

# Metabolic syndrome, inflammation and atherosclerosis

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**Abstract:** The inflammatory component of atherogenesis has been increasingly recognized over the last decade. Inflammation participates in all stages of atherosclerosis, not only during initiation and during evolution of lesions, but also with precipitation of acute thrombotic complications. The metabolic syndrome is associated with increased risk for development of both cardiovascular disease and type-2 diabetes in humans. Central obesity and insulin resistance are thought to represent common underlying factors of the syndrome, which features a chronic low-grade inflammatory state. Diagnosis of the metabolic syndrome occurs using defined threshold values for waist circumference, blood pressure, fasting glucose and dyslipidemia. The metabolic syndrome appears to affect a significant proportion of the population. Therapeutic approaches that reduce the levels of proinflammatory biomarkers and address traditional risk factors are particularly important in preventing cardiovascular disease and, potentially, diabetes. The primary management of metabolic syndrome involves healthy lifestyle promotion through moderate calorie restriction, moderate increase in physical activity and change in dietary composition. Treatment of individual components aims to control atherogenic dyslipidemia using fibrates and statins, elevated blood pressure, and hyperglycemia. While no single treatment for the metabolic syndrome as a whole yet exists, emerging therapies offer potential as future therapeutic approaches.

**Keywords:** metabolic syndrome, systemic inflammation, coronary artery disease

## Metabolic syndrome

It has been known for more than 40 years that the risk factors for coronary heart disease (CHD) include hypertension, elevated levels of low-density lipoprotein cholesterol (LDL-C), smoking, and type-2 diabetes. Yet, extensive research has established that several of these cardiovascular risk factors cluster to a greater degree than can be explained by chance. In the last few years, this clustering of symptoms has been ascribed to a specific condition: the metabolic syndrome (MS). The MS is a cluster of the most dangerous heart attack risk factors: diabetes or prediabetes, abdominal obesity, changes in cholesterol and high blood pressure (Eckel et al 2005). The basis for this aggregation of metabolic disorders has been investigated in an epidemiological analysis carried out in the adult population of a small Pacific island, leading to the identification of four independent factors that explained 73% of the total variance (Shmulewitz et al 2001). This refinement in the clustering, however, is lost when factors are all packaged together. In a re-analysis of the West of Scotland Coronary Prevention Study (WOSCOPS), risk prediction increased with the number of metabolic abnormalities (Sattar et al 2003). Evidence suggests that it is the exact nature of the cluster which appears to bring additional risk over and above that which would be expected from each of the components (Reilly and Rader 2003). It has been argued, though, that the combination of risk factors does not add up to a more significant or higher cardiovascular risk than the individual components (Kahn et al

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2005). Whether or not it is accepted that MS is a specific disease entity or just a constellation of factors, the prevalence of this condition is increasing worldwide, and patients need to improve these risk factors through either lifestyle or pharmacological approaches to reduce the odds of developing diabetes and cardiovascular disease.

MS appears to affect a significant proportion of the population. While up to 80% of the almost 200 million adults worldwide with diabetes will die of cardiovascular disease, people with MS are also at increased risk, being twice as likely to die from, and three times as likely to have a heart attack or stroke compared with people without the syndrome (Isomaa et al 2001). People with MS have a 5-fold greater risk of developing type-2 diabetes if not already present (Stern et al 2004). This puts MS and diabetes way ahead of HIV/AIDS in morbidity and mortality terms, yet the problem is not as well recognized.

## Definitions and prevalence of MS

Two somewhat different definitions of the syndrome have been proposed: the first one by the World Health Organization (WHO) (Alberti and Zimmet 1998), and the second by the US National Cholesterol Education Program (NCEP) in 2001 (NCEP 2001). Both definitions share the essential components: glucose intolerance, obesity, hypertension, and dyslipidemia. They do differ, however, in detail and criteria (Table 1). Building on the earlier

definitions, the new consensus definition proposed by the International Diabetes Federation in April 2005 is mainly based on abdominal obesity as a central core of the syndrome. It avoids the need for measurements that may only be available in research settings. For a person to be defined as having MS, the new definition requires the presence of central obesity, plus two of the following four additional factors: raised triglycerides, reduced high-density lipoprotein cholesterol (HDL-C), raised blood pressure, or raised fasting plasma glucose level. Gender and, for the first time, ethnicity-specific cut-points for central obesity as measured by waist circumference are included (Table 1). It should be pointed out that these are operational definitions and a definition using cluster analysis with likelihood of having high risk cluster as continuous variable may be more useful.

