Metabolic syndrome: pharmacological treatment

P.A. van Zwieten[1,2] and F.C. Visser[2]
[1]Departments of Pharmacotherapy, Cardiology and Cardiothoracic Surgery, Academic Medical Centre, Amsterdam, The Netherlands, and [2]Department of Cardiology, Free University Medical Centre, Amsterdam, The Netherlands

Correspondence: Prof.Dr P.A. van Zwieten, Departments of Pharmacotherapy, Cardiology and Cardiothoracic Surgery, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
Tel: +31 20 566 49 76; fax: +31 20 696 8704

Abstract

Patients with the metabolic syndrome have a clustering of the following risk factors: detrimental changes in glucose tolerance and insulin resistance, abdominal (visceral) obesity, atherogenic dyslipidemia, hypertension. In addition to appropriate changes in lifestyle, the majority of patients with the syndrome will require pharmacological treatment, usually for the remainder of their lives. We present here an exhaustive and critical review of the drug treatment of the risk factors associated with the metabolic syndrome. Emphasis will be upon antihypertensive treatment and on the influence of various drugs on insulin resistance, an important background to the metabolic syndrome.
■ *Heart Metab.* 2006;30:15–20.

Keywords: Metabolic syndrome, insulin resistance, antihypertensive drugs, diabetes mellitus (type 2), obesity, hyperlipidemia

Introduction

The most relevant components of the metabolic syndrome [1,2] can be listed as follows:

- unfavorable changes in glucose tolerance (↓) and insulin resistance (↑);
- abdominal (visceral) obesity;
- atherogenic dyslipidemia;
- hypertension.

Taking into account the complex character of the metabolic syndrome, it is not surprising that its definition and nomenclature have been subject to considerable and even polemic discussions and debate. Secondary to the initial term 'syndrome X', other names for metabolic syndrome have been proposed, such as 'insulin resistance syndrome', 'Reaven's syndrome' and 'metabolic cardiovascular syndrome' [3].

Both the National Cholesterol Education Programme (NCEP) and the World Health Organization (WHO) have established definitions of the metabolic syndrome that are fairly similar. Both definitions comprise markers for abdominal obesity, glucose and lipid metabolism, and blood pressure. The WHO definition contains, in addition, criteria for urinary albumin excretion as a marker for renal damage, and in more general terms as a sensitive predictor for cardiovascular disease in an early stage [4].

The pathophysiological backgrounds of metabolic syndrome, a very heterogenous syndrome, are complex. Two major issues are discussed as possible common backgrounds of the metabolic syndrome: (a) insulin resistance/glucose intolerance (see *Figure 1*) and (b) hyperactivity of the sympathetic nervous system. Both phenomena and their relationship with the metabolic syndrome have been discussed exhaustively in recent reviews [5,6].

Metabolic syndrome is associated with important cardio/cerebrovascular and metabolic risks. Prevention and treatment are therefore of great importance. Preventive measures involving lifestyle are mandatory. In addition, patients with the metabolic syndrome will

