

MANAGEMENT OF THE METABOLIC SYNDROME

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Summary

The metabolic syndrome consists of a constellation of factors that raise the risk for cardiovascular diseases and type 2 diabetes. Although therapeutic lifestyle modification is the first-line therapy for the metabolic syndrome and thus deserves initial attention, drug therapy may be necessary in many patients to achieve recommended goals regarding lipid profile, blood pressure and blood glucose control. The growing prevalence and high-risk nature of the metabolic syndrome highlights the need to identify individuals with this condition and to treat them with an aggressive multitargeted approach.

Introduction

In 1988, Reaven introduced the term syndrome X, with insulin resistance as a common denominator for a syndrome in which a clustering of atherosclerotic risk factors is present (1). Several other synonyms have been attached to this constellation of risk factors : deadly quartet, insulin resistance syndrome, metabolic syndrome, plurimetabolic syndrome, dysmetabolic syndrome, cardiometabolic syndrome, etc. (2,3,4). Such a syndrome comprises a cluster of abnormalities that occur as a result of perturbations in multiple metabolic pathways, leading to insulin resistance and hyperinsulinaemia, hyperglycaemia, atherogenic dyslipidaemia, hypertension, fibrinolytic abnormalities, etc. Numerous other disturbances have been progressively added to the syndrome, including a prothrombotic state (5), endothelial dysfunction (6) and inflammation (7), all conditions associated with cardiovascular diseases (CVD). In 1998, the World Health Organization (WHO) recommended a unifying definition and chose the term “metabolic syndrome” (MetS), primarily because current data did not establish insulin resistance as the cause of all components of the syndrome (8). An alternative definition has been proposed in 2001 by the National Cholesterol Education Program (NCEP) Expert Panel (9). This definition is easier to use in clinical practice and widely accepted (4). According to this definition, patients were considered to have the MetS if they exhibit three or more of the following criteria 1) abdominal obesity : waist circumference > 102 cm in men and > 88 cm in women; 2) hypertriglyceridaemia : ≥ 150 mg/dl; 3) low HDL cholesterol : < 40 mg/dl in men and < 50 mg/dl in women; 4) high blood pressure : $\geq 130/85$ mm Hg; and 5) high fasting glucose : ≥ 110 mg/dl.

Individuals with MetS (or insulin resistance syndrome) are at increased risk for type 2 diabetes mellitus (10,11) and at increased risk of mortality from CVD (12-15). Thus, the primary goals of treating MetS are prevention of type 2 diabetes and cardiovascular events. The importance of prevention of diabetes in high-risk individuals (such as people with MetS) is highlighted by the substantial and worldwide increase in the prevalence of diabetes in recent years (16). The NCEP Adult Treatment Panel III (NCEP ATP III) guidelines emphasize the importance of treating patients with MetS to prevent CVD (9,17). The association between MetS and CVD raises important questions about the underlying pathological process(es), especially for designing targeted therapeutic interventions (14,15). Cardiovascular risk reduction in individuals with MetS should include at least three levels of

intervention : 1) control of obesity and lack of physical activity; 2) control of insulin resistance; and 3) control of the individual components of MetS (18).

In the present review, we will consider three levels of intervention in individuals with MetS : 1) management of underlying risk conditions by controlling weight excess, enhancing regular physical exercise and promoting healthy diet; 2) management of metabolic risk factors such as dyslipidaemia, hypertension, hyperglycaemia and prothrombotic state; and 3) targeting insulin resistance, a metabolic abnormality that is considered to be in the core of MetS. Owing to the complex pathophysiology and phenotypic expression of MetS, lifestyle changes are crucial as they are able to positively and simultaneously influence almost all components of the syndrome. If such measures are not sufficient or not adequately followed, a pharmacological intervention should be considered. One may dream of either a magic bullet that could completely reverse the underlying cause of the syndrome (possibly insulin resistance ?) and thus all secondary metabolic abnormalities (19) or of a “polypill” that will contain several active compounds targeting each of the components of MetS (20,21).

