The dysmetabolic syndrome, insulin resistance and increased cardiovascular (CV) morbidity and mortality in type 2 diabetes: aetiological factors in the development of CV complications

E Eschwège

SUMMARY
Insulin resistance often clusters with other cardiovascular risk factors, such as obesity, impaired glucose tolerance (IGT), hypertension, dyslipidaemia and impaired fibrinolysis. Collectively, these endocrine and metabolic disturbances are described as the dysmetabolic syndrome, which is also commonly called the “insulin resistance syndrome”, the “metabolic syndrome”, or “syndrome X”. Insulin resistance, working in concert with the other components of the dysmetabolic syndrome, induces deleterious changes to the vascular endothelium and lipid profiles that directly and indirectly promote the progression of atherosclerosis. Insulin resistance in adipocytes, leading to decreased suppression of lipolysis by insulin, may be especially important in this regard. Reduced suppression of lipolysis by insulin in obese subjects is associated with increased levels of fatty acids that damage the arterial wall and promote atherosclerosis. The lipid profiles of insulin-resistant subjects are often characterised by the appearance of hypertriglyceridaemia and small, dense LDL-cholesterol, together with low HDL-cholesterol. In addition, adipocytes are highly active endocrine organs and secrete a range of substances that reduce insulin sensitivity further. The net result of these derangements is a vicious circle, wherein the development of insulin resistance is strongly associated with atherogenic lipid profiles and endothelial dysfunction which, in turn, exacerbates insulin resistance. The consequences for the individual with dysmetabolic syndrome include an increased risk of cardiovascular disease of up to 4-fold compared with subjects without the dysmetabolic syndrome.

Key-words: Dysmetabolic syndrome · Syndrome X · Insulin resistance · Clinical outcomes · Coronary heart disease · Type 2 diabetes.

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Insulin resistance and its metabolic consequences, such as hyperglycaemia, dyslipidaemia, hypertension, are potent risk factors for adverse clinical outcomes, including cardiovascular death and peripheral vascular disease [1, 2]. Insulin resistance is already present in the vast majority of patients before type 2 diabetes is diagnosed, at which time a decline in β-cell function typically marks the transition to type 2 diabetes [3]. Moreover, insulin resistance commonly occurs as part of a cluster of cardiovascular risk factors, which also includes hypertension, dyslipidaemia, obesity, and impaired haemostasis [4]. These risk factors, known collectively as the “dysmetabolic or metabolic syndrome”, the “insulin resistance syndrome” or “syndrome X”, are common in the type 2 diabetic population, and are undoubtedly responsible for much of the excess cardiovascular mortality observed in this type 2 diabetic population [1, 5].

Insulin resistance and the dysmetabolic syndrome are closely associated. Indeed, more than 95% of men with dysmetabolic syndrome may be insulin resistant [6]. Research carried out during the last decade has clarified the central role of insulin resistance and the dysmetabolic syndrome in the genesis and development of macrovascular diabetic complications. Insulin resistance, with its attendant hyperinsulinaemia, not only contributes to the hyperglycaemia of type 2 diabetes, but has also been associated, directly and indirectly, with deleterious changes in the vasculature, including the progression of atherosclerosis that may ultimately lead to myocardial infarction and stroke. This review explores the relationships between insulin resistance, the dysmetabolic syndrome, and the genesis and progression of cardiovascular disease in patients with type 2 diabetes.

Table I
Definitions of the metabolic syndrome from the World Health Organisation (WHO) [7], the European Group for the Study of Insulin Resistance (EGIR) [8] and the US National Cholesterol Education Program (NCEP) [9].

