

# Metabolic Consequences of Hyperglycemia and Insulin Resistance

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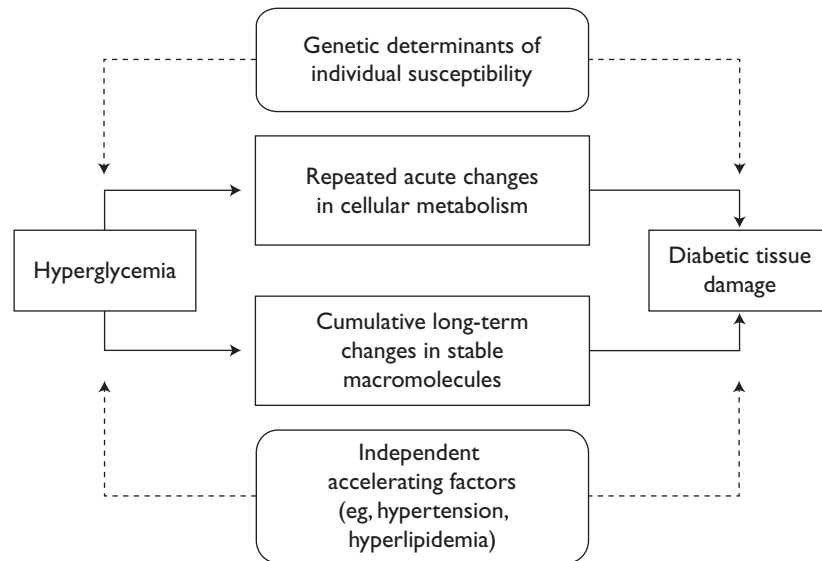
Insulin is a pleiotropic hormone that exerts a multitude of effects on metabolism and various cellular processes in the body. The main metabolic actions of insulin are to stimulate glucose uptake in skeletal muscle and the heart and to suppress the production of glucose and very-low-density lipoprotein in the liver. Other metabolic effects of insulin include inhibition of glucose release from the liver, inhibition of the release of free fatty acids (FFAs) from adipose tissue, and stimulation of the process by which amino acids are incorporated into protein. Insulin resistance (IR) is a condition in which defects in the action of insulin are such that normal levels of insulin do not trigger the signal for glucose absorption. An excess of FFAs is implicated in the pathogenesis of IR. The effects of this condition can have profound pathophysiologic effects on various organs and tissues of the body. For example, IR is associated with impaired insulin signaling, impaired fibrinolysis, and inflammation. The clinical consequences include hyperglycemia-induced tissue damage, hypertension, dyslipidemia, metabolic syndrome, and cardiovascular disease. Pharmacotherapies that target IR include metformin and the thiazolidinediones. Endocannabinoid antagonists, agents that target obesity and associated cardiovascular and metabolic risk factors, are currently being developed. (*Clinical Cornerstone*. 2007;8[Suppl 7]:S30–S42). Copyright © 2007 Excerpta Medica, Inc.

A recent study reported a statistically significant correlation between blood glucose levels and mortality.<sup>1</sup> In this study, data on exposure to higher than optimum blood glucose levels were collected from 65 data sources in 52 countries, representing 74% of the world population. The data sources included individual-level data from population-representative health examination surveys, exposure data from systematic reviews of published studies, data provided by individual investigators, and empirically derived models. In addition, relative risks for ischemic heart disease and stroke mortality were obtained from a meta-analysis of >200,000 participants in the Asia-Pacific region extrapolated to all populations, with adjustment for other cardiovascular risk factors. The investigators found that higher than optimum blood glucose levels account for 21% of deaths from ischemic heart disease and 13% of deaths from stroke worldwide. This burden of mortality is >2 times greater than that due to diabetes alone. They concluded that higher than optimum blood glucose is a leading cause of cardiovascular mortality in most regions of the world. Other studies also suggest a positive continuous association between

blood glucose levels and cardiovascular risk.<sup>2</sup> The hyperglycemia that occurs with insulin resistance (IR) can have deleterious effects on organs and tissues in the body (Figure 1).<sup>3</sup> This paper will review the pathophysiology of hyperglycemia and IR, describe the metabolic consequences of IR at the cellular and organ levels, and present pharmacotherapeutic options that target IR and obesity and the associated cardiovascular and metabolic risk factors.

## **NORMAL ACTIONS OF GLUCOSE AND GLUCOSE METABOLISM**

Glucose is the required metabolic fuel for the brain under physiologic conditions. Other organs, however, can use both glucose and fatty acids to generate energy. The process of glucose homeostasis maintains plasma glucose levels within a narrow range, usually between 60 and 150 mg/dL (3.3 and 8.3 mmol/L).<sup>4</sup> Because glucose is a hydrophilic molecule, specific carrier proteins—glucose transporter (GLUT) proteins—are required to allow glucose to cross cell membranes down its concentration gradient. Five GLUT proteins have been identified. One of



**Figure 1. General features of hyperglycemia-induced tissue damage. Adapted with permission.<sup>3</sup>**

these proteins, GLUT-4, is located on the cell membranes of muscle cells and adipocytes. In the absence of insulin, GLUT-4 exists in membrane vesicles located within the cytosol of cells. Insulin binding to its receptor initiates a signaling cascade that promotes the translocation of GLUT-4 to the plasma membrane, thus permitting the movement of glucose into the cell.

