

# Metabolic Syndrome and Insulin Resistance

## Perioperative Considerations

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Metabolic syndrome represents a constellation of risk factors associated with increased incidence of cardiovascular disease and progression to diabetes mellitus. Insulin resistance, a state of decreased biologic response to physiologic concentrations of insulin, is a key component of this syndrome and seems to be the result of a primary defect at the skeletal muscle glucose transporter. Acute illness and the perioperative period are characterized by a state of insulin resistance that manifests as hyperglycemia and leads to various other metabolic and biochemical alterations that adversely affect end organ function. Hyperglycemia in acutely ill patients adversely affects outcome. Achieving euglycemia seems beneficial in certain clinical situations, but considerable disagreement exists regarding the target blood sugar levels, the duration of therapy, and the modality. Pharmacotherapy, exercise, and nutrition to improve insulin sensitivity seem promising but require further evaluation to confirm their efficacy for perioperative risk reduction. This review discusses the pathophysiology and the clinical implications of metabolic syndrome and insulin resistance in the acutely ill patient with an emphasis on perioperative modulation strategies.

METABOLIC syndrome represents a cluster of related cardiovascular risk factors that include central obesity, insulin resistance, atherogenic lipid profile, and hypertension. Several definitions of metabolic syndrome exist that share the core components but differ in the criteria required to diagnose the syndrome. Among these, the World Health Organization definitions and the National Cholesterol Education Program Adult Treatment Panel III (table 1) are widely accepted.<sup>1,2</sup>

The use of various criteria hampered comparison of

data from different studies as each definition identified different sets of the population as having metabolic syndrome. Further, none of the definitions were found to be universally superior when applied to different populations. The International Diabetes Federation (IDF) thus recognized the need for a simple, easily applicable tool for the diagnosis of the syndrome that could be used universally. In 2006, the IDF consensus group proposed new criteria (essential and additional) for defining metabolic syndrome recognizing the ethnic variations in the identification of obesity and focused on the prediction of coronary vascular disease and diabetes.<sup>3</sup> Metabolic syndrome, which affects an estimated 20–25% of the general population, has been identified as the central player in the growing epidemic of diabetes and cardiovascular disease.<sup>3</sup>

## Pathophysiology of Metabolic Syndrome

### Central (Visceral) Obesity

Abnormal fat distribution plays a key role in the pathogenesis of metabolic syndrome. Obesity is associated with an increased risk of diabetes and cardiovascular disease. Furthermore, visceral fat by itself is a strong determinant of insulin sensitivity and B-cell function.<sup>3,4</sup> Waist circumference is found to be superior to the body mass index as a measure of visceral adiposity and is widely used to quantify central obesity in clinical practice.<sup>3</sup> Further, visceral adiposity as measured by waist circumference correlates better with the risk of diabetes or coronary vascular disease than total obesity as measured by body mass index.<sup>5,6</sup> Central obesity also shares a strong relation with other components of metabolic syndrome. The IDF definition draws attention to the fact that waist circumference may be population specific because differences have been observed between various ethnic groups and thus may warrant the use of different cutoff values while defining metabolic syndrome.<sup>3</sup>

Adipose tissue is an active endocrine organ that secretes numerous bioactive substances, including hormones, growth factors, and cytokines. Central (visceral) obesity represents dysfunctional adipose tissue whose dysregulated metabolism leads to increased free fatty acid (FFA) flux in the liver and muscle. This contributes to insulin resistance that further worsens the dyslipide-

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**Table 1. Definitions of Metabolic Syndrome**

Criteria	WHO (1999) <sup>1</sup>	NCEP ATP III (2001) <sup>2</sup>	IDF (2006) <sup>3</sup>
Essential	Diabetes mellitus, IFG, IGT, or insulin resistance (assessed by clamp studies) and at least two of the following:	Three or more of the following five risk factors:	Central obesity plus any two of the following four factors:
Central obesity	Waist-to-hip ratio >0.90 in men and >0.85 in women or BMI >30 kg/m <sup>2</sup>	Waist circumference >102 cm in men and >88 cm in women	Waist circumference (Europid) ≥94 cm in men and ≥80 cm in women (ethnic specific values for other population groups as applicable)
Insulin resistance	Diabetes mellitus or IFG or IGT or insulin resistance by clamp studies	FPG ≥100 mg/dl (5.6 mm)	FPG ≥100 mg/dl (5.6 mm) or previously diagnosed type II diabetes
Lipid profile	Serum triglycerides ≥1.7 mm and/or HDL-C <0.9 mm (35 mg/dl) in men and <1.0 mm (39 mg/dl) in women	Triglyceride ≥150 mg/dl (1.7 mm)  HDL-C <40 mg/dl (1.03 mm) in men and <50 mg/dl (1.29 mm) in women	Triglyceride ≥150 mg/dl (1.7 mm) or specific treatment for this lipid abnormality  HDL-C <40 mg/dl (1.03 mm) in males and <50 mg/dl (1.29 mm) in females or specific treatment for this lipid abnormality
Hypertension	Blood pressure ≥140/90 mmHg	Systolic BP ≥130 or diastolic BP ≥85 mmHg	Systolic BP ≥130 or diastolic BP ≥85 mmHg, or treatment of previously diagnosed hypertension
Others	Urinary albumin excretion rate >20 μg/min or albumin to creatinine ratio ≥30 mg/g		Additional metabolic criteria supportive of but not essential for the diagnosis

BMI = body mass index; BP = blood pressure; FPG = fasting plasma glucose; HDL-C = high-density lipoprotein cholesterol; IDF = International Diabetes Federation; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; WHO = World Health Organization.

mia.<sup>7</sup> Visceral fat also secretes proinflammatory cytokines interleukin 6 and tumor necrosis factor  $\alpha$ . Together with the reduced secretion of adiponectin, it further aggravates insulin resistance.<sup>8</sup>