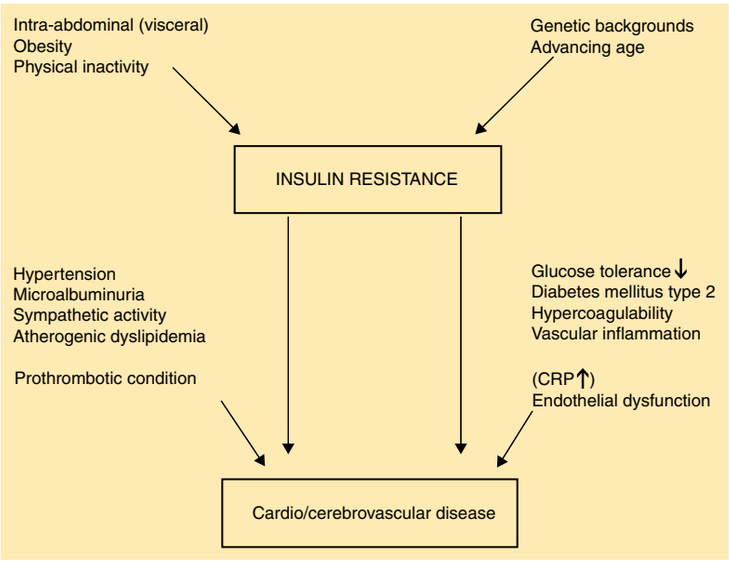

Figure 1. Pathological processes that have roles in the metabolic syndrome and can hence lead to cardio/cerebrovascular diseases. Insulin resistance appears to be of pivotal importance as a background to several pathological mechanisms.

require pharmacological treatment, usually for the remainder of their lives.

Taking into account the heterogenous character of the metabolic syndrome and its various components, the pharmacological interventions are bound to be complex. Consequently, the evaluation of pharmacological interventions will require appropriately designed, rather complicated clinical trials.

The present survey will deal with the various aspects of pharmacological treatment of the metabolic syndrome, including some newer therapeutic approaches.

Prevention and general aspects of intervention

It goes without saying that prevention is a crucial approach for reducing the various risks brought about by the metabolic syndrome. The preventive approach holds for virtually all important components of metabolic syndrome, such as glucose intolerance/insulin resistance, diabetes mellitus type 2, obesity, hyperlipidemia, and hypertension. Generally speaking, the recommended changes in lifestyle run parallel to reduction of risk for these pathophysiological processes. Accordingly, the following recommendations for intervention should be taken into account as preventive measures [7]:

- Obesity, glucose intolerance, insulin resistance, diabetes mellitus type 2: correction of overweight by adequate changes in diet (Mediterranean diet, less saturated fat, fewer calories, reduction of alcohol consumption), and by more and regular physical activity.
- Hyperlipidemia: as discussed above for obesity etc.
- Hypertension: as discussed above for obesity etc.; in addition, moderation of salt (Na^+) and alcohol consumption.

From a more general perspective, all patients are urgently advised to stop smoking. On the basis of the concept that the metabolic syndrome is associated with sympathetic hyperactivity, preventive measures aiming at reducing this hyperactivity could be considered. Correction of overweight and enhanced physical activity may be expected to reduce sympathetic hyperactivity somewhat. Prevention of the prothrombotic condition can be achieved only by drug treatment.

Drug therapy and the metabolic syndrome

General aspects

Although the preventive measures described above should always be the primary approach to intervention in patients with the metabolic syndrome, this approach is not always successful, in particular in the long term. Accordingly, the vast majority of patients with the metabolic syndrome require pharmacological treatment, in spite of all the good intentions with respect to prevention and lifestyle improvements. Once established, drug treatment has to be followed daily, and usually for the remainder

of the patient's life. Guidelines on prevention of cardiovascular disease do not usually make extensive reference to the metabolic syndrome [8]. When they do, they usually advise that this condition is predominantly approached by improvements in lifestyle. It is likely that this conservative approach will change in the future towards a more interventional one, with a more important role of pharmacological treatment [8].

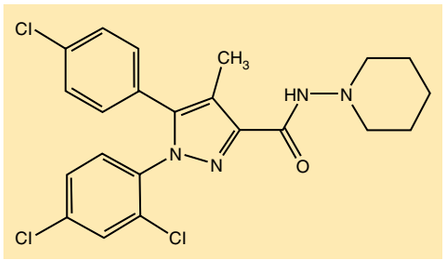

Figure 2. Chemical structure of rimonabant, an inhibitor of the cannabinoid (CB_1) receptor in the endocannabinoid system.

Obesity

Pharmacological treatment of obesity had been attempted for several decades, but so far this approach has been disappointing. In most European countries, two drugs are registered for the treatment of obesity: sibutramine and orlistat.