### NORMAL ACTIONS OF INSULIN

Insulin is a pleiotropic hormone that exerts a multitude of effects on metabolism and various cellular processes in different tissues and organs of the body. The main metabolic actions of insulin are to stimulate glucose uptake in skeletal muscle and the heart and to suppress the production of glucose and very-low-density lipoprotein (VLDL) in the liver.<sup>5</sup> Other metabolic effects include inhibition of glucose release from the liver, inhibition of the release of free fatty acids (FFAs) from adipose tissue, and stimulation of the process by which amino acids are incorporated into protein.<sup>6</sup>

Some of the actions of insulin can be considered antiatherogenic.<sup>5</sup> For example, in blood vessels, insulin increases the production of nitric oxide (NO), which has a vasodilatory effect.<sup>7</sup> Insulin also inhibits platelet aggregation<sup>8</sup> and type-1 plasminogen activator inhibitor (PAI-1).<sup>9</sup> Insulin has been hypothesized to be a growth factor that stimulates vascular cell growth and synthesis of matrix proteins.<sup>10,11</sup>

### KEY POINT

**The main metabolic actions of insulin are to stimulate glucose uptake in skeletal muscle and the heart and to suppress the production of glucose and VLDL in the liver.**

### GLUCOSE PRODUCTION AND UTILIZATION

The balance between glucose production and utilization is regulated by a network of hormones, neural pathways, and metabolic signals. Insulin plays a pivotal role in this process. In the fasting state, insulin secretion is suppressed, which leads to increased gluconeogenesis in the liver and kidneys and increased glucose generation by the breakdown of liver glycogen. In the fed state, insulin released from pancreatic  $\beta$ -cells reverses this process by inhibiting glycogenolysis and gluconeogenesis, enhancing peripheral glucose uptake and utilization, and reducing lipolysis and proteolysis. The net result is that excess glucose is converted into glycogen, triglycerides (TGs), and proteins. When more glucose is present in liver cells than can be metabolized or stored as glycogen, insulin causes the excess glucose to be converted into FFAs. These FFAs are packaged as TGs in VLDL, transported in the blood in this form, and deposited as fat in adipose tissue.<sup>12</sup>

## NEGATIVE ACTIONS OF GLUCOSE AND CONSEQUENCES OF HYPERGLYCEMIA

When cells are exposed to abnormally high levels of glucose, they generally are able to reduce the transport of glucose into the cytoplasm, thus maintaining internal glucose concentrations at normal levels. However, some cells cannot quickly decrease glucose transport rates, which results in high glucose levels inside the cell.<sup>3</sup> Examples of these cells include capillary endothelial cells in the retina, mesangial cells in the renal glomerulus, and neurons and Schwann cells in peripheral nerves.<sup>3</sup> The results can be visual and renal impairment, and neuropathy.

Hyperglycemia also produces global or systemic effects. For example, glucose induces vascular inflammation.<sup>13</sup> Hyperglycemia impairs the immune status of an individual by stimulating inflammatory cytokines and cell adhesion molecules and by inhibiting leukocyte function.<sup>14</sup> Furthermore, hyperglycemia can produce excessive levels of superoxide in endothelial cells, which can then activate the various pathways of microvascular damage.<sup>15</sup> Finally, hyperglycemia rapidly suppresses endothelium-dependent vasodilation, probably through increased production of oxygen-derived free radicals,<sup>16</sup> which suggests that hyperglycemia might play a role in the development and progression of atherosclerosis.

## INSULIN SENSITIVITY

Insulin sensitivity refers to the ability of insulin to support glucose homeostasis by signaling insulin-sensitive tissues or organs to absorb glucose. These signals include stimulating glucose utilization in both muscle and adipose tissue and suppressing the production of glucose by the liver. Both responses act to decrease plasma glucose concentration. The degree of impairment of glucose metabolism is influenced both by the insulin sensitivity of cells within the body and by pancreatic  $\beta$ -cell reserve capacity.<sup>17</sup>

### KEY POINT

**Insulin sensitivity refers to the ability of insulin to support glucose homeostasis by signaling insulin-sensitive tissues or organs to absorb glucose.**

## INSULIN RESISTANCE

IR is a condition in which defects in the action of insulin are such that normal levels of insulin do not trigger the signal for glucose absorption. The result is hyperinsulinemia to maintain euglycemia.<sup>6</sup> The pancreas compensates for the decreased insulin response by increasing insulin secretion until reserve capacity is exceeded by metabolic demands and insulin secretion is no longer adequate.<sup>18</sup> As blood glucose levels rise, impaired glucose tolerance and then type 2 diabetes develops. Thus, there is a continuous spectrum of insulin responsiveness, ranging from normal insulin sensitivity to severe IR.<sup>19</sup> Similarly, there is a concurrent spectrum of glucose tolerance that ranges from normoglycemia to impaired glucose tolerance and impaired fasting glucose and, finally, to diabetes.<sup>19</sup> Other genetic or acquired conditions that may cause IR are shown in **Table I**.<sup>12</sup>