#### *Insulin Resistance*

Insulin resistance can be defined as “a state where there is a reduced biologic effect for any given concentration of insulin.”<sup>9</sup> It is a central feature of metabolic syndrome, showing a strong association with most components of the syndrome.<sup>3,10</sup> The prevalence of insulin resistance in the general population has seen a phenomenal increase in the past decade.<sup>7</sup> It may be seen during pregnancy or starvation but is more widely recognized in patients with type II diabetes mellitus. Transient insulin resistance may often develop with surgical and nonsurgical trauma and critical illness.<sup>11</sup>

Insulin resistance manifests as a broad clinical spectrum evolving progressively from hyperinsulinemia to glucose intolerance and eventually to frank diabetes. Therefore, the diagnosis of insulin resistance in the various definitions of metabolic syndrome has required the presence of one or more features from this spectrum. Genetic susceptibility, along with environmental factors such as lifestyle, diet, stress, and smoking, can trigger the development of insulin resistance.<sup>8</sup> The metabolic consequences, hyperinsulinemia, hyperglycemia, and lipid and lipoprotein dysregulation, act in synergy to potentiate and sustain the pathologic state of insulin resistance. With the evolution of insulin resistance, endothelial dysfunction, inflammation, and atherosclerosis worsen progressively.<sup>7,12</sup>

#### *Atherogenic Dyslipidemia*

The combination of increased triglycerides and reduced high-density lipoprotein (HDL) cholesterol together with increased apolipoprotein B and small-dense low-density lipoprotein (LDL) particles best describes the atherogenic lipid profile associated metabolic syndrome.<sup>3,7</sup> Alterations in the lipid and lipoprotein metabolism are closely linked with hepatic and peripheral insulin resistance. The small-dense LDL is highly atherogenic and therefore has become the main target for lipid lowering therapy.<sup>13</sup>

#### *Hypertension*

The mechanism of hypertension in metabolic syndrome is multifactorial and may be related, among other factors, to obesity and dietary thermogenesis.<sup>14</sup> Insulin-related alteration in renal sodium handling and salt sensitivity, central activation of the sympathetic nervous system, along with angiotensin II and endothelin 1-mediated vasoconstriction might also contribute.<sup>12</sup>

#### *Thrombogenicity*

Metabolic syndrome predisposes to a prothrombotic state as a result of elevated fibrinogen levels along with decreased fibrinolytic activity due to increased plasminogen activator inhibitor 1. Platelet function is also disturbed, leading to increased aggregation and thrombin generation.<sup>15</sup>

#### *Inflammation and Endothelial Dysfunction*

Metabolic syndrome is a proinflammatory state. Insulin resistance and the atherogenic dyslipidemia cause up-

regulation of inflammatory adipokine tumor necrosis factor  $\alpha$ , interleukin 6, and C-reactive protein and a decrease in adiponectin.<sup>7</sup> Overexpression of the inflammatory proteins further interferes with insulin signaling pathways, enhances lipid peroxidation, and increases FFA flux.

### Systemic Effects of Metabolic Syndrome

Patients with metabolic syndrome are at a greater risk of developing coronary artery disease and major adverse vascular events (table 2).<sup>16-18</sup> A threefold increase in the risk of myocardial infarction (MI) or stroke with twice the mortality from such an event is reported in patients with metabolic syndrome as compared with those without the syndrome.<sup>19</sup> While the individual components of metabolic syndrome have been recognized as independent risk factors of coronary vascular disease, clustering of these adverse metabolic factors may further intensify the risk.<sup>3</sup>

Patients with metabolic syndrome have fivefold higher risk for developing diabetes. Insulin resistance and altered glucose metabolism, the key component of the syndrome, may be responsible for this increased risk.<sup>20</sup>

Metabolic syndrome and its individual components are risk factors for acute stroke in the elderly. Stroke patients with metabolic syndrome exhibited an atherogenic profile with higher concentrations of triglycerides and lower HDL cholesterol.<sup>21</sup> Patients, especially women, with metabolic syndrome and atherosclerotic disease were at an increased risk for ischemic stroke or transient ischemic attack even in the absence of diabetes. Further, hypertension and fasting hyperglycemia were stronger predictors of cerebrovascular events than other components of metabolic syndrome.<sup>22</sup>

The individual components of metabolic syndrome adversely affect the kidney initiating loss of renal function. The constellation of the syndrome acts in synergy, the risk increasing progressively with the number of components involved, to accelerate renal damage from microalbuminuria to eventual end-stage renal disease.<sup>23</sup> Metabolic syndrome has also been identified as an important risk factor for diabetes mellitus, chronic renal graft dysfunction, and graft loss after renal transplantation.<sup>24</sup>

Metabolic syndrome has been shown to be associated with nonalcoholic fatty liver disease and nonalcoholic steatohepatitis.<sup>25</sup> Nonalcoholic steatohepatitis is characterized by hepatocellular inflammation and necrosis along with elevated transaminases and may progress to cirrhosis.<sup>7</sup> Insulin resistance may be the main causative factor because improving insulin sensitivity has been shown to decrease hepatic fat and inflammation, improve metabolic profile, and resolve the histologic changes.<sup>7,26</sup>

A retrospective study of a large cohort of pregnant women showed that features of metabolic syndrome before pregnancy were linked to a higher risk of placen-

tal dysfunction, including fetal growth retardation and demise. The study also found that this risk increased progressively with the number of components of metabolic syndrome involved, with the odds ratio increasing from 3.1 for one feature to 7.7 when three or four components were affected.<sup>27</sup> Metabolic syndrome has also been linked with an increased risk of adverse vascular events and venous thrombosis.<sup>17,28</sup>

The pathophysiology of metabolic syndrome may have important implications for the surgical patient. Obesity, hypertension, and diabetes mellitus are well-recognized perioperative risk factors that contribute to morbidity and mortality.<sup>29,30</sup> It is possible that the clustering of these cardiometabolic risk factors may further potentiate surgical risk and impact outcome. The incidence and degree of insulin resistance may also be related to the clustering of features of metabolic syndrome.<sup>10</sup> In the context of perioperative or acutely ill patients, insulin resistance may be one of the only features that is easily amenable to modulation and that may lead to an improvement in outcome.