Management of underlying risk conditions

The underlying conditions that promote the development of MetS and diabetes mellitus are overweight and obesity, physical inactivity, and an atherogenic diet (22). Therefore, lifestyle modification is first-line therapy to prevent and treat MetS. The most important therapeutic intervention effective in subjects with MetS should focus on modest weight reduction and regular leisure-time physical activities (3,17). The Finnish Diabetes Prevention Study (23) and the Diabetes Prevention Program (DPP) in the United States (24) performed in overweight subjects with impaired glucose tolerance (IGT) have both shown that as little as a 5 % reduction in weight, obtained with a balanced moderately hypocaloric diet and regular physical activity, can reduce the risk of developing diabetes by over 50 %. Further data from the DPP (only published as abstracts) showed that the subjects enrolled in the intensive lifestyle intervention group have lower levels of LDL-cholesterol, lower triglyceride concentrations and less hypertension than the subjects of other groups. In addition, intensive lifestyle intervention lowered the level of C-reactive protein and improved fibrinolytic potency as expressed by the level of tissue plasminogen activator. Although the three years of follow-up seem insufficient to draw conclusions applicable at large, lifestyle modifications seem to substantially reduce the need for both lipid-lowering and

antihypertensive therapies in subjects with impaired glucose tolerance. Finally, the influence of intensive lifestyle intervention on the emergence of metabolic syndrome was studied in the DPP. At baseline, about one half of the participants showed at least three constituents of MetS. Lifestyle modification was superior to other treatments in reducing abdominal obesity and offered the best protection against the development of MetS. This highly successful lifestyle intervention applied in the DPP was based on empirical literature in nutrition, exercise, and behavioural weight control. It has been described extensively (**24a DPP**) and was designed to achieve and maintain at least a 7 % weight loss and 700 calories/week of physical activity (a minimum of 150 min of exercise equivalent to brisk walking) in all lifestyle participants.

Weight loss

Although obesity is thought to be the main predisposing factor for MetS, how it relate to insulin resistance is not precisely established, because not all obese people develop insulin resistance (25) and not all individuals with MetS are obese (26). Abdominal obesity was identified as being particularly associated with several of the components of MetS (27,38). Although the precise answer to the question whether it is nature (genetic) or nurture (environment) is not known, it seems that it is probably both, to some extent. Nevertheless, it is clear that the current epidemic of obesity, and as correlate of MetS, is related to modern lifestyles that emphasize overconsumption of high-caloric food and lack of physical activity (29,30).

Effective for long-term weight loss are reduced-energy diets, consisting of a 500- to 1000-calorie/day reduction. A realistic goal for weight reduction is to reduce body weight by 7 to 10 % over a period of 6 to 12 months. Numerous studies have shown that significant improvement of several abnormalities of MetS, including dyslipidaemia, hyperglycaemia and, to some extent, hypertension, can be observed, even with a modest amount of weight loss (31,32). The impact of weight reduction on diabetes mellitus is particularly impressive (33). Regarding MetS, treatment of obesity needs to focus on high risk abdominally obese patients (34).

Unfortunately, long-term success of diet treatment is rather poor in most obese individuals (35). If combined therapy with low-calorie diet and increased physical exercise is not successful after at least 6 months, pharmacotherapy may be considered as adjunct therapy to promote weight loss and weight maintenance (29,30). Weight loss drugs approved for long-term therapy may be useful for some patients with a BMI > 30 kg/m² with no concomitant

risk factors or diseases. The risk factors (or co-morbidities) that warrant consideration of weight-loss drugs at a lower BMI (between 27 and 30 kg/m²) are hypertension, dyslipidaemia, type 2 diabetes mellitus, thus all features of MetS, as well as sleep apnoea and clinical CVD. Anti-obesity agents, including the newly available sibutramine and orlistat (36), offer for some overweight persons the possibility of improving many of the features of MetS. Orlistat has been shown to improve glucose tolerance, reduce insulin resistance, lower elevated triglycerides and LDL cholesterol and reduce hypertension (37,38) while sibutramine was associated with an impressive increase in HDL cholesterol level in the STORM trial (39).

The XENDOS (Xenical in the prevention of diabetes in Obese Subjects) study tested the hypothesis that adding a weight-reducing agent such as the lipase inhibitor orlistat to lifestyle changes may lead to an even greater decrease in body weight, and thus the incidence of type 2 diabetes, in obese patients (40). After 4 years of follow up and compared with lifestyle changes alone, orlistat plus lifestyles changes resulted in a greater weight loss (5.8 vs 3.0 kg, $p < 0.001$) and in a greater reduction in the incidence of type 2 diabetes (6.2 versus 9.0 %, corresponding to a risk reduction of 37.3 %; $p = 0.0032$) in a clinically representative obese population. Difference in diabetes incidence was detectable only in the group with IGT despite similar weight loss in subjects with or without IGT. Interestingly, treatment with orlistat plus lifestyle changes resulted in early and significant improvements in cardiovascular risk factors that were sustained throughout the study, including waist circumference, blood pressure, and lipids. Total and LDL cholesterol and the LDL-to-HDL cholesterol ratio decreased significantly more with orlistat than with placebo.