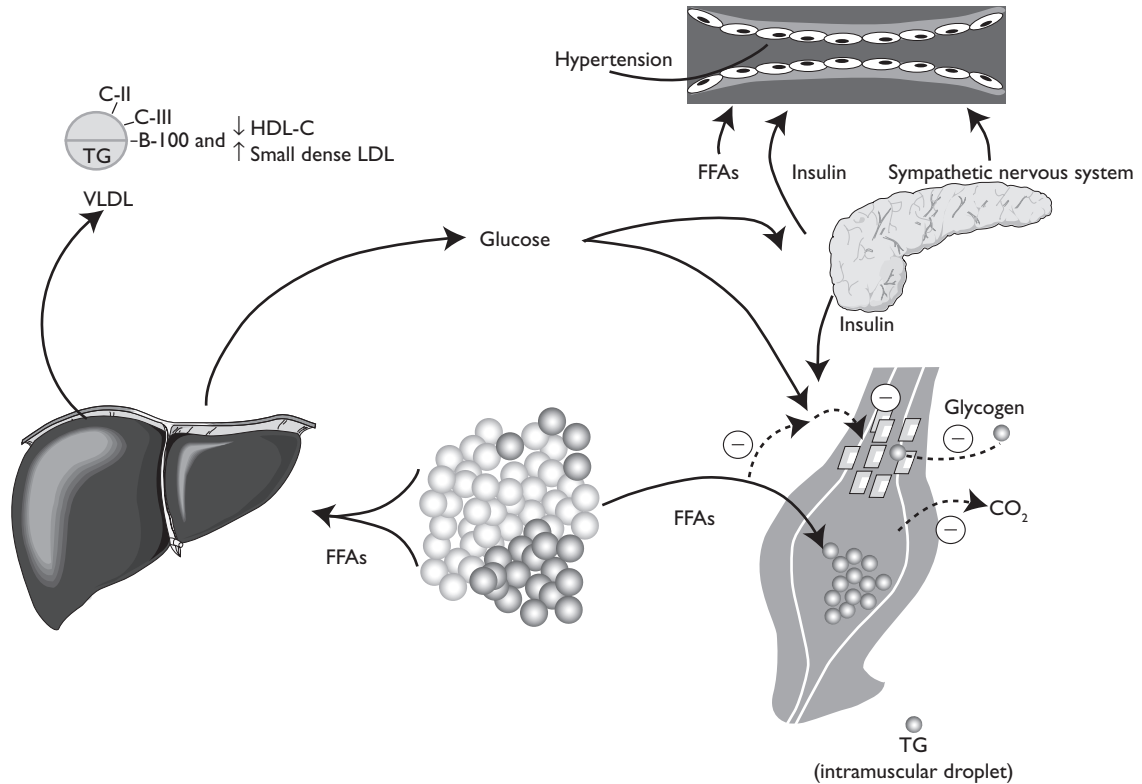
**TABLE I. GENETIC OR ACQUIRED CONDITIONS THAT MAY CAUSE INSULIN RESISTANCE.**

Obesity/overweight (especially excess visceral adiposity)
Excess glucocorticoids (Cushing's syndrome or steroid therapy)
Excess growth hormone (acromegaly)
Pregnancy, gestational diabetes
Polycystic ovary disease
Lipodystrophy (acquired or genetic; associated with lipid accumulation in the liver)
Autoantibodies to the insulin receptor
Mutations of the insulin receptor
Mutations that cause genetic obesity

Adapted with permission.<sup>12</sup>

## EXCESS FREE FATTY ACIDS INDUCE INSULIN RESISTANCE

The 2 main adipose tissue depots in man are subcutaneous and visceral fat, both of which take up and store FFAs. An excess of FFAs is implicated in the pathogenesis of IR (**Figure 2**).<sup>6</sup> FFAs released from increased adipose tissue, as in overweight or obesity, are deposited in the liver, which results in an increased production of glucose and TGs and an increased secretion of VLDL. Other lipid abnormalities that occur include a decrease in high-density lipoprotein cholesterol (HDL-C) and an increase in low-density lipoprotein cholesterol (LDL-C).



