Nutrition in Metabolic Syndrome

Module 24.4

Pharmacological treatment

Learning Objectives

• To review some drug treatments which, together with diet and changes in lifestyle, are able to improve some metabolic aspects related to MetS, such as the progression rate towards the development of type 2 diabetes or the cardiovascular risk;
• To review special implications of cardiovascular risk factors treatment in patients with the MetS;
• To understand the MetS not only as the treatment for each one of its components, but also as a whole risk-reduction strategy.

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Key Messages

• The metabolic syndrome predicts the development of both diabetes and cardiovascular disease: reducing these risks should therefore be the main goals of treatment;
• After diet and lifestyle changes, consider antiobesity drugs when weight loss is still needed;
• Insulin sensitizers (metformin and glitazones) should be used in diabetic individuals with the metabolic syndrome and perhaps in people with impaired glucose tolerance. There is no evidence for using them in MetS with normal glucose metabolism;
• Conventional cardiovascular risk factors such as lipids, blood pressure or prothrombotic state should also be treated.
1. Introduction

The metabolic syndrome (MetS) is a clinical entity precipitated by multiple underlying risk factors, the most important of them being abdominal obesity and insulin resistance, which predispose the individual to an increased risk of cardiovascular disease and developing diabetes. Therefore, the primary goal of clinical management of the MetS will be to reduce those risks. Today, dietary and lifestyle changes remain the cornerstones when looking for a “pathophysiological” treatment for the MetS. Currently, there is no single pharmacological treatment for the MetS although, obviously, the idea of reducing multiple risk factors with just a single drug or a drug combination is somewhat attractive. Current consensus statements address at treatment for each one of the components of the MetS (1): obesity, atherogenic dislipidemias, elevated blood pressure, impaired glucose metabolism, and prothrombotic and proinflammatory states. Nevertheless, evidence is available regarding some drug treatments, together with diet and lifestyle changes, which are able to improve some metabolic aspects related to MetS, such as the progression rate towards the development of type 2 diabetes or cardiovascular risk. That is the reason why we consider of interest to underline here those aspects as a possible coadjuvant treatment. As we will see, candidate drugs for treatment of the MetS as a whole are weight-loss drugs, peroxisome proliferator-activated receptor (PPAR)-alpha agonists (fibrates), PPAR-gamma agonists (thiazolidinediones), and dual PPAR agonists (2).

Considering the components and pathogenetic mechanisms of the MetS, we understand that treatment of the MetS would involve: a) Treatment of abdominal obesity; b) Treatment for the insulin resistance; c) Treatment for each one of the risk factors involved in the syndrome (Fig. 1).

![Figure 1 Metabolic syndrome and role of the pharmacological treatment](image)

2. Obesity Treatment

Treatment with either sibutramine or orlistat has shown to be effective as adjuvant to dietary treatment and lifestyle changes in reducing weight and cardiovascular factors related to overweight (3, 4, 5, 6). Furthermore, in the ORListat and CARdiovascular risk profile in patients with metabolic syndrome and type 2 DIabetes (ORLICARDIA) study, the combination of orlistat with a hypocaloric diet for 6 months reduced the proportion of patients meeting the diagnostic criteria of the MetSyn by 35% while hypocaloric diet alone only reduced it by 9% in patients with both diabetes and the MetSyn (Fig. 2) (7).
As orlistat, sibutramine results not only in weight loss, but also reduces waist circumference (8) and visceral fat reduction is associated with improvements in risk factors associated with the MetS such as fasting blood glucose, insulin levels, HDL cholesterol and triglycerides (9). Direct comparative studies between these two antiobesity drugs are still limited, but it has been suggested that sibutramine is better tolerated and causes greater weight loss (10, 11), although patients taking orlistat experienced more decrease in waist circumference (3.4 cm vs 1.8 cm for sibutramine) per unit decrease in BMI (Fig. 3) (12). Furthermore, orlistat may be more powerful in improving blood glucose control (13) despite this lower antiobesity effect compared to sibutramine, perhaps because of a greater improvement of insulin sensitivity related to the reduced fat absorption. Combination therapy seems to add no significant benefit in terms of added weight loss.

When addressing the issue of a possible role of weight-reducing drugs to decrease the risks associated to the MetS, we should refer to the XENDOS study (Xenical in the Prevention of Diabetes in Obese Subjects) (14), which demonstrated that orlistat was able to decrease the incidence of type 2 diabetes mellitus by 37% vs placebo (Fig. 4). On the other hand, the
The Sibutramine Cardiovascular Outcome (SCOUT) Study is ongoing to demonstrate if long-term weight loss with sibutramine plus lifestyle modifications results in health benefits and improve cardiovascular prognosis.

