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*Diab Vasc Dis Res* 2007; 4; 13

DOI: 10.3132/dvdr.2007.001

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# The insulin resistance syndrome: physiological considerations

SANGEETA R KASHYAP, RALPH A DEFRONZO

## Abstract

**T**he insulin resistance syndrome, also referred to as the 'metabolic syndrome' or 'syndrome X', is associated with a primary cellular defect in insulin action (insulin resistance) and a compensatory increase in insulin secretion. The combination of insulin resistance and subsequent hyperinsulinaemia causes a number of metabolic and cardiovascular changes that result in a syndrome typically characterised by type 2 diabetes, obesity, dyslipidaemia, coronary artery disease and hypertension. Moreover, disturbances in sleep (sleep apnoea) and ovarian dysfunction are also characterised by insulin resistance. The pathophysiological basis for these disturbances reflects the impact of variable genetic and environmental influences. At a molecular level, insulin resistance involves defects of insulin signalling such as reduced insulin receptor tyrosine kinase activity and reduced post-receptor phosphorylation steps that impinge on metabolic and vascular effects of insulin.

*Diabetes Vasc Dis Res* 2007;4:13–19

**Key words:** insulin resistance, visceral adiposity, type 2 diabetes, obesity, hypertension, coronary artery disease.

## Introduction

Insulin resistance and associated hyperinsulinaemia contribute to a syndrome that typically includes several or all of: impaired glucose tolerance or type 2 diabetes, obesity, dyslipidaemia, raised blood pressure and coronary artery disease (table 1).

The evolution of type 2 diabetes requires the presence of defects in both insulin secretion (beta-cell dysfunction) and insulin action (insulin resistance). Both defects have a recognised genetic component as well as an acquired component that includes age, obesity, glucotoxicity and lipotoxicity.<sup>1–3</sup> The earliest detectable abnormality in type 2 diabetes is an impairment in the body's ability to respond to insulin. This

**Table 1. Insulin resistance syndrome**

Obesity
Diabetes/IGT
Hypertension
Ageing
Hyperlipidaemia
Increased PAI-1
Endothelial dysfunction
ASCVD
Hyperinsulinaemia
Insulin resistance

**Key:** IGT = impaired glucose tolerance; ASCVD = atherosclerotic cardiovascular disease; PAI-1 = plasminogen activator inhibitor 1

is counterbalanced by a compensatory increase in insulin secretion by pancreatic beta cells (hyperinsulinaemia) to maintain normal glucose tolerance.

When the fasting plasma glucose concentration exceeds about 140 mg/dL (7.7 mmol/L), however, the beta cell can no longer maintain its elevated rate of insulin secretion, and the fasting insulin concentration declines progressively, resulting in impaired glucose tolerance (IGT) and, eventually, overt type 2 diabetes (figure 1).<sup>4,5</sup> It is important to note that, at this stage, plasma insulin levels remain elevated in absolute terms, but the hyperinsulinaemia is no longer sufficient to offset the severe degree of insulin resistance, and the relative lack of insulin leads to a frankly diabetic state. Only when the diabetic state deteriorates further and fasting plasma glucose concentrations exceed 180–200 mg/dL (9.9–11.0 mmol/L) do mixed meal and glucose-stimulated insulin responses become reduced in absolute terms. Even at this point, however, the fasting plasma insulin concentration remains elevated.<sup>4,5</sup>

Studies have demonstrated conclusively that hyperinsulinaemia, which develops in response to insulin resistance, precedes the development of type 2 diabetes.<sup>6–8</sup> Studies using minimal model, euglycaemic insulin clamp and insulin suppression techniques have provided quantitative evidence that progression to glucose intolerance is associated with the development of marked insulin resistance, whereby plasma insulin concentrations are elevated both in the post-absorptive and prandial states (figure 2). Therefore, the plasma insulin concentration has become a widely accepted surrogate measure of insulin resistance.

