の合併等により効果がなくなったり、不十分となる場合があるので、食事摂取量、血糖値、感染症の有無等に留意の上、常に投与継続の可否、薬剤の選択等に注意すること。 (6)本剤投与により、血清クレアチニンの上昇又はeGFRの低下がみられることがあるので、腎機能を定期的に検査するとともに、腎機能障害患者における治療にあたっては経過を十分に観察すること。 (7)尿路感染及び性器感染を起こすことがあるので、症状及びその対処方法について患者に説明すること。また、腎盂腎炎等の重篤な感染症を起こすおそれがあるので、十分な観察を行うなど尿路感染及び性器感染の発症に注意し、発症した場合には適切な処置を行うとともに、状態に応じて休薬等を考慮すること。 (8)本剤の利尿作用により多尿・頻尿がみられることがある。また、体液量が減少することがあるので、適度な水分補給を行うよう指導し、観察を十分に行うこと。脱水、血圧低下等の異常が認められた場合は、休薬や補液等の適切な処置を行うこと。体液量減少を起こしやすい患者(高齢者や利尿剤併用患者等)においては、脱水や糖尿病性ケトアシドーシス、高浸透圧高血糖症候群、脳梗塞を含む血栓・塞栓症等の発現に注意すること。[「**3.相互作用**」及び「**5.高齢者への投与**」の項参照] (9)本剤の作用機序により、血糖コントロールが良好であっても尿中ケトン体陽性又は血中ケトン体増加がみられることがある。患者の症状、血糖値等の臨床検査を確認し、インスリンの作用不足によるケトン体増加と区別して糖尿病の状態を総合的に判断すること。 (10)インスリン分泌能が低下している患者では、糖尿病性ケトアシドーシスの発現に注意すること。 (11)排尿困難、無尿、乏尿あるいは尿閉の症状を呈する患者においては、その治療を優先するとともに他剤での治療を考慮すること。 (12)本剤投与による体重減少が報告されているため、過度の体重減少に注意すること。 (13)本剤とインスリン製剤、GLP-1受容体作動薬との併用における有効性及び安全性は検討されていない。 (14)低血糖症状を起こすことがあるので、高所作業、自動車の運転等に従事している患者に投与するときは注意すること。

3.相互作用
本薬は主としてCYP2C18、CYP4A11、CYP4F3B及びアルコール脱水素酵素等により代謝される。[**【薬物動態】**の項参照]
併用注意(併用に注意すること) 薬剤名等 糖尿病用薬:スルホニルウレア剤、速効型インスリン分泌促進薬、α-グルコシダーゼ阻害剤、ビグアナイド系薬剤、チアゾリジン系薬剤、DPP-4阻害薬、インスリン製剤、GLP-1受容体作動薬等 血糖降下作用を増強する薬剤:β-遮断薬、サリチル酸剤、モノアミン酸化酵素阻害剤、フィブラート系薬剤等 血糖降下作用を減弱する薬剤:副腎皮質ホルモン、甲状腺ホルモン等 利尿作用を有する薬剤:ループ利尿剤、チアジド系利尿剤等 プロベネシド

4.副作用
臨床試験において、1,060例中397例(37.5%)に副作用が認められた。主な副作用は血中ケトン体増加117例(11.0%)、口渇80例(7.5%)、頻尿80例(7.5%)等であった。(承認時)
(1)重大な副作用
低血糖:他の糖尿病用薬(特にスルホニルウレア剤(14.7%))との併用で低血糖(初期症状:脱力感、高度の空腹感、発汗等)があらわれることがある。また、他の糖尿病用薬と併用しない場合も低血糖(3.3%)が報告されている。低血糖症状が認められた場合には、糖質を含む食品を摂取させるなど適切な処置を行うこと。ただし、α-グルコシダーゼ阻害剤との併用により低血糖症状が認められた場合にはブドウ糖を投与すること。[「**1.慎重投与**」、「**2.重要な基本的注意**」、「**3.相互作用**」及び**【臨床成績】**の項参照]