<table>
<thead>
<tr>
<th>WHO</th>
<th>EGIS</th>
<th>NCEP</th>
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<tbody>
<tr>
<td><strong>Insulin resistance</strong> (glucose uptake below lowest quartile for background population under investigation)</td>
<td><strong>Hyperinsulinaemia</strong> (fasting insulin concentration above the upper quartile of the non-diabetic population)</td>
<td><strong>Fasting plasma glucose ≥ 6.1 mmol/L (110 mg/dL)</strong></td>
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<td>and/or</td>
<td><strong>Hyperglycaemia</strong> (fasting plasma glucose ≥ 6.1 mmol/L [110 mg/dL] and/or 2 h post-load plasma glucose &gt; 7.8 mmol/L [140 mg/dL])</td>
<td><strong>Blood pressure ≥ 130/85 mmHg</strong></td>
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<tr>
<td><strong>Impaired glucose regulation</strong> (fasting plasma glucose ≥ 6.1 mmol/L [110 mg/dL] and/or 2 h post-load plasma glucose ≥ 7.8 mmol/L [140 mg/dL])</td>
<td><strong>Hypertension</strong> (systolic blood pressure ≥ 140 mmHg, and/or diastolic blood pressure ≥ 90 mmHg, and/or receiving treatment for hypertension)</td>
<td><strong>Triglycerides ≥ 1.7 mmol/L (150 mg/dL)</strong></td>
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<tr>
<td><strong>Raised triglycerides, low HDL-cholesterol</strong> (plasma triglycerides &gt; 1.7 mmol/L [150 mg/dL] and/or HDL-cholesterol &lt; 0.9 mmol/L [35 mg/dL] for men or &lt; 1.0 mmol/L [39 mg/dL] for women)</td>
<td><strong>Dyslipidaemia</strong> (plasma triglycerides &gt; 2.0 mmol/L [180 mg/dL] and/or HDL-cholesterol &lt;1.0 mmol/L [40 mg/dL] and/or treatment for dyslipidaemia)</td>
<td><strong>HDL-cholesterol &lt; 1.0 mmol/L (40 mg/dL) in men, &lt; 1.3 mmol/L (&lt; 50 mg/dL) in women</strong></td>
</tr>
<tr>
<td><strong>Central obesity</strong> (waist/hip ratio &gt; 0.90 for men or &gt; 0.85 for women and/or body mass index &gt; 30 kg/m²)</td>
<td><strong>Central obesity</strong> (waist girth ≥ 94 cm for men, ≥ 80 cm for women)</td>
<td><strong>Abdominal obesity</strong> (waist girth &gt; 102 cm in men, &gt; 88 cm in women; some men with waist girth &gt; 94 cm may develop metabolic risk factors through a genetic predisposition to insulin resistance, and would benefit from similar lifestyle interventions to men with waist girth &gt; 102 cm)</td>
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<tr>
<td><strong>Microalbuminuria</strong> (urinary albumin excretion rate ≥ 20 mg/min or albumin/creatinine ratio &gt; 30 mg/kg)</td>
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Definitions and prevalence of the dysmetabolic syndrome

Three definitions of the dysmetabolic syndrome are currently in use (Table I). The World Health Organisation (WHO) has proposed a definition based on the occurrence of either hyperinsulinaemia (a surrogate for insulin resistance) or impaired fasting glucose, together with abdominal obesity, dyslipidaemia and obesity [7]. However, the European Group for the Study of Insulin Resistance (EGIR) have recommended a modification to the original WHO definition. While the original definition includes a measure of obesity based on either waist-hip ratio or body mass index, EGIR suggested that a waist girth measurement should be used [8]. The National Cholesterol Education Program (NCEP) in the USA have proposed a further definition for clinical practice,
Insulin resistance and cardiovascular outcomes

based on the presence of three cardiovascular risk factors from elevated fasting plasma glucose, hypertriglyceridaemia, low HDL-cholesterol, hypertension, and abdominal obesity [9].

The EGIR definition provided a rather lower prevalence of the dysmetabolic syndrome in men, compared with the WHO definition (11% vs 15% for men aged < 40 years, 16% vs 23% for men aged 40-55 years, and 23% vs 33% for men aged > 55 years) [10]. The prevalence figures for women, however, were almost identical (4% in each case for women aged < 40 years, 9% vs 10% for women aged 40-55 years and 16% in each case for women aged > 55 years). A recent analysis has pooled the data from a number of European studies [11]. While the prevalence according to the WHO syndrome was again somewhat higher than that of the EGIR, the general pattern was the same, with a step increase with increasing age, and a higher prevalence in men than in women (Fig 1).