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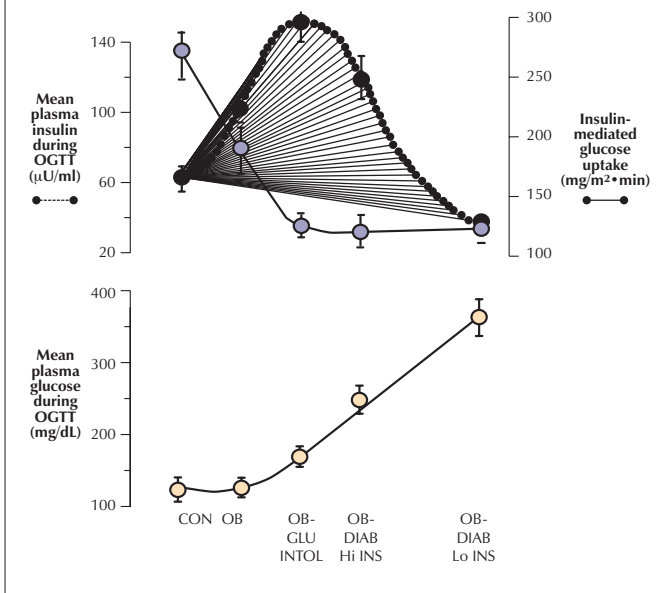
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**Figure 1. Natural history of type 2 diabetes**

Data are obtained during 75 g oral glucose tolerance testing (OGTT) from lean control subjects (CON), obese (OB) glucose-tolerant, obese glucose-intolerant (OB GLU INTOL), obese type 2 diabetes with high insulin secretion (OB DIAB Hi INS), and obese type 2 diabetes with low level insulin secretion (OB DIAB Lo INS) subjects. Mean plasma insulin levels during OGTT for all five groups is a bell-shaped curve called the 'Starling curve of the pancreas'. Peak plasma insulin levels during OGTT occur in obese glucose-intolerant subjects and correspond with lowest levels of glucose disposal rates. Progression to type 2 diabetes is characterised by a decline in mean plasma insulin levels and no further worsening of insulin-mediated glucose uptake. To convert glucose from mg/dL to mmol/L, multiply by 0.055