The ongoing SCOUT (Sibutramine Cardiovascular

Bariatric surgery has been shown to have favourable effects on most components of MetS, including improvement of insulin sensitivity (41), atherogenic dyslipidaemia (42), type 2 diabetes and hypertension (43), and liver steatosis (44). Such a therapeutic approach is, however, limited to those subjects with severe or morbid obesity (45).

Physical exercise

As regular exercise and fitness have been shown to improve several metabolic risk factors, physical inactivity should be considered as an important contributor of the development of MetS (46). Low levels of leisure-time physical activity and cardiorespiratory fitness predict development of MetS (47). Despite it has been long a controversial issue, it is

now accepted that exercise alone is an effective strategy for reducing obesity and related comorbidities (48). Current physical activity guidelines recommend practical regular, and moderate-intensity physical activity for the management of obese subjects (49) and of patients with type 2 diabetes (50). The standard exercise recommendation is a daily minimum of 30 minutes of moderate-intensity physical activity. Increasing the level of physical activity appears to further enhance beneficial effect while more exercise (i.e., 1 hour daily) is even more efficacious for weight control. A remarkable analysis of all data published on exercise and MetS noted that an exercise program could positively affect many of the abnormalities found (51). An “ideal programme” has been created that is preferably aerobic at 40 to 65 % of maximal oxygen consumption (VO₂ max) for 20 to 45 minutes per session, three to four times weekly.

Healthy diet

ATP III recommendations for diet composition for patients with MetS are consistent with general dietary recommendations (9). Guidelines for healthy anti-atherogenic diet call for : 1) low intake of saturated fats, *trans* fats, and cholesterol; 2) reduced consumption of simple sugars; 3) increased intakes of fruits, vegetables, and whole grains (17,52). Such principles also concern diet recommendations for the treatment and prevention of diabetes mellitus and related disorders (53,54). The so-called Mediterranean diet is in agreement with these basic recommendations and thus may be expected to improve or even correct some of the main metabolic abnormalities present in MetS. **It has been show to significantly reduce the incidence of CVD in high risk patients (DeLorgeril).**

In the DPP, the initial focus of the dietary intervention was on reducing total fat rather than calories (24a). This allowed participants to accomplish a reduction in caloric intake while at the same time emphasizing overall healthy eating. After several weeks, the concept of calorie balance and the need to restrict calories as well as fat was introduced. In the DPP, the fat and calorie goals were used as a means to achieve the weight loss goal rather than as a goal in and of itself.

An important question is whether individuals with MetS will benefit from a shift to relatively more unsaturated fats. Indeed, the risk that very high-carbohydrate diets may accentuate atherogenic dyslipidaemia may be reduced by isocalorically substituting a higher intake of unsaturated fats. However, recent small clinical trials indicate that improvement of

atherogenic dyslipidaemia by increasing unsaturated fat consumption is relatively small when compared with standard dietary recommendations (52).

Medical nutrition therapy for the management of hypertension has focused on weight reduction and reducing sodium intake (55,56). In both normotensive and hypertensive individuals, a reduction in sodium intake lowers blood pressure. In hypertensive patients, the goal should be to reduce sodium intake to 2,400 mg (100 mmol) or sodium chloride (salt) to 6,000 mg/day. Other nutritional variables that have been considered include alcohol, potassium calcium and magnesium intake. An association between high alcohol intake (> 3 drinks/day) and elevated blood pressure has been reported. However, there is no major difference in blood pressure between people who consume < 3 drinks/day and nondrinkers. Clinical trials have reported a beneficial effect of potassium supplementation on lowering blood pressure. Such high potassium intake can be provided by high intake of fruits and vegetables (five to nine servings/day). In contrast, evidence for a beneficial effect from calcium and magnesium supplementation is lacking.

Management of metabolic risk factors

The starting point for treatment of MetS is lifestyle changes (17). Treatment must address the multipathological process of MetS, with each component identified and aggressively targeted for treatment. When lifestyle changes are not sufficient, a multidrug regimen will be needed to achieve the desired goals regarding blood pressure, lipid profile and blood glucose control (57). Treatment of clinical risk factors (dyslipidaemia, hypertension, hyperglycaemia) should be even more intensive than called for by current guidelines based on the “additive” global risk reported for the syndrome itself. At present, no consensus optimal targets for LDL cholesterol or blood pressure in the treatment of MetS have been determined (17).