Overall, about a quarter of the population above the age of 55 years were found to have the dysmetabolic syndrome according to the WHO or EGIR definition. A similar prevalence estimate was obtained from a recent analysis based on a cohort of 1,005 middle-aged Finnish men followed up for 4 years [6]. In the USA, the age-adjusted prevalence of dysmetabolic syndrome according to the NCEP and WHO definitions in the 20,050 people studied within the third National Health and Nutrition Examination Survey (NHANES III) was 24% and 25%, respectively [12]. The prevalence was comparable for men and women in the general US population, but was substantially higher for women in some ethnic groups, such as African Americans and Mexican Americans (Fig 2).

![Figure 1](image1.png)

**Figure 1**

![Figure 2](image2.png)

**Figure 2**
Age-adjusted prevalence of the dysmetabolic syndrome in the USA [12].
Insulin resistance, dysmetabolic syndrome and clinical outcomes

Type 2 diabetes

Individuals with insulin resistance are at a markedly increased risk of developing type 2 diabetes. Data from the Paris Prospective Study, based on a population of 5,042 white, middle-aged men, who were strictly normoglycaemic, found that fasting hyperinsulinaemia was strongly and significantly associated with the risk of developing type 2 diabetes during a 3-year follow-up period [13]. Similar data are available from the Micronesian population of Nauru, where plasma C-peptide increased in parallel with 2-h post-load glucose levels, suggesting that an increase in insulin resistance was associated with the onset of type 2 diabetes [14]. Further evidence comes from the USA, where a 7-year study of 714 Mexican-American subjects revealed that the risk of developing type 2 diabetes increased in line with fasting insulin [15]. The relative risks of developing diabetes in the second, third and fourth (highest) quartiles of fasting insulin were 1.5, 2.0 and 3.7, relative to the first (lowest) quartile (p < 0.0001). A similar and highly significant (p < 0.001) relationship was observed when the ratio between insulin and glucose concentrations 30 minutes after an oral glucose load was measured instead of fasting insulin. The dysmetabolic syndrome is also strongly associated with the development of type 2 diabetes. In the observational study in 1,005 Finnish men, described above, individuals with WHO or EGIR dysmetabolic syndrome were roughly 7-9 times more likely to develop type 2 diabetes, compared with individuals without the dysmetabolic syndrome (Fig 3) [6].

Cardiovascular events

Epidemiological studies have clearly defined the relationships between insulin resistance and the dysmetabolic syndrome and poor cardiovascular outcomes. For example, the Botnia Study surveyed a total of 4,483 subjects aged 35-70 years in Finland and Sweden, with the dysmetabolic syndrome defined using the WHO criteria [16]. The subjects were stratified for the presence of absence of dysmetabolic syndrome, and the prevalence of coronary heart disease (defined as a diagnosis of, or treatment for, angina pectoris or a previous myocardial infarction), previous myocardial infarction, or previous stroke (Fig 4). Type 2 diabetic patients were more likely to suffer a cardiovascular event, compared with individuals who were either normoglycaemic at baseline or who had less advanced forms of dysglycaemia, as would be expected. The relative risks of cardiovascular dis-

Figure 3
The presence of components of the dysmetabolic syndrome is associated with an increased risk of developing type 2 diabetes [6].

Vertical bars are 95% CI.

<table>
<thead>
<tr>
<th>Odds ratios for developing type 2 diabetes</th>
<th>Waist-hip ratio&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Waist girth&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Waist &gt; 102 cm</th>
<th>Waist &gt; 94 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified WHO definitions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCEP definition&lt;sup&gt;c&lt;/sup&gt;</td>
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<sup>a</sup>Adiposity defined as waist/hip ratio > 0.90 or body mass index > 30 kg/m²; <sup>b</sup>abdominal obesity defined as waist girth > 94 cm; <sup>c</sup>see definitions relating to abdominal obesity shown in Table I. Vertical bars are 95% CI.
ease associated with the dysmetabolic syndrome were generally higher in diabetic subjects, though the presence of dysmetabolic syndrome was strongly and significantly associated with adverse cardiovascular outcomes, irrespective of the glycaemic status at baseline.