**Figure 2. Pathophysiology of insulin resistance.** Free fatty acids (FFAs) released from adipose tissue increase production of glucose and triglycerides (TGs) and secretion of very-low-density lipoprotein (VLDL) in the liver. Associated lipid/lipoprotein abnormalities include decreased levels of high-density lipoprotein cholesterol (HDL-C) and increased levels of small dense low-density lipoprotein (LDL) particles. FFAs also reduce insulin sensitivity in muscle by inhibiting insulin-mediated glucose uptake. Increases in circulating glucose increase pancreatic insulin secretion, resulting in hyperinsulinemia. Hyperinsulinemia may result in enhanced sodium reabsorption and increased sympathetic nervous system activity. It also may contribute to the development of hypertension. Adapted with permission.<sup>6</sup>

**Table II** lists various proteins and molecules that play a role in obesity and IR.

FFAs are believed to induce IR in muscle at the level of insulin-mediated glucose transport by impairing the insulin-signaling pathway.<sup>20</sup> In a study of nondiabetic men and women, IR appeared 2 to 4 hours after an acute increase in plasma FFA concentration and took a similar amount of time to disappear after plasma FFA levels returned to normal.<sup>21,22</sup>

Excess FFAs can also increase the level of oxidative stress.<sup>23</sup> The reactive oxygen radical species (ROS) that are produced as a result can activate various pathways that contribute to the pathogenesis of IR.<sup>24</sup> Because insulin promotes hepatic uptake of FFAs, IR in liver tissue may contribute to elevated plasma FFA levels.<sup>20</sup> As

more FFAs are released from adipose tissue there is a decrease in FFA uptake by muscle tissue.<sup>18</sup> The net result may be an increased influx of FFAs to the liver, which again exacerbates IR.

### KEY POINT

**FFAs are believed to induce IR in muscle at the level of insulin-mediated glucose transport by impairing the insulin-signaling pathway.**

**TABLE II. SUBSTANCES THAT PLAY A ROLE IN OBESITY AND INSULIN RESISTANCE.**

Substance*	Full Name	Function(s)
Adiponectin (anti-inflammatory cytokine)		Secreted by adipocytes; improves insulin sensitivity; synthesis stimulated by insulin
CRP (proinflammatory cytokine)	C-reactive protein	Produced in liver; concentration frequently used as an index of inflammation
GLUT (protein)	Glucose transporter	Translocated to the plasma membrane to facilitate glucose transport into the cell
IL-6	Interleukin-6	Inflammatory mediator; interferes with/inhibits insulin signaling; inhibits adipogenesis and secretion of adiponectin
Leptin (hormone)		Secreted predominantly by adipose tissue; signals sufficiency of energy and decreased food intake and increases energy expenditure; produces sympathetic stimulation
MCP-1	Monocyte chemoattractant protein-1	Impairs insulin-stimulated glucose uptake; promotes atherosclerosis by attracting macrophages to vessel walls
NF-κB	Nuclear transcription factor κB	Affects gene transcription; inhibited by adiponectin; activated by TNF-α (see below)
PAI-1	Plasminogen activator inhibitor-1	Associated with visceral obesity, insulin resistance, and metabolic syndrome; exerts prothrombotic activity
PPAR-γ	Peroxisome proliferator-activated receptor-gamma	Activation stimulates free fatty acid (FFA) catabolism; thiazolidinediones (TZDs) are PPAR-γ agonists
Resistin		Secreted predominantly by visceral but also subcutaneous adipose tissue; function is unknown
TNF-α	Tumor necrosis factor-alpha	Inflammatory mediator; main factor triggering secretion of FFAs from adipose tissue into the circulation; inhibits insulin signaling

\*These substances include proteins, molecules, and adipokines (ie, hormones and cytokines released by adipose tissues).

## CELLULAR AND MOLECULAR CONSEQUENCES OF INSULIN RESISTANCE

### Impaired Insulin Signaling

The metabolic consequences of IR result from abnormalities in key molecules of the insulin-signaling pathways, including overexpression of phosphatases and downregulation and/or activation of protein kinase cascades.<sup>18</sup> The net result is that insulin signaling is impaired, and because ≥3 different pathways are involved in insulin signaling, multiple pathologic consequences can occur. Impaired insulin signaling is associated with abnormalities in the expression and action of various peptides, growth factors, and cytokines.<sup>25</sup>

### Impaired Fibrinolysis

Fibrinogen is a blood plasma globulin that is converted into fibrin by the action of thrombin to produce blood coagulation. The endogenous fibrinolytic system is regulated by activators of plasminogen (primarily tissue type

plasminogen activator) and inhibitors of these activators (such as PAI-1). Because low-grade coagulation is continually occurring in the blood, maintaining the fluidity of blood requires fibrinolytic activity. Consequently, excessive inhibition of fibrinolysis will lead to coagulation and thrombosis.

Plasma PAI-1 activity is elevated in a wide variety of patients with IR. Even in patients with normal glucose tolerance, elevated levels of fasting insulin are associated with impaired fibrinolysis and hypercoagulability.<sup>26</sup> An important consequence and component of IR is impaired fibrinolysis, which likely contributes significantly to the increased risk of cardiovascular events.<sup>25</sup> A clinical feature of IR, therefore, is the prothrombotic state characterized by an elevation of PAI-1 and fibrinogen levels.<sup>27</sup>