Although the use of different definitions up until now has made it difficult to estimate the prevalence of MS and make comparisons between nations, recent data from Australia and the US provides a broad estimate of 20%–25% of the adult population (Dunstan et al 2002; Ford et al 2002). Of the 8608 participants in the Third US National Health and Nutrition Examination Survey (NHANES III), all aged at least 20 years, the age-adjusted prevalence of MS was approximately 25%. The incidence rate increases with age and the prevalence of CHD is increased in patients with this condition. Most importantly, MS heavily affects

**Table 1** Definitions of the metabolic syndrome

World Health Organization	NCEP ATP III	International Diabetes Federation
<p>At least one of the following criteria of <i>insulin resistance and impaired glucose regulation</i></p> <p>impaired FPG <math>\geq 110</math> mg/dL</p> <p>impaired PG tolerance (2h PG <math>\geq 140</math> mg/dL)</p> <p>elevated insulin levels (4th quartile of reference) diabetes</p> <p>Plus two or more of the following:</p> <p>Systolic BP <math>\geq 140</math> mm Hg and/or diastolic BP <math>\geq 90</math> mm Hg</p> <p>TG <math>\geq 150</math> mg/dL and/or HDL-C <math>&lt; 35</math> mg/dL for men and <math>&lt; 40</math> mg/dL for women</p> <p>Central obesity: waist/hip ratio <math>&gt; 0.90</math> for men and <math>0.85</math> for women and/or BMI <math>&gt; 30</math> kg/m<sup>2</sup></p> <p>Microalbuminuria: urinary albumin excretion rate <math>\geq 20</math> mg/ml or albumin/creatinine ratio <math>\geq 30</math> mg/g</p>	<p>Abdominal obesity as defined by:</p> <p>waist circumference <math>&gt; 102</math> cm in men</p> <p>waist circumference <math>&gt; 88</math> cm in women</p> <p>TG <math>\geq 150</math> mg/dL</p> <p>HDL-C in men <math>&lt; 40</math> mg/dL, in women <math>&lt; 50</math> mg/dL</p> <p>BP <math>\geq 130/85</math> mm Hg</p> <p>FPG <math>\geq 110</math> mg/dL</p>	<p>Central obesity defined as:</p> <p>waist circumference <math>\geq 94</math> cm for European men</p> <p>waist circumference <math>\geq 80</math> cm for European women</p> <p>with ethnicity specific values for other groups</p> <p>Plus any two of the following four factors:</p> <p>raised TG level: <math>\geq 150</math> mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality</p> <p>reduced HDL-C: <math>&lt; 40</math> mg/dL (1.03 mmol/L) in males and <math>&lt; 50</math> mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality</p> <p>raised BP: systolic BP <math>\geq 130</math> or diastolic BP <math>\geq 85</math> mm Hg, or treatment of previously diagnosed hypertension</p> <p>raised FPG <math>\geq 100</math> mg/dL (5.6 mmol/L), or previously diagnosed type-2 diabetes</p> <p>If above 5.6 mmol/L or 100 mg/dL, oral glucose tolerance test is strongly recommended but is not necessary to define presence of the syndrome.</p>

**Abbreviations:** ATP, Adult Treatment Panel; BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; PG, plasma glucose; TG, triglycerides.

the younger generations. Looking at more than 1900 children and teenagers aged 12 to 19 living in the US, over 60% of them have at least one metabolic abnormality using a pediatric definition based on the NCEP criteria and almost 10% have MS (de Ferranti et al 2004). The racial and ethnic distribution for MS in this study was similar to that seen in adults, whereby Mexican-Americans have the greatest prevalence (13%) followed by non-Hispanic whites (11%). Thus, the clustering of metabolic abnormalities in children raises major concerns and warrants risk-reducing interventions in the form of a population approach. In a rather similar study, the effect of different degrees of obesity in children on the prevalence of MS and its relationship to insulin resistance was examined in 439 obese, 31 overweight, and 20 nonobese children and adolescents. In this cohort, the overall prevalence of MS is 38.7% in moderately obese subjects and 49.7% in severely obese subjects (Weiss et al 2004). C-reactive protein (CRP) and interleukin 6 (IL-6), which are established biomarkers of inflammation and potential predictors of adverse cardiovascular outcomes, rise with the degree of obesity whereas adiponectin, a biomarker of insulin sensitivity, decrease as obesity increased. These data suggest that pathophysiological mechanisms related to MS in adults are already operative in childhood, which predisposes to increased risk for development of both CHD and type-2 diabetes.