Dyslipidaemia

The atherogenic lipid profile associated with MetS consists of the following : 1) increased apolipoprotein B, plasma triglyceride, and intermediate density lipoprotein levels; 2) reduced HDL cholesterol concentration; and (3) smaller, dense, cholesterol ester-depleted LDL particles (1-4). In most cases, the LDL cholesterol concentration is normal or only

marginally elevated. Several components of MetS have proatherogenic properties and have an adverse impact on the vascular endothelium, producing endothelial dysfunction. The clinical approach to treatment of patients with dyslipidaemia associated with MetS requires a broad-based strategy that includes reversal of lipid abnormalities and improvement of insulin resistance (58). Lifestyle modifications (balanced diet and increased physical exercise), although the cornerstone of dyslipidaemia management, are seldom sufficient to reduce lipid parameters. Thus, the treatment of these patients often requires addition of lipid-lowering drugs targeting high (small-dense) LDL cholesterol, hypertriglyceridaemia and low HDL cholesterol. For that purpose, several types of drugs are available. Fibrates represent an attractive choice of first-line drug therapy for patients with dyslipidaemic components of MetS, but statins have brought the best evidence of protection against CVD in randomised clinical trials (59).

The benefits of statin therapy in people with diabetes and IGT or impaired fasting glucose, classical markers of MetS, have been observed from post hoc analyses of several major statin trials (60, 61). The benefit is assumed to be related to statin-induced LDL cholesterol lowering and, possibly, to the statins' pleiotropic antiatherogenic properties (62,63). As demonstrated by the Heart Protection Study (HPS), reductions in major cardiovascular events were found in a wide range of patients, including those with a total cholesterol level of < 190 mg/dl and LDL cholesterol < 100 mg/dl (64). Thus, regardless of the levels of blood cholesterol, a statin should be considered for anyone with a history of heart disease, stroke or peripheral occlusive disease, as well as for individuals with an absolute coronary risk above 20 % at 10 years. The recently reported subanalysis of the diabetic patients enrolled in the HPS provided remarkable results with a 25 % reduction of having a vascular event with simvastatin therapy as compared to placebo, irrespective of initial LDL cholesterol levels (65). However, initial HDL cholesterol levels appears to play a crucial role. For instance, diabetic patients with low HDL cholesterol levels treated with simvastatin had a CHD event rate that was higher than in diabetic patients with normal HDL cholesterol levels who received a placebo for five years. The lack of normalisation of risk in statin-treated patients with features of the MetS clearly emphasises the need to develop alternative or additional therapies.

Drugs in the fibric acid group typically reverse the dyslipidaemia associated with MetS (66). The presence of low HDL cholesterol levels along with normal LDL cholesterol levels may lead the clinician to favour a fibrate over a statin, particularly when the patient has abdominal obesity and MetS. Therapy with gemfibrozil in the Veterans Administration HDL

Intervention Trial (VA-HIT) led to triglycerides lowering of 31 %, HDL cholesterol raising of 6 %, and no change in LDL cholesterol (67). Most of the patients participating to this trial had MetS as nearly 40 % were obese and approximately had diabetes or IGT. A significant 24 % reduction in coronary events (nonfatal myocardial infarction and coronary death) was observed during follow-up as compared to placebo. The benefits conferred by the fibrate were particularly significant in the subgroup of patients with diabetes or hyperinsulinaemia, and with obesity, thus in patients with MetS (68). **In the BIP (“Bezafibrate ...”) study (69), the protective effect of bezafibrate versus placebo was only observed in the subgroup of patients with high triglyceride levels and low HDL concentration, two major components of MetS.** In the DAIS (“Diabetes Atherosclerosis Intervention Study”), treatment with fenofibrate significantly reduced progression of coronary atherosclerosis in diabetic patients (70). As compared with placebo, fenofibrate treatment was associated with a substantial improvement in atherogenic lipid profile (reduction in total cholesterol, LDL cholesterol, and triglycerides, and increase in HDL cholesterol). Furthermore, fenofibrate treatment induced a significant increase in LDL particle size in association with slowed progression of coronary atherosclerosis as compared with the placebo group (71). Although the DAIS trial was not designed to examine clinical end-points, there were fewer CV events and less coronary revascularization in the fenofibrate group than in the placebo group (- 23 %, NS) (70). In this respect, the results of the largest prospective trial in diabetic subjects ever, the FIELD (“**Fenofibrate ... Diabetes**”) study, addressing the effect of fenofibrate on cardiovascular events, will be of great value in confirming the benefits of this fibrate in patients with type 2 diabetes and MetS.