### Pathophysiology and Molecular Mechanisms of Perioperative Insulin Resistance

Insulin is secreted mainly in response to plasma glucose.<sup>31</sup> With the onset of insulin resistance, normoglycemia is achieved by increasing the secretion of insulin from pancreatic  $\beta$ -cells resulting in hyperinsulinemia. This state of "prediabetes" manifests clinically as impaired fasting glucose and/or impaired glucose tolerance.<sup>7,32</sup> Further resistance to insulin results in a failure to achieve normoglycemia despite increased insulin secretion, resulting in diabetes mellitus. Eventually, a "burnout" of  $\beta$  cells results, followed by decreased insulin levels along with further failure of glucose homeostasis<sup>7,31</sup> (fig. 1). Hyperinsulinemia, glucose intolerance, hyperglycemia, and frank diabetes thus represent a clinical continuum of abnormal glucose homeostasis and insulin resistance. Features of this clinical continuum often coexist, and it may not always be possible to dissect the effects of hyperglycemia *per se* from the state of insulin resistance.

The stress of acute illness and surgery induces transient but reversible acceleration of the progression of insulin resistance.<sup>33</sup> The magnitude of insulin resistance and the metabolic response to surgical stress may be linked to the invasiveness of the surgery. Blood loss may also have a direct and independent correlation with postoperative insulin resistance.<sup>33</sup> Whether the body cavity operated on influences the magnitude of insulin resistance is not known and remains open to speculation. Stress response may also be related to the duration of the surgical trauma, because glucose utilization seems to be reduced after prolonged surgery.<sup>34</sup> Physical status and postsurgery rehabilitation may further influence the development of insulin resis-

**Table 2. Clinical Outcomes of Metabolic Syndrome**

Investigators	Study Design	Population	Metabolic Criteria	Assessment	Results
Valantine <i>et al.</i> , <sup>16</sup> 2001	Prospective, n = 66, follow-up 8 yr	Heart transplant	NCEP ATP III	Transplant CAD	Markers of MetSyn predict the development transplant coronary artery disease and death. Plasma insulin levels independently correlated with intimal thickness and subsequent development of stenosis.
Marchesini <i>et al.</i> , <sup>25</sup> 2003	Prospective, n = 304	NAFLD without overt DM	NCEP ATP III	Steatohepatitis (NASH)	High prevalence of MetSyn in patients with NAFLD. Presence of MetSyn is associated with increased risk of progression to steatohepatitis in patients with NAFLD.
Chen <i>et al.</i> , <sup>23</sup> 2004	Cross-sectional, n = 7,832, subsample of NHANES III	Age >20 yr	NCEP ATP III	Chronic kidney disease and microalbuminuria	MetSyn is a strong and independent risk factor for chronic kidney disease and microalbuminuria. The risk increases with increasing number of features of the syndrome.
Saely <i>et al.</i> , <sup>17</sup> 2005	Prospective cohort study, n = 750	Established or suspected CAD	NCEP ATP III, IR-HOMA	Adverse vascular events, follow-up 2.3 yr	MetSyn and insulin resistance are strong independent predictors of adverse vascular events among patients with or at risk of CAD. Increased vascular events with increasing MetSyn score.
Koren-Morag <i>et al.</i> , <sup>22</sup> 2005	Prospective, n = 14,284	CAD	NCEP ATP III	Ischemic stroke/TIA, follow-up 4.8–8.1 yr	Presence of MetSyn predicts the risk for ischemic stroke/TIA in patients with coronary artery disease. Impaired fasting glucose and hypertension were strongest predictors of the risk of ischemic cerebrovascular event.
Milionis <i>et al.</i> , <sup>21</sup> 2005	Prospective case-control study, n = 392	Age >70 yr	NCEP ATP III	Ischemic nonembolic stroke	High prevalence of MetSyn in stroke patients. MetSyn is associated with an increased risk of acute ischemic nonembolic stroke in elderly individuals with significant contribution from individual components.
Ray <i>et al.</i> , <sup>27</sup> 2005	Retrospective cohort study, n = 1.03 million	Pregnant women	NHLBI and AHA	Placental dysfunction	Women with features of MetSyn before pregnancy had a higher risk of placental dysfunction and fetal demise. The risk increased with increasing features of MetSyn.
Agno <i>et al.</i> , <sup>28</sup> 2006	Prospective case-control study, n = 210	Confirmed DVT diagnosis	NCEP ATP III	Idiopathic DVT	MetSyn is independently associated with an increased risk of idiopathic DVT. Among the features of MetSyn, central obesity and increased triglycerides are independently associated with DVT.
Hu <i>et al.</i> , <sup>18</sup> 2006	Retrospective case-control study, n = 2,596	CAD	Modified IDF (BMI used instead of waist circumference)	Major adverse cardiac and cerebral events	Increased incidence of major cardiac and cerebral events in patients with MetSyn on long-term follow-up.
Porrini <i>et al.</i> , <sup>24</sup> 2006	Prospective cohort study, n = 230	Renal transplant	Modified NCEP ATP III	PTDM, graft function, patient survival	MetSyn prominent risk factor for PTDM, chronic graft dysfunction, graft loss, and mortality in renal transplant recipients.