### **MS is associated with excess mortality**

According to the NCEP definition, roughly one third of middle-aged men and women in most Western countries have MS. This represents a potential public health issue, as MS is associated with an increased risk of mortality from CHD, cardiovascular disease, and from all causes. In a prospective cohort study, 1209 Finnish men aged 40 to 60 at baseline (1984–1989), who were free of cardiovascular disease, cancer or diabetes, were followed through 1998. In this cohort, men with MS were 3 to 4 times more likely to die of CHD than were those without the syndrome (Lakka et al 2002). Using data from 11 large population- or occupational-based prospective cohort studies comprising 6156 nondiabetic men and 5356 women, the prevalence of MS was found to be slightly higher in men (15.7%) than in women (14.2%). These individuals have a 1.4-fold increased risk of all-cause mortality and a 2.3 to 2.8 increased risk of cardiovascular death (Hu et al 2004). Accordingly, a recent

prospective study describing the prevalence of MS in acute myocardial infarction (AMI) and assessing its impact on hospital outcomes demonstrates that almost half of all AMI patients also suffer from MS (Zeller et al 2005). In this study, the prevalence of MS was examined in 633 patients hospitalized with AMI within 24 hours of the onset of symptoms. Participants were diagnosed with MS according to the NCEP definition and MS was more prevalent in women and older patients. Analysis of the predictive value of each of the five metabolic-syndrome components for severe heart failure showed that hyperglycemia is the major determinant. Given the ever-increasing prevalence of MS worldwide, this finding has important clinical implications and suggests the importance of evaluating glycemic control during the acute phase of MI.

### **Factors contributing to the development of MS**

While the underlying cause of MS is still the subject of intense debate, both abnormal abdominal fat distribution and insulin resistance have been identified as potential, inter-related causes. The flux of non-esterified fatty acids to the liver is tied into visceral fat accumulation as a contributing factor. Accordingly, MS in older men and women is associated with excess accumulation of visceral abdominal or intramuscular fat, even in normal-weight individuals (Goodpaster et al 2005). This study examined 3035 adults aged 70 to 79, of whom 42% were African Americans. Prevalence of MS was 39% in the entire cohort and highest in obese men and women. Using computed tomography to assess fat distribution, it was found that visceral adipose tissue was nearly 50% higher in participants with MS. Higher subcutaneous adipose tissue as well as higher intermuscular adipose tissue was significantly associated with MS in normal-weight and overweight, but not in obese men, and not in women. Regional fat distribution clearly discriminates those with MS, particularly among the non-obese. This implies that older men and women can have normal body weight and even have relatively lower total body fat but still have MS, due to the amount of adipose tissue located intra-abdominally or interspersed within the musculature.

Like steroid hormone receptors, nuclear peroxisome proliferator-activated receptors (PPAR) are ligand-activated, metabolic transcription factors containing ligand binding and DNA binding domains. PPAR activation by specific ligands results in either induction of repression of target

gene expression. PPAR $\alpha$ , which is expressed in tissues with high-energy demands, is involved in the  $\beta$ -oxidation of fatty acids. PPAR $\gamma$ , which is expressed predominantly in adipose tissue, participates in adipogenesis, glucose homeostasis, and lipid metabolism. PPAR activation can improve metabolic parameters like glucose and lipid levels, but also directly alter relevant vascular responses through regulation of target genes including those encoding adhesion molecules, the ATP-binding cassette transporter 1 (ABCA1), lipoprotein lipase, cytokines, and chemokines (Chinetti-Gbaguidi et al 2005). There have been indications that PPAR $\alpha$  are involved in the pathogenesis of insulin resistance. For instance, PPAR $\alpha$  knock-out mice are protected from diet-induced insulin resistance probably because of inhibition of PPAR $\alpha$ -dependent fatty acid oxidation (Tordjman et al 2001). By contrast, genetic defects in PPAR $\gamma$  can recapitulate all the salient features of MS in humans (Savage et al 2003). Therefore, PPARs are likely to be involved in the development of MS and, accordingly, can serve as potential therapeutic targets for the prevention and treatment of MS (Berger et al 2005).