Sibutramine, an anorexant chemically derived from amphetamine, inhibits the reuptake of both norepinephrine and serotonin by their respective nerve endings, in both the periphery and the central nervous system. Consequently, appetite is reduced and energy expenditure is increased. Adverse responses to sibutramine can be problematic as a result of activation of the sympathetic nervous system. Long-term beneficial effects of the drug are the subject of debate.

Orlistat reduces the intestinal absorption of nutritional fat by inhibition of the enzyme lipase in the pancreas and the stomach. Orlistat, indeed, appears to be able to reduce body weight in the long term, but its adverse reactions (mainly gastrointestinal) are most unpleasant, leading to poor patient compliance.

Metformin, a biguanide-type antidiabetic agent, is not classified as an anti-obesity drug, but in diabetic patients treated with this agent, body weight is usually decreased [9].

Rimonabant, an antagonist of cannabinoid (CB_1-type) receptors in the endocannabinoid system of the brain, offers a new approach in the management of obesity. Stimulation of CB_1 receptors is involved in an increase in appetite, increased accumulation of fat in adipocytes, and increased motivation to smoke. Conversely, blockade of the CB_1 receptor by an antagonist will counteract both hyperphagia/obesity and the increased motivation to smoke. Rimonabant (*Figure 2*), the first clinically applicable CB_1 receptor antagonist, exhibits these beneficial effects, to date in studies lasting 1 year [10]. Further and large-scale studies will be required to establish the position of rimonabant, which appears to offer a new approach in the management of obesity, including in patients with the metabolic syndrome.

Overall, the pharmacological treatment of obesity has to date been largely disappointing. Appropriate improvements are highly desirable. In this respect, the endocannabinoid system and its receptors can be thought of as an interesting target for new drugs.

In recent years, several hormones involved in the regulation of appetite and saturation have been discovered, such as leptin*, ghrelin, resistin and peptide PYY. It is conceivable that derivatives, analogs, agonists, or antagonists of these hormones may provide the basis for the development of new drugs that can be used to counteract obesity.

Glucose intolerance, insulin resistance, and type 2 diabetes mellitus

In addition to the classical oral antidiabetic drugs (tolbutamide and related sulfonylurea derivatives, glinides, and acarbose), the biguanide, *metformin*, has experienced a renaissance of interest since it was discovered that it exhibits insulin-sensitizing activity. For this and other reasons, metformin is considered the oral antidiabetic drug of choice in patients with metabolic syndrome [9].

Glitazones, such as pioglitazone and rosiglitazone, are the newer type of insulin sensitizer. They reduce insulin resistance via the activation of the peroxisome-proliferator-activated receptor subtype γ (PPAR-γ). On theoretical grounds, they would be beneficial oral antidiabetic agents in patients with metabolic syndrome. Their position will be established by means of current clinical trials [11].

Insulin resistance

As insulin resistance is now widely recognized as an important background to the various components of the metabolic syndrome, it appears useful to review the differential influences of the various cardiovascular and antidiabetic drugs used in the management of the metabolic syndrome [12]. As summarized in *Table I*, insulin resistance can be modulated in a differential manner by various types of drugs. In particular, various types of antihypertensive agent display a clearly differential activity. As will be discussed in the next paragraph, this issue is of vital importance, in particular with respect to the long-term

Table I. Overview of the effects of cardiovascular and antidiabetic drugs that influence insulin resistance.