AHA = American Heart Association; BMI = body mass index; CAD = coronary artery disease; DM = diabetes mellitus; DVT = deep vein thrombosis; IDF = International Diabetes Federation; IR-HOMA = Insulin Resistance by Homeostasis Model Assessment; MetSyn = metabolic syndrome; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; NHANES III = Third National Health and Nutrition Examination survey; NHLBI = National Heart, Lung, and Blood Institute; PTDM = posttransplant diabetes mellitus; TIA = transient ischemic attack.

tance by affecting skeletal muscle glucose uptake. Nutrition may be another contributing factor. A diet inadequate in calories, besides causing negative nitrogen balance, has been shown to alter the metabolic environment and give rise to insulin resistance.<sup>31</sup> Although the biochemical man-

ifestation of this transient state of insulin resistance is obvious, the underlying mechanisms remain poorly understood.

Several alterations in the skeletal muscle, adipose tissue, hormones, and cytokines are proposed to explain

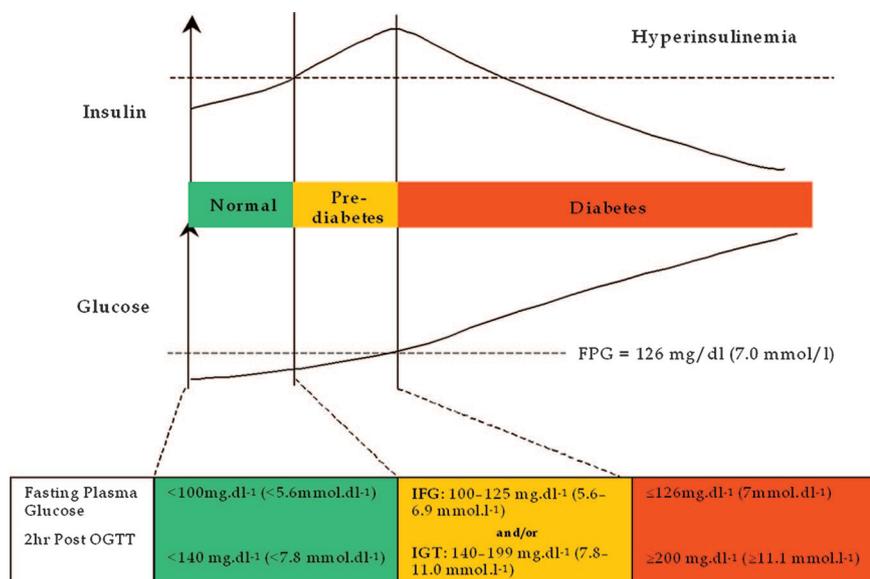


Fig. 1. Schematic representation of the temporal progression of insulin resistance. FPG = fasting plasma glucose; IFG = impaired fasting glucose, elevated fasting glucose levels but with normal response to oral glucose tolerance test (OGTT); IGT = impaired glucose tolerance, abnormal postprandial glucose excursion but with normal fasting glucose levels.

the pathogenesis of perioperative insulin resistance. It is now increasingly recognized that perioperative insulin resistance is predominantly an extrahepatic phenomenon, primarily affecting the skeletal muscle. It is characterized by a decrease in peripheral glucose uptake with an increase in endogenous glucose production.<sup>11,33</sup> Insulin facilitates glucose entry in insulin sensitive tissues such as muscle and adipose tissue by increasing the number of GLUT4 transporters.<sup>31</sup> These receptors are stored in intracellular vesicles, and insulin-mediated activation of phosphoinositol-3-kinase causes fusion of the vesicles with the cell membrane, thereby resulting in insertion of the transporter into the cell membrane and increasing glucose entry into the cell. A defect at this GLUT4 transporter prevents insulin-stimulated glucose uptake and subsequent glycogen synthesis in skeletal muscle. This is now considered the principal abnormality underlying insulin resistance.<sup>11,33,35,36</sup> Studies on muscle biopsies from patients undergoing hip replacement seem to corroborate the role of skeletal muscle GLUT4 transporter in the pathogenesis of peripheral insulin resistance.<sup>36</sup> Furthermore, with insulin resistance there is upregulation of insulin-independent GLUT1–3 transporters that are found in neurons, renal cells, erythrocytes, and immunocytes, exposing them to excess glucose load and glucotoxicity (fig. 2).<sup>11</sup> Skeletal muscles also contain a subpopulation of GLUT4 transporters that translocate to the cell membrane in response to exercise and enhances glucose uptake independent of insulin. Limitation of physical exercise results in down-regulation of these GLUT4 transporters, aggravating insulin resistance.<sup>31,37</sup>

Lipid and lipoprotein dysregulation are closely linked to the insulin-resistant state. Defects in FFA storage and metabolism result in increased FFA flux in primary insulin sensitive tissues like the liver and skeletal muscle. The FFAs and their metabolites decrease phosphoinositide-3-

kinase activity that ultimately leads to failure of GLUT4 translocation and insulin signaling mechanisms. The resulting insulin-resistant state further enhances lipolysis, setting up a vicious cycle (fig. 3).<sup>7</sup>

Insulin resistance and the inflammatory stress response seem to be interlinked. Plasma insulin levels and interleukin 6 follow a similar pattern during the perioperative period.<sup>38</sup> Whereas inflammatory cytokines such as interleukin 6 seem to inhibit insulin sensitivity by their effects on lipid peroxidation, and FFA flux, and GLUT4 expression, adipokines such as tumor necrosis factor  $\alpha$  and resistin decrease insulin sensitivity by modulating lipid metabolism and GLUT4 activity.<sup>7,31,38</sup>