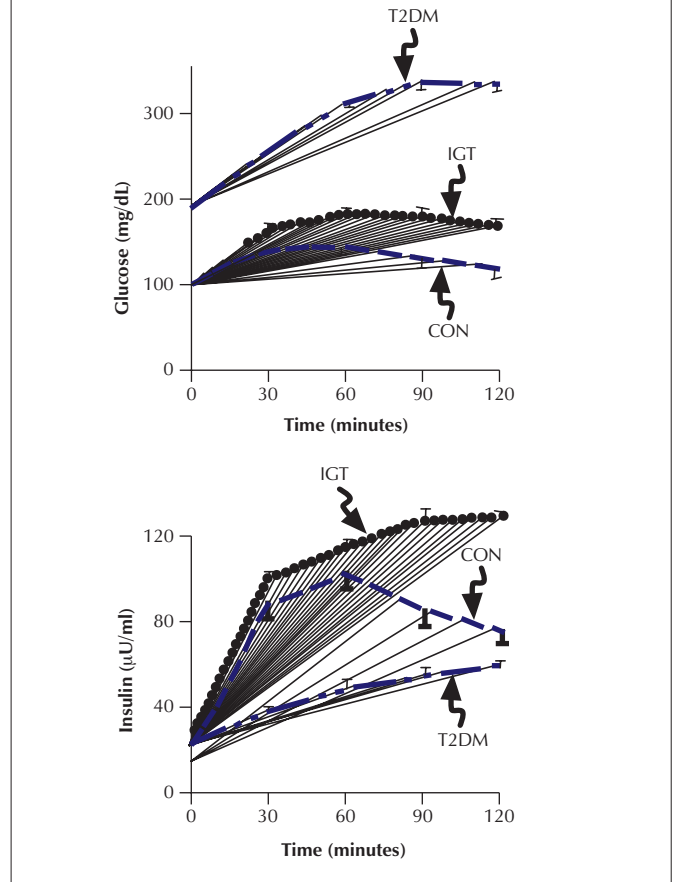


Interestingly, approximately 25% of the healthy glucose-tolerant population exhibits significant insulin resistance by this measure.<sup>9</sup> This was demonstrated in euglycaemic hyperinsulinaemic clamp and hyperglycaemic clamp studies performed in 32 non-obese women with normal oral glucose tolerance tests.<sup>9</sup> The subjects were stratified into quartiles based upon their insulin-mediated rate of glucose uptake during the euglycaemic insulin clamp. Total body glucose disposal varied three-fold, and a highly significant reciprocal relation was identified between insulin-mediated glucose uptake during the euglycaemic insulin clamp (a measure of insulin sensitivity) and pancreatic insulin secretion during the hyperglycaemic clamp studies. These results demonstrate that normal glucose tolerance is maintained by a finely regulated balance between the level of whole-body insulin sensitivity and the demand for insulin secretion by the pancreatic beta cells. Consequently, deterioration of glucose tolerance is heralded by pancreatic beta-cell dysfunction with no further worsening of insulin resistance at peripheral tissues (figure 2).

In the San Antonio Metabolism study, investigators examined the plasma insulin response to glucose levels in relation to glycaemic stimulus and severity of insulin resistance in three groups comprising 138 subjects with normal glucose

**Figure 2. Schematic representation of glucose tolerance and the insulin response to a 75 g oral glucose tolerance test (OGTT)**

Data show the area under the curve (AUC) glucose and insulin levels during OGTT in lean normal glucose-tolerant subjects (CON), impaired glucose-tolerant subjects (IGT) and type 2 diabetes subjects (T2DM). Progression to hyperglycaemia, a characteristic feature of diabetes, is heralded by decreasing plasma insulin levels signifying pancreatic beta-cell dysfunction. Subjects with impaired glucose tolerance are markedly hyperinsulinaemic with maximal plasma AUC insulin levels. To convert glucose from mg/dL to mmol/L, multiply by 0.055



tolerance, 49 with impaired glucose tolerance and 201 with type 2 diabetes. The results indicated a progressive deterioration of pancreatic beta-cell function, beginning as early as in 'normal' glucose-tolerant individuals.<sup>10</sup> Similarly, metabolic studies in genetically predisposed, normal glucose-tolerant individuals with a strong family history of type 2 diabetes have demonstrated marked hyperinsulinaemia in response to the presence of insulin resistance,<sup>11</sup> though the degree of hyperinsulinaemia may not be sufficient to compensate for the severity of insulin resistance. Moreover, subjects with impaired glucose tolerance are reported to be as insulin-resistant as subjects with overt type 2 diabetes.<sup>1-3</sup>

**Visceral adiposity and insulin resistance**

While the relationship between insulin resistance and overall obesity is well established in cross-sectional and longitudinal studies, debate continues about which of the fat

**Table 2. The overflow hypothesis**

Adipocytes represent a storage depot for energy (i.e. fat). When the capacity of adipocytes to store fat is exceeded, there is an overflow of fat to:

Muscle → insulin resistance

Liver → ↑ HGP (GN)

Pancreas → ↓ insulin secretion

Arteries → atherosclerosis

**Key:** HGP = hepatic glucose production; GN = gluconeogenesis

depots, visceral adipose tissue (VAT) or subcutaneous adipose tissue (SAT), is of greater importance in this relationship.<sup>12,13</sup> As part of the Insulin Resistance Atherosclerosis Study (IRAS) family study, Wagenknecht and colleagues studied insulin sensitivity, acute insulin response and disposition index (insulin secretion x insulin sensitivity) in almost 1,500 Hispanic and African-American adults.<sup>12</sup> They found a strong independent relationship between both visceral and subcutaneous adiposity and insulin resistance. Increased levels of fat in these depots were significantly associated with lower insulin sensitivity; VAT was a more potent predictor of insulin resistance than SAT. In another study of 63 subjects with type 2 diabetes, Gastaldelli and colleagues determined that visceral fat accumulation decreased peripheral insulin sensitivity and enhanced hepatic gluconeogenesis.<sup>14</sup>