Figure 4 XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Finally, rimonabant is a cannabinoid receptor antagonist, which exerts its action equally at a central and at a peripheral level (15). The RIO studies (16, 17, 18, 19) results show that rimonabant is effective in body weight control together with diet and lifestyle changes, achieving weight-losses around 5% (Table 1). Besides, it also improves metabolic derangements related to MetS. Across all 4 studies, rimonabant increased HDL-cholesterol and decreased triglyceride levels. Adiponectin, measured only in the RIO-Lipids study, increased on rimonabant compared with placebo, and HbA1c, measured only in RIO-Diabetes, along with fasting insulin in the non-diabetic patients, were both significantly reduced with rimonabant. Moreover, weight-independent beneficial effects on HDL-cholesterol, triglycerides, Hb A1c, insulin, and adiponectin have been recently postulated for rimonabant (Table 2) (20).

Table 1 RIO studies (Results with 20 mg)

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of patients</th>
<th>n</th>
<th>Duration</th>
<th>Waist</th>
<th>Weight</th>
<th>HDL-C</th>
<th>Tg</th>
<th>Insulin sensitivity</th>
<th>Met S</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIO</td>
<td>Obese/Overweight</td>
<td>304</td>
<td>2 years</td>
<td>↓8</td>
<td>↓5% in</td>
<td>↑24,5</td>
<td>↓9,9%</td>
<td>Improved</td>
<td>↓</td>
</tr>
<tr>
<td>North</td>
<td></td>
<td>3</td>
<td>(1+1) cm</td>
<td>62,5%</td>
<td>%</td>
<td></td>
<td></td>
<td></td>
<td>1/3</td>
</tr>
<tr>
<td>America</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>RIO</td>
<td>Obese/Overweight</td>
<td>150</td>
<td>2 years</td>
<td>↓8,5</td>
<td>↓8,6</td>
<td>↑27%</td>
<td>↓10,6</td>
<td>Improved</td>
<td>↓1/</td>
</tr>
<tr>
<td>Europe</td>
<td></td>
<td>7</td>
<td>cm Kg</td>
<td>%</td>
<td>%</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>
### Table 2: Cardiometabolic Effects of Rimonabant Independent of Weight Loss
(*Mean difference vs placebo at 1 year; \( P < .001 \) for all comparisons.)

<table>
<thead>
<tr>
<th>Cardiometabolic Parameter</th>
<th>Overall Effect*</th>
<th>Effect Beyond That of Body Weight Loss Alone*</th>
<th>Overall Effect Beyond That of Body Weight Loss Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-cholesterol (%)</td>
<td>8.0</td>
<td>3.6</td>
<td>45%</td>
</tr>
<tr>
<td>Triglycerides (%)</td>
<td>-14.0</td>
<td>-6.5</td>
<td>46%</td>
</tr>
<tr>
<td>Fasting insulin (mcIU/mL)</td>
<td>-2.74</td>
<td>-1.34</td>
<td>49%</td>
</tr>
<tr>
<td>Adiponectin (mcg/mL)</td>
<td>1.5 (0.2)</td>
<td>0.85</td>
<td>57%</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>-0.67</td>
<td>-0.37</td>
<td>55%</td>
</tr>
</tbody>
</table>
3. Treatment of Insulin Resistance and Impaired Glucose Metabolism

Diabetes in a patient with MetS should be initially treated with metformin or thiazolidinediones considering these drugs will not only improve glycemic control but will also have an effect on some other components of the MetS. Besides, metformin, thiazolidinediones and acarbose (21) could lower risk for type 2 diabetes mellitus in people with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Two large multicenter studies lasting 3 years, the Finnish Diabetes Prevention Study and the Diabetes Prevention Program (DPP) (22, 23), reported that a decrease of 5-7% of body weight brought a 58% decrease in the conversion rate to type 2 diabetes of people with previous IGT, while the decrease was 31% on treatment with metformin (Fig. 5). In the DPP study, 53% of the participants had the MetS at baseline, but the incidence was reduced by 41% in the lifestyle group and by 17% in the metformin group (24).

Figure 5 US Diabetes Prevention Program

Figure 6 US Diabetes Prevention Program: risk of developing MetS
The thiazolidinediones (glitazones), pioglitazone and rosiglitazone, are agonists for the nuclear receptor peroxisome proliferator-activated receptor gamma which lessen insulin resistance and modestly improve other metabolic risk factors (25) (Table 3). The Troglitazone in the Prevention of Diabetes (TRIPOD) study found a 50% reduction in the incidence of diabetes in women with previous gestational diabetes who were treated with troglitazone for up to 5 years. Even after troglitazone was discontinued, the protective effect persisted for months. This cohort is now being followed up on pioglitazone in the Pioglitazone in the Prevention of Diabetes, or PiPOD, study (26). Pioglitazone is also associated with significant improvements in triglycerides, HDL cholesterol, LDL particle concentration, and LDL particle size (27).