Insulin-like growth factors (IGFs) and their binding proteins may also play a role in the pathophysiology of perioperative insulin resistance. IGFs are polypeptides secreted by the liver that mediate the anabolic effects of growth hormone. Most IGF-1 in the plasma is bound to IGF-binding proteins 1–6. Free IGF-1 binds specifically to IGF receptors and weakly to insulin receptors, both of which are tyrosine kinases that enhance glucose uptake.<sup>31,33</sup> Levels of IGF-binding protein 1 are elevated in the perioperative period, whereas IGF-1 levels remain unchanged or even decrease, resulting in altered bioavailability of IGFs in the perioperative period.<sup>33</sup> The neuroendocrine system also contributes to the development of insulin resistance. Elevated circulating cortisol, growth hormone, and catecholamines seen during surgical stress exert an antiinsulin effect resulting in enhanced hepatic glucose output.<sup>39</sup>

### Insulin Resistance and Hyperglycemia

There is mounting evidence attesting to the detrimental effects of hyperglycemia on outcomes in diverse clinical settings (table 3).<sup>40,41–48</sup> The impact of hyperglycemia on

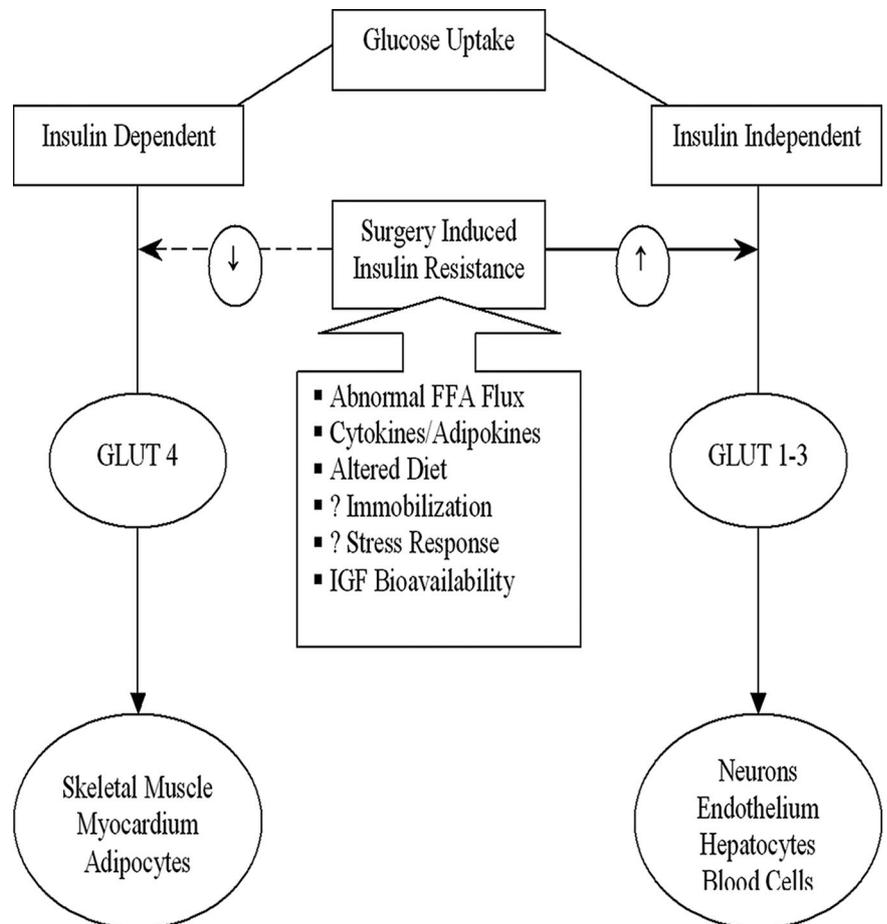


Fig. 2. Physiology of glucose uptake and biochemical alterations contributing to perioperative insulin resistance. FFA = free fatty acid; GLUT1–4 = glucose transporters; IGF = insulin-like growth factor.

outcome in critically ill patients was first evaluated prospectively in the Leuven study by van den Berghe *et al.*<sup>40</sup> It was found that tight glycemic control (blood glucose <110 mg/dl or 6.1 mm) reduced morbidity and mortality among surgical intensive care patients irrespective of their diabetic status.<sup>40</sup> Among medical intensive care patients, van den Berghe *et al.* reported that intensive insulin therapy to achieve blood glucose levels of 80–110 mg/dl (4.4–6.1 mm) while reducing morbidity did not affect mortality. However, a reduction in mortality with intensive insulin therapy was observed in patients who required intensive care for more than 3 days.<sup>49</sup> An observational study involving critically ill patients showed that glycemic control and not insulin dosage seemed to explain mortality benefits of intensive insulin therapy.<sup>46</sup> Therefore, the primary benefits of intensive insulin therapy may be related to its glucose-decreasing effect and maintenance of normoglycemia.<sup>46,50</sup>

Hyperglycemia is a frequent metabolic disturbance observed in patients with MI. Stress-induced insulin resistance mediates decreased availability of glycolytic substrate, and increased fatty acid utilization may impair myocardial contractility and increase oxygen requirements, promoting arrhythmias and pump failure.<sup>51</sup> A meta-analysis reviewing the risk of in-hospital mortality after MI in patients with stress hyperglycemia found that

nondiabetic patients with blood glucose in the range 6.1–8 mm (100–140 mg/dl) had 3.9-fold increased risk of death than patients who had blood glucose of 6.1 mm (100 mg/dl) or less. Admission hyperglycemia corresponded with the risk of in-hospital mortality, congestive cardiac failure, and cardiogenic shock after MI in both diabetic and nondiabetic patients, with more pronounced effects in the latter.<sup>52</sup> A prospective study involving nondiabetic patients with acute MI reported increasing mortality with fasting glucose levels of 6.1 mm (110 mg/dl) or greater. Fasting glucose was also found to be better at predicting short-term mortality after acute MI than admission glucose levels.<sup>53</sup> Patients without previous history of diabetes with admission hyperglycemia (fasting glucose >7 mm [>125 mg/dl] or random >11.1 mm [>200 mg/dl]) on general surgical and medical wards were found to have higher mortality and poorer outcome as compared with normoglycemic patients. Further, these patients had higher rates of intensive care unit admissions and greater risk of infection and acute neurologic events.<sup>54</sup> The American Diabetes Association and the American Association of Clinical Endocrinologists have subsequently issued guidelines recommending fasting glucose level less than 6.1 mm (110 mg/dl) in hospitalized patients irrespective of their clinical history.<sup>55</sup>