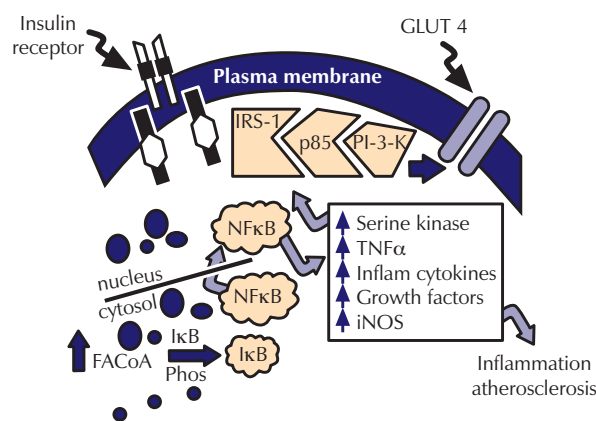
On the other hand, Abate and colleagues found that SAT was more strongly correlated with insulin resistance than VAT in male patients with type 2 diabetes.<sup>15</sup> It appears, however, that the deeper of the two histologically different layers of SAT has an association with insulin resistance that bears resemblance to the pattern for VAT whereas the superficial layer has a weaker association.<sup>16</sup>

It also seems that accumulation of fat within the liver and muscle leads to insulin resistance in these tissues, resulting in elevated fasting plasma glucose levels (due to accelerated hepatic glucose production) and postprandial hyperglycaemia (due to decreased insulin-mediated glucose uptake by muscle).<sup>17-19</sup> Imaging studies of these tissues have demonstrated a linear relationship between the severity of insulin-mediated glucose disposal and the presence of intramyocellular and hepatic fat.<sup>20</sup> Similarly, Greco and colleagues demonstrated that lipid deprivation selectively depletes inter- and intra-myocellular lipid stores and reverses insulin resistance despite a persistent excess of total body fat mass.<sup>21</sup> Moreover, findings from recent animal studies suggest a direct relationship between the accumulation of intracellular fatty acid-derived metabolites in the liver or muscle and insulin resistance in those tissues, mediated via alterations in the insulin signalling pathway.<sup>22</sup>

In addition to the accumulation of visceral fat, insulin resistance of adipose tissue is present in insulin-resistant states such as obesity and type 2 diabetes and is characterised by mean elevations in plasma free fatty acid (FFA) levels which are not suppressed normally after ingestion of a

**Figure 3. The effect of fatty acids on insulin signal transduction pathways**

Fatty acids accumulate in muscle and liver as long-chain fatty acyl CoAs. These intermediate forms lead to NF kappa activation from the nucleus, which in turn initiates inflammatory pathways including cytokine and growth factor production that interfere with insulin-mediated, IRS associated PI3-kinase activation



**Key:** NFκB = nuclear factor kappa B; IκB = inhibitor kappa B; IRS1 = insulin receptor substrate 1; PI-3-K = phosphatidylinositol-3-kinase; p85 and p110 are subunits of PI3K; GLUT4 = glucose transporter isoform 4; TNFα = tumour necrosis factor alpha; iNOS = inducible nitric oxide synthase

mixed meal or oral glucose load.<sup>1,10,11</sup> Insulin is a potent inhibitor of lipolysis and reduces the release of FFA from adipocytes by inhibiting the enzyme hormone-sensitive lipase. In insulin-resistant states such as obesity, hypertension and type 2 diabetes, the ability of insulin to inhibit lipolysis is impaired, resulting in chronically elevated plasma FFA. It is now recognised that plasma FFA are a central component of the insulin resistance syndrome in accordance with the 'overflow hypothesis' (table 2), in that when adipocyte storage capacity is exceeded, there is an overflow and accumulation of FFA in the form of toxic ceramide, long-chain fatty acyl CoA and sphingolipid in muscle, liver, pancreas and arteries, resulting in physiological features of insulin resistance.<sup>10,11</sup> Plasma FFA also contribute to activation of several inflammatory pathways, as shown in figure 3, that hamper insulin signal transduction pathways in muscle tissue.