Drug	Effects on insulin resistance (IR)	Details
Thiazolidinediones (glitazones)	IR ↓ (favorable)	PPAR-γ receptor agonism
Metformin	IR ↓ (favorable)	Hepatic glucose production ↓
α_1-Adrenoreceptor antagonists (eg, doxazosin)	IR ↓ (favorable) Weak effect	
Calcium antagonists	No direct effect (neutral)	
ACE inhibitors	IR ↓ (favorable)	Possibly via angiotensin II/endothelium
Angiotensin II receptor antagonists (AT_1-blockers; ARBs; sartans) Exception: telmisartan	No effect IR ↓ (favorable)	PPAR-γ receptor agonism
Thiazide diuretics	IR ↑ (unfavorable)	Pancreatic insulin release ↓
β-Blockers	IR ↑ (unfavorable)	
Centrally acting antihypertensives (clonidine; α-methyl-DOPA; moxonidine; rilmenidine)	IR ↓ (probably) Weak effects	Via depression of sympathetic nervous system activity

ACE, angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blocking agent; AT_1, angiotensin II type 1; DOPA, dihydroxyphenylalanine; PPAR, peroxisome proliferator activated receptor.

treatment of essential hypertension, which is usually continued for several decades.

Hypertension

Taking into account that patients with the metabolic syndrome are clearly at increased cardio/cerebrovascular risk, strict control of blood pressure is mandatory, aiming at values of 130/85 mm Hg or even less. Although it has not been studied in a specific trial, it seems very likely that patients with the metabolic syndrome including hypertension would also benefit from decreasing their blood pressure by pharmacological treatment, probably almost irrespective of the type of drug used. However, in this connection it should be borne in mind that the development of diabetes and other metabolic problems are associated with the long-term use of certain antihypertensive agents.

The European Society of Hypertension/European Society of Cardiology 2003 guidelines proposed five groups of antihypertensive drugs as first-line treatment of hypertension: thiazide diuretics, β-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor antagonists (angiotensin II type 1 [AT_1] blockers; angiotensin II type 1 receptor blocking agents; sartans).

Other drugs that can be considered are the α-blockers and the older centrally acting antihypertensives such as clonidine and α-methyl-dihydroxyphenylalanine. If used correctly, these various agents have largely comparable blood pressure decreasing activities. However, recent investigations indicate that the metabolic changes associated with the various categories of antihypertensive agent are differential, and therefore highly relevant within the framework of the metabolic syndrome.

A recent review paper by Opie and Schall [13] dealt in detail with the metabolic, and in particular the diabetogenic, actions of various groups of antihypertensive agents. In this connection, 'older' and 'modern' antihypertensive drugs were distinguished. Thiazide diuretics and β-blockers were classified as the 'older' antihypertensive agents, whereas calcium antagonists, ACE inhibitors and AT_1 receptor blockers were considered to be the 'modern' antihypertensive drugs. These two categories of drug were compared by means of a meta-analysis, including seven large-scale intervention trials, involving 58 010 patients. In a follow-up period of 4 years, particular attention was paid to newly developed diabetes. ACE inhibitors and AT_1 blockers reduced the number of new cases of diabetes by 20%, whereas for the calcium antagonists this reduction amounted to 16%. In contrast, the 'older' antihypertensives significantly increased the incidence of new cases of diabetes, probably by a factor of 4.

Furthermore the Antihypertensive Treatment and Lipid Profile in the North of Sweden Efficacy Evaluation (ALPINE) trial [14], performed in patients with hypertensive metabolic syndrome, has demonstrated important metabolic differences between two different treatment regimens: hydrochlorothiazide + atenolol, and candesartan + felodipine. Both treatment schedules caused a satisfactory and similar control of blood pressure. Interestingly, treatment with the diuretic + β-blocker combination appeared to be associated with a significantly larger number of new cases of diabetes mellitus type 2, and was accompanied by higher plasma triglyceride concentrations. In contrast, treatment with combination candesartan + felodipine, leading to the same degree of decrease in blood pressure, was not accompanied by any significant metabolic/endocrine changes. The former treatment also enhanced the occurrence of new cases of the

metabolic syndrome, whereas the latter treatment did not [14].

Taking together the findings of Opie and Schall and ALPINE, the potential diabetogenic action of thiazide diuretics and β-blockers would speak against their use in patients with the metabolic syndrome, for whom the more modern antihypertensive agents (ACE inhibitors, AT_1 receptor blockers, calcium antagonists) appear to be preferable [15].

