

## Insulin Resistance

### WHAT IS INSULIN RESISTANCE?

Insulin resistance (IR) is often defined as a decreased sensitivity or responsiveness of target tissues to the metabolic actions of insulin. IR can be viewed as a spectrum that if not arrested in the earlier stages can lead to the development of Type 2 diabetes—the ultimate illustration of IR. Initially, IR is characterized by decreased insulin-mediated glucose disposal into skeletal muscle and other peripheral tissues (peripheral IR). Impaired inhibition of hepatic gluconeogenesis (hepatic IR) occurs secondary to peripheral IR. Peripheral IR usually occurs first; because these tissues are responsible for 70-90% of glucose disposal following a carbohydrate load, it often results in postprandial hyperglycemia. In an effort to maintain normal glucose levels, there is a compensatory postprandial hyperinsulinemia as long as there is sufficient pancreatic beta cell function.<sup>1</sup> Hence, an elevated after-meal glucose level coupled with an increase in plasma insulin levels is associated with peripheral IR. Hepatic IR is manifested by overproduction of glucose, and less storage of glycogen after a meal, and correlates more with fasting hyperglycemia and fasting hyperinsulinemia than peripheral IR does.

### HOW COMMON IS INSULIN RESISTANCE?

The prevalence of insulin resistance (IR) depends on the method of determination. Currently, there is no single test that is generally accepted as the gold standard in the clinical assessment of IR. A number of well-established tests are used in research, but there are problems with each of these tests. For example, in several epidemiological studies insulin resistance has been determined by mathematical models calculated by measuring both fasting glucose and insulin (e.g., the homeostasis model assessment of insulin resistance [HOMAIR], and the quantitative insulin sensitivity check index [QUICKI]). The problem with these models is that they are based on fasting glucose and insulin levels so it is much more reflective of hepatic IR which occurs later, than it is for peripheral or skeletal muscle IR.<sup>2</sup> What may emerge as a simple and reliable laboratory marker of IR is measurement of serum adiponectin, which correlates with both HOMAIR and QUICKI.

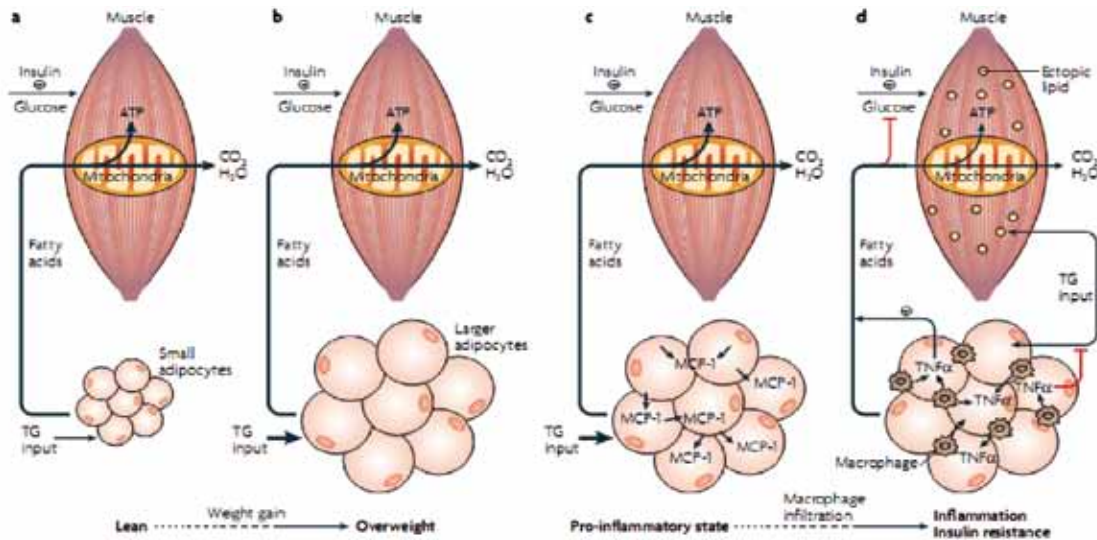
The most practical clinical tool for the determination of IR may simply be assessing a patient's body weight and fat distribution pattern, as the majority of overweight and obese

individuals have some degree of insulin resistance.<sup>3</sup> The association between obesity, specifically central obesity, and skeletal muscle insulin resistance is well-established.<sup>4</sup> In 2003-2004, 17.1% of US children and adolescents were overweight and 66.3% of adults were either overweight or obese.<sup>5</sup> Therefore, the true prevalence of IR probably parallels these numbers.