### Inflammation

Inflammation has been linked to the development of IR and the pathogenesis of type 2 diabetes.<sup>28</sup> In fact, data

suggest that IR is not only associated with but may be a result of an overproduction of proinflammatory cytokines (ie, interleukin [IL]-6, resistin, tumor necrosis factor [TNF], and C-reactive protein [CRP]) and a relative deficiency of anti-inflammatory cytokines (ie, adiponectin), resulting from the increased adipose tissue associated with obesity.<sup>6</sup> The proinflammatory role of adipose tissue was first demonstrated by Hotamisligil and colleagues<sup>29</sup> and Feinstein and colleagues,<sup>30</sup> who showed that the proinflammatory cytokine TNF- $\alpha$  was able to induce IR in experimental animals. The proinflammatory state of IR is characterized by a rise in the level of CRP, an acute-phase protein produced by the liver in response to the production of various proinflammatory cytokines (IL-6, IL-1, TNF- $\alpha$ ).<sup>25</sup>

## CLINICAL CONSEQUENCES OF INSULIN RESISTANCE

### Hyperglycemia-Induced Tissue Damage

IR is manifested primarily by muscle and adipose tissue, while other tissues retain their sensitivity to insulin. The compensatory hyperinsulinemia required to maintain glucose homeostasis has an adverse impact on the tissues that remain insulin sensitive. Thus the differential insulin sensitivity of various tissues in the body results in the abnormalities and clinical syndromes associated with IR.<sup>31</sup> For example, alterations in the vascular endothelium that occur in patients with IR are shown in **Table III**.<sup>25</sup> The underlying cause of these abnormalities is the hyperglycemia associated with IR.

The first step in the process of hyperglycemia-induced tissue damage is the high flux of glucose across endothelial cell membranes. This flux exceeds the capacity of the mitochondrial electron transport system, resulting in the production of ROS.<sup>32</sup> In addition to the formation of oxygen radicals, intracellular advanced

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glycation end products (AGEs) are produced.<sup>33</sup> The resulting increased oxidative stress that occurs decreases the bioavailability of NO by converting the available NO to peroxynitrite. AGEs also induce the production of vascular cell adhesion molecules. The net result is an enhanced interaction of the vascular endothelium with circulating monocytes and the initiation of an inflammatory cascade.<sup>34,35</sup> Endothelial dysfunction, characterized by a decrease in the bioavailability of endothelial NO and the production of oxygen-derived free radicals, may play an important role in the pathogenesis of atherosclerosis and has been seen during acute episodes of hyperglycemia, even in individuals with normal glucose tolerance.<sup>16</sup>

### Hypertension

There is clinical evidence for a link between IR and hypertension, as many patients with essential hypertension exhibit IR and hyperinsulinemia.<sup>31</sup> Normotensive first-degree relatives (ie, parents, siblings) of patients with essential hypertension were found to be relatively insulin resistant and hyperinsulinemic as compared with a matched control group.<sup>31</sup> Furthermore, hyperinsulinemia, as a surrogate estimate of IR, has been shown to predict the development of hypertension in normotensive individuals.<sup>31</sup> However, the link between IR and hyper-

**TABLE III. ALTERATIONS IN THE VASCULAR ENDOTHELIUM ASSOCIATED WITH INSULIN RESISTANCE.**

Abnormality	Significance
Decreased release of and responsiveness to nitric oxide	Impaired endothelial function and reactivity
Increased adhesion-molecule expression	Increased monocyte adhesion to vessel wall
Increased adhesion of platelets and monocytes	Foam cell formation, thrombosis, and inflammation
Increased procoagulant activity	Thrombosis
Impaired fibrinolytic activity	Decreased clot breakdown

Adapted with permission.<sup>25</sup>

tension is not absolute because half of the patients with essential hypertension do not exhibit IR.<sup>31</sup>

There are several ways in which IR might influence the development of hypertension. High levels of FFAs have a proinflammatory effect that can produce a relative vasoconstriction, whereas insulin is an anti-inflammatory hormone that suppresses FFA concentrations to produce a vasodilatory effect.<sup>36</sup> The decrease of endothelium-derived NO that occurs in the insulin-resistant state can exacerbate the vasoconstriction produced by FFAs. In an individual with IR, the insulin-stimulated reabsorption of sodium in the kidney can be increased.<sup>6</sup> At the same time, the stimulation of the sympathetic nervous system by insulin is maintained.<sup>37</sup> Both of these factors play a role in the development of hypertension. Finally, the endothelial dysfunction summarized in **Table III** can further contribute to the development of essential hypertension.<sup>25</sup>

### Dyslipidemia

Dyslipidemia has been reported to be the most common complication of IR and type 2 diabetes.<sup>18</sup> Very specific changes in the plasma lipid and lipoprotein profile occur in conjunction with IR. These changes, including elevated TG levels (VLDL), decreased HDL-C levels, and formation of small dense low-density lipoprotein (LDL) particles, produce a highly atherogenic dyslipidemic profile that increases the risk of cardiovascular disease (CVD) in patients with IR.<sup>18</sup>