本剤は新医薬品であるため、厚生労働省告示第97号(平成20年3月19日付、平成18年厚生労働省告示第107号 一部改正)に基づき、平成27年5月末まで1回14日分を限度として投薬すること。

2014年5月(第1版)の添付文書より

★添付文書の改訂に十分ご留意ください。
★その他の使用上の注意は添付文書をご参照ください。
★資料は当社医薬情報担当者にご請求ください。

新発売

選択的SGLT2阻害剤－2型糖尿病治療剤－

薬価基準収載

アプルウェイ®錠20mg

処方せん医薬品 (注意－医師等の処方せんにより使用すること)

Apleway

トホグリフロジン水和物錠

詳しくは製品情報サイトをご覧ください。e-MR

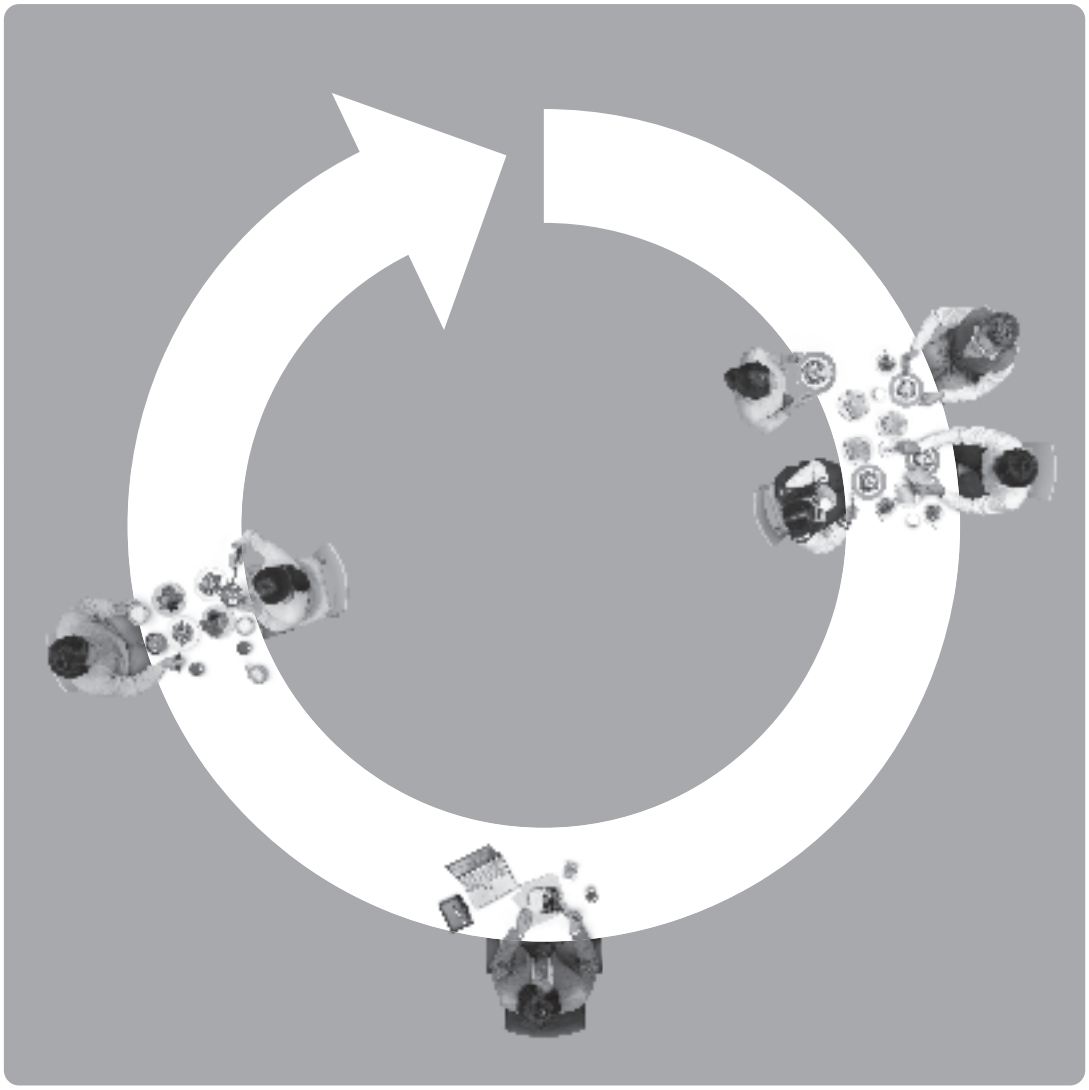
e-MR 検索

2014年5月作成 JP.TOF.14.04.52 (APW1032B)

製造販売:サノフィ株式会社
〒163-1488
東京都新宿区西新宿三丁目20番2号

SANOFI DIABETES

Going beyond together



Selective DPP-4 inhibitor -Type 2 Antidiabetic agent- Listed on the NHI drug price list

TENELIA® Tablets 20mg

(Teneligliptin Hydrobromide Hydrate)

Prescription drug (Caution-Use only pursuant to the prescription of a physician,etc.)

Please refer to the package insert about details of indications and usage, dosage and administration, precautions including contraindications.