### WHY DOES INSULIN RESISTANCE OCCUR?

Recently, the role of the adipocyte itself has emerged as the source of the key underlying factors that contribute to the development of IR. When adipocytes, particularly those around the abdomen, become full of fat (triacylglycerols) they secrete a number of biological products (e.g., resistin, tumor necrosis factor, free fatty acids) that dampen the effect of insulin, impair glucose utilization in skeletal muscle, promote glucose production by the liver, and impair insulin release by pancreatic beta cells. As the number and size of these adipocytes increases, this leads to a reduction in the secretion of compounds that promote insulin action, including a novel protein produced by fat cells known as adiponectin. Adiponectin is associated with improved insulin sensitivity; it also has anti-inflammatory activity, lowers triglycerides, and blocks the development of atherosclerosis.<sup>6</sup> The net effect of all of these actions by fat cells is that they severely stress blood sugar control mechanisms as well as lead to the development of the major complication of diabetes—atherosclerosis. Because of all of these newly-discovered hormones secreted by fat cells (now known as adipokines), many experts now consider the adipose tissue a member of the endocrine system. Measuring blood levels of adiponectin may turn out to be the most meaningful indicator of IR as well as predictor of the likelihood of developing Type 2 diabetes. Furthermore, measuring serum adiponectin levels may be an important monitor for improvement in insulin sensitivity.

Serum adiponectin is lower in those with obesity and Type 2 diabetes and increases with weight reduction. Lower levels of serum adiponectin correlates with the adverse features of the Metabolic Syndrome and other associated features of insulin resistance and conventional cardiovascular risk factors including serum insulin, total cholesterol, low-density lipoprotein (LDL), apolipoprotein B-100, triglycerides, plasma glucose, HbA1c, lower high-density lipoprotein (HDL), and smaller



**Figure 1\*** Chronic inflammation in adipose tissue triggers insulin resistance in skeletal muscle. **a)** In the lean state, small adipocytes efficiently store fatty acids as triglyceride (TG input, arrow), which can be mobilized and used to generate ATP through the mitochondrial oxidation pathway in muscle during periods of caloric need. Insulin-stimulated glucose uptake under these conditions is normal. **b)** Excess caloric intake leads to metabolic overload, increased TG input and adipocyte enlargement. Nonetheless, in non-diabetic overweight individuals, TG storage by adipose cells and oxidation in muscle can often be maintained to prevent insulin resistance. **c)** On further overloading with TG, hypertrophy of adipocytes and increased secretion of macrophage chemoattractants occurs, including the secretion of monocyte chemoattractant protein-1 (MCP-1; arrows), which recruits additional macrophages. **d)** Macrophage recruitment in turn results in a pro-inflammatory state in obese adipose tissue. Infiltrating macrophages secrete large amounts of tumour-necrosis factor (TNF), which results in a chronic inflammatory state with impaired TG deposition and increased lipolysis (arrow and plus signal). The excess of circulating TG and free fatty acids results in the accumulation of activated lipids in the muscle (yellow dots), disrupting functions, such as mitochondrial oxidative phosphorylation and insulin-stimulated glucose transport, thus triggering insulin resistance.

LDL particle size. Serum adiponectin levels also negatively correlate with body mass index (BMI), waist circumference, waist/hip ratio, intra-abdominal fat, and percentage of body fat.<sup>7</sup> Additionally, serum adiponectin levels are linked to blood glucose levels in oral glucose tolerance testing, the insulin sensitivity indices HOMA and QUICKI, and insulin sensitivity markers in frequently sampled intravenous glucose tolerance testing and clamp studies. These relationships are independent of adiposity, BMI and hyperglycaemia. Adiponectin has been found to increase insulin signaling efficiency, predict intra-hepatic and muscle triglyceride content, decrease liver glucose production, increase the capacity for fat oxidation, and increase muscle glucose uptake and utilization.

