MSDA 2006

Metabolic Syndrome, type II Diabetes and Atherosclerosis congress

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The 3rd Congress MSDA (Metabolic Syndrome, Type II Diabetes and Atherosclerosis) was held in Marrakesh from May 24th to 28th, 2006. This congress was organized by the "International Task force for Prevention of Coronary Disease", the "Moroccan Association of Atherosclerosis", the "Foundation Heart and Arteries" (France), placed under the aegis of the "Association of French Language for the Study of the Diabetes and the Metabolic Diseases", the "International Atherosclerosis Society", "The New French Association of Atherosclerosis" and supported by the laboratories Sanofi-Aventis, AstraZenecca, Bayer Pharma, Fournier (member of the Group Solvay), Kowa, Merck, Bayer HealthCare Pharmaceuticals, and Boehringer Ingelheim. This 3rd MSDA congress made it possible to give a progress report on the physiopathology of the metabolic syndrome, its criteria of diagnosis, strategies intended to prevent it and to treat it, like on the last pharmacological tests of prevention of the cardiovascular risk using the statins and the fibrates. Moreover, data of recent fundamental research relating to the metabolism of the lipids and glucose were presented.

Metabolic syndrome:
From epidemiology towards prevention and treatment

1 - Definition and criteria of diagnosis of the metabolic syndrome - "Guidelines":

The diagnosis of metabolic syndrome is based on the identification of biological abnormalities (overweight, high blood pressure, low HDL-cholesterol, hypertriglyceridemia, high fasting glucose level). Pr. Zimmet (Australia) recalled that intra-abdominal obesity was a major element

of diagnosis and that the new consensus of the “International Diabetes Federation” (IDF) had established these criteria of diagnosis. According to the IDF, central obesity corresponds to a waist measurement >94 cm (male) and >80 cm (female). Nevertheless, it appears that the thresholds defining abdominal obesity are not identical from an ethnic group to another. Pr. Sadikot (India) showed starting from PODIS (Prevalence off Diabetes in India Study) that the use of BMI or of waist measurement intended to establish the overweight and abdominal obesity according to criteria's of the World Health Organization or of ATP-III underestimated the risk of metabolic syndrome in the rural and urban indian populations. The criteria of the IDF make it possible to establish a better adequacy between the evaluation of the risk of metabolic syndrome and the results of PODIS, but do not take into account the anthropometric differences highlighted between the rural and urban populations of India. The criteria of IDF of the waist measurement applied about type 2 diabetics and subjects with impaired glucose tolerance of PODIS over-estimate the metabolic risk in the urban populations and underestimate it in the rural populations, perpetuating the inaccurate concept that the risk of diabetes is weak in the Indian rural populations. This error results in being unaware of the importance of the risk of diabetes in the indian rural populations by the “National Diabetes Program Prevention”.

The japanese “Guidelines” allowing to establish the diagnosis of the metabolic syndrome were introduced by Pr. Matsuzawa (Japan). According to the study of the “National Labor Ministry”, the japanese workers presenting 3 of the biological criteria defining the metabolic syndrome have a 38,8 fold increased in cardiovascular risk in comparison with those having no biological criteria of metabolic syndrome. In addition, Pr. Matsuzawa indicated that the japanese population was more sensitive than the western populations to the effects of statins allowing to divide the doses of these drugs by two in the japanese population.

2-Epidemiology of obesity:

The prevalence of obesity in children increases in the whole world, according to WHO 10% of the children are in overweight or obese and 16% of the children and the teenagers of the USA are obese (Pr. Delisle, Canada). Countries of the Middle-East, from Latin America and North Africa, as well as the Asian cities and of Sub-Saharian Africa have a high prevalence of chilhood obesity. The loss of the traditional mode of nutrition to the profit of Western dietetics involves an over nutrition, who while interfering in certain countries with one early period of malnutrition induced

the increase in obesity in children. It is of primary importance to develop interventions in educational circle, in the families and the social environments to promote a way of life and a food adapted to human physiology in order to stop the progression of obesity in children and teenagers (Pr. Delisle, Canada).