<table>
<thead>
<tr>
<th>Component</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central obesity</td>
<td>↓ Visceral fat ↑ Subcutaneous fat</td>
</tr>
<tr>
<td></td>
<td>↓ Hepatic fat ↑ Muscular fat</td>
</tr>
<tr>
<td></td>
<td>Small initial increases in weight gain which stabilise after 6 months</td>
</tr>
<tr>
<td>Hypertension</td>
<td>↓ Systolic blood pressure (slight) ↓ Diastolic blood pressure (slight)</td>
</tr>
<tr>
<td>Dyslipidemia (more marked</td>
<td>↓ Triglycerides</td>
</tr>
<tr>
<td>improvements with pioglitazone)</td>
<td>↑ HDL-C</td>
</tr>
<tr>
<td>Pro-coagulation</td>
<td>↑ LDL-C ↓ LDL particle concentration</td>
</tr>
<tr>
<td></td>
<td>↑ Time to intra-arterial thrombus formation</td>
</tr>
<tr>
<td></td>
<td>↓ PAI-1 expression ↓ PAI-1 release</td>
</tr>
<tr>
<td>Endotelial dysfunction,</td>
<td>↓ C-reactive protein</td>
</tr>
<tr>
<td>inflammation and</td>
<td>↑ Adiponectin</td>
</tr>
<tr>
<td>atherosclerosis</td>
<td>↓ Intima-media thickness</td>
</tr>
</tbody>
</table>

Nevertheless, no clinical trial evidence indicates that metformin or thiazolidinediones will reduce risk for cardiovascular disease events in non-diabetic patients with the metabolic syndrome. Some studies are underway examining various diabetes prevention strategies: The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication, or DREAM, study, and the ACTOS NOW study, which is evaluating whether pioglitazone can prevent or delay the development of diabetes in individuals with IGT. Currently, it is at least controversial whether insulin sensitizers should be used in the pharmacological treatment of the metabolic syndrome in non-diabetic subjects.

In a near future, we will have dual PPAR agonists combining PPAR-alpha and PPAR-gamma agonism in a single agent, known as the glitazar class of medications (muraglitazar, tesaaglitazar), with favorable effects on both glucose and lipid metabolism (Fig. 7) (28, 29). Other drugs for the future include the incretin mimetics, as exenatide, which mimic the effects of the gut peptide glucagon-like peptide (GLP)-1 and reduce body weight in the setting of diabetes. Although significant reductions in both triglycerides and diastolic blood pressure and an increase in HDL-C have been claimed, its role in the treatment of the Met S has to be determined (30).
4. Treatment of the Other Components of the Metabolic Syndrome

4.1 Atherogenic Dislipidemias

The ATP III guidelines (31) recommend LDL-C as the primary target of lipid-lowering therapy when a patient's triglyceride level is below 500 mg/dL. Statins have shown to reduce risk for major cardiovascular events in patients with the MetS (Fig. 8) (32), although a possible protective role to reduce the incidence of new-onset diabetes has been postulated (33, 34) but not confirmed (35, 36). Nonetheless, hypertriglyceridemia and low HDL-C levels are characteristic features of the MetS, and when triglycerides are >500 mg/dL, they are the primary target of treatment because of the risk of acute pancreatitis. Fibrates are PPARα agonists which effectively decrease triglyceride and increase HDL-C levels. They produce a modest decrease of LDL-C levels but they reduce the proportion of atherogenic small dense LDL particles. Moreover, antiinflammatory properties of PPARα agonists have been documented in in vitro and animal studies (37). Some clinical studies with fibrates have shown variable reductions in the relative risks for cardiovascular events, which could apply for the MetS. In the VA-HIT study, which included a huge proportion of patients with features of the metabolic syndrome, treatment with gemfibrozil reduced non-fatal MI and CHD death at five years by 22% and treatment was more effective in patients with hyperinsulinaemia and diabetes (38). However, these findings contrast with those of FIELD, in which patients with MetS, did not obtain significantly greater benefit from fenofibrate than patients without MetS (39). In summary, evidence is inconclusive to strongly recommend treatment with fibrates as a primary option to prevent cardiovascular disease in patients with the MetS.
Figure 8 Reduction of cardiovascular events by simvastatin in nondiabetic coronary heart disease patients with (•) or without ( ) the metabolic syndrome: subgroup analyses of the 4S Study.