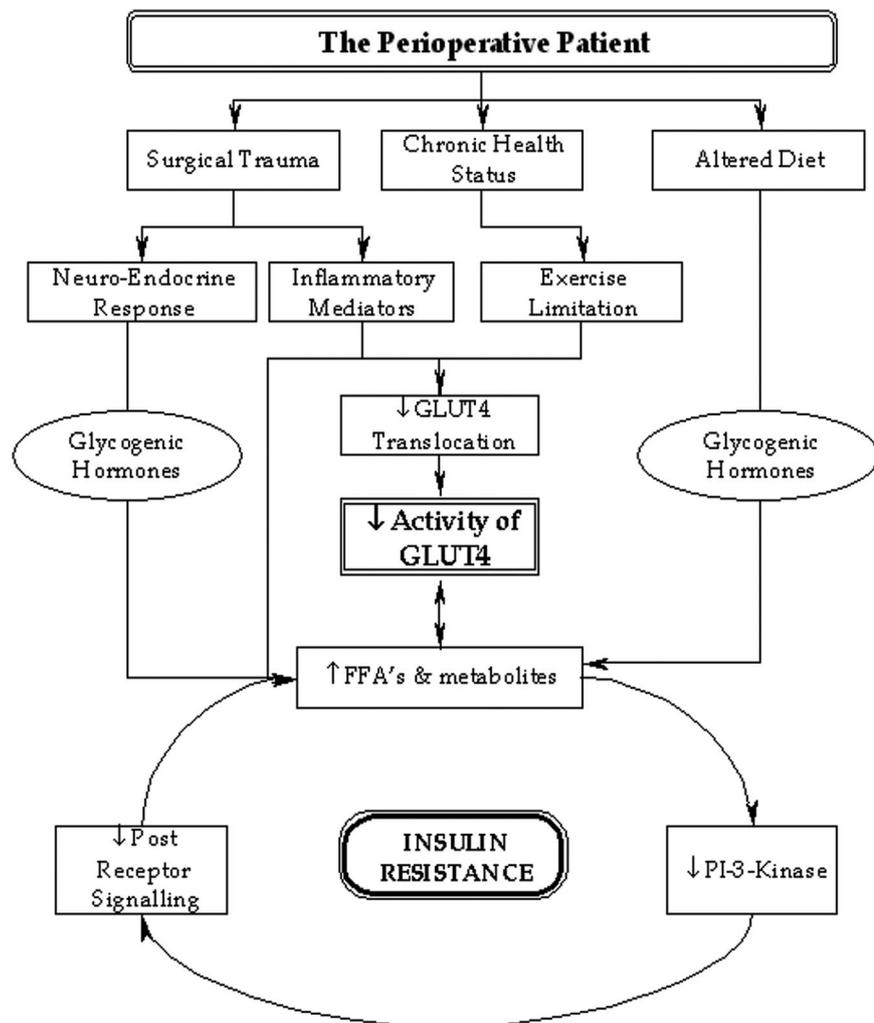


Fig. 3. Mechanisms of insulin resistance during the perioperative period. FFA = free fatty acid; GLUT = glucose transporter; PI-3 = phosphoinositide-3.

The insulin resistance and hyperglycemia frequently observed during cardiac surgery occurs as a result of release of inflammatory cytokines during cardiopulmonary bypass, use of heparin, release of stress hormones, and iatrogenic catecholamine use, among others. Hyperglycemia during cardiopulmonary bypass and after cardiac surgery has been associated with increased mortality among both diabetics and nondiabetics.<sup>48,56,57</sup> In a study involving diabetic patients undergoing coronary artery bypass graft, plasma glucose levels greater than 175 mg/dl (9.7 mm) were related to higher mortality principally from cardiac causes. Achieving glycemic control with continuous insulin infusion improved survival in these patients by reducing cardiac mortality.<sup>58</sup> Others have reported similar improvements in morbidity and mortality using insulin infusion to achieve tight glycemic control.<sup>40,59</sup>

The potential diabetogenicity of uremia and peritransplant therapy may be aggravated further by surgical stress. Glucose uptake into renal tubular cells is insulin independent, making them vulnerable to glucotoxicity related to hyperglycemia.<sup>11</sup> Perioperative hyperglycemia has been shown to be associated with acute rejection in known diabetics.<sup>60</sup> Thomas *et al.*,<sup>61</sup> however, reported

that 71% of nondiabetic renal transplant recipients whose postoperative blood glucose levels were greater than 8 mm (144 mg/dl) developed acute rejection. Acute hyperglycemia due to insulin resistance may enhance ischemia-reperfusion injury and antigen presentation, escalating the inflammatory response that mediates graft rejection.<sup>61</sup>

Insulin resistance seems to play a central role in the pathophysiology of the glucose intolerance commonly observed in brain-dead donors. Detrimental effects include osmotic diuresis, electrolyte disturbances, and impairment of end-organ function. Insulin therapy to maintain blood glucose levels between 4.4 and 8.3 mm (80 and 150 mg/dl) and avoidance of hypotonic dextrose solutions have been recommended. Treatment of insulin resistance during the process of graft harvest and transplantation may improve the number and viability of the organs procured.<sup>62</sup>