These lipid abnormalities are a direct result of excess FFA levels in the blood. The increased FFA flux to the liver results in increased production of apolipoprotein B-containing TG-rich VLDL.<sup>38</sup> The decrease in HDL-C levels is a consequence of changes in high-density lipoprotein (HDL) composition and metabolism due to the presence of hypertriglyceridemia,<sup>6</sup> as well as an increased clearance of HDL-C from the circulation.<sup>39</sup> The density of LDL particles has been found to be concentrated in 5 discrete subfractions, the main subfractions of which are abnormally small and dense.<sup>40</sup> Both the number and relative distribution of the subfractions are dependent on the extent of hypertriglyceridemia.<sup>40</sup> Small dense LDL is thought to be more atherogenic than larger, more buoyant LDL because it is more toxic to the endothelium, it is better able to transit through the endothelial basement membrane, and it has increased susceptibility to oxidation.<sup>6</sup>

### Metabolic Syndrome

The term *metabolic syndrome* is used to describe a constellation of metabolic abnormalities that are all risk factors for CVD.<sup>6</sup> These abnormalities include glucose intolerance (which can manifest as impaired glucose tolerance or impaired fasting glucose), IR, central obesity, dyslipidemia, and hypertension.<sup>6</sup> The fundamental defect in patients with metabolic syndrome is resistance to the cellular actions of insulin, particularly resistance to insulin-stimulated glucose uptake.<sup>18</sup> IR results in hyperinsulinemia, hyperglycemia due to enhanced hepatic gluconeogenesis and glucose output, and an increase in plasma FFAs due to reduced suppression of lipolysis in adipose tissue.<sup>18</sup> High levels of FFAs result in increased hepatic VLDL secretion, which results in hypertriglyceridemia and reduced plasma levels of HDL-C.<sup>18</sup>

Other potential subclinical metabolic abnormalities associated with metabolic syndrome are shown in **Table IV**.<sup>41</sup> Endothelial dysfunction, for example, which is characterized by changes in coagulation factors and the production of proteins involved in fibrinolysis (eg, PAI-1), can result in atherogenic lesions and hypercoagulability.<sup>42</sup> The level of oxidative stress and/or the level of ROS in patients with metabolic syndrome is increased, possibly due to the oxidative state of the lipoproteins.<sup>42</sup> Oxidative stress, in turn, results in changes in the production of cytokines secreted by adipose tissues.<sup>42</sup> With a resulting lower concentration of adiponectin, the catabolism of VLDL decreases and the catabolism of HDL increases. The net result is an increase in the levels of FFAs secreted from adipose tissue.<sup>42</sup> Various proinflammatory cytokines, such as TNF- $\alpha$ , play an important role in metabolic syndrome by regulating multiple processes and molecules such as PAI-1. Thus, metabolic syndrome exhibits multiple effects related to IR at both cellular and organ levels, including hepatic, muscular, adipose, and vascular endothelium levels.<sup>42</sup>

### Cardiovascular Disease

As mentioned, many of the metabolic abnormalities that occur as a consequence of hyperglycemia and IR are well-known risk factors for CVD (**Table V**).<sup>43</sup> It has been suggested that the excess risk for CVD associated with hyperinsulinemia and glucose intolerance may partially result from an enhanced potential for acute thrombosis.<sup>25</sup> **Figure 3** illustrates the links between oxidative stress, IR, and CVD.<sup>44</sup> The dyslipidemia, endothelial dysfunction,

**TABLE IV. POTENTIAL SUBCLINICAL METABOLIC ABNORMALITIES ASSOCIATED WITH METABOLIC SYNDROME.**

Abnormality	Result(s)
Insulin resistance	Hyperinsulinemia Decreased insulin-mediated glucose disposal in muscle, liver, and fat Altered glucose transporter-4 expression
Dyslipidemia	Increased free fatty acids Increased very-low-density lipoproteins (triglycerides) Decreased low-density lipoprotein particle size
Altered renal function	Sodium retention Increased renin-angiotensin-aldosterone system
Altered adipose tissue physiology	Increased visceral fat accumulation Decreased adiponectin
Cardiovascular system disorders	Increased sympathetic adrenergic activity Left ventricular hypertrophy
Prothrombotic disorders	Increased plasminogen activator inhibitor-1 Hyperfibrinogenemia Increased plasma/blood viscosity
Endothelial dysfunction/low-grade inflammation	Impaired skeletal muscle vasodilation Increased plasma concentration of vascular adhesion molecules Increased concentrations of inflammatory biomarkers (eg, C-reactive protein) Alterations in the tumor necrosis factor- $\alpha$ system
Altered liver function	Increased glucose production Decreased insulin removal Increased hepatic lipase activity
Altered skeletal muscle	Increased intramuscular triglycerides Altered plasma membrane phospholipids Increased type II-a skeletal muscle fibers (slow twitch)

Adapted with permission.<sup>41</sup>

tion, and inflammation that occur as a result of IR all influence the risk of CVD. Consequently, pharmacotherapies that target obesity and IR have the potential to reduce morbidity and mortality due to CVD.

