Management of metabolic syndrome and associated cardiovascular risk factors

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Abstract

Patients with metabolic syndrome have a 1.5- to 3-fold increase in the risk of coronary heart disease and stroke. The association between metabolic syndrome and cardiovascular diseases raises important questions about the underlying pathological processes, especially for designing targeted therapeutic interventions. Cardiovascular risk reduction in individuals with metabolic syndrome should include at least three levels of interventions : 1) control of obesity, unhealthy diet and lack of physical activity ; 2) control of the individual components of metabolic syndrome, especially atherogenic dyslipidaemia, hypertension, dysglycaemia and prothrombotic state ; and 3) control of insulin resistance, a defect closely linked to metabolic syndrome.

Metabolic syndrome generally precedes and is often associated with type 2 diabetes. Because of this intimate relationship, appropriate management of metabolic syndrome should be able to prevent the progression from impaired glucose tolerance to frank diabetes and thus to prevent type 2 diabetes, another important cardiovascular risk factor. The importance of prevention of diabetes in high-risk individuals (such as people with metabolic syndrome are) is highlighted by the substantial and worldwide increase in the prevalence of type 2 diabetes in recent years.

Owing to the complex pathophysiology and phenotypic expression of metabolic syndrome, 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 may be considered. However, no official guidelines are available yet concerning the pharmacological management of individuals with metabolic syndrome. (Acta gastroenterol. belg., **2010**, 73, **261-267**).

Key words : metabolic syndrome, insulin resistance, cardiovascular risk factor, obesity, lifestyle, drug therapy.

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). 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 (low HDL cholesterol and hypertriglyceridaemia), hypertension, fibrinolytic abnormalities, etc. Numerous other disturbances have been progressively added to the syndrome, including a prothrombotic state, endothelial dysfunction and inflammation, all conditions associated with cardiovascular disease, and with nonalcoholic fatty liver disease (2). In 1998, the World Health Organization (WHO) recommended a unifying definition and chose the term "metabolic syndrome" (MetS). An alternative definition has been proposed in 2001 by the National Cholesterol Education Program (NCEP) Expert Panel (3). This definition was easier to use in clinical practice and widely accepted (3). 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 : ≥ 130/85 mm Hg ; and 5) high fasting glucose : ≥ 110 mg/dL (decreased to 100 mg/dL later on).

In 2005, the International Diabetes Federation proposed a new definition, which emphasized the role of abdominal obesity (5). Because waist circumference is increasingly recognized as a simple means of identifying abdominal obesity, this criterion became a prerequisite for the diagnosis of MetS. Furthermore, the threshold of waist circumference was adjusted according to ethnicity and the cut-ff was decreased from 102 cm to 94 cm in men and from 88 cm to 80 cm in women. However, in an attempt to unify criteria, a recent joint statement of several major organizations agreed that there should not be an obligatory component, but that waist measurement would continue to be a useful preliminary screening tool (6). While it may be considered useful as an educational concept, MetS has limited practical utility as a diagnostic or management tool according to the conclusions of a recent WHO Expert Consultation (7). Nevertheless, individuals with MetS are at increased risk for type 2 diabetes mellitus (T2DM) (8) and at increased risk of mortality from CVD (9). Thus, the primary goals of treating MetS are prevention of T2DM and cardiovascular events.

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 MetS-associated 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 (10).

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Management of underlying risk conditions with lifestyle changes

The underlying conditions that promote the development of MetS and T2DM are abdominal adiposity associated with overweight and obesity, physical inactivity, and an atherogenic diet (11). Therefore, lifestyle modification is the first-line therapy to prevent and treat MetS (10). The most important therapeutic intervention effective in subjects with MetS should focus on modest weight reduction and regular leisure-time physical activities (12). The Finnish Diabetes Prevention Study (13) and the US Diabetes Prevention Program (DPP) (14) performed in overweight subjects with impaired glucose tolerance (IGT) have both shown that as little as a 5% reduction in body weight, obtained with a balanced moderately hypocaloric diet and regular physical activity, can reduce the risk of developing T2DM by over 50%. 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 IGT. Finally, the influence of intensive lifestyle intervention on the emergence of MetS 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 (cumulative incidence over 3 years reduced to 34% versus 45% in the metformin group and 51% in the placebo group) (15).