3- The causes of the metabolic syndrome and obesity:

- Genetic and epigenetic causes:

The recruitment of important cohorts of subjects will make it possible to establish the genetic factors supporting the development of the metabolic syndrome which in addition increases the cardiovascular risk. Pr. Scott (U.K.) has described the "LOLIPOP" cohort (London Life Sciences Futurology Study) which incorporates Londoners of north-European and south-Asian origin and which is intended to establish the genetic factors of risk by employing the genomic, the proteomic and the metabonomic technology. Polymorphisms of different genes have already been identified to alter the metabolism of glucose and lipids. Pr. Froguel (France) reported that one SNP variant of the adiponectin gene promoter (- 11391G/A) increased by 1,6 fold the risk to develop type 2 diabetes. In the same way another SNP variant of the adiponectin gene (- 11377C/G) increases the serum concentration of this protein and predisposes to obesity while decreasing the risk of type 2 diabetes in female. Pr. Junien (France) exposed the role of the epigenetic programming during the first phases of the fetal life in the development of obesity and of the metabolic syndrome. Placental disorders as well as an unsuited maternal nutrition are involved in the development of the metabolic syndrome. The epigenetic transmission of the metabolic syndrome from generation to generation could be possible. Results of fundamental research which are in progress to identify if the epigenetic modifications are unstable or not and could be transmit from a generation to another have been presented.

- Food causes:

Pr. Ailhaud (France) showed that the excess of omega 6 fatty acids (Acid linoleic) with the costs of omega 3 fatty acids (Acid linoleic) in the mother's milk and the humanized cow's milk was partly responsible for the development of obesity in children.

- Environmental causes: sedentarity lifestyle

According to Pr. Tremblay (Canada), if the deficit of physical activity takes part in the epidemic development of obesity by unbalancing energy balance by a reduction in the number of burned

calories, the evolution of the nature of employment to the profit of “intellectual” jobs and thus to the costs of “physical” jobs worsen this energy imbalance beyond the simple reduction in calorie burning related to the loss of physical activity. Indeed, "intellectual" jobs induce alteration in neurological and endocrine functions (reduction in the time of sleep…) who disturb the metabolism of glucose and increases the appetite and the consumption of food and calories which will not be burned because the daily physical activity is reduced.

4-Prevention of the metabolic syndrome and obesity:

Pr. Horton (the USA) showed starting from the results of the “Diabetes Program Prevention” that modifications of the lifestyle alone or in partnership with drugs (metformine) allowed to decrease the development of the metabolic syndrome among high-risk patients and to reduce the cardiovascular risk in subjects with a metabolic syndrome or type 2 diabetes. The association of the increase in the physical activity and the loss of weight constitute the cornerstone of the prevention and of the treatment of the patients being likely to develop a metabolic syndrome, or having already developed it (Pr. Horton, The USA). A daily physical activity of approximately 30 minutes inducing a heating consumption of approximately 1000 Kcal/week decreases the cardiovascular risk and also improves the muscular and skeletal system (Pr. Farino, Italy), suggesting that the national programmes of prevention of the cardiovascular risk should include the improvement of the way of life like a top priority.

According to Pr. Holman (U.K.), 71% of the patients with type 2 diabetes which had been recruited in the “United Kingdom Prospective Diabetes Study” (UKPDS) presented a metabolic syndrome but this percentage decreased to 60% after 3 months of a diet which reduced by 5% the body weight.

In France, the “French Agency of Medical Safety of Food” (AFSSA) worked out several recommendations aiming at reducing the prevalence of obesity in children. Pr. Turck (France) indicated that the AFFSA had advised with the Ministry for Health to remove the morning collation given in schools. This collation had as a role to bring a food intake to children not having profited from a breakfast at home. The recommendation of the suppression of this collation was justified by the fact that it was not licit in term of public health to bring an excess of calories to 90% of the children who had profited from an adequate breakfast at home.