Irrespective of the occurrence of the metabolic syndrome, it should be assumed that young hypertensive patients will be treated for several decades. Accordingly, these modern antihypertensive agents appear to be preferable over the metabolically unfavorable thiazide diuretics or β-blockers.

Finally, it may be of interest to note the dual activity of the AT_1 blocker, *telmisartan*, which is also an insulin sensitizer, thanks to its PPAR-γ-stimulating activity [16]. The clinical relevance of these dual activities remains to be established.

Atherogenic dyslipidemia

Improvement in the diet, already mentioned with respect to prevention and general measures, remains the cornerstone of the treatment of atherogenic dyslipidemia; this is true also for patients with the metabolic syndrome. A significant percentage of the latter patients additionally require treatment with lipid-decreasing drugs (antilipemics, hypolipemics). In this context, antilipemic drug treatment will be mandatory more and more often in patients with hypertension or type 2 diabetes mellitus, or both.

The management of hyperlipidemia in patients with the metabolic syndrome is performed according to the same principles as in patients without this syndrome, and is based upon aberrations in the plasma lipids. The hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins) have acquired and maintained a very important position. In most countries, several statins are registered. To date, it is not possible to express a preference for one particular preparation to be used in patients with the metabolic syndrome. The widest experience in various categories of patients has been acquired with simvastatin, now available as a generic preparation.

The importance of the high triglyceride concentrations in patients with the metabolic syndrome may require the additional use of fibrates, nicotinic acid or its derivatives, or both. (For reviews of lipid decreasing treatment, see references [17] and [18].)

Enhanced coagulability (prothrombotic state)

If necessary, enhanced coagulability can be corrected by means of an antithrombotic drug; in practice, acetylsalicylic acid (ASA, aspirin), a classic antiplatelet drug, has always been used. According to the general advice of the American Heart Association, aspirin prophylaxis should be applied in patients with a $\geq$ 10% risk of developing a coronary event within a period of 10 years, based upon the criteria of the Framingham risk schedule [19]. Some, but not all, patients with the metabolic syndrome will meet these criteria.

Conclusions and perspectives

The awareness of the metabolic syndrome as a well-defined and relevant pathological entity has stimulated interest in pharmacological intervention. The heterogenous backgrounds of the syndrome mean that clinical trials concerning drug treatment of the syndrome are bound to be complex and difficult to design. Furthermore, drug treatment targeting the various components of the metabolic syndrome has been demonstrated to be largely differential for the categories of the drugs required for this purpose.

The recognition that insulin resistance is an important background to the metabolic syndrome has led to a new classification of *antihypertensive drugs*, to be differentiated into 'old' and 'new' categories. Newer drugs, such as ACE inhibitors, AT_1 blockers (ARBs), and probably also the calcium antagonists, appear to offer a better metabolic profile than the older thiazide diuretics and β-blockers, in particular for the long-term treatment of young patients who have hypertension and the metabolic syndrome. The same holds for the treatment of *type 2 diabetes mellitus*, for which the newer insulin sensitizers, the thiazolidinediones (glitazones), offer a potentially more favorable metabolic profile than the classical oral antidiabetic agents.

The pharmacological treatment of atherogenic dyslipidemia has made substantial progress, in particular owing to the development of the statins. Although little studied in specific trials targeting the metabolic syndrome, the use of statins in patients with the metabolic syndrome who have hyperlipidemia appears to be mandatory, although to date none of the statins can be put forward as preferable over the others. Furthermore, the relevance of decreasing increased triglyceride concentrations and increasing high-density lipoprotein concentrations by means of fibrates or derivatives of nicotinic acid is now accepted widely, including in patients with the metabolic syndrome.