Controlling weight excess

Interestingly, modest weight loss as low as 5-10% of initial body weight can reduce or eliminate disorders associated with obesity, especially MetS components and T2DM. The proposed explanation is that 5-10% weight loss is sufficient to induce a 30% reduction in visceral adipose tissue, an entity closely linked to various metabolic disturbances (16). In a large Dutch cohort followed over three consecutive five-year periods, weight loss (> 2.5 kg) and weight gain (> 2.5 kg) was associated with a lower and higher rate ratio, respectively, for the number of components of the MetS (17). The potential contribution of anti-obesity agents such as orlistat, an specific inhibitor of gastrointestinal lipase, in addition to lifestyle changes remains controversial (18), although this drug has been shown to promote weight loss and prevent new-onset T2DM in overweight/obese patients, especially in those with IGT (19).

Thus, initially, the target of weight loss programme should be to reduce body weight by about 10%. It should be remembered that even a 5% weight reduction in those who are overweight or obese improves cardiovascular risk factors. Once this has been achieved, a new target can be set, either weight maintenance or further weight reduction.

Physical exercise

As regular exercise and high fitness have been shown to improve several metabolic risk factors, physical inactivity should be considered as an important contributor of the development of MetS. Exercise alone is an effective strategy for reducing obesity and related comorbidities (20). Current physical activity guidelines recommend regular and moderate-intensity physical activity for the management of obese subjects and patients with T2DM. 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 (21).

Healthy diet

NCEP-ATP III recommendations for diet composition in patients with MetS are consistent with general dietary recommendations (3,12). Guidelines for healthy anti-atherogenic diet include : 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 (22). 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.

In the US DPP, the initial focus of the dietary intervention was the reduction of total fat rather than calories (14,15). 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.

Management of metabolic risk factors with pharmacological approaches

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. At present, no consensus exists regarding optimal targets for LDL cholesterol or blood pressure in the treatment of MetS (12).

Dyslipidaemia

The atherogenic lipid profile associated with MetS consists of the following characteristics : 1) increased apolipoprotein B, plasma triglycerides, and intermediate density lipoprotein levels ; 2) reduced high-density lipoprotein (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. The clinical approach to treatment of patients with dyslipidaemia

associated with MetS requires lifestyle modifications (balanced diet and increased physical exercise, as previously mentioned), but also 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.

The cardiovascular benefits of statin therapy in people with diabetes and IGT or impaired fasting glucose have been observed from post hoc analyses of several major statin trials (23). The benefit is assumed to be related to statin-induced LDL cholesterol lowering, irrespective of baseline cholesterol levels, and pleiotropic antiatherogenic properties have been attributed to statins (24). A post hoc analysis of the Treating to New Targets (TNT) study assessed whether intensive lowering of LDL cholesterol with high-dose (80 mg) versus low-dose (10 mg) atorvastatin therapy results in cardiovascular benefits for patients with both coronary heart disease and MetS (23). Irrespective of treatment assignment, significantly more patients with MetS (11.3%) had a major cardiovascular event at a median of 4.9 years than those without MetS (8.0% ; hazard ratio 1.44 ; $p < 0.0001$). This increased risk was significantly reduced by intensive therapy with atorvastatin 80 mg beyond that achieved with atorvastatin 10 mg, suggesting that the presence of MetS may help select patients requiring high statin dose (25). It is noteworthy, however, that a collaborative meta-analysis of randomised statin trials recently showed that statin therapy is associated with a slightly increased risk of development of diabetes, but the risk is low both in absolute terms and when compared with the reduction in coronary events (26). Therefore, clinical practice in patients with high cardiovascular risk or existing cardiovascular disease, including those with MetS known to be at higher risk to develop T2DM, should not change and should include statin therapy.