The Ministry for Health endorsed the suppression of this morning school collation in September

2004. The new law of September 2005 removed in the schools the distribution by food automats of "fun food" (Fatty, sweetened, salted etc) as well as sweetened drinks. Certain schools followed the recommendations of the AFSSA aiming at installing cooled water fountains. The AFSSA recommended the suppression of TV publicities for food intended for the children. To date the French government did not make a decision on this subject.

5-Treatment of the biological disorders of the metabolic syndrome:

5-1: Obesity:

- Therapeutic strategies:

At the teenagers, obesity obeys to specific pathological determinants which are related on the hormonal modifications of puberty and on the stressing of the sexual differentiation in relationship also to new social behaviours (Pr. Frelut, France). Moderate obesity is generally dependent on an increase in sedentarity and a reduction in the number of the meals taken "at home" facilitating the consumption of high quantity of fatty and sweetened food. The consumption of fatty and sweetened food is promoted by the publicities specifically intended for the teenagers. When the overload is modest, to discuss these behaviours with the teenagers generally makes it possible to channel them in a favourable direction. On the other hand, the therapeutic strategy of severe obesity is very complex because multiple factors can interfere (genes, hormones, psychological and/or psychiatric disorders (depression, psychosis, food behavioural problems), metabolic disorders (insulin-resistance, diabetes), cardio-respiratory diseases, etc). Patients can be treated in specialized units in or one multi-specialized centre, with in case of morbid obesity the necessity to be hospitalized. The forecast of severe obesity is poor. An effective, early and prolonged prevention policy is essential.

- Drugs:

Acid arachidonic derivatives (amandamide etc) constitute the endocannabinoid system in the nervous central system and various organs. Endocannabinoids bind on receptors: CB1 receptor (Central Nervous system, adipocytes, liver, muscles, cells alpha and beta of the pancreas) and CB2 receptor (Immune system). The over activity of the endocannabinoid system in overweight or obese subjects would take part in the pathological mechanisms of obesity and its clinical consequences (Pr. Maldonado, Spain). Pr. Després (Canada) brought back the favourable effects of the inhibition of CB-1 receptors by rimonabant on the weight loss in patients with abdominal

obesity like on the markers of the cardiovascular risk in these patients (HDL-cholesterol, small, dense LDL, insulinemia, glycemia, usCRP).

6- Dyslipidemias in the metabolic syndrome and in the cardiovascular risk:

6-1- The different types of dyslipidemia:

Pr. Davignon (Montreal) showed that the installation of combined family hyperlipidemia could preceded the development by the metabolic syndrome and that this syndrome would be a late complication of the combined family hyperlipidemia.

According to the Pr. Bruckert (Paris), the prevalence of low-HDL-cholesterol is 40% in the women and 33% in the men in a cohort of dyslipidemic patients recruited in 11 European countries.

6-2- Biological diagnosis of dyslipidemias:

Overweight, decrease in insulin sensitivity and type 2 diabetes cause triglyceride increase and HDL-cholesterol decrease, without significant increase in LDL-cholesterol. On the other hand LDL are small and dense and their number are increased in the serum, resulting in an increase in the apo B concentration, because there is one molecule of apo B by LDL particle. Small, dense LDL are more atherogenic than large LDL. Pr. Hayden (Canada) reported that in the general population apo B level is equivalent to that of LDL-cholesterol level to predict the cardiovascular risk. On the other hand, the apo B predictive capacity is more important than that of LDL-cholesterol to evaluate the cardiovascular risk in patients treated with statins, like that of the patients with metabolic syndrome or type 2 diabetes.