As in many patients with MetS statin therapy alone will not correct abnormalities in triglycerides and low HDL, consideration can be given to adding a second-lipid lowering drug (niacin or fibrate), especially when MetS occurs in high-risk patients (72). Unfortunately, the combination of statin + fibrate carries increased risk for severe myopathy. A clinical advisory reviewed selection of patients and reasonable precautions when statin therapy is used (73). Clinicians should be selective in the use of combined therapy in patients at high risk. Furthermore, with this combination, it is prudent to avoid high doses of statins. A combination therapy should be considered by the physician if the patient’s absolute risk is elevated to the point that a combined statin-fibrate pharmacotherapy would be more likely to have an advantageous risk/benefit ratio.

Elevated blood pressure

Among the characteristic features of MetS, hypertension has been the most challenged, and is probably the least consistently associated with or most independent of the features of the syndrome (3). Nevertheless, most of the persons with hypertension in the context of MetS are overweight or obese. Consequently, as already pointed out, specific attention should be directed first toward weight loss and sodium reduction (55,56). However, in abdominally obese subjects with MetS, a recent study showed that weight loss is associated with a decrease in blood pressure that is transient despite weight maintenance (74). These observations are in agreement with those of the Swedish Obese Subjects study in which initial blood pressure reduction after bariatric surgery vanished with time (in contrast to the sustained reduction in the incidence of diabetes mellitus), despite persistence of a substantial weight loss, as compared to control obese subjects treated with medical means (75). Thus, in most obese patients with MetS and hypertension, pharmacological intervention should be considered to reach the targets of blood pressure (55,56). Furthermore, to achieve the desired reduction in blood pressure (< 130/80 mm Hg), most of these patients may require two, three or more antihypertensive drugs. In most, if not all, hypertensive patients with MetS, therapy should be started gradually, and target blood pressure values achieved progressively through several weeks (56). It appears reasonable to initiate therapy either with a low dose of a single agent or with a low-dose combination of two agents. There are advantages and disadvantages with either approach (56).

Patients' responses to individual pharmacological agents should be monitored, and factors other than the blood pressure response should be monitored. For instance, use of high dose of diuretics has been associated with deterioration in glycaemic control while beta-blockers have been shown to be related to weight gain. Furthermore, both thiazide diuretics and non-selective beta-blockers can worsen insulin resistance and atherogenic dyslipidaemia. Finally in some population studies, both pharmacological classes have been reported to favour the development of type 2 diabetes. However, the long-term safety and efficacy of these classical antihypertensive agents have been effectively demonstrated in many clinical trials (55,56). Angiotensin-converting enzyme inhibitors and AT1 angiotensin receptors blockers may carry advantages over other drugs in patients with insulin resistance and diabetes. Several, although not all, clinical trials suggested that they may improve insulin sensitivity and recent large prospective trials in hypertensive patients reported that they are able to reduce the incidence of new onset type 2 diabetes (76). Because of the renin-angiotensin system is linked to the pathophysiology of various conditions such as hypertension, insulin

sensitivity, and inflammation, and is active in central adipocytes, its inhibition may potentially provide benefits beyond blood pressure lowering. Nevertheless, in the more recent consensus (17,55,56), it is mentioned that no particular antihypertensive agents have been identified as being preferable for hypertensive patients who also have MetS.

Microalbuminuria is a marker of renal dysfunction in patients with diabetes mellitus, but is also an independent risk marker for the development of CVD and a predictor of cardiovascular mortality in the diabetic population (87 Donnelly 2003). Microalbuminuria is associated with insulin resistance, endothelial dysfunction, dyslipidaemia, central obesity, and the loss of normal nocturnal lowering of blood pressure (15) and is part of the components of MetS according to the WHO definition (8). Again, ACE inhibitors and AT1 angiotensin receptors blockers have proven their remarkable potency to reduce microalbuminuria, essentially in patients with diabetes mellitus, an effect that appears to occur beyond the specific antihypertensive effect. This effect may represent a further argument to include a molecule that inhibits the renin-angiotensin system as first choice drug and in all combinations used to control blood pressure in patients with MetS (REF ??).

Elevated blood glucose

Most patients with MetS have at least modest hyperglycaemia, both in the fasting state (“impaired fasting glucose”) and after an oral glucose load (IGT) (78). Both impaired fasting glucose and IGT states are highly predictive of progression towards type 2 diabetes. An improvement in life-style habits and certain medications (orlistat, metformin, acarbose, troglitazone) may lessen the risk of progression to diabetes mellitus (16). Besides, the presence of MetS in patients with type 2 diabetes conveys a particularly high risk for CVD.