Persistent hyperglycemia 48 h after thromboembolic stroke seems to increase mortality, whereas achieving euglycemia seems to improve outcome. Normoglycemia was reported to be an independent predictor of survival after stroke. This effect seemed to be independent of the

**Table 3. Studies Investigating the Effects of Hyperglycemia on Perioperative Outcome**

Investigators	Study Design	Surgery	Subjects	Threshold of Poor Control	Outcomes
McGirt <i>et al.</i> , <sup>43</sup> 2006	Retrospective review, n = 1,201	Carotid endarterectomy	Diabetic and nondiabetic	Preoperative >200 mg/dl	Perioperative hyperglycemia (>200 mg/dl) is an independent risk factor for perioperative MI, stroke, TIA, and death after carotid endarterectomy irrespective of diabetes history.
Malmstedt <i>et al.</i> , <sup>44</sup> 2006	Retrospective review, n = 91	Peripheral vascular	Diabetic	Mean postoperative glucose (area under curve)	Poor postoperative glycemic control associated with unfavorable outcome (wound infection, graft occlusion, major amputation, death).
Pomposelli <i>et al.</i> , <sup>45</sup> 1998	Prospective observational study, n = 100	Abdominal and cardiovascular	Diabetic	Postoperative glucose >220 mg/dl	Postoperative hyperglycemia (>220 mg/dl) is an independent risk factor for nosocomial infection.
Thomas <i>et al.</i> , <sup>61</sup> 2000	Retrospective record review, n = 230	Renal transplant	Nondiabetic	Postoperative >144 mg/dl	Postoperative hyperglycemia (>144 mg/dl) associated with increased risk of allograft rejection. Poor early glycemic control independently predicts acute rejection.
Thomas <i>et al.</i> , <sup>60</sup> 2001	Retrospective record review, n = 50	Renal transplant	Diabetic	Postoperative >200 mg/dl	Postoperative hyperglycemia >200 mg/dl is associated with increased risk of allograft rejection and infection.
Ouattara <i>et al.</i> , <sup>57</sup> 2005	Prospective interventional (insulin therapy), n = 200	Cardiac	Diabetic	Intraoperative >200 mg/dl	Intraoperative hyperglycemia >200 mg/dl associated with higher postoperative in-hospital morbidity (cardiovascular, respiratory, renal, neurologic).
Doenst <i>et al.</i> , <sup>48</sup> 2005	Prospective, n = 6,280	Cardiac	Diabetic and nondiabetic	Intraoperative peak glucose >360 mg/dl	Hyperglycemia during bypass is an independent risk factor for death and morbidity in both diabetic and nondiabetic subjects.
Gandhi <i>et al.</i> , <sup>56</sup> 2005	Retrospective review, n = 409	Cardiac	Diabetic and nondiabetic	Intraoperative mean and peak glucose levels	Intraoperative hyperglycemia is an independent risk factor for complications and death after cardiac surgery.

MI = myocardial infarction; TIA = transient ischemic attack.

method used for blood glucose control.<sup>63</sup> Hyperglycemia has also been reported to be associated with poor neurologic outcome after traumatic brain injury in both adults and children.<sup>47,64</sup>

Hyperglycemia has been shown to have detrimental effects on the immune system. Acute hyperglycemia impairs monocyte activation and oxidative burst as well as phagocytic capacity of macrophages.<sup>65,66</sup> It may also lead to glycosylation of immunoproteins.<sup>11</sup> Another effect observed is an exaggeration of injury-induced inflammatory response. These effects, in conjunction with

the enhanced protein breakdown caused by insulin resistance, may predispose to systemic and surgical site infections, impair wound healing, and delay recovery.<sup>40,59,67</sup> Amelioration of hyperglycemia may partly account for the beneficial immunomodulating effects of insulin therapy.

### Assessment of Insulin Resistance

Hyperinsulinemic euglycemic clamp remains the accepted standard for assessment of insulin resistance.<sup>68</sup>

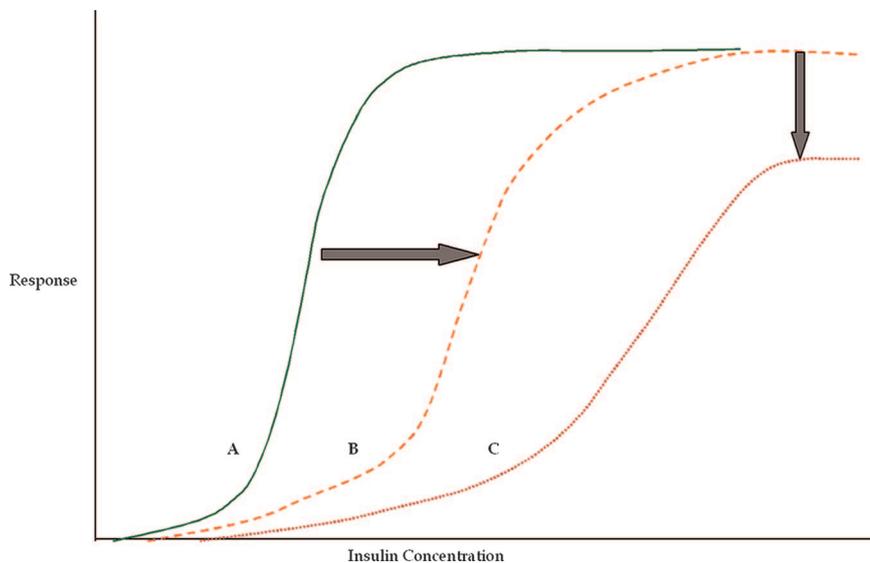


Fig. 4. Representation of insulin dose-response curve. A represents normal state of insulin sensitivity. B depicts insulin response curve shifted to right, showing decremented response to insulin. C depicts decreased maximal response to insulin secretion. B and C represent progression of the insulin-resistant state.