Despite achieving targets for LDL cholesterol, patients with dyslipidaemia remain at high residual risk of vascular events. Atherogenic dyslipidaemia, characterized by elevated triglycerides and low levels of HDL cholesterol, often with elevated apolipoprotein B and non-HDL cholesterol, is common in patients with established CVD, T2DM or MetS and contributes to both macrovascular and microvascular residual risk (27). The lack of normalisation of risk in statin-treated patients with features of the MetS may emphasise the need to develop alternative or additional therapies, with the use of fibrates or nicotinic acid in addition to statin.

The results of FIELD ("Fenofibrate Intervention and Event Lowering in Diabetes") study, addressing the effect of fenofibrate on cardiovascular events, have been relatively disappointing in patients with T2DM. However, as shown in a post-hoc analysis of this study, MetS components identify higher CVD risk, so the absolute benefits of fenofibrate are likely to be greater when MetS features are present. The highest risk and greatest benefits of fenofibrate are seen among those with marked hypertriglyceridaemia (28). In the recent ACCORD study in patients with T2DM who were at high risk for CVD, the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone (29). However, prespecified subgroup analyses suggested a possible interaction according to lipid subgroup, with a possible benefit for patients with both a high baseline triglyceride level and a low baseline level of HDL cholesterol, the two lipid abnormalities defining MetS (- 37% of cardiovascular events, $P = 0.057$ for interaction).

Another option may be the association of nicotinic acid, a drug known to reduce triglycerides and to increase HDL cholesterol. A European Consensus Panel recommended the combination of nicotinic acid and a statin, together with lifestyle modification, as a useful strategy to lower CHD risk in patients with T2DM and MetS (30). Prolonged-release nicotinic acid with improved tolerability (especially when combined with laropiprant, an inhibitor of prostaglandin responsible for flush) compared with previous formulations may have obvious advantages for use in this setting.

Clinicians should be selective in the use of combined therapy in patients at high risk. A combination therapy should be considered by the physician if the patient's absolute risk is elevated to the point that a combined 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 (4). 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 (31). However, in abdominally obese subjects with MetS, it has been showed that weight loss is associated with a decrease in blood pressure that is transient despite weight maintenance. Thus, in most obese patients with MetS and hypertension, pharmacological intervention should be considered to reach the targets of blood pressure (30). 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 cases, if not all hypertensive patients with MetS, therapy should be started gradually, and target blood pressure values achieved progressively through several weeks. 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 (31).

Angiotensin-converting enzyme inhibitors and AT1 angiotensin receptors blockers may carry advantages

over other antihypertensive agents (especially, diuretics and beta-blockers) in patients with insulin resistance and diabetes. Several clinical trials suggested that they may improve insulin sensitivity, and large prospective trials in hypertensive patients reported that they are able to reduce the incidence of new-onset T2DM (32). Because of the renin-angiotensin system is linked to the pathophysiology of various conditions such as hypertension, insulin resistance, and inflammation, and is active in central adiposity, its inhibition may potentially provide benefits beyond blood pressure lowering. Nevertheless, in the most recent European guidelines on hypertension management, no specific recommendation is proposed for individuals with MetS (31).

Elevated blood glucose

Most patients with MetS have at least modest hyperglycaemia, both in the fasting state ("impaired fasting glucose" or IFG) and after an oral glucose load (IGT) (4). Both IFG and IGT states are highly predictive of progression towards T2DM. An improvement in lifestyle habits and certain medications (metformin, acarbose, glitazones) may lessen the risk of progression to diabetes mellitus (33). Besides, the presence of MetS in patients with T2DM conveys a particularly high risk for CVD.

Several pharmacological agents may be used to directly or indirectly improve glucose tolerance and to improve associated metabolic disorders, such as metformin, acarbose and thiazolidinediones (or glitazones) (see below) (34).