6-3- Pharmacological treatments of the cardiovascular risk and of dyslipidemias targeting LDL-cholesterol with statins:

The recent results of the “SPARCL” study have reported that the risk to develop a second stroke decreased by 16% when patients were treated with a high dose of statin (Atorvastatin, 80 mg/d) (Pr. Amarenco, France). Pr. Carmena (Spain) and Pr. Fruchart (France) have shown (TNT (CHD patients)) that patients with a metabolic syndrome, type 2 diabetes or free of these pathologies had drawn a more important benefit from an aggressive treatment by a high dose of statin (Atorvastatin 80 mg/d) in term of secondary prevention of coronary heart disease that those

treated by the conventional dose (10 mg/d). The decrease of the relative risk between the 2 groups of patients to present a new coronary event was 29% when the metabolic syndrome was not associated with type 2 diabetes and 35% in the contrary case. This study also showed that the aggressive treatment by atorvastatin (80 mg/d) decreased the relative risk of stroke by 25% in secondary prevention of the coronary risk in subjects with a metabolic syndrome, in comparison with the conventional treatment (10 mg/d). On the whole, a reduction in LDL-cholesterol to less than 0,70 g/L by statin decreased at the same time the coronary (- 29%) and the cerebro-vascular risks (-25%) in secondary prevention of the coronary risk in patients with the metabolic syndrome compared to those whose LDL-cholesterol was brought to 1,0 g/L .

It has been reminded that to begin an aggressive treatment by a statin in the early phase of a myocardial infarction (MIRACL, PROVIT, With to Z) decreases the risk to develop a second myocardial infarction (Pr. Lablanche, France) and it has been shown that this treatment was beneficial in both diabetic and non diabetic patients (In PROVIT the relative risk decreased by 28,8% in these two groups of patients). Pr. Betteridge (the U.K.) recalled that the guidelines relating to the reduction of the cardiovascular risk reflected the results of CARDS and HPS studies. These studies have suggested that the diabetics of more than 40 years were to be treated by a statin if their total cholesterol levels were higher than 3.5 mmol/L, independently of their LDL-cholesterol concentrations before starting treatment.

Pr. Fruchart (France) reported that a decrease in LDL-cholesterol to 0.61 g/L (- 53.2%) by rosuvastatine (ASTEROID) decreased by approximately 50% the surface of atheroma of coronary stenosis extending over 40 mm length and reducing of more than 20% but of less than 50% the coronary lumina (5.81 mm2 at the end of the treatment versus 10.16 mm2 before treatment).

The therapeutic goals in term of LDL-cholesterol are achieved only in 50% of the patients treated with statins. Pr. Shepherd (Scotland) pointed out the interest to associate an inhibitor of the intestinal absorption of cholesterol (Ezetimibe) with statins in order to achieve therapeutic goals while decreasing in certain cases the doses of statins.

A new statin (Pitavastatin) at the dose of 2 mg/d decreased the LDL-cholesterol by 45% without modifying HDL-cholesterol, nor apo AI, nor pre-beta-lipoproteins, but by causing a reduction in the LCAT activity and a non significant increase in HDL2-cholesterol. Just like atorvastatin, pitavastatin increased the expression of some genes involved in the reverse cholesterol transport

(PPAR-alpha, LXR, SRB-I) in macrophage, but decreased the expression of ABCA1 (HDL-receptor) (Pr. Tada, Japan).

6-4- Pharmacological treatments of the cardiovascular risk and of dyslipidemias not targeting specifically LDL-cholesterol:

In a whole, clinical trials indicate that the use of statins decreases the absolute cardiovascular risk by 15% in primary and secondary prevention (mixed diabetics and non diabetic patients) of the cardiovascular risk. In fact, 85% of the absolute persist, suggesting that LDL-cholesterol should not be any more the only lipoprotein target in case of dyslipoproteinemia. Being given the capacity of HDL to reduce the cardiovascular risk in epidemiological studies, pharmacological treatment should also have for objective to increase HDL-cholesterol (Pr. Chapman, France). Pr. Brown (USA) has shown that when HDL-cholesterol was increased by niacine (in the presene or not of fibrate) , while LDL-cholesterol was decreased in a suitable way, the cardiovascular risk was decreased by 60-70%, whereas in mono-therapy statins decreased it only by 25-30%. The injection of delipidated HDL in patients induced a regression of coronary atherosclerosis (Pr. Brewer, USA).