### TARGETING INSULIN RESISTANCE

The 2 classes of drugs currently prescribed that have direct effects on IR are biguanides (eg, metformin) and thiazolidinediones, or TZDs (eg, pioglitazone, rosiglitazone).<sup>25</sup> Both classes simultaneously lower blood glucose levels and plasma insulin concentrations, however, they do so with different mechanisms of action. Metformin mainly acts in the liver by increasing insulin sensitivity of that organ, while TZDs act primarily in muscle tissue and adipocytes by increasing insulin-mediated glucose uptake.<sup>45</sup>

### Biguanides

The biguanide metformin is considered an insulin-sensitizing agent. It has the following proposed mechanisms of action: (1) decreases hepatic glucose production, (2) improves peripheral glucose uptake in skeletal muscle and adipocytes, (3) decreases appetite and caloric

### KEY POINT

**Many of the metabolic abnormalities that occur as a consequence of hyperglycemia and IR are well-known risk factors for CVD.**

**TABLE V. CHARACTERISTICS OF INSULIN RESISTANCE AND METABOLIC SYNDROME ASSOCIATED WITH INCREASED CARDIOVASCULAR DISEASE RISK.**

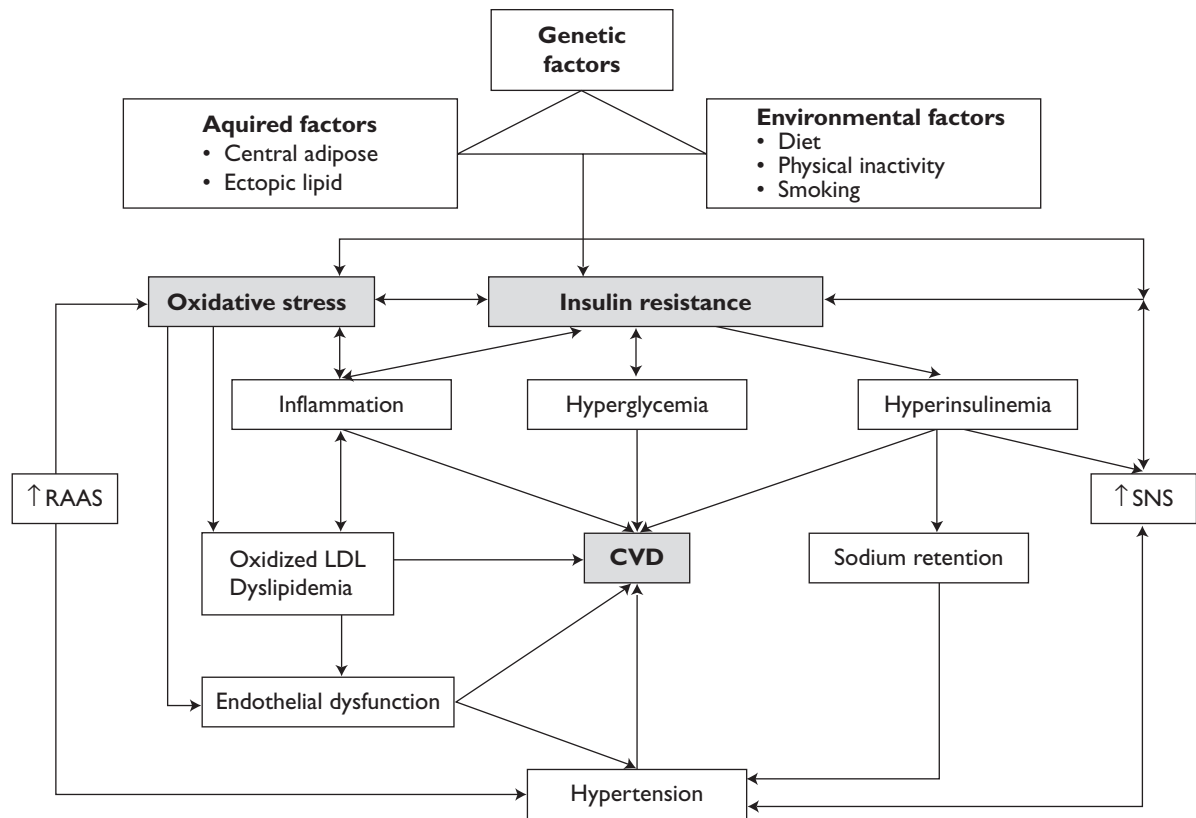
- Low serum high-density lipoprotein cholesterol levels
- High serum triglyceride levels
- Increased serum apolipoprotein B levels
- Small dense low-density lipoprotein particles
- Increased serum fibrinogen levels
- Increased serum C-reactive protein levels
- Increased production of interleukin-6
- Increased blood viscosity
- Premature atherosclerosis
- Enhanced tissue renin-angiotensin-aldosterone system
- Salt sensitivity
- Endothelial dysfunction

Adapted with permission.<sup>43</sup>

intake in the gut, and (4) may improve pancreatic insulin secretion.<sup>46</sup> The pharmacologic effects of metformin also include a reduction in FFAs and an improvement in endothelial dysfunction.<sup>47</sup> Metformin has been associated with beneficial effects on lipid parameters, for example, decreasing LDL-C levels<sup>48,49</sup> and increasing HDL-C concentrations.<sup>50-52</sup> Although lactic acidosis is the most publicized possible adverse effect of therapy with biguanides,<sup>53,54</sup> gastrointestinal symptoms (diarrhea, abdominal discomfort, and anorexia) are the most common adverse effects.<sup>55</sup>