### Type 2 diabetes and obesity

Both type 2 diabetes and obesity are associated with severe insulin resistance and compensatory hyperinsulinaemia.<sup>4</sup> In type 2 diabetes, insulin resistance is a substantially inherited metabolic defect, whereas obesity and its consequent insulin resistance may be due to either excessive caloric intake or an inherited disturbance in thermogenesis or intermediary metabolism.<sup>5</sup> Both in the basal state and after a hyperglycaemic stimulus, obese people display a level of hyperinsulinaemia that correlates with the degree of insulin resistance, in order to maintain normal glucose tolerance.<sup>17</sup> A number of factors present in obesity (elevated FFA levels, decreased adiponectin and increased adipocytokine levels) are respon-

sible for induction of insulin resistance. However, as in the development of type 2 diabetes, progressive deterioration of the metabolic state results in eventual failure of endogenous hyperinsulinaemia to compensate fully for the insulin resistance, and impaired glucose tolerance develops.<sup>4,5</sup>

Recently, studies have highlighted the inflammatory nature of adipose tissue in the setting of weight gain and obesity and thus have provided another mechanism to the development of insulin resistance.<sup>23</sup> A high body mass index (BMI), increased visceral fat and insulin resistance are associated with increased circulating inflammatory markers such as the acute phase protein, pro-inflammatory cytokines and soluble cell adhesion molecules.<sup>24-26</sup> In rodent models fed a high fat 'western diet', the occurrence of hyperinsulinaemia corresponded to an infiltration of activated macrophages into fat tissue. Moreover, in obese, insulin-resistant individuals circulating mononuclear cells (precursor cells of tissue macrophages) were reported to be in a pro-inflammatory state.<sup>27</sup> Conversely, weight loss was shown to be associated with a reduction of inflammatory mediators such as MCP-1.<sup>28,29</sup> Such observations have led to the hypothesis that low-grade inflammation generated by adipose tissue and FFA is a key player in the development of insulin resistance and endothelial dysfunction, leading ultimately to the manifestation of diabetes and atherosclerosis. Several studies have noted elevated mean circulating cytokine levels (tumour necrosis factor [TNF], interleukin [IL]6) as well as plasma FFA that, in a paracrine approach, inhibit insulin signalling pathways in peripheral tissues and result in decreased whole body insulin-mediated glucose disposal.<sup>24</sup> A small clinical trial of salicylates in rodents and humans has shown improvement in insulin resistance and type 2 diabetes.<sup>23</sup>

### Commonalities between diabetes, obesity and hypertension

Hypertension is prevalent in obesity and in type 2 diabetes, both of which are associated with insulin resistance. Various prospective and cross-sectional studies have now documented a correlation between insulin resistance, hyperinsulinaemia and elevated blood pressure.<sup>30-32</sup> In all of these studies, the major defect in insulin action is diminished non-oxidative glucose disposal, which primarily affects muscle and involves the glycogen synthetic pathway.<sup>4,5</sup> This is the same cellular defect that characterises the insulin resistance of obesity and of diabetes.

From an aetiological standpoint, a number of well-established mechanisms explain the association between hyperinsulinaemia, insulin resistance and hypertension.<sup>5</sup> These include renal sodium retention, sympathetic nervous system activation, stimulation of vascular smooth muscle cell growth and altered cell electrolyte composition. An example of the latter is increased  $\text{Na}^+\text{-H}^+$  pump activity, which may enhance the sensitivity of vascular smooth muscle cells to the pressor effects of norepinephrine, angiotensin and sodium chloride loading.<sup>5</sup> Resistance of the  $\text{Na}^+\text{-K}^+$ -adenosine triphosphatase pump to insulin activity increases intracellular sodium concentrations and decreases intracellular potassium concentrations, which are characteristic abnormalities in hypertension. Finally, decreased  $\text{Ca}^{2+}$ -adenosine triphos-

phatase activity as a result of insulin resistance increases intracellular calcium, leading to vascular hyper-reactivity and hypertension. In the beta cell, this could facilitate compensatory hyperinsulinaemia.