A similar comparison was made within two groups of 85 type 2 diabetic patients, with and without dysmetabolic syndrome (WHO definition), who were matched for age, gender, duration of diabetes and the level of glycaemic control [17]. The patients with the dysmetabolic syndrome were more likely to have cardiovascular disease (52% vs 21%, p < 0.001), albuminuria (23% vs 7%, p = 0.003) or peripheral neuropathy (16% vs 6%, p = 0.048), compared with the group who did not have the dysmetabolic syndrome. Elevated HbA1C, on the other hand, correlated significantly with the risk of neuropathy, retinopathy and microalbuminuria, but not with coronary heart disease. This analysis is consistent with the results of the larger analysis, described above.

Two prospective observational studies in Scandinavia have added further to the evidence base for adverse cardiovascular outcomes in subjects with the dysmetabolic syndrome. The Kuopio Ischaemic Heart Disease Risk Factor Study followed up 1,209 Finnish men with the dysmetabolic syndrome, but without cardiovascular disease or diabetes at baseline, for an average of 11.6 years [18]. The presence of the dysmetabolic syndrome was associated with a 3-4-fold increase in the risk of death from coronary heart disease or cardiovascular disease (Fig 5). The second study evaluated a population of 6,851 diabetic and 249 non-diabetic middle-aged (50-59 years) men in Sweden. Their clinical outcomes were stratified on the basis of their glycaemic status and cardiovascular risk factor profile at baseline [19]. Individual risk factors characteristic of the dysmetabolic syndrome exerted a markedly greater influence on cardiovascular risk in diabetic men, compared with non-diabetic men (Fig 6). This study underlines the urgency of an aggressive cardiovascular risk factor management in patients with type 2 diabetes.

Insulin resistance and hyperinsulinaemia, within the dysmetabolic syndrome, therefore appear to play a central role in the pathogenesis of cardiovascular disease in type 2 diabetic patients. The Paris Prospective Study evaluated the impact of various metabolic and disease factors on clinical outcomes in 6,903 middle-aged men (45-53 years at baseline) during a follow-up period of 23 years [20]. Elevated levels of fasting plasma insulin, corresponding to the fourth and fifth quintiles of this parameter, were positively and significantly (p < 0.05) associated with the risk of death from coronary heart disease after adjustment for age (Fig 7). Although the relationship between hyperinsulinaemia and coronary or cardiovascular death was no longer significant after adjustment for other risk factors, elevated fasting insulin remained an independent risk factor for all-cause mortality (p < 0.001).
Figure 5
Cumulative incidence of coronary heart disease and cardiovascular disease in subjects with the dysmetabolic syndrome (DMS) [18].

Figure 6
Influence of risk factors characteristic of the dysmetabolic syndrome on deaths from coronary heart disease (CHD) in non-diabetic and diabetic men: data from a prospective cohort study in 7,100 middle-aged men [19].

Figure 7
Association between hyperinsulinaemia and adverse cardiovascular outcomes: 23-year data from the Paris Prospective Study [20].
Clinical mechanisms

Mechanisms of atherogenesis

The process of atherogenesis depends on a series of pathophysiological processes occurring in concert. An atherogenic lipid profile, dysfunction within the vascular endothelium, the recruitment of inflammatory cells, all work hand in hand, among other factors, to drive the production of an atherosclerotic plaque. The process may be considered to begin with the accumulation of lipoproteins within the extracellular matrix of the endothelial surface [21]. Inflammatory cells, such as primed polymorphonuclear leukocytes, then bind to adhesion molecules presented on the endothelial surface [22]. These cells then enter the vascular wall, where they are transformed into macrophages under the influence of locally-generated cytokines. The newly-generated macrophages avidly take up lipids and become foam cells. The accumulation and degradation of foam cells generates, first, fatty streaks within the vessel wall, followed by the establishment of the lipid core of an atherosclerotic plaque. The subsequent rupture of the plaque provides the substrate for the formation of a thrombus that gives rise to a myocardial infarction or stroke.

All of these processes are exacerbated by insulin resistance and/or the dysmetabolic syndrome. Their contributions to some key steps in atherogenesis are considered separately below.