### Inflammation: the missing link?

The measurement of markers of inflammation has been proposed as a method to improve global cardiovascular risk prediction. Among them are markers of systemic inflammation produced in the liver, such as CRP. When determined with a high sensitivity test, CRP is an independent predictor of future cardiovascular events and adds prognostic information to lipid screening. A wealth of prospective studies relates baseline CRP levels to the risk of first cardiovascular events among individuals with no prior history of cardiovascular disease (Ridker 2003). Although CRP level was not considered a MS marker by NCEP ATP III, it is also increased in patients affected by this syndrome. Ridker et al (2003) noted a gradual increase in median CRP levels in relation to the number of markers of MS in an 8-year follow-up of 14 719 initially healthy American women. In middle-aged Finnish men who participated in a population-based cohort study, CRP concentrations above 3 mg/L were associated to the development of MS, but the relationship was no longer significant after adjustment for lifestyle- and insulin resistance-related factors (Laaksonen et al 2004). It has been argued that statin therapy reduces coronary events by virtue of decreased levels of CRP independent from the effects on LDL-C (Nissen et al 2005; Ridker et al 2005). Statins display

a variety of pleiotropic properties, including their ability to induce dose-dependent decreases in the levels of CRP and other inflammatory biomarkers (Albert et al 2001). Secondary prevention data also demonstrate that therapies designed to reduce inflammation after acute coronary ischemia may improve cardiovascular outcomes (Hansson 2005).

Increasing evidence suggests that chronic, subclinical inflammation is part of MS. The first demonstration thereof pointed out that various components of MS are related to inflammatory markers (CRP, fibrinogen, white cell count) and that dyslipidemia, abdominal obesity, low insulin sensitivity and hypertension parallel increasing levels of CRP (Festa et al 2000). Results are consistent across a variety of ethnic groups that differ in insulin sensitivity. In addition, it is known that glucose and macronutrient intake causes oxidative stress and inflammatory changes while insulin displays antiinflammatory effects. As a result, increased concentrations of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and IL-6 might interfere with insulin action by suppressing insulin signal transduction (Dandona et al. 2004).

Several features of MS, including visceral obesity, are associated with a low-grade inflammatory state (Table 2). Highly sensitive CRP (hsCRP) levels in plasma tend to be elevated in subjects with insulin resistance and obesity; elevated levels of hsCRP are predictors of both CHD and diabetes. The adipose tissue is a source of several molecules, such as leptin, plasminogen activator inhibitor 1 (PAI-1), TNF- $\alpha$ , angiotensinogen and IL-6, that are collectively called adipokines and directly contribute to oxidative damage and vascular inflammation (Dandona et al 2005). Leptin was described to have procoagulant and

**Table 2** The inflammatory component of the metabolic syndrome

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#### Vascular dysfunction

Endothelial dysfunction

Microalbuminuria

#### Proinflammatory state

Elevated hsCRP and SAA

Elevated inflammatory cytokines (TNF- $\alpha$ , IL-6)

Decreased adiponectin levels

#### Prothrombotic state

Increased antifibrinolytic factors (PAI-1)

Increased fibrinogen

#### Insulin resistance

#### Visceral adiposity

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**Abbreviations:** hsCRP, high sensitivity C-reactive protein; IL-6, interleukin 6; PAI-1, plasminogen activator inhibitor 1; SAA, serum amyloid A; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

antifibrinolytic properties. Furthermore, leptin supports thrombus formation and atherogenesis by amplifying vascular inflammation and proliferation (Nieuwdorp et al 2005). TNF- $\alpha$  and leptin can also inhibit insulin-mediated glucose uptake. Thus, increasing evidence implicates the adipocyte as a pathophysiologic contributor to insulin resistance and vascular disease. In contrast, adiponectin, also derived from adipose tissue, circulates in low levels in obese subjects and, importantly, inhibits inflammation and promotes insulin sensitivity. Adiponectin decreases endothelial expression of adhesion molecules (intercellular adhesion molecule-1[ICAM-1], vascular cell adhesion molecule-1[VCAM-1], P-selectin), inhibits foam cell formation in vitro and decreases macrophage phagocytic activity (Yokota et al 2000). Yet resistin, which is expressed primarily in macrophages and is correlated with markers of inflammation (Reilly et al 2005), increases the expression of VCAM-1 and ICAM-1 while enhancing that of monocyte chemoattractant protein-1 (Verma et al 2003). Therefore, adiponectin and resistin interfere with monocyte adherence to vascular endothelium, further promoting monocytic migration to the subendothelial space, one of the key events in the development of atherosclerosis.