In addition to the role of adipokines contributing to IR, when adipose tissue is overloaded with triacylglycerol, the buffering capacity for lipid storage in adipocytes is decreased.<sup>8</sup> As a result, there is an increase in macrophage infiltration in the visceral adipose tissue (VAT) and an excess of triglyceride and circulating free fatty acids (FFAs) are deposited into non-adipose fat stores, such as muscle, especially after meals. The increased infiltration and activation of macrophages subsequently lead to an increased production and secretion of a wide range of inflammatory molecules including TNF- $\alpha$  and interleukin-6 (IL-6), which not only have local effects on VAT physiology, but also systemic effects on other

organs including promotion of insulin resistance (See Figure 1). This inflammation within VAT is also the underlying factor that leads to alterations in adipokines, such as an increased secretion of resistin and decreased secretion of adiponectin; these further promote inflammation, inhibit cellular energy production, and interfere with normal insulin signaling.<sup>9</sup>

### INSULIN RESISTANCE, CHRONIC INFLAMMATION, AND ENDOTHELIAL DYSFUNCTION

The systemic effects of these actions within VAT are best illustrated by looking at the vascular endothelium. The systemic inflammation and the reduction of adiponectin levels leads to IR in the vascular endothelium, as well as increased free radical damage and resultant activation of the NF-kappaB and JNK systems. In addition, the IR seen in the vascular endothelium is selective. Insulin activation produces two somewhat diametrically-opposed actions. When insulin activates the phosphatidylinositol-3-kinase (PI3K) pathway it promotes glucose uptake in insulin-responsive tissues and nitric oxide (NO) production in the endothelium. NO induces vasodilation and inhibits platelet aggregation and vascular smooth muscle cell growth. By contrast, insulin activation of the mitogen-activated protein kinase (MAPK) leads to vasoconstriction and pathologic vascular cellular growth. In states of insulin resistance, insulin activation of PI3K is selectively impaired, whereas the MAPK pathway is spared and activated

normally. In the endothelium, selective impairment of insulin-mediated NO production plays a central role in the development of hypertension, endothelial dysfunction, atherogenesis, and further insulin resistance.<sup>10, 11</sup>

### WHAT ARE THE CONSEQUENCES OF IR?

Insulin resistance is recognized as playing a role in the pathogenesis of a wide range of conditions, including Type 2 diabetes and cardiovascular disease (e.g., hypertension, dyslipidemia, hepatic steatosis, coronary artery disease, and stroke). Some research also suggest that insulin resistance is linked to the development of late-onset forms of Alzheimer's disease and neurodegeneration associated with Type 2 diabetes.<sup>12</sup>

Insulin resistance mediates many of these consequences through a number of mechanisms, including the facilitation of the formation of advanced glycation end products (AGEs), free fatty acids, and small and dense LDL. It does so by blunting NO production, impairing thrombolysis, and by stimulating the production of inflammatory mediators (See Figure 2).<sup>13</sup> As cells become more resistant to the effects of insulin, insulin levels are raised to overcome this resistance.

### POSTPRANDIAL HYPERGLYCEMIA

Increasingly, it is becoming recognized that postprandial hyperglycemia, for which insulin resistance is a chief determinant, has a very important role in determining cardiovascular disease risk, specifically in the occurrence of microvascular and macrovascular complications (See Figure 3). Recent epidemiological studies strongly indicate that hyperglycemia, specifically postprandial hyperglycemia, was a greater risk factor for the risks of morbidity and mortality in Type 2 diabetes, and for the development of cardiovascular disease than fasting glucose.<sup>14, 15</sup> Additionally, reductions in HbA1c do not necessarily indicate a reduction in postprandial hyperglycemia,

which may explain why the reductions in HbA1c did not significantly reduce cardiovascular disease risk in recent studies.<sup>16</sup>

### HOW IS IR TREATED?

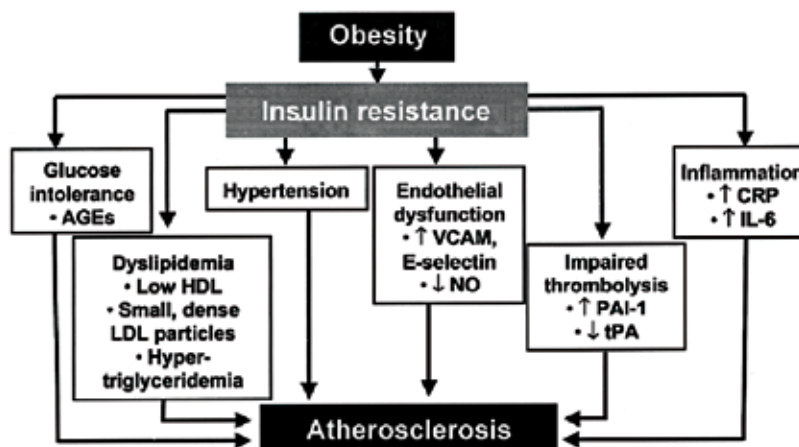
The primary goal in the treatment of IR is weight loss, specifically the reduction in the size of VAT, coupled with insuring the daily intake of nutrients required for proper insulin action (e.g., B vitamins, chromium, manganese, magnesium, etc.).