Damage to the vascular endothelium

The vascular endothelium is intimately involved in the maintenance of vascular function [23]. The endothelium also releases potent vasoconstrictors (such as endothelin-1 and angiotensin II) and vasodilator substances (such as prostacyclin and nitric oxide) that regulate vascular tone and blood flow. In addition, endothelium-derived tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) regulate fibrinolysis, and increased secretion of PAI-1 may facilitate the process of atherosclerosis in insulin-resistant individuals [24]. Endothelial cells also secrete a range of growth factors that influence the growth and migration of vascular smooth muscle cells, and provide an anchor point for adhesion molecules (such as LAM, ICAM and VCAM), which provide the means for inflammatory cells to access to sub-endothelial vascular tissue.

Insulin resistance or the dysmetabolic syndrome is often associated with impaired endothelial function, leading to vasoconstriction and a pro-coagulant state that may predispose towards a vascular occlusive event. Evidence from type 2 diabetic patients without clinical evidence of cardiovascular disease suggests that endothelial dysfunction is one of the earliest cardiovascular abnormalities to appear during the progression of type 2 diabetes. This was determined in 72 type 2 diabetic patients who had achieved good glycaemic control on diet therapy and were free of clinical manifestations of cardiovascular disease or diabetic complications [25]. Patients were stratified into those with and without microalbuminuria, a component of the dysmetabolic syndrome which itself confers an elevated cardiovascular risk, patients with microalbuminuria had more evidence of endothelial dysfunction, indicated by an altered redox balance and elevated secretion of endothelial markers including PAI-1, tPA, and endothelin-1, compared with either diabetic patients without microalbuminuria, or non-diabetic control subjects.

Insulin resistance of lipolysis may also be an important factor involved in the impairment of endothelial dysfunction in type 2 diabetes. A study in 53 insulin resistant first-degree relatives of type 2 diabetic patients correlated the extent of endothelium-mediated vasodilation in the brachial artery with the effectiveness of insulin in suppressing circulating non-esterified fatty acid (NEFA) levels during a euglycaemic, hyperinsulinaemic glucose clamp [26]. Circulating NEFA levels were similar in subjects with good or impaired endothelial function in the resting state. However, the degree of impairment of endothelial function correlated significantly with elevations in NEFA levels during the clamp. Further evidence from type 2 diabetic or hypertensive patients subjected to a hyperinsulinaemic clamp suggests an association between whole-body insulin sensitivity, insulin/glucose-mediated vasodilation, and endothelial function [27]. Reduced insulin-mediated suppression of fatty acid levels may therefore provide a link between insulin resistance and impaired vascular function in man.

Oxidative processes may underlie much of the endothelial damage that occurs in diabetes. Elevated fatty acids induce an intracellular signalling cascade that includes the generation of active oxygen species [28]. Some studies indicate that oxidation of lipoproteins increases their atherogenic potential, and that lipids from diabetic subjects are more susceptible to oxidation than lipids from normoglycaemic individuals [29]. Advanced glycation end-products also generate an oxidative environment in the region of the endothelium, which may contribute to the development of endothelial dysfunction and impaired vascular function [23].

Pharmacological interventions which improve insulin sensitivity (metformin or thiazolidinediones) have been shown to improve endothelial function in parallel, in a manner consistent with the above observations [30, 31]. Similarly, interventions designed to reduce triglyceride levels, such as lipid-lowering drugs [32, 33], antioxidant treatment [34] or dietary fish oil supplementation [35] have been shown to reduce circulating triglyceride levels and improve endothelial function in parallel. The Biguanides and the Prevention of the Risk of Obesity (BIGPRO) study recruited a population of subjects who were likely to be insulin resistant due to the presence of central obesity [36]. Study subjects were randomly assigned to 1 year of double-blind treatment with metformin or placebo, each in addition to lifestyle advice. Reductions in body weight, observed in both groups, were accompanied by a 30% reduction in plasminogen activator inhibitor-1 (PAI-1) activity, and a 40% reduction in PAI-1 antigen. In addition, significantly greater reductions in the
secretion of tissue plasminogen activator antigen and von Willebrand factor occurred in the metformin group, relative to placebo. These changes are consistent with improved endothelial function.