Manufactured & Marketed by
Mitsubishi Tanabe Pharma Corporation
2-6-18, Kitahama, Chuo-ku, Osaka 541-8505, Japan

Marketed by
DAIICHI SANKYO CO., LTD.
3-5-1, Nihonbashi-honcho, Chuo-ku, Tokyo 103-8426, Japan

2013年9月作成

血清脂質を良好にコントロール
1日1回のリピディル錠が key

【禁忌】(次の患者には投与しないこと)
(1)本剤の成分に対して過敏症の既往歴のある患者　(2)肝障害のある患者　(3)中等度以上の腎機能障害のある患者(目安として血清クレアチニン値が2.5mg/dL以上)　(4)胆のう疾患のある患者　(5)妊婦又は妊娠している可能性のある女性、授乳婦

【原則禁忌】(次の患者には投与しないことを原則とするが、特に必要とする場合には慎重に投与すること)
腎機能に関する臨床検査値に異常が認められる患者に、本剤とHMG-CoA還元酵素阻害薬を併用する場合には、治療上やむを得ないと判断される場合にのみ併用すること。

【効能・効果】　高脂血症(家族性を含む)

〈効能・効果に関連する使用上の注意〉
1)総コレステロールのみが高い高脂血症(Ⅱa型)に対し、第一選択薬とはしないこと。
2)カイロミクロンが高い高脂血症(Ⅰ型)に対する効果は検討されていない。

【用法・用量】

通常、成人にはフェノフィブラートとして1日1回106.6mg～160mgを食後経口投与する。なお、年齢、症状により適宜減量する。1日160mgを超える用量は投与しないこと。