Several studies have also demonstrated that endothelial dysfunction (which is an early abnormality in the development of atherosclerosis) is a common link among obesity, insulin resistance, diabetes and hypertension, because it has been independently correlated with each of these conditions.<sup>33-35</sup> Caballero *et al.* demonstrated impaired brachial artery reactivity and endothelial activation in subjects with increasing severity of insulin resistance.<sup>36</sup> In line with this, *in vitro* studies have documented resistance to insulin in endothelial, vascular smooth muscle and mononuclear cells that results in decreased production of the vasodilatory effects of nitric oxide, and increased endothelin-1 levels.<sup>37,38</sup>

### Commonalities between diabetes, dyslipidaemia and coronary artery disease

Insulin resistance is associated with an atherogenic plasma lipid profile (pattern B: smaller, more atherogenic low-density lipoprotein [LDL] cholesterol, high plasma triglycerides, elevated very-low-density lipoprotein [VLDL] cholesterol, and decreased high-density lipoprotein [HDL] cholesterol concentrations).<sup>39,40</sup> Subjects with an elevated total cholesterol:HDL cholesterol ratio were found to have higher systolic and diastolic blood pressures, in addition to being insulin-resistant, glucose-intolerant and hypertriglyceridaemic.<sup>41</sup> Decreased apolipoprotein A1 levels, increased Lp(a) and increased apolipoprotein B levels further suggest a more atherogenic lipid profile found in subjects with type 2 diabetes.<sup>42</sup>

The combination of augmented VLDL synthesis (secondary to the compensatory hyperinsulinaemia of insulin resistance, elevated circulating plasma FFA and elevated glucose levels) and impaired VLDL removal (secondary to diminished insulin action on lipoprotein lipase) causes a net increase in plasma VLDL and triglycerides and, ultimately, LDL cholesterol. The defect in lipoprotein lipase activity also contributes to the decrease in plasma HDL cholesterol observed in insulin-resistant states.<sup>22</sup>

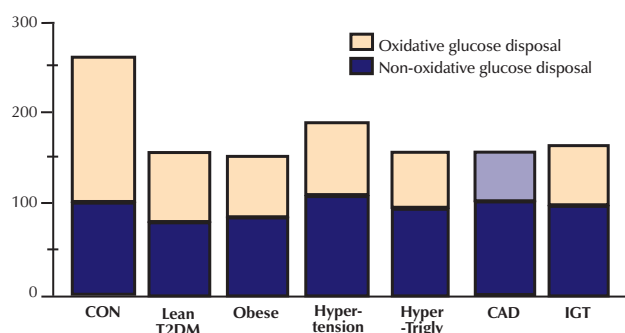
Clinically, the relationship of insulin resistance and dyslipidaemia has been linked to angiographically documented coronary artery disease (CAD). In a study of normal weight, normotensive, healthy glucose-tolerant subjects with angiographically documented CAD versus controls, subjects with CAD had moderate-to-severe insulin resistance (the magnitude of which correlated positively with the severity of CAD) and hyperinsulinaemia.<sup>43</sup>

### Insulin resistance is the underlying link

Taken together, these data suggest that insulin resistance is the common metabolic defect underlying all of these disorders – type 2 diabetes, obesity, hypertension, dyslipidaemia and CAD (figure 4). Clinical evidence for this observation comes from the Barilla Factory Study, in which 647 subjects free of disease were divided into quartiles, based on their plasma insulin response to a glucose challenge at baseline, then observed for 15+ years for the development of IGT/type

**Figure 4. Representative glucose disposal rates determined by euglycaemic hyperinsulinaemic clamp with indirect calorimetry in subjects with insulin resistance syndrome**

Open bars represent oxidative glucose disposal. Shaded bars represent non-oxidative glucose disposal (glycogen synthesis). Compared to control subjects, all groups of subjects have markedly reduced glucose disposal rates characteristic of whole body insulin resistance



Adapted from Bressler and DeFronzo, *Diabetologia* 1996;**39**:1345-50.

**Key:** CON = control; T2DM = type 2 diabetes mellitus; CAD = coronary artery disease; IGT = impaired glucose tolerance; Trigly = triglycerides

2 diabetes, hypertension or coronary heart disease.<sup>44</sup> At follow-up, the 25% of the study population with the lowest level of insulin sensitivity (i.e. the most insulin-resistant subjects) had significant increases in the incidence of IGT or type 2 diabetes (eight-fold), hypertension (two-fold) and coronary heart disease (three-fold) compared with those from the other quartiles.