-Fibrates

The goal of FIELD was to study the capacity of fenofibrate to reduce the cardiovascular risk in type 2 diabetic patients. The number of coronary events (death of coronary origin + nonfatal myocardial infarction) did not fall to a significant degree (RR:-11%) (Pr. Scott, Australia). The number of nonfatal infarction decreased (RR significantly: -24%), as well as the number of revascularisation (RR:-21%) but the number of cardiovascular death increased, in a non significant way, in the treated group. Microangiopathies were reduced in the fenofibrate treated group. The number of cancers was not significantly different between the two groups, on the other hand the number of major venous thrombosis and of pancreatitis was slightly increased in the fenofibrate treated group. This study brings the following informations (Pr. Zambon, Italy): 1- In type 2 diabetic patients statins are to be prescribed in first intention to reduce the cardiovascular risk. The association of fenofibrate to a statin can bring an additional benefit (reduction in the microangiopathies and in arteritis), 2- It is the first study showing that one hypolipidemic drug reduced at the same time the number of macrovascular and of microvascular

events, 3- Fenofibrate alone or associated with statins is well tolerated and does not involve adverse effects, 4- Fenofibrate represents a therapeutic option intended to reduce the number of the cardiovascular events and the progression of retinopathies and of arteritis, in the early phase of type 2 diabetes in patients free of cardiovascular antecedent, with a good control of the glycemia and when HDL-cholesterol is decreased and triglycerides moderately increased, without increase in LDL-cholesterol.

7- High blood pressure:

High blood pressure is one of the major cardiovascular risk factors and is frequently present in the metabolic syndrome. The role of the renin angiotensin aldosterone system is essential in the development of high blood pressure in the metabolic syndrome (Pr. Valensi, France; Pr. Henry, France), in particular that of angiotensin 2. Recent meta-analyzes have shown that the treatment of arterial hypertension by angiotensin converting enzyme (ACE) inhibitors or angiotensin 2 receptor antagonists (ARA2) decreased the risk to develop type 2 diabetes by 25% (Pr. Vergés, France). In type 2 diabetic patients with albuminuria and renal insufficiency ARA2 decrease proteinuria and induce a nephroprotection (Pr. Halimi, France). Some ARA2 are PPAR-gamma activators, as the anti-diabetic drugs of the glitazone's family. Recent clinical studies indicate that these specific ARA2 could in that way reduce the number of type 2 diabetes and that they could induce nephroprotection in patients (Pr. Halimi, France). Arterial hypertension and type 2 diabetes could be a common target of telmisartan (Pr. Vaisse, France).

8- Inflammation:

The role of inflammation in the physiopathology of the metabolic syndrome and of atherosclerosis has been exposed by Pr. Libby (USA). Abdominal obesity is responsible for an inflammatory state related to the release of cytokines by adipocytes. These cytokines stimulate the production of CRP and fibrinogen by the liver. Adipocytes also release an inhibitor of the fibrinolysis (PAI-1). On the whole haemostatic balance is moved in the pro-thrombotic pathway in patients with atherosclerosis (Pr. Libby, The USA). Statins and the fibrates decrease the vascular inflamation. Pr. Staels (France) reported that PPARalpha (The nuclear receptor activated by fibrates) is implies in the anti-inflammatory effects of simvastatin in the mouse (Reduction in iNOS and IL-6 expression in macrophages). PPARalpha activators increase the concentrations of

thioredoxine in cells whereas PPARgamma activtors decreases it. Thioredoxine modifies the secretion of cytokines by the macrophages, as well as apoptosis (Pr. Rouis, France).
The dosage of inflammatory markers in plasma could help to evaluate the cardiovascular risk. Nevertheless, the clinical interpretation of the dosage of inflammatory markers is complex. Pr. Koenig (Germany) has reported that CRP plasma levels are increased in men but not in women with cardiovascular disease. On the other hand, CRP plasma levels are increased in women but not in men with type 2 diabetes. These differences between the sexes are not explained. IL-6 plasma levels are increased in both men and women with cardiovascular disease. IL-18 plasma levels are not increased in patients with cardiovascular disease but are increased in patients with type 2 diabetes.