When combination therapy with a statin is needed, fenofibrate combined with a statin seems to be less likely to cause myopathy than is gemfibrozil (40) and higher doses of the statin should be used. Patients with impaired glucose metabolism who are treated with nicotinic acid should follow careful monitoring for possible worsening of hyperglycemia. On the other hand, resins are not recommended in MetS patients because of their triglyceride-raising effect. When LDL goals are not met on statin therapy, the addition of ezetimibe, a new selective inhibitor of intestinal cholesterol absorption, could provide a further 15-20% LDL-C lowering in patients with either DM or MetS (41). In patients with high triglycerides, omega 3 fatty acids could be useful as they have shown to decrease triglyceride levels and improve insulin resistance, although their effect on total mortality, combined cardiovascular events, or cancer has not been proven in a recent systematic review (42). In Table 4, efficacy patterns of current lipid-lowering agents are shown (43).

Table 4 Efficacy patterns of current lipid-lowering agents (modified from Vega)

<table>
<thead>
<tr>
<th>Drugs/supplements</th>
<th>Site of action</th>
<th>LDL cholesterol reduction</th>
<th>HDL cholesterol increase</th>
<th>Triglyceride reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>HMG-CoA reductase</td>
<td>20%-60%</td>
<td>5%-15%</td>
<td>10%-30%</td>
</tr>
<tr>
<td>Fibrates</td>
<td>PPAR-alpha</td>
<td>10%-20%</td>
<td>10%-15%</td>
<td>20%-50%</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>PUMA-G and HM74 receptors??</td>
<td>10%-25%</td>
<td>15%-35%</td>
<td>20%-50%</td>
</tr>
<tr>
<td>Ezitimibe</td>
<td>Niemann-Pick C1 like 1 protein</td>
<td>14%-18%</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Enterohepatic circulation of bile acids</td>
<td>15%-30%</td>
<td>3%-5%</td>
<td>5%-25%</td>
</tr>
</tbody>
</table>
**4.2 Elevated Blood Pressure**
The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (44) provides guidelines for intensive treatment of hypertension. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) are better first-line therapy for MetS patients, especially when diabetes is present, but the issue of the most effective drug has not been absolutely solved. Recently, the study ASCOT-BPLA (45) has shown the first evidence of greater cardiovascular protective effects of newer as compared to old antihypertensive drug treatments. An antihypertensive regimen based on the long acting dihydropyridine calcium antagonist amlodipine very often associated to the ACE inhibitor perindopril showed significantly lower rates of cardiovascular and total mortalities, cardiovascular events, new diabetes or renal impairment as compared to the atenolol-based combination drug regimen (with thiazide as required).

**4.3 Prothrombotic State**
Low-dose aspirin or other antiplatelet drugs should be recommended in patients with established cardiovascular disease unless contraindicated. In patients with type 2 diabetes in the absence of cardiovascular disease, they are widely recommended although their efficacy has not been clearly established. In other people with the MetS, aspirin (75 to 325 mg/day) (46) should be used when the risk for cardiovascular disease events is judged to be moderately high (10-year risk 10% or greater) (47).

**4.4 Proinflammatory State**
Lifestyle therapies, especially weight reduction, will reduce concentrations of elevated cytokine and acute phase reactants in the MetS and thus mitigate an underlying inflammatory state. Although no specific anti-inflammatory drugs were available to treat the proinflammatory state, several drugs used to treat other metabolic risk factors – such as statins, fibrates, and thiazolidinediones—have been reported to reduce concentrations of C-reactive proteins (48, 49). The drugs, however, should not be recommended to reduce proinflammatory state independently of other risk factors. A recent report has pointed out a role for an anti-inflammatory drug such as etanercept in patients with the metabolic syndrome, which reduces C-reactive protein levels and tends to improve other inflammatory cardiovascular risk indexes (increases adiponectin levels, decreases fibrinogen and interleukin 6 levels) (50).

**5. Summary**
The metabolic syndrome (MetS) is a clinical entity which predisposes the individual to an increased risk of cardiovascular disease and developing diabetes. Therefore, the primary goal of clinical management of the MetS will be to reduce those risks. Today, dietary and lifestyle changes remain the cornerstones when looking for a “pathophysiological” treatment for the MetS. Currently, there is no single pharmacological treatment for the MetS although, obviously, the idea of reducing multiple risk factors with just a single drug or a drug combination is somewhat attractive. Current consensus statements adress at treatment for each one of the components of the MetS, but evidence is available regarding some drug treatments, together with diet and lifestyle changes, are able to improve some metabolic aspects related to MetS, such as the progression rate towards the development of type 2 diabetes or cardiovascular risk. Candidate drugs for treatment of the MetS as a whole are weight-loss drugs (orlistat, sibutramine and especially rimonabant, a cannabinoid receptor
antagonist which also also improves metabolic derangements related to MetS), peroxisome proliferator-activated receptor (PPAR)-alpha agonists (fibrates), PPAR-gamma agonists (thiazolidinediones), and dual PPAR agonists.

References