### Hyperinsulinaemia is atherogenic

In addition to mediating metabolic effects in muscle, liver and adipose tissue, insulin is a vascular hormone.<sup>45</sup> In physiological doses and in lean healthy subjects, insulin is a vasodilator.<sup>46</sup> However, in conditions of insulin resistance and hyperinsulinaemia, insulin causes vasoconstriction in response to intra-arterial infusions of vasodilatory agents such as acetylcholine (which stimulates production of nitric oxide). This suggests that insulin or hyperinsulinaemia may induce endothelial dysfunction in insulin-resistant individuals by interfering with generation of vaso-dilatory and vaso-constrictive substances such as nitric oxide and endothelin-1. There is also much evidence to suggest that insulin is an atherogenic hormone. It has been shown to increase formation and decrease regression of lipid plaques, cause proliferation of smooth muscle cells, increase collagen formation, increase LDL receptor activity, and stimulate growth factors.<sup>45,46</sup>

The results of several animal studies have demonstrated the atherogenicity of insulin *in vivo* convincingly. In one experiment, investigators found that continuous infusion of low-dose insulin into the femoral artery of dogs caused marked intimal and medial proliferation with the accumulation of cholesterol and fatty acids on the insulin-infused side

but had no effect on the contralateral femoral artery or other blood vessels in the body.<sup>47</sup> In another study, cholesterol-fed rabbits that developed severe generalised atherosclerosis were rendered diabetic and insulinopenic with alloxan.<sup>48</sup> The result was marked attenuation of the atherosclerosis. Conversely, insulin replacement in alloxan-induced diabetic rabbits led to severe atherosclerosis. Neither change could be attributed to differences in serum cholesterol concentrations.

These data suggest that the metabolic link between insulin resistance/hyperinsulinaemia and cardiovascular risk factors may explain the 'ticking clock' hypothesis for CAD and type 2 diabetes.<sup>49</sup> According to this hypothesis, the clock for atherosclerosis/CAD begins to tick at birth and is related to the inheritance of the insulin resistance genes and compensatory hyperinsulinaemia, which expose the vasculature to insulin resistance, hyperinsulinaemia and a more atherogenic cardiovascular risk profile for decades before the onset of overt hyperglycaemia. On the other hand, the clock for diabetic microvascular complications does not begin until much later and starts with the onset of overt hyperglycaemia.

All of these data suggest that in addition to diet, exercise, weight loss and aggressive treatment of the individual components of the metabolic syndrome, we should consider earlier treatment of the underlying metabolic defect (that is, insulin resistance) with an insulin-sensitising agent. Although there are multiple treatment strategies and emerging clinical trials for the treatment of the insulin resistance syndrome, this topic is beyond the scope of this review.

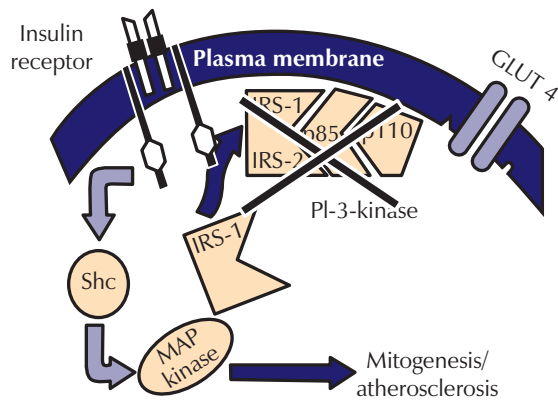
### Molecular aetiology of the insulin resistance syndrome

In order to exert its biological effects on glucose metabolism, insulin must first bind to specific receptors present on the cell surface of insulin target tissues. Once this happens, second messengers are generated that initiate a series of events involving a cascade of phosphorylation-dephosphorylation reactions that result in the stimulation of intracellular glucose metabolism (figure 5).<sup>1</sup> The first step is insulin receptor phosphorylation of the  $\beta$  subunit, with subsequent activation of insulin receptor tyrosine kinase. Activated insulin receptor tyrosine kinase phosphorylates specific intracellular proteins, including insulin receptor substrate-1 (IRS-1) (pivotal for glycogen synthesis in muscle) and IRS-2 (which mediates the effect of insulin on hepatic glucose production, gluconeogenesis and glycogen formation). Activation of phosphatidylinositol-3-kinase results in stimulation of glucose transport and activation of glycogen synthase. IRS-1 activation also activates the mitogen-activated protein-signalling pathway, which promotes cell growth and proliferation. Following the initial steps in insulin signalling, glucose transport is activated by GLUT 4 transporters in muscle. Free glucose is metabolised by a series of enzymatic steps that are under the control of insulin. The most important are glucose phosphorylation (by hexokinase), glycogen synthase (which regulates glycogen synthesis), and phosphofructokinase and pyruvate dehydrogenase (which regulate glycolysis and glucose oxidation, respectively).