Metformin acts primarily on hepatic glucose production and has additional modest effects on peripheral insulin sensitivity (35). In patients with T2DM, 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 (31). It may also positively influence some markers of MetS and appears to have some beneficial effects on lipid metabolism, clotting factors, and platelet function, which may contribute to its positive effects on micro- and macrovascular complications of patients with T2DM (36). Metformin is now considered as first-line antidiabetic drug in obese diabetic patients, provided that classical contra-indications (essentially renal insufficiency) have been excluded (37). The US Diabetes Prevention Program showed that treatment with metformin significantly reduced the progression from IGT to T2DM by 31% compared to placebo (13). This protective effect was mainly observed in obese patients and in subjects younger than 60 years of age. Furthermore, metformin slightly reduced the progression to MetS as compared to placebo (45 versus 51%) (14). In a recent post-hoc analysis of the French BIGPRO-1 trial focusing on the IFG/IGT patients, significant differences in 1-year changes were observed for systolic blood pressure, which decreased markedly more in the metformin group than in the placebo group, and for fasting plasma glucose, and total and LDL cholesterol, which decreased slightly in the metformin group, but increased in the placebo group (38). Further work to explore the therapeutic potential of metformin on related features of MetS and the CVD risk in individuals with MetS is clearly warranted (39).

Another approach not directly interfering with insulin sensitivity would be to competitively inhibit intestinal α-glucosidase enzymes. This pharmacological effect directly reduces postprandial hyperglycaemia and improves other associated metabolic disorders. In the STOP-NIDDM trial, acarbose has been shown to prevent the development of new-onset diabetes and to reduce the incidence of cardiovascular events in patients with IGT (40).

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 as well as by a higher degree of platelet aggregation. The risk for thrombotic events can be reduced by aspirin therapy in high-risk patients (41). Aspirin prophylaxis has been recommended in patients with diabetes and in those with MetS provided that their 10-year risk for coronary heart disease is $\geq$ 10% (12). However, according to recent data, the role of aspirin in prevention of cardiovascular events remains controversial in patients with MetS, even in patients with diabetes (42).

Management of insulin resistance

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. Thus, insulin resistance is widely believed to be at the heart of MetS, even though this has been disputed by Reaven himself (43). However, 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 IFG/IGT. 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 compensatory hyperinsulinaemia are independent risk factors for CVD (8). However, this association has not yet been confirmed in controlled studies. Furthermore, the mechanistic link between insulin resistance and some of the components of MetS remains unclear.

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 because smoking increases both insulin resistance and cardiovascular risk.

Thiazolidinediones (TZDs) (rosiglitazone, pioglitazone) are pharmacological compounds that work by enhancing insulin action. These so-called "insulin sensitizers" act as PPAR ("Peroxisome Proliferator Activated Receptor")-gamma agonists (44). Thus, they are potentially interesting in insulin-resistant obese diabetic patients. Numerous studies have demonstrated that TZDs improve blood glucose control in (obese) patients with TD2M, either treated with diet alone, sulphonylureas, metformin, or insulin (43). Several studies also demonstrated that TZDs, although they may increase subcutaneous fat deposition (thus promoting some weight gain), decrease visceral adipose tissue and hepatic fat content, thus contributing to attenuate lipotoxicity (34). In addition to their favourable action on insulin sensitivity and glucose control, TZDs can also improve other vascular risk factors. Several controlled trials have shown that both pioglitazone and rosiglitazone are able to dramatically reduce new-onset diabetes in high risk individuals (33). However, TZDs are associated with various side effects such as weight gain, fluid retention and congestive heart failure or peripheral bone fractures. In the Proactive trial, pioglitazone, increased body weight and the risk of congestive heart failure, but reduced the incidence of cardiovascular death, myocardial infarction and stroke in patients with antecedents of CVD disease and with T2DM treated with diet alone, metformin/sulfonulyurea monotherapy/combined therapy or insulin, most of them known to have MetS (45). In contrast, the cardiovascular safety of rosiglitazone has been challenged so that this compound is contra-indicated for the patients with antecedents of coronary heart disease (46).

To date, management of insulin resistance with insulin-sensitizing agents in the absence of diabetes has not been shown to reduce CVD risk profile, despite a significant increase in adiponectin levels, so that they cannot be recommended for this purpose (47).

Conclusions

Individuals with MetS have an increased risk of T2DM 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 leisure-time physical activities. From a practical point of view, 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, especially in patients with T2DM. 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. The role of insulin sensitizers such as metformin and TZDs in patients with MetS remain controversial despite these agents have shown that they can prevent the development of T2DM and in some instances CVD.

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.

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