The chemical pathology of insulin resistance and the metabolic syndrome

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Over the past decade the metabolic syndrome has become prominent in the literature in addition to emerging as a major public health concern. The metabolic syndrome presents many diagnostic problems for clinicians and laboratorians alike. The metabolic syndrome is a constellation of symptoms and signs that include central obesity, insulin resistance, dysglycemia, dyslipidemia, and hypertension. The definition has many subtleties and clinically, there are a multitude of presentations. Included in the current understanding of the metabolic syndrome is a subtext of a proinflammatory and a prothrombotic state.

There is certainly no agreement on any single causative agent; however, it is clear that the modern calorie-rich Western diet in the setting of little or no regular exercise plays a central role. A recent concise review on metabolic syndrome was published in this journal. The current review addresses the biology of insulin resistance, viz., what is it and how does it present? The insulin resistance of the metabolic syndrome remains somewhat of an enigma, but a number of plausible models have come to light in recent years.

Here we review: (a) the many metabolic actions of insulin, (b) the pathogenesis of type 2 diabetes mellitus, (c) insulin resistance (in general), (d) the ectopic fat hypothesis of insulin resistance, (e) the possible role of the hormones leptin, resistin, and adiponectin, and (f) the connection between insulin resistance and islet amyloid.

Insulin and insulin resistance

Insulin is an essential polypeptide hormone produced under conditions of feeding by the beta cells of the pancreatic islets of Langerhans. Insulin is critical for entry of glucose into multiple tissues, including skeletal muscle and adipose tissue (via activation of the glucose transporter molecule GLUT4), but is not necessary for glucose entry into erythrocytes, liver, or brain. Insulin promotes the oxidation of glucose to carbon dioxide and water by tissues and also blocks “new” glucose biosynthesis (i.e., gluconeogenesis) by hepatic tissue. Insulin is also very important in promoting the storage of glucose in the form of glycogen by liver and muscle.

The drive of glucose into the cells with its subsequent oxidation is the basis for the glucose-lowering effect of insulin. Insulin also has major effects on lipid metabolism. It blocks the breakdown of triacylglycerols (triglycerides) by adipose tissue and promotes the biosynthesis of fatty acids and triacylglycerols by liver and adipose tissue. In short, insulin promotes fat storage.

This summary of insulin’s many actions helps to clarify the effects of insulin deficiency. In the absence of sufficient insulin, glucose (now unable to enter cells) accumulates in excess within the extracellular fluid. This has two major effects: (a) the cells undergo a functional starvation and (b) the high plasma glucose has many untoward physiologic effects, including osmotic problems and tissue damage from protein glycation. Cell starvation manifests as increased synthesis of ketone bodies. Furthermore, there is adipose tissue breakdown with production and release of fatty acids. The latter are delivered to the liver in such high quantities that hepatic lipoprotein synthesis is increased and the liver puts out abundant very low-density lipoproteins (VLDLs). Insulin is required for VLDL breakdown in the capillary beds via lipoprotein lipase and so, in cases of insulin deficiency, these large triglyceride-rich lipoproteins persist.

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Diabetes is a disease that results from decreased insulin action. Insulin action is a product of insulin concentration and tissue insulin sensitivity. For many decades, researchers have been aware of the essential differences between type 1 and type 2 diabetes. In type 1 diabetes, there is a true deficiency of insulin due to pancreatic beta-cell damage by an autoimmune, cell-mediated response. Insulin concentrations are very low. In type 2 diabetes, insulin concentrations may be normal or even high. In type 2 diabetes, there is an insensitivity of the tissues to the effects of insulin — an effect termed insulin resistance. Insulin is present, but it cannot get its message through to the cells. What has happened? Before addressing this, let us review what normally happens when insulin interacts with a cell.

In order to initiate its many metabolic effects, insulin must interact with a specific cell-surface receptor that belongs to a family of receptor-enzymes known as tyrosine kinases. The binding of insulin to the insulin receptor initiates a complex chain of events that ultimately generates a multitude of intracellular second messengers (Figure 1). The latter eventually produce the characteristic effects of insulin, for example, by promoting the movement of GLUT4 molecules to the cell surface. Although cases of insulin resistance have been described due to specific mutations in the insulin cell-surface receptor tyrosine kinase, these are rather rare and constitute only a minority of cases. They have, however been extensively studied and have shed much light on the biology of insulin action. The insulin resistance of the common type 2 diabetes is not related to receptor mutations, but is somehow related to the amount of fat in the body. The remainder of the review will address this subject.