**Obesity, hypertriglyceridaemia and accelerated atherosclerosis**

The hepatic metabolism of lipoproteins is to a large extent controlled by insulin, which has implications for the lipids profiles of insulin resistant individuals. Indeed, the dyslipidaemia associated with insulin resistance is commonly characterised by hypertriglyceridaemia, often in conjunction with low HDL-cholesterol and abdominal obesity [5, 37]. The development of obesity, especially abdominal obesity, is an important driving force behind the development of both insulin resistance and atherogenic lipid profiles. Indeed, the presence of concomitant visceral obesity and hypertriglyceridaemia appears to identify a phenotype of insulin resistant patients who are at especially high (20-fold) risk of developing coronary disease [38]. Furthermore, a study in obese women demonstrated that the severity of insulin resistance was correlated with the extent of visceral adiposity [39].

Overall, it appears that insulin resistance in the fat cells of obese individuals may lead to reduced suppression of lipolysis by insulin, which in turn leads to increased circulating levels of free fatty acids. These may then further impair the actions of insulin, setting up a vicious circle of metabolic impairment [40]. For example, a cross sectional study in 200 subjects stratified for glycaemic control showed that triglyceride levels were independently correlated with levels of endothelin-1 in insulin-resistant subjects with IGT or type 2 diabetes [41]. Furthermore, other factors derived from adipocytes, including adiponectin, leptin, tumour necrosis factor-alpha and resistin, may influence insulin sensitivity adversely [42]. These data provide a mechanistic link between insulin resistance, dyslipidaemia and impaired endothelial function.

Hypertriglyceridaemia is associated with the formation of small, dense LDL-cholesterol particles which are believed to be especially atherogenic [43, 44]. This phenomenon was observed in the study of 170 type 2 diabetic subjects, described above, in which the occurrence of dysmetabolic syndrome was associated with the presence of significantly smaller (p < 0.001), triglyceride-rich LDL-cholesterol particles compared with patients without the dysmetabolic syndrome [17]. A further study in 391 healthy individuals, of whom 58 had dysmetabolic syndrome and 81 had fasting plasma glucose > 5.6 mmol/L and/or insulin resistance (hyperinsulinaemia) confirms these associations [45]. The extent of atherosclerosis in the carotid and femoral arteries was quantified by measurement of arterial intima-media thickening, which is indicative of the presence of atherosclerosis. On average, LDL-cholesterol particles were significantly smaller (p < 0.001), and intima-media thickening was significantly greater, in subjects with the dysmetabolic syndrome compared with subjects with no risk factors (p < 0.001). In addition, subjects without evidence of atherosclerosis had larger LDL-cholesterol particles, on average, than subjects who had well-established atherosclerotic plaques (p < 0.05).

LDL-cholesterol receptors are present in platelets, and their activation results in rises in cytosolic calcium concentrations. Activation of platelets in this way is consistent with an increased likelihood of platelet aggregation or binding of platelets to the endothelium, both of which would increase the risk of thrombus formation. The sensitivity of platelets to activation by LDL-cholesterol was studied in platelets from 41 patients with NIDDM. The extent of activation of platelets by LDL-cholesterol was significantly greater in platelets from type 2 diabetic subjects, compared with platelets from non-diabetic control subjects [46]. Moreover, insulin infusions did not mimic this effect, which thus appeared to be associated with long-term insulin resistance, rather than hyperinsulinaemia *per se*.

**Conclusions**

Insulin resistance, in concert with the other cardiovascular risk factors that make up the dysmetabolic syndrome, plays a central role in the pathogenesis of type 2 diabetes and adverse cardiovascular outcomes. The impairment of endothelial function, increased oxidative stress and atherogenic lipid profiles in subjects with the dysmetabolic syndrome all combine to increase the rate of development of atherosclerotic plaques, with the associated increase in the risk of an adverse cardiovascular event. It is essential that we address the metabolic and endocrine defects that give rise to insulin resistance if we are to effectively prevent or to effectively manage type 2 diabetes.

**References**