〈用法・用量に関連する使用上の注意〉
1)総コレステロール及びトリグリセライドの両方が高い高脂血症(Ⅱb及びⅢ型)には、1日投与量を106.6mgより開始すること。なお、これらの高脂血症患者において、高血圧、喫煙等の虚血性心疾患のリスクファクターを有し、より高い治療目標値を設定する必要のある場合には1日投与量を159.9mg～160mg[注]とすること。　注)159.9mgは53.3mg錠を3錠、160mgは80mg錠を2錠用いる。
2)トリグリセライドのみが高い高脂血症(Ⅳ及びⅤ型)には、1日投与量53.3mgにおいても低下効果が認められているので、1日投与量を53.3mgより開始すること。
3)肝機能検査に異常のある患者又は肝障害の既往歴のある患者には、1日投与量を53.3mgより開始すること(「慎重投与」の項参照)。　4)**急激な腎機能の悪化を伴う横紋筋融解症**(「副作用(1)重大な副作用」の項参照)があらわれることがあるので、投与にあたっては患者の腎機能を検査し、血清クレアチニン値が2.5mg/dL以上の場合には投与を中止し、血清クレアチニン値が1.5mg/dL以上2.5mg/dL未満の場合は53.3mgから投与を開始するか、投与間隔を延長して使用すること。　5)本剤はフェノフィブラートの吸収を高めるため、固体分散体化した製剤であり、本剤106.6mg(53.3mg製剤2錠)は微粉化フェノフィブラートカプセル製剤134mgと、また本剤160mg(80mg製剤2錠)は微粉化フェノフィブラートカプセル製剤200mgと生物学的に同等である(【薬物動態】の項参照)。

【使用上の注意】　―― 抜粋 ――

1.慎重投与(次の患者には慎重に投与すること)
(1)肝機能検査に異常のある患者又は肝障害の既往歴のある患者　(2)軽度な腎機能障害のある患者(目安として血清クレアチニン値が1.5mg/dL以上2.5mg/dL未満)　(3)胆石の既往歴のある患者　(4)抗凝血剤を投与中の患者　(5)HMG-CoA還元酵素阻害薬(プラバスタチンナトリウム、シンバスタチン、フルバスタチンナトリウム等)を投与中の患者　(6)高齢者

2.重要な基本的注意
(1)本剤の適用にあたっては、次の点に十分留意すること。1)適用の前に十分な検査を実施し、**高脂血症の診断が確立した患者**に対してのみ本剤の適用を考慮すること。2)あらかじめ高脂血症の基本である**食事療法**を行い、更に**運動療法**や、高血圧、喫煙等の虚血性心疾患のリスクファクターの軽減等も十分に考慮すること。3)投与中は**血清脂質値を定期的に検査**し、本剤の効果が認められない場合には漫然と投与せず、中止すること。
(2)本剤は肝機能及び肝機能検査値に影響を及ぼすので、使用にあたっては次の点に十分留意すること。1)肝障害を悪化させることがあるので、肝障害のある患者には投与しないこと(「禁忌」の項参照)。2)肝機能検査値の異常変動があらわれるおそれがあるので、肝機能検査に異常のある患者又は肝障害の既往歴のある患者には慎重に投与すること(「慎重投与」の項参照)。3)AST(GOT)、ALT(GPT)、γ-GTP、LDH、ALPの上昇、黄疸、並びに肝炎があらわれることがあるので、**肝機能検査は投与開始3カ月後までは毎月**、その後は3カ月ごとに行うこと。異常が認められた場合には、減量又は中止等の適切な処置を講ずるとともに、少なくとも1カ月以内に肝機能検査を実施すること。なお、AST(GOT)又はALT(GPT)が継続して正常上限の2.5倍あるいは100単位を超えた場合には投与を中止すること。

3.相互作用
(1)[原則併用禁忌](原則として併用しないこと)
腎機能に関する臨床検査値に異常が認められる患者では原則として併用しないこととするが、治療上やむを得ないと判断される場合にのみ慎重に併用すること。 薬剤名等:HMG-CoA還元酵素阻害薬(プラバスタチンナトリウム、シンバスタチン、フルバスタチンナトリウム等)　(2)[**併用注意**](併用に注意すること)薬剤名等:**抗凝血剤**(ワルファリン)／HMG-CoA還元酵素阻害薬(プラバスタチンナトリウム、シンバスタチン、フルバスタチンナトリウム等)／**スルホニル尿素系血糖降下薬**(グリベンクラミド、グリメピリド等)／**陰イオン交換樹脂剤**(コレスチラミン)／**シクロスポリン**