The standard model of type 2 diabetes is that the body tissues progressively become more insulin resistant, so that ever-higher blood concentrations of the hormone are needed to produce the identical effect. In the early stages of the disease, plasma insulin concentrations tend, therefore, to be higher than normal. The insulin resistance eventually achieves a level where the person is relatively insulinopenic. He has above-normal concentrations of insulin, but the circulating insulin nevertheless is not sufficient to fully activate the insulin-resistant tissues, such as skeletal muscle and adipose tissue. There is a price to pay for this profligate expenditure of insulin. The beta cells cannot keep up with the demand and begin to fail — an event that may also be promoted by body-fat content. Such individuals enter a stage where they are truly insulinopenic. Indeed, even when the beta cells are still able to secrete large amounts of insulin, the temporal pattern of insulin secretion is no longer normal.

Initially, the insulin resistance is most likely subclinical, since insulin is not routinely measured in the clinical labora-

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**CLINICAL ISSUES**

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**Figure 2.** Adipose tissue

Adipose tissue is an active endocrine organ that secretes:

1. Leptin - controls lipid "ectopia"
2. Resistin - may produce insulin resistance (controversial)
3. Adiponectin - promotes insulin sensitivity.

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**Figure 3.** Normal total body fat stores

- Adipose tissue
- Liver
- Skeletal muscle
- Islet beta cells

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Body fat and insulin resistance

How does body-fat content produce insulin resistance? First, it appears that it is particularly intra-abdominal fat (also termed visceral fat) that is the culprit here. Intra-abdominal fat is adipose tissue associated with the abdominal viscera. Subcutaneous fat is much less of a problem. One hypothesis suggests that a process that is central to the pathogenesis of insulin resistance is fat ectopia.6,7 In the simplest terms, adipose tissue can only hold a certain amount of fat, and if excessively loaded with fat, there is a spillover or redistribution of lipid to ectopic sites, including liver and skeletal muscle (Figures 2-5). In support of this, hepatic steatosis8 is frequently observed in individuals with the metabolic syndrome. Nonalcoholic fatty liver disease has a prevalence of 57% to 74% in obese individuals.8 It is the most common cause of abnormal liver function tests in the United States. The ectopic triglyceride deposition in nonadipose tissue, such as liver and skeletal muscle, has deleterious effects (Figure 6). There is both tissue damage (lipotoxicity) and the development of insulin resistance.

Another aspect of the lipid ectopia hypothesis is that the beta cells themselves are damaged by the deposition of the fat. This results in a gradual failure to produce sufficient insulin, making the insulinopenia worse. The evidence that this hypothesis has some validity comes from rare cases of lipodystrophic diabetes. Congenital lipodystrophies9 are conditions where body fat is significantly reduced or almost absent. The dearth of normal fat-storage capacity leads to early fat ectopia with deposition of fat (triglycerides) in skeletal muscle and liver and the development of insulin resistance despite the absence of obesity (Figure 5).

Conversely, in the Prader-Willi syndrome, where significant obesity is a major feature, insulin resistance is uncommon. These individuals appear to have an expanded capacity to store fat, so their risk of fat ectopia and type 2 diabetes is...
less than average. Additional support of this hypothesis derives from studies of low-birth-weight infants. As adults, these individuals are predisposed to insulin resistance. It appears that they have reduced amounts of adipose tissue and, therefore, a reduced capacity to store fat. They are more likely to experience spillover or fat ectopia, according to the hypothesis outlined above. Further evidence comes from the use of a class of drugs termed PPAR-gamma agonists (thiazolidinediones). These compounds stimulate the development of new adipose tissue, allowing the redistribution or normalization of fat stores. Fat leaves the ectopic tissues and re-enters the new adipose tissue. Thiazolidinediones are known to be effective in treating type 2 diabetes.

**Leptin, resistin, and adiponectin**

The hormone leptin may be important in this fat ectopia/lipotoxicity scenario. Leptin is a 167-amino-acid polypeptide with a molecular mass of about 16 kDa that is produced by adipose tissue. It is known to regulate body adipose tissue. The ob/ob mouse is genetically deficient in leptin production, while the db/db mouse or the fa/fa (ZDF) rat have mutations in the leptin receptor. In these animal models, there is either a deficiency of leptin or there is a nonfunctional leptin receptor. These animals display hyperphagia and obesity as well as steatosis liver, skeletal muscle, and pancreatic islets. Leptin is believed to reduce appetite and control thermogenesis via actions on the hypothalamus. Growing evidence suggests that leptin can also act directly on adipose tissue and that this may well be a major site of its action. It has been proposed that, in this setting, leptin normally prevents steatosis in nonadipose tissue — it blocks the ectopic deposition of fat and thus prevents lipotoxicity. In leptin-deficient or leptin-resistant animals, this control is absent and ectopic fat deposition (steatosis) with consequent lipotoxicity continues unabated. A similar situation is found in individuals with congenital lipodystrophies. In the latter case, the lack of adipose tissue is responsible for the leptin deficiency. In human diet-induced obesity, leptin levels initially are high, preventing ectopic fat deposition. Resistance to leptin ultimately occurs, however, and control over the ectopic deposition of fat is lost.