Several pharmacological agents may be used to directly or indirectly improve insulin sensitivity and reduce metabolic risk factors associated to insulin resistance, especially metformin, a biguanide compound, acarbose, an alpha-glucosidase inhibitor, and thiazolidinediones (or glitazones), PPAR (“Peroxisome Proliferator Activated Receptor”)-gamma agonists (19,33).

Metformin acts primarily on hepatic glucose production and has additional effects on peripheral insulin sensitivity (79,80). Its major antihyperglycaemic effect is mediated through reduction in hepatic gluconeogenesis. In type 2 diabetic patients, metformin lowers plasma glucose levels without increasing (and even by concomitantly decreasing) circulating

insulin concentrations. Unlike other antidiabetic agents (sulfonylureas, glitazones, insulin), metformin does not promote weight gain and may even cause weight reduction in obese patients. It may also favourably influence some markers of the metabolic insulin resistance syndrome (81) and appears to have beneficial effects on lipid metabolism, clotting factors, and platelet function. Metformin is now considered as first-line antidiabetic drug in obese diabetic patients, provided that classical contra-indications (essentially renal insufficiency) have been excluded (33,80). The landmark United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that metformin monotherapy was associated with a significant reduction in diabetes-related complications and cardiovascular morbidity when compared with diet alone or even with intensive therapy using sulphonylureas or insulin in obese subjects with newly diagnosed type 2 diabetes (82). The randomized, placebo-controlled BIGPRO (“BIGuanides and the Prevention of the Risk of Obesity”) trial studied 324 non-diabetic subjects with excessive body weight and high waist:hip ratio, who were treated with metformin for one year (83,84). The metformin group demonstrated larger improvements in body weight, plasma insulin and fibrinolytic parameters (tissue type plasminogen activator [tPA] antigen and von Willebrand factor), together with a better maintenance of fasting plasma glucose and cholesterol. However, blood pressure and triglyceride levels were not significantly affected. It should be pointed out that of the BIGPRO population, only 21 % had impaired glucose tolerance, while 33 % were hypertensive, and the mean triglyceride concentration was 1.6 mmol/l. Accordingly, a further trial was conducted on 168 men with a high waist:hip ratio, hypertension and elevated triglyceride level (> 1.7 mmol/l with an average of 2.8 mmol/l) (85). The results of this new study were consistent with those of the former trial, demonstrating significant improvement in insulin sensitivity and parameters related to fibrinolysis. Again neither blood pressure nor triglyceride levels decreased significantly in the metformin-treated group as compared to the placebo-treated group. Finally, the Diabetes Prevention Program showed that treatment with metformin at a dose of 850 mg twice daily significantly reduced the progression from impaired glucose tolerance to diabetes mellitus by 31 % compared to placebo (24) This protective effect was mainly observed in obese patients and in subjects younger than 60 years of age. Thus, further work to explore the therapeutic potential of metformin on visceral adipose tissue and related features of the metabolic syndrome is clearly warranted (86).

Acarbose, an alpha-glucosidase inhibitor, reduces postprandial hyperglycaemia and hyperinsulinaemia. It may represent a useful adjunct therapy for the obese diabetic patient insufficiently controlled by diet alone or in combination with other classical antidiabetic drugs (87) as well as potential pharmacological tool to prevent type 2 diabetes (88). The recently published STOP-NIDDM trial demonstrated that acarbose is able to significantly reduce the progression from IGT to overt type 2 diabetes in obese patients (hazard ratio : 0.75; 95 % CI 0.63-0.90; p = 0.0013) (89) and acarbose treatment is associated with a significant reduction in the risk of CVD (hazard ratio : 0.51; 95 % CI 0.28-0.95; p = 0.03) and hypertension (hazard ratio : 0.66; 95 % CI 0.49-0.89; p = 0.006) (90). These protective effects remained statistically significant even after adjusting for major risk factors. These observations are compatible with the hypothesis that postprandial hyperglycaemia, an important component of MetS, is a risk factor for cardiovascular disease and provide further arguments for screening and treating subjects with IGT.