4.副作用
フェノフィブラートカプセル製剤の承認時の臨床試験及び市販後の使用成績調査4,687例中623例(13.29%)に副作用が認められた。主な副作用はAST(GOT)上昇、ALT(GPT)上昇等の肝機能検査値異常、胃部不快感、嘔気等の胃腸障害、発疹、そう痒感等の皮膚及び皮下組織障害、CK(CPK)上昇等であった。
フェノフィブラートカプセル製剤の承認時:臨床試験1,256例中70例(5.57%)に副作用が認められた。主な副作用は、胃部不快感、嘔気等の消化器症状が36例(2.87%)、発疹等の皮膚症状が24例(1.91%)、黄疸1例(0.08%)、筋症状1例(0.08%)であった。臨床検査値異常は442例(35.19%)に認められた。主なものは、AST(GOT)上昇239件、ALT(GPT)上昇251件、γ-GTP上昇218件等の肝機能検査値異常318例(25.32%)、CK(CPK)上昇95例(8.48%)、BUN上昇44件、クレアチニン上昇38件等の腎機能検査値異常63例(5.02%)、好酸球の増加20例(2.04%)、赤血球数等の減少17例(1.48%)であった。
フェノフィブラートカプセル製剤の再審査終了時: 使用成績調査3,431例中553例(16.12%)に副作用が認められた。主な副作用は、AST(GOT)上昇119件(3.47%)、γ-GTP上昇118件(3.44%)、ALT(GPT)上昇115件(3.35%)等の肝機能検査値異常364例(10.61%)、肝機能異常21件(0.61%)、肝障害16件(0.47%)等の肝胆道系障害40例(1.17%)、血中クレアチニン増加34件(0.99%)、BUN上昇32件(0.93%)等の腎機能検査値異常52例(1.52%)、CK(CPK)上昇49例(1.43%)、胃部不快感15件(0.44%)、嘔気11件(0.32%)等の胃腸障害39例(1.14%)等であった。
(1)重大な副作用
1)**横紋筋融解症**(0.1%未満)　2)**肝障害**(0.1～5%未満)　3)**膵炎**(頻度不明)