How does leptin exert its action to prevent steatosis? It enhances fatty-acid oxidation by tissues, leading to the generation of both ATP and heat. It also reduces de novo fatty acid biosynthesis and reduces synthesis of triglycerides. In the absence of leptin, these processes are blocked and triglycerides accumulate in nonadipose tissue. Furthermore, these metabolic studies have shed light on the lipotoxicity of ectopic fat deposition. In the absence of leptin, and when intracellular triglycerides accumulate, fatty acids enter a pathway of nonoxidative metabolism. This leads to increased ceramide formation. Ceramide is a sphingolipid, derived from sphingosine (an amino alcohol) joined to a fatty acid. Ceramide promotes apoptosis (programmed cell death).

Recent studies in adipose tissue biology have lead to the discovery of a another new hormone (termed resistin) that (like leptin) is produced by adipose tissue. Initial evidence pointed to resistin playing a major role in the pathogenesis of insulin resistance by virtue of its ability to oppose certain actions of insulin. This was supported by the observation that thiazolidinedione drugs that activate the transcription factor PPAR-gamma decrease adipose tissue resistin secretion and, therefore, help to reverse insulin resistance. Since its initial description, the role of resistin has been somewhat less clear with conflicting reports in the literature. A study published in 2002 showed, however, that the removal of visceral fat from Zucker diabetic rats prevented the development of insulin resistance, and that resistin expression in visceral fat was much higher than subcutaneous fat. The role of resistin in human biology however, remains rather uncertain.

Adiponectin is yet another adipose tissue-derived protein...
with endocrine effects. Adiponectin is a 244-amino-acid protein (30 kDa) with a collagen-like domain. Part of the molecule shares structural similarities with the cytokine tumor necrosis factor-alpha (TNF- alpha). Plasma concentrations of adiponectin are lowered in obesity and insulin resistance, in contrast to many other adipose-derived cytokines. Adiponectin production is associated with insulin sensitivity; conversely, low adiponectin concentrations produce insulin resistance. Adiponectin also stimulates fatty-acid oxidation and lowers plasma triglycerides. In addition, adiponectin appears to have antiatherogenic effects. When adiponectin “knock-out” mice were given high-fat, high-sucrose diets, they developed insulin resistance. Of relevance to the metabolic syndrome, visceral fat accumulation is associated with lowered adiponectin concentrations. TNF-α, which is also known to be associated with insulin resistance, inhibits adiponectin gene expression.

### Increased fatty-acid concentrations cause insulin resistance

In the course of a normal physiologic response to starvation, free fatty acids or FFA have a carbohydrate-sparing effect so that glucose can be preserved for oxidation by the central nervous system. Fatty acids are also elevated in obese individuals, and these have direct effects on carbohydrate metabolism. Fatty acids decrease glucose uptake, glycogen synthesis, and glycolysis, effects normally promoted by insulin. The evidence from the original studies suggested the effect of fatty acids to be at the level of glucose transport or phosphorylation. Furthermore, fatty acids inhibit insulin suppression of hepatic glucose production, leading to increased hepatic glucose production.

### Summary and conclusion

In this review, we have examined the phenomenon of insulin resistance, a central manifestation of the metabolic syndrome. While it is by no means clear-cut, many new and exciting hypotheses have been proposed to explain this puzzling and enigmatic phenomenon. These studies have also led to a new way of looking at adipose tissue — it is no longer a passive repository of fat. It now actually appears to be a very active endocrine organ. A disturbance in this endocrine function helps contribute to the metabolic syndrome.

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**Insulin resistance has important effects on the vascular bed.**

**Islet amyloid**

Another development in the field of type 2 diabetes has been the identification of islet amyloid and its relationship to beta-cell failure. The standard model of type 2 diabetes, as described above, raises the question: Is the beta-cell failure that occurs as the disease advances simply a result of cell exhaustion? Is it due to the lipotoxicity described above? There is evidence that islet amyloid may be important, too, although it probably is not the only factor. Amyloid is a proteinaceous fibrillar deposit that is seen in tissues during certain pathologic processes and that can fold into beta-pleated sheets. Amyloid has a characteristic electron-microscopic appearance, as well as a green birefringence in polarizing light microscopy when stained with Congo Red. Islet amyloid is a form of local amyloidosis, since it is confined to the islets of Langerhans.

Islet amyloidosis is frequently observed in individuals with type 2 diabetes mellitus. The amyloid appears to promote beta-cell damage and death. Is there any connection with insulin resistance? There may well be. A major component of islet amyloid is a 37-amino-acid polypeptide termed islet amyloid polypeptide (IAPP) or amylin, produced and secreted by the islet beta cells. In the setting of insulin resistance, not only does insulin secretion by the beta cell increase, IAPP production follows suit. Although the IAPP sequence is normal, the high polypeptide concentrations promote amyloid fibril formation, leading to localized islet amyloidosis. This ultimately may contribute to beta-cell failure. Thus, insulin resistance leads to islet amyloid, which, in turn, promotes insulin lack of.

**References**


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