Among the most powerful tools for restoring insulin sensitivity and reducing the complications of its effects are: the use of PolyGlycopeX (PGX), along with the adoption of a low glycemic, Mediterranean diet that is high in monounsaturated fats, combined with an increase in aerobic and muscle strength training. PGX exerts the following benefits:

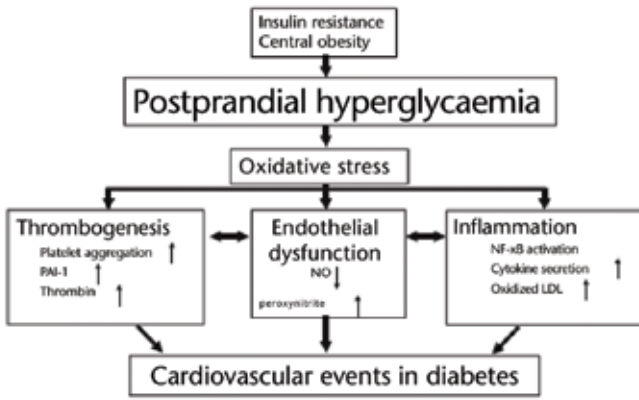
- Reduces postprandial (after-meal) blood glucose levels
- Increases insulin sensitivity
- Reduces appetite and promote effective weight loss
- Improves diabetes control
- Lowers blood cholesterol

PGX typically lowers after-meal blood glucose levels by approximately 35 to 70% and also lowers insulin secretion by approximately 40%, producing a whole body insulin sensitivity index improvement of nearly 60%—a phenomenal accomplishment that is unequalled by any drug or natural health product. For more information, see the *PGX Product Monograph*.

Regarding supportive therapy to PGX, a trial of nearly 600 adults with pre-diabetes, diet and lifestyle interventions over six years was found to prevent or delay diabetes for up to 14 years after the active intervention.<sup>17</sup> In another trial of



**Figure 2** Association of insulin resistance with cardiovascular risk factors and atherosclerosis. AGEs = advanced glycation end products; CRP = C-reactive protein; HDL = high density lipoprotein; IL-6 = interleukin-6; LDL = low density lipoprotein; NO = nitric oxide; PAI-1 = plasminogen activator inhibitor-1; tPA = tissue plasminogen activator; VCAM = vascular cell adhesion molecule; ↑ = increased; ↓ = decreased.

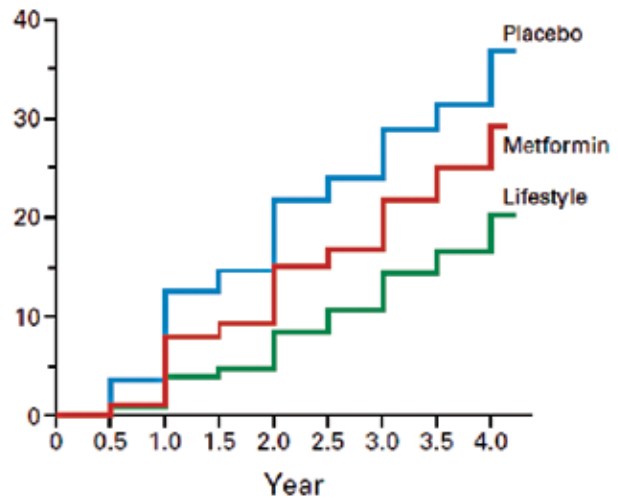


**Figure 3** Molecular mechanisms for postprandial hyperglycaemia-elicited cardiovascular disease in diabetes.

over 3,000 pre-diabetic individuals with elevated fasting and post-load plasma glucose concentrations, lifestyle interventions reduced the incidence of Type 2 diabetes by 58%, while the commonly-prescribed drug metformin by only 31% compared with placebo—the lifestyle intervention was significantly more effective than metformin (See Figure 4). Interventions were designed to achieve a 7% weight loss, and 150 minutes aerobic exercise (walking) per week.<sup>18</sup> Since the weight loss was rarely achieved, the benefits were largely attributed to exercise.

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**Figure 4** Cumulative incidence of diabetes according to study group.

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**FIGURES**

1. Guilherme A., Virbasius J.V., Puri V., Czech M.P., "Adipocyte dysfunctions linking obesity to insulin resistance and Type II diabetes," *Nat Rev Mol Cell Biol*, 2008 May; 9(5): 369.
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