One of the receptor defects in type 2 diabetes is a signif-

### Figure 5. Schematic representation of insulin signal transduction pathway that leads to intracellular glucose metabolism

Signalling through PI-3-K is crucial for insulin-mediated glucose transport and activity of this enzyme is reduced in insulin-resistant states. However, IRS-associated MAP kinase activation is intact in subject with insulin resistance, leading to production of growth factors that contribute to atherosclerosis



**Key:** IRS-1 = insulin receptor substrate-1; PI-3-K = phosphatidylinositol-3-kinase; MAP-K = mitogen-activated protein kinase; GLUT 4 = glucose transporter isoform 4; Shc and MAP kinase are signalling intermediates and p85 and p110 are subunits of PI-3-K

icant reduction in insulin-stimulated tyrosine kinase activity. Correction of this defect has been achieved with weight loss and near normalisation of fasting plasma glucose concentration.<sup>1</sup> In addition, the ability of insulin to activate tyrosine phosphorylation of the insulin receptor and of IRS-1 and the association of p85 protein and phosphatidylinositol-3-kinase activity with IRS-1 are significantly reduced in obese subjects without diabetes and in subjects with type 2 diabetes.<sup>50</sup> Downstream insulin signalling defects such as AKT activation and FOXO1 activation have also been implicated in decreased nitric oxide generation and glucose as well as lipid metabolism.<sup>51,52</sup>

In contrast to the marked insulin resistance of the PI-3-kinase signalling pathway, the ability of insulin to stimulate mitogen-activated protein kinase pathway activity in insulin-resistant type 2 diabetes and obese non-diabetic individuals is intact (figure 5). Hyperinsulinaemia increases MEK1 activity and ERK1/2 phosphorylation and activity to the same extent in lean healthy subjects as in insulin-resistant obese non-diabetic and type 2 diabetes patients. ERKs can phosphorylate IRS-1 on serine residues, and serine phosphorylation of IRS-1 and the insulin receptor itself has been implicated in desensitisation of insulin receptor signalling.<sup>53</sup> Stimulation of the mitogen-activated protein kinase pathway can lead to smooth muscle cell proliferation, endothelin-1 activation, increased collagen formation and increased production of growth factors and inflammatory cytokines, possibly explaining the accelerated rate of atherosclerosis in individuals with type 2 diabetes.<sup>50</sup>

### Summary

The insulin resistance, or metabolic, syndrome is associated with a primary cellular defect in insulin action (insulin resistance) and a compensatory increase in insulin secretion. This combination of insulin resistance and hyperinsulinaemia causes a number of metabolic and cardiovascular changes that result in a syndrome characterised by type 2 diabetes, obesity, dyslipidaemia, CAD and hypertension. One clinical implication of this scenario is consideration of earlier treatment of the underlying metabolic defect (that is, insulin resistance) with an insulin-sensitising agent.

Insulin receptor defects responsible for insulin resistance include reduced insulin-stimulated tyrosine kinase activity, reduced activation of tyrosine phosphorylation of the insulin receptor and of IRS-1, and decreased association of p85 protein and phosphatidylinositol-3-kinase activity with IRS-1. Treatments targeting insulin resistance such as biguanides, thiazolidinediones and weight loss therapies targeting the endocannabinoid system as well as future incretin hormone therapies (such as exenatide, DPP4 inhibitors) are promising agents for treatment of insulin resistance as the underlying cause. Future studies are needed to examine the molecular and clinical implications for new insulin-sensitising therapies.

### Conflict of interest

SK is on the speaker bureau for Merck. RD has received research grants from Amylin, Lilly, Novartis, Pfizer and Takeda. He is a consultant for all of these companies. He is also on the speaker bureau for Amylin, Lilly and Takeda.

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