Thiazolidinediones (troglitazone, rosiglitazone, pioglitazone, ...) are a new class of pharmacological compounds which work by enhancing insulin action ("insulin sensitizers") and thus promoting glucose utilization in peripheral tissues and suppressing gluconeogenesis in the liver (91). Thus, they are potentially interesting in insulin-resistant obese diabetic patients. Thiazolidinediones act through a member of the nuclear hormone receptor superfamily ("Peroxisome Proliferator Activated Receptor" or PPAR-gamma) and enhance the expression of a number of genes encoding proteins involved in glucose and lipid metabolism (92). Thiazolidinediones stimulate adipogenesis and reduce plasma FFA concentrations. Stimulation of PPAR-gamma may decrease the release by the adipocytes of various signalling molecules, such as FFA, leptin and TNF- α which all are able to counteract the hypoglycaemic action of insulin (91,92). Numerous studies have demonstrated that thiazolidinediones improve blood glucose control in (obese) type 2 diabetic patients, either treated with diet alone, sulphonylureas, metformin, or insulin. Several studies also demonstrated that thiazolidinedione compounds may increase subcutaneous fat deposition, but in contrast decrease visceral fat, thus contributing to a redistribution of adipose tissue, and hepatic fat content, thus contributing to attenuate lipotoxicity (33, **REF 93**). As visceral fat exerts much more deleterious effects than subcutaneous fat, this may result in a favourable metabolic effect, even despite global moderate weight gain. In addition to their favourable action on insulin sensitivity, and glucose control, thiazolidinediones can also improve other vascular risk factors (94). However, although the

concept is appealing (95), there is no direct evidence demonstrating that the currently available thiazolidinediones prevent the development of diabetes or CVD.

Prothrombotic state

A prothrombotic state is common in individuals with MetS. It is characterized by elevations of fibrinogen, PAI-1, and other coagulation factors such as von Willebrand factor, factor VII, and thrombin (84) as well as by a high degree of platelet aggregation (5). The risk for thrombotic events can be reduced by aspirin therapy (96). Aspirin prophylaxis is recommended in patients with diabetes (97) and in patients with MetS provided that their 10-year risk for CHD is $\geq 10\%$ (17). The impact of aspirin in the patient with diabetes or MetS is twofold. The major effect of this cyclooxygenase inhibitor agent is to reduce platelet aggregation. However, its anti-inflammatory properties may be just as important as inflammation plays a key role in the pathology of MetS (98 **Garg 2003 ou NEJM**). By blocking the production of proinflammatory prostaglandins, aspirin may reduce the inflammatory processes in the arterial wall and the resultant cardiovascular pathology.

Management of insulin resistance

Insulin resistance is widely believed to be at the heart of MetS (1), even though there is as yet little clinical trial evidence that a reduction in insulin resistance will substantially improve any of the components of MetS other than glucose intolerance (3). It is generally accepted that insulin resistance is the primary underlying abnormality that precedes and contributes to most metabolic and other perturbations seen in MetS. Although insulin resistance is strongly associated with atherogenic dyslipidaemia (increased small dense LDL, low HDL, high triglyceride levels), it is less tightly associated with hypertension. Some epidemiological data support the concept that insulin resistance and its associated hyperinsulinaemia are independent risk factors for CVD (14,15). However, this association has not yet been confirmed in controlled studies. Furthermore, the mechanistic link between insulin resistance and most of the components of MetS remains unclear.

As insulin resistance is a common feature of many of the components of MetS, many investigators believe that it plays a key pathogenic role. Insulin sensitivity may be improved by reducing weight excess, by limiting intake of saturated fats and by enhancing physical

activity. For this reason, lifestyle modification represents first-line clinical therapy of MetS. Smoking cessation, of course, is paramount.

To date, management of insulin resistance with insulin-sensitizing agents in the absence of diabetes has not been shown to reduce CVD risk so that they cannot be recommended for this purpose.

“Magic bullet” or “polypill” strategy ?

In theory, it is possible to treat each of the symptoms of MetS using the currently optimal method or pharmacological agent. This will result in treating obesity, treating hypertension, treating dyslipidaemia, treating hyperglycaemia, treating exaggerated platelet aggregation, each with a different mode. This may, of course, lead to separate treatments for numerous disorders. The focus of today’s efforts is toward discovering and applying methods that simultaneously mitigate several of the morbid features of MetS, perhaps best exemplified by treating the underlying link or cause, if there is one, rather than by treating each discrete manifestation (3). As already discussed, insulin resistance may be a good candidate although MetS can not be exclusively linked to insulin resistance. As emphasized by Després et al (34), abdominal obesity is probably an excellent target as it is closely related to the metabolic risk and CVD complications. For the moment, we cannot answer the question of whether MetS is one disease or simply a cluster of many aging or maturity-related risk factors. Whenever insulin resistance is in the core of MetS, one may expect that a magic drug that could completely reverse cellular insulin resistance will also be able to reverse MetS phenotype. Unfortunately, neither metformin, nor currently available glitazones are able to fulfil such criteria. New insulin-sensitizers are currently in development, especially PPAR γ -PPAR α agonists (3,19).