Carbohydrate and lipid metabolism: Fundamental research

Pr. Assman (Germany) pointed out the part played by HDL in the reduction in the cardiovascular risk and described the molecular effects of HDL on cells with mechanisms by which the HDL acted on the cells while insisting on the activation of AKT. ABCA1 and ABGC1 HDL receptors are involved in cellular cholesterol efflux. Pre-beta HDL (nascent HDL = phospholipid poor HDL (apoA-I)) bind to ABCA1 to capture cellular free cholesterol, whereas mature HDL bind to ABCG1 to capture this cholesterol (Pr. Von Eckardstein, Switzerland).
The decrease in insulin sensitivity and the metabolic syndrome are associated with a low HDL-cholesterol plasma level. Recent data fom the research on ABCA1 make it possible to establish a link between HDL metabolism and insulin insensitivity. A decrease in ABCA1 expression induces a decrease in HDL-cholesterol plasma level (Total deficit = Tangier disease) and conversely. In addition, a low HDL-cholesterol plasma level is associated with an alteration in beta-cell function in pancreas (Pr. Assman, Germany). It has been recently discovered that ABCA1 controlled glycemia and insulin-secretion homeostasis. This mechanism could take part in the anti-diabetic properties of rosiglitazone, because this drug increases the expression of ABCA1 in the pancreatic beta-cells. Drugs increasing specifically the expression of ABCA1 could improve beta-cell function in type 2 diabetes, independently of their effects on HDL-cholesterol. The research of molecules specifically capable to increase ABCA1 expression could

also correspond to an effective strategy to discover drugs capable to increase HDL-cholesterol (Hayden, The USA).

Pr. Van Tol (Nedherland) has reported the effects of the atorvastatin (10 and 80 mg/d) in hypertriglyceridemic (1,5 - 6,0 mmol/L) type 2 diabetic patients (DALI study). Atorvastatin decreased triglyceride, apo AV, apo C-III and apo E plasma levels. Before starting the treatment triglyceridemia was mainly determined by apo C-III concentrations and secondarly by apo A-V concentrations. After treatment, triglyceride plasma levels were always primarily correlated with apo C-III concentrations but partly only to those of apo A-V. The study of genetic polymorphisms of apo A-V suggested that the plasma concentrations of this protein would be correlated with different gene polymorphisms. Apo A-V concentrations are very low in plasma (168 ng/ml) and there is only one molecule of apo A-V for 100 VLDL particles and 7000 HDL particles, consequently apo A-V would not control the metabolism of triglycerides in the seric compartment; on the other hand apo A-V could act by controlling the secretion VLDL particles by hepatocytes. Apo A-V would have only one slight impact in the development of hypertriglyceridemia in type 2 diabete.

Conclusion

The different conferences of the 3rd MSDA Congress have confirmed the importance of the extension of the epidemic of obesity and of metabolic syndrome. The clinical criteria to diagnose the metabolic syndrome become increasingly rigorous and different according to populations' concerning abdominal obesity. The role of the environment (nutrition, sedentarity, types of occupation etc) is essential in the progression of obesity and of the metabolic syndrome, but the research undertaken in genetics confirms the genetic existence of polymorphism supporting the clinical expression of an inadequate way of life. The environment could moreover exert one noxious effect by supporting a transmission from one generation to another one of obesity and metabolic syndrome (epigenetic).

The lecturers agree to express the absolute need for implementing programmes of prevention of obesity and diabetes.

Statins have confirmed their effectiveness in the prevention of the cardiovascular risk in type 2 diabetes and now have shown their interest in the prevention of stroke. New drugs increasing HDL-cholesterol could reduce the cardiovascular risk.