●その他の使用上の注意等の詳細は、製品添付文書をご参照ください。

高脂血症治療剤　**薬価基準収載**

処方せん医薬品　注意－医師等の処方せんにより使用すること

リピディル®錠 53.3mg 80mg

(フェノフィブラート錠)　**LIPIDIL® Tab.**

発売元　科研製薬株式会社
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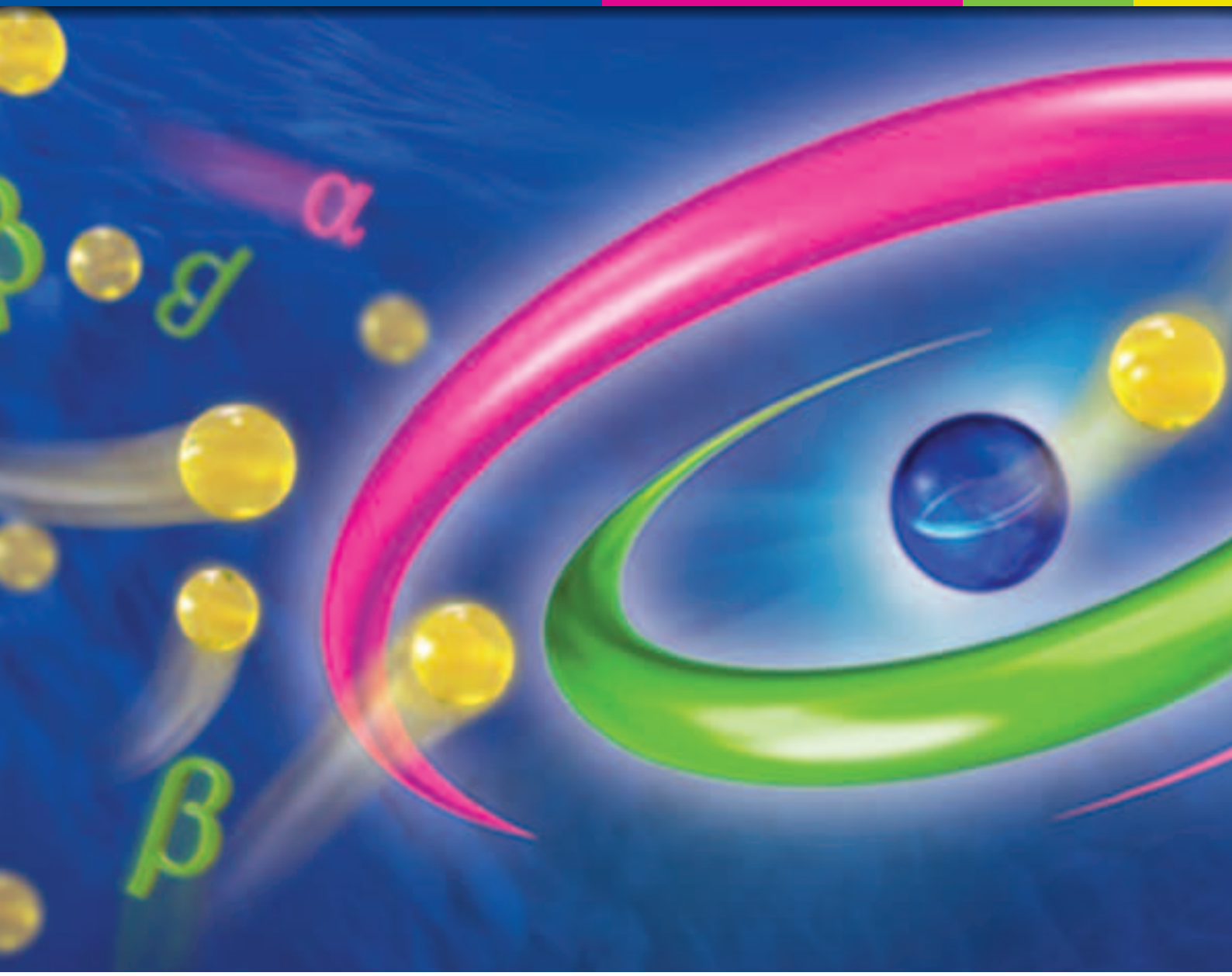
提携　Laboratoires FOURNIER S.A.(France)

(2014年8月作成)　LPD02AP

リピディル製品情報サイト　http://lipidil.jp/



Selective DPP-4 inhibitor/for type 2 diabetes mellitus (Listed on the NHI drug price list)

Januvia® Tablets 12.5mg 25mg 50mg 100mg

[Sitagliptin Phosphate Hydrate Tablets]

Prescription drug: note-use only pursuant to the prescription of a physician, etc.
Please refer to the package insert for CONTRAINDICATIONS, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION and PRECAUTIONS.

MSD

MSD K.K.
Kitanomaru Square, 1-13-12 Kudan-kita, Chiyoda-ku,
Tokyo 102-8667 JAPAN http://www.msd.co.jp/

2013年12月作成
JAN13AD428-1218

Better Health, Brighter Future

There is more that we can do to help improve people's lives. Driven by passion to realize this goal, Takeda has been providing society with innovative medicines since our foundation in 1781.

Today, we tackle diverse healthcare issues around the world, from prevention to care and cure, but our ambition remains the same: to find new solutions that make a positive difference, and deliver better medicines that help as many people as we can, as soon as we can.

With our breadth of expertise and our collective wisdom and experience, Takeda will always be committed to improving the future of healthcare.


Today Astellas is working to meet unmet medical needs.
All around the world there are diseases
for which no medicine has been developed.
Such unmet medical needs are the battleground of Astellas.
Our mission is to change tomorrow
for millions of lives, one drug at a time.
Changing tomorrow
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