Finally, the pharmacological treatment of *obesity* remains a difficult and disappointing issue. The two drugs registered for this purpose (sibutramine and orlistat) are far from optimal and are difficult to use in the long term. New approaches based on modulating

the endocannabinoid system by means of the CB_1 receptor antagonist, rimonabant, do at least offer a potentially new route of intervention. In addition, improved knowledge of the several hormones involved in the control of body weight regulation (such as ghrelin, leptin, PYY) may offer new approaches to the pharmacological treatment of obesity.

Generally speaking, it can be concluded that the drug treatment of hypertension and atherogenic dyslipidemia, including that in patients with metabolic syndrome, can be considered to be satisfactory. The management of type 2 diabetes remains a more difficult and less successful issue, although the introduction of the newer insulin sensitizers may offer better perspectives. The drug treatment of obesity, a very major component in the metabolic syndrome, also continues to be disappointing. A few newer perspectives for this purpose are emerging, and improvements in this field are highly desirable. ■

* See glossary for definition of these terms.

REFERENCES

1. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005;365:1415–1428.
2. Grenrodic SM, Brewer HB, Cleeman JI, et al. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation*. 2004;109: 433–438.
3. Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome. *Circulation*. 2005;11:1448–1454.
4. Pedrinelli R, Dell'Omo G, Penno G, et al. Microalbuminuria, a parameter independent of metabolic influences in hypertensive men. *J Hypertens*. 2003;21:1163–1169.
5. Malik S, Wong ND, Franklin SS, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, and all causes in United States adults. *Circulation*. 2004;110:1245–1250.
6. Isomaa B. A major health hazard: the metabolic syndrome. *Life Sci*. 2003;73:2395–2411.
7. Grundy SM, Hansen B, Smith SC Jr et al. Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management. *Circulation*. 2004;109:551–556.
8. De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and other Societies on Cardiovascular Disease in Clinical Practice. *Eur J Cardiovasc Prev Rehabil*. 2003;10:S1–S78.
9. Hundal RS, Inzucchi SE. Metformine. *Drugs*. 2003;63:1879–1894.
10. Van Gaal LF, Rissanen AM, Scheen AJ, et al., for the RIO-Europe Study Group. Effects of the cannabinoid-1-receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet*. 2005;365:1389–1397.
11. Yki-Järvinen H. Thiazolidinediones. *N Engl J Med*. 2004;351: 1106–1118.
12. Kendale DM, Sobel BE, Coulston AM, et al., for the Partners Against Insulin Resistance Advisory Panel. The insulin resistance syndrome and coronary artery disease. *Coron Artery Dis*. 2003;14:335–348.
13. Opie LH, Schall R. Old antihypertensives and new diabetes. *J Hypertens*. 2004;22:1453–1458.
14. Lindholm LH, Persson M, Alanpovic P, Carlberg B, Svensson A, Samuelsson O. Metabolic outcome during 1 year in newly detected hypertensives: results of the Antihypertensive Treatment and Lipid Profile in the North of Sweden Efficacy Evaluation (ALPINE-study). *J Hypertens*. 2003;21:1563–1574.
15. Ruilope LM, Segure J, Schiffrin E. ACE-inhibition of angiotensin receptor blockade: which should we use in diabetic patients? *J Renin Angiotensin Aldosterone Syst*. 2003;4:74–79.
16. Schupp M, Janke J, Clasen R, Unger T, Kintscher U. Angiotensin type I receptor blockers induce peroxisome proliferator-activated receptor activity. *Circulation*. 2004;109: 2054–2057.
17. Low MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ*. 2003;326:1423–1427.
18. Vrecer M, Turk S, Drinovec J, Mrhar A. Use of statins in primary and secondary prevention of coronary heart disease and ischemic stroke. Meta-analysis of randomized trials. *Int J Clin Pharmacol Ther*. 2003;41:567–577.
19. Peasson TA, Blair SM, Daniels SR, et al., for the American Heart Association Science Advisory and Coordinating Committee. AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update. Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. *Circulation*. 2002;106:388–391.