One alternative strategy may consist in prescribing a so-called “polypill” (20). An extensive literature survey based on various large meta-analyses of the efficacy and safety of the reduction of four cardiovascular risk factors (cholesterol, arterial blood pressure, platelet aggregation, homocysteine) leads to the conclusion that a combined pharmacological intervention should reduce ischaemic heart disease events by 88 % and strokes by 80 % in at risk individuals. Therefore, a new paradigm is proposed for the prevention of CVD. This new strategy would consist in the systematic prescription to people with a history of heart attack or stroke, those with any form of obliterative atherosclerotic

vascular disease or diabetes, and everyone aged 55 and older of a fixed combination of 6 pharmacological agents independently of initial risk factor profile. Obviously, such polypill may be prescribed in individuals with MetS and high risk for CVD. The proposed pharmacological formulation should contain a statin, three blood pressure lowering drugs (each at half standard dose), aspirin (75 mg/day) and folic acid (0.8 mg/day). However, the efficacy of such « polypill » remains to be demonstrated in a large controlled clinical trial as well as its superiority as compared to a classical approach of cardiovascular prevention based upon the individual optimal correction of each risk factor thanks a dose titration of each pharmacological compound.

The Steno-2 Study (99) compared the effect of a targeted, intensified, multifactorial intervention (n = 80) with that of a conventional treatment (n = 80) on modifiable risk factors for cardiovascular disease in patients with type 2 diabetes and microalbuminuria. After a mean follow-up of 7.8 years, the risk of cardiovascular events was reduced by 53 % in the intensive group, and the risk of microvascular events (nephropathy, retinopathy, autonomic neuropathy) by 58-63 %. Thus, a target-driven, long-term, intensified intervention aimed at multiple risk factors should be recommended in patients with type 2 diabetes and microalbuminuria.

A polypill that may correct all the abnormalities of MetS should theoretically comprise numerous pharmacological agents targeting all the causes and consequences of the syndrome One can imagin that such a polypill for treating MetS should contain metformin, a glitazone, acarbose, a statin, a fibrate, aspirin, an ACE inhibitor (or a AT1 receptor antagonist), etc (**Slama Diabetes met ???**). However, only targeting both elevated blood pressure and dylipidaemia would already be a successful strategy (100). Overall, in patients with MetS, reducing the three risks attributed to blood pressure, LDL cholesterol and HDL cholesterol to “normal-optimal” levels would theoretically decrease coronary events by 51 to 80 % in men and by 43 to 82 % in women, respectively. Thus, the potential benefit of controlling lipid parameters and/or blood pressure in patients with MetS is well worth emphasising as a way to prevent most coronary events. **VOIR REF 21 SLAMA**

Conclusions

Individuals with MetS have an increased risk of diabetes mellitus and CVD. The occurrence of multiple risk factors necessitates multifactorial therapy that includes glycaemic control, lipid-lowering therapy, blood pressure control and antiplatelet treatment. The most

important therapeutic intervention effective in subjects with MetS is lifestyle change, with the focus on modest weight reduction and regular leisure-time physical activities. Some patients would require the aid of pharmacological therapy, such as insulin-sensitizing agents like metformin or thiazolidinediones. Ongoing trials should be able to identify the most effective pharmacological interventions.

From a practical point of view, lifestyle modification, including regular physical exercise, health diet and smoking cessation, should be recommended first in individuals with MetS. In addition, treatments specifically targeting dyslipidaemia, hypertension or hyperglycaemia should be considered for patients with any of these conditions. In many cases, a combination of different drugs has to be proposed to reduce the risk of major adverse outcomes. However, the optimal manner in which the existing drugs should be used in patients with MetS has yet to be defined, including the optimal doses, regimens, and treatment combinations.

Public health trends and lifestyle patterns clearly suggest that nurture is the biggest contributor to the epidemic, and serious attention and public health measures are needed to curb the epidemic of obesity, MetS, diabetes, and CVD. Early identification, treatment, and prevention of the MetS present a major challenge for health care professionals and public health policy makers facing an epidemic of overweight and sedentary lifestyle. While prevention of MetS is the primary goal for the next decades, today new treatments are under development and greatly needed. There are indeed many candidate agents or areas of pharmaceutical development that may be promising for the future treatment of the syndrome.

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