**Peroxisome Proliferator-Activated Receptor Agonists**

A very different approach to the treatment of IR and type 2 diabetes is to decrease plasma FFA levels. The peroxisome proliferator-activated receptor (PPAR) family of receptors plays an important role in lipid metabolism, and agonists to 2 subtypes of PPARs have been developed.<sup>20</sup> Fibrates selectively activate the



**Figure 3. Selected factors (genetic, acquired, and environmental) linking oxidative stress, insulin resistance, and cardiovascular disease (CVD). RAAS = renin-angiotensin-aldosterone system; LDL = low-density lipoprotein; SNS = sympathetic nervous system. Adapted with permission.<sup>44</sup>**

PPAR- $\alpha$  subtype of receptors. These PPAR- $\alpha$  activators help to decrease plasma FFA and triglyceride concentrations and to increase FFA uptake and oxidation. TZDs have a high affinity for the PPAR- $\gamma$  subtype of receptors, and because PPAR- $\gamma$  is expressed at highest concentrations in adipose tissue, the primary action of TZDs is considered to be on adipose tissue. It is thought that TZDs improve insulin sensitivity by redistributing fat from visceral to subcutaneous adipose tissue, lowering plasma levels of FFAs, and increasing adiponectin levels.

TZDs may also have beneficial effects on various risk factors associated with IR.<sup>25</sup> For example, TZDs exert an anti-inflammatory effect at the cellular and molecular level<sup>56–58</sup> and have been shown to improve endothelial function, inflammation, and fibrinolysis.<sup>59,60</sup> In a 26-week randomized, double-blind, placebo-controlled study of patients with type 2 diabetes, rosiglitazone significantly reduced mean plasma CRP levels.<sup>61</sup> However, TZDs have been shown to increase total cholesterol and LDL-C levels, as well as body weight.<sup>60</sup>

The first TZD approved for the treatment of type 2 diabetes, troglitazone, was removed from the market because of an increased risk of idiosyncratic hepatotoxicity. The 2 TZDs currently available—pioglitazone and rosiglitazone—do not appear to share this same risk and may even improve liver function in patients with nonalcoholic steatohepatitis.<sup>62</sup> However, a recent meta-analysis showed a significant increase in the risk of myocardial infarction and a borderline significant risk of death from cardiovascular causes with rosiglitazone.<sup>63</sup> It is not yet known whether the observed cardiovascular risks represent a class effect; nonetheless, these risks should be considered when determining whether treatment with a TZD, and especially rosiglitazone, is the appropriate course of action.<sup>63</sup>

## TARGETING OBESITY AND ASSOCIATED CARDIOVASCULAR AND METABOLIC RISK FACTORS

### Endocannabinoid Antagonists

The endocannabinoid system (ECS) produces endogenous substances—cannabinoids (CBs)—that play an important role in activating the drive for food ingestion, energy storage, and hepatic lipogenesis. Overactivation of the ECS is implicated in obesity and dyslipidemia; therefore, the ECS represents a new target for

the treatment of obesity and associated cardiovascular and metabolic risk factors.<sup>64</sup> The CB<sub>1</sub> receptor is found extensively in the brain<sup>65</sup> and appears to regulate the activity of mesolimbic dopamine neurons, thus influencing reward behaviors mediated by dopamine.<sup>66,67</sup> In animal studies, rimonabant, a selective CB<sub>1</sub> receptor blocker, suppressed eating<sup>68,69</sup> and reduced the preference for sweet foods.<sup>70,71</sup> In several clinical trials, rimonabant promoted weight reduction, reduced waist circumference, and improved metabolic risk factor profiles in patients without diabetes.<sup>72,73</sup> Similar results were observed in 1047 overweight and obese patients with type 2 diabetes who were being treated with background metformin or sulfonylurea monotherapy.<sup>74</sup> In this 1-year, placebo-controlled trial, treatment with rimonabant 20 mg QD produced a statistically significant and clinically meaningful 0.7% decrease in glycosylated hemoglobin levels, along with a modest 3.9 kg weight loss ( $P < 0.0001$  vs placebo). Although discontinuation rates due to adverse events were comparable among all groups, more patients in the rimonabant groups than in the placebo group dropped out of the study prematurely. The most common adverse events leading to discontinuation were depressed mood disorders, nausea, and dizziness.

## CONCLUSIONS

IR can have profound pathophysiologic effects on various organs and tissues of the body. Hyperglycemia-induced tissue damage, hypertension, dyslipidemia, metabolic syndrome, and CVD are among the many clinical consequences of IR. Current pharmacotherapy targeting IR includes metformin and the TZDs. Endocannabinoid antagonists, which target both obesity and associated cardiovascular and metabolic risk factors, are currently in development.

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