The relationship of adiponectin with markers of inflammation, adiposity and insulin resistance was investigated in obese individuals with and without MS. Subjects with MS have significantly lower adiponectin and higher TNF- $\alpha$  compared with subjects without MS. Despite rapid weight loss through caloric restriction for 4–6 weeks, adiponectin and TNF- $\alpha$  concentrations did not change (Xydakis et al 2004). Patients with MS commonly have additional less well-defined metabolic abnormalities including hyperuricemia and raised CRP levels that may be associated with increased cardiovascular risk. As chronic subclinical inflammation appears to participate in the progression of MS and other metabolic disorders, it has been hypothesized that periodontal disease is one such subclinical inflammation (Nishimura and Murayama 2001; Nishimura et al 2005), because successful periodontal treatment may improve metabolic control via reduction of circulating TNF- $\alpha$  concentrations.

The newly proposed definition of MS from the International Diabetes Federation does not include inflammatory parameters. However, the proinflammatory state is regarded as an additional metabolic criterium that appears to be related to MS (Table 2). Elevated hsCRP and serum amyloid protein A (not to be confused with Alzheimer amyloid), elevated inflammatory cytokines (TNF- $\alpha$ , IL-6),

and decreased adiponectin plasma levels should be included in research studies to help determine the predictive power of these extra criteria for cardiovascular disease and/or diabetes. The use of these additional factors in research is intended to allow further modification of the definition and its validation in different ethnic groups.

## Treatment of MS

While no single treatment for the metabolic syndrome as a whole exists yet, it is well established that lifestyle changes, for example, changes in diet and an increase in exercise, form the underlying strategy of treatment (Table 3). When the lifestyle approach seems to be inadequate, it is necessary to treat the individual components of MS so that a reduction in the individual risk associated with each component will likely contribute to reduce the overall impact on cardiovascular disease and diabetes risk (Table 3).

The relevance of diet as a therapeutic strategy in MS is emphasized in a recent study by Esposito and colleagues (2004), who randomized 180 men and women with MS to either a Mediterranean diet or a “prudent diet.” The nutrient composition of the two diets (50%–60% carbohydrates, 15% protein, <30% fat) was similar. After two years, while physical activity levels had increased in both groups to the same degree, patients on the Mediterranean diet lost more weight than the control group and had lower plasma levels of CRP and IL-6, as well as less insulin resistance. Likewise,

**Table 3** Current therapeutic approaches to the treatment of metabolic syndrome

### Primary prevention

*Healthy lifestyle promotion*

Small weight loss

Moderate physical activity

Dietary restriction in calorie intake

Change in dietary composition

### Drug intervention for treatment of individual components

*Atherogenic dyslipidemia*

Statins

Fibrates

Nicotinic acid

*Elevated blood pressure*

No particular agent is preferred, although ACE inhibitors and angiotensin receptor blockers may carry advantage in patients with metabolic disorders

*Insulin resistance and hyperglycemia*

Metformin

Thiazolidinediones

Acarbose

Orlistat

**Abbreviations:** ACE, angiotensin-converting enzyme.

participants on the Mediterranean diet saw their total cholesterol and triglycerides fall and their HDL-C rise over the course of the study significantly more than did participants on the prudent diet. In addition, endothelial function improved in the Mediterranean diet group but remained stable in the control group, although this difference was not quite statistically significant, suggesting a potential mechanistic explanation of benefit. Strikingly, after two years on their respective diets, only 40 out of 90 patients in the Mediterranean diet still had features of MS, compared with 78 out of 90 in the control group. The results of this study represent the first demonstration that a Mediterranean-style diet rich in whole grains, fruits, vegetables, legumes, walnuts, and olive oil might be effective in reducing both the prevalence of MS and its associated cardiovascular risk. The benefits of the diet might be through a reduction in low-grade inflammation associated with MS. Conversely, there are indications that marked reductions in fat intake associated with exercise lead to increased levels of circulating cytokines likely due to enhanced activity of the immune system (Meksawan et al 2004).

In the Diabetes Prevention Program, more than 3200 men and women with impaired glucose tolerance were examined and followed for 3 years (Orchard et al 2005). These subjects were randomized to intensive lifestyle changes (diet and exercise interventions), metformin therapy (850 mg twice daily) or placebo. Incidence of MS at baseline was over 50%. Among participants who did not have MS at baseline, 53% of those in the placebo group went on to develop MS over the mean 3.2 years of follow-up, compared with 47% in the metformin group and 38% in the lifestyle-intervention group. The risk reduction for MS development, as evaluated by proportional hazard analysis, was 41% in the lifestyle group and 17% in the metformin group compared with placebo. Lifestyle interventions appeared to have a positive impact on all of the parameters of MS but HDL-C. By contrast, metformin was effective only at reducing waist circumference and fasting glucose levels. Lifestyle intervention not only prevented new cases of MS but also led to an overall decline in the proportion of participants with MS.

In a substudy from the Arterial biology for the investigation of the treatment effects of reducing cholesterol (ARBITER-2) trial (Taylor et al 2004) supporting the addition of extended-release niacin to statin therapy to increase HDL-C in patients with abnormal glucose tolerance, changes in HDL-C were independently associated with changes in carotid intima-media thickness in patients

with MS after controlling for individual MS determinants (Taylor et al 2005). The utilization of nicotinic acid in diabetic patients has, in the past, been considered problematic due to its glucose-raising effects. Recent data, however, indicate that despite the modest increase in serum glucose levels the overall benefit of nicotinic acid treatment is a marked reduction in cardiovascular events (Canner et al 2005). A new post-hoc analysis of the Bezafibrate Infarction Prevention (BIP) trial identified 1470 patients with MS and revealed that in those patients treatment with bezafibrate (400 mg/d) was associated with a reduced risk of MI as compared with placebo, and cardiac mortality showed borderline significance towards reduction (Tenenbaum et al 2005). Even greater was the effect of bezafibrate treatment on cardiac mortality reduction in those patients with augmented features of MS, ie, with at least four features of MS according to the ATPIII definition. Similarly, a subgroup analysis from the Veterans Affairs HDL Intervention Trial (VA-HIT) shows that the combined events of MI, CHD death, and stroke were reduced more with gemfibrozil at all levels of HDL-C or triglycerides with insulin resistance than without insulin resistance. Unexpectedly, the increases in HDL-C and decreases in triglycerides with therapy were least in the presence of insulin resistance for which the clinical benefit of drug was greatest, suggesting that other properties of fibrate therapy may be more beneficial than changes in lipid concentrations (Robins et al 2003). Whereas statins remain the drug of choice for patients who need to achieve the LDL-C goal, fibrate therapy may represent an alternative for those with a lipid profile typical of MS (Robins 2003). The concomitant use of fibrates could be attractive in patients whose LDL-C is controlled by statin therapy but whose HDL-C and/or triglycerides are still inappropriate.

Ligands that activate PPAR $\gamma$  (thiazolidinediones) may also prove useful because they have antiinflammatory properties and exert direct effects on skeletal muscle that promote insulin action and protect vascular endothelium from the atherosclerotic process (Staels and Fruchart 2005). The antiinflammatory properties of synthetic PPAR $\gamma$  agonists may be explained, in part, by their ability to inhibit production of TNF- $\alpha$  and other proinflammatory cytokines as well as to increase adiponectin expression and secretion (Cabrero et al 2002). Recent thiazolidinedione studies have also demonstrated efficacy in delaying or preventing type-2 diabetes in patients with impaired glucose tolerance (IGT) and insulin resistance (Buchanan et al 2002; Durbin 2004). It has not been ascertained yet whether any of the currently

available thiazolidinediones reduce the risk of cardiovascular disease in subjects with MS, IGT, or diabetes.

New therapies are on the horizon that may address several of the risk factors concurrently, which may have a significant impact on reducing both cardiovascular and diabetes morbidity and mortality. The multiple risk factor approach has been tested in high-risk diabetic patients who were assigned to an intensive multifactorial pharmacological treatment including aspirin, angiotensin-converting enzyme (ACE) inhibitors, dietary supplements, and other medications to control known risk factors. This approach reduced cardiovascular events as well as additional disease conditions by about half with respect to standard therapy (Gaede et al 2003). Clinical data should become available soon for the new generation of PPAR agonists, which interact with both PPAR $\alpha$  and  $\gamma$ -receptors (the glitazars), thereby combining lipid and glycaemic effects. In addition, emerging therapies such as incretin mimetics (exenatide), dipeptidyl peptidase IV inhibitors, protein tyrosine phosphatase 1B inhibitors, leptin receptor antagonists, and cannabinoid receptor blocking agents offer potential as future therapies for MS.

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