With this method, blood glucose is “clamped” at a predetermined level by titrating glucose infusion against a fixed rate of insulin infusion. The degree of insulin resistance is inversely related to the amount of glucose required to maintain the target concentration when steady state is achieved. The clamp technique provides a quantitative measure of insulin-mediated glucose disposal and also defines the site of insulin resistance.<sup>68</sup> In the insulin-resistant state, the insulin-mediated glucose disposal curve is typically shifted to the right, often with reduction in the maximal effect of insulin (fig. 4). This is reflected in clinical practice by increasing insulin requirements to achieve blood glucose control.<sup>9</sup>

Several other validated tests are available for the assessment of insulin resistance and are summarized in table 4. These are useful research tools and may provide valuable input for clinical management. Insulin resistance may be quantified by mathematical models, clamp techniques, insulin infusion tests, or by glucose tolerance tests.<sup>9,68</sup> Due consideration should be given to the method of assessment of insulin resistance when comparing different studies.

### Strategies for Metabolic Management

The complex cellular and molecular mechanisms underlying insulin resistance and metabolic syndrome may be further altered by the dynamics of surgical trauma and the associated stress response, analgesia, nutritional status, and bed rest, among other factors. Active modulation of the altered metabolic status may improve outcome after a surgical injury.

#### *Insulin Therapy and Glucose Control*

Insulin, endogenous and exogenous, has long been recognized as a metabolic hormone. Its primary effect is on glucose homeostasis, *i.e.*, enhanced peripheral glu-

cose uptake with inhibition of glycogenolysis and hepatic gluconeogenesis. It promotes protein anabolism while also inhibiting fatty acid breakdown. The non-metabolic effects of insulin are increasingly being recognized. It is believed to have an antiinflammatory effect while enhancing phagocyte function and opsonic activity. It may maintain fibrinolytic activity, prevent platelet activation, and improve vascular reactivity and endothelial function. These effects may act in synergy with the metabolic effects to promote and maintain organ function.<sup>11</sup> However, it should be noted that persistent hyperinsulinemia might be associated with detrimental effects, such as coronary stenosis in transplanted hearts.<sup>16</sup>

Insulin therapy for the management of insulin resistance and the potential benefits of glycemic control among acutely ill subjects has been well studied (table 5).<sup>40,42,49</sup> Although data from heterogeneous surgical populations are sparse, several authors have addressed the effect of insulin therapy in cardiac surgery.<sup>40,58,59,69</sup> Furthermore, in practice, the glycemic target, timing, and duration of therapy vary widely. A common method of insulin therapy in acutely ill patients is intravenous insulin infusion. Other methods used include glucose-insulin-potassium infusions, subcutaneous injections, dextrose infusions with insulin boluses, and insulin clamp techniques.

The Leuven study by van den Berghe *et al.*<sup>40</sup> was a prospective, randomized controlled trial of surgical intensive care patients, more than two thirds of whom had had cardiac surgery. It showed that intensive insulin therapy to maintain glucose at or below 110 mg/dl (6.1 mM) was associated with a reduction in morbidity and mortality. Furthermore, there was reduced mortality from multiorgan failure irrespective of a history of diabetes, reduced duration of stay in intensive care, and lower requirement for mechanical ventilation and renal

**Table 4. Methods of Assessment of Insulin Resistance<sup>9,68</sup>**

Method	Procedure	Advantage/Limitations	Application
Fasting plasma insulin	Plasma insulin concentration measured after overnight fast. High plasma insulin values reflect presence of insulin resistance.	Inexpensive and easy to perform Correlates well with clamp. Insulin concentrations vary widely both among normal and diabetics. Marked interassay variability exists. Insulin secretion, distribution and degradation also determine plasma insulin concentrations. No defined cutoff values indicating IR.	Population-based studies
HOMA	Mathematical estimate of basal state of IR from fasting glucose and insulin concentration. $HOMA = \text{fasting insulin } (\mu\text{U/ml}) \times \text{fasting glucose (mm)}/22.5$ . High HOMA values indicate low insulin sensitivity.	Simple, correlates well with clamp	Epidemiologic studies; assess evolution of IR within an individual
CIGMA	Mathematical model assessing glucose and insulin responses to low-dose glucose infusion. Model based on known physiologic data of glucose and insulin kinetics from healthy, lean subjects.	Scarce data to benchmark results	Epidemiologic studies; assess evolution of IR within an individual
Clamps	Blood glucose "clamped" at a predetermined level by titrating glucose infusion against a fixed rate of insulin infusion. Insulin resistance inversely related to amount of glucose required to maintain target concentration at steady state.	Accepted standard; time consuming, complex, labor intensive, expensive	Research tool
OGTT	IR estimated from log of plasma insulin concentration after 75 g oral glucose load.	Correlates well with hyperinsulinemic euglycemic clamp. Less expensive and labor intensive than clamp test. Several insulin sensitivity indices are available.	Epidemiologic studies, interventional trials
Insulin tolerance test	Estimate of IR by plasma glucose decline after fixed insulin bolus. Faster decline in glucose concentration reflects greater insulin sensitivity.	Risk of hypoglycemia	Physiologic studies

CIGMA = continuous infusion of glucose with model assessment; HOMA = homeostasis assessment model; IR = insulin resistance; OGTT = oral glucose tolerance test.

replacement therapy. Intensive insulin therapy was also associated with reduced episodes of septicemia and lower levels of inflammatory markers.<sup>40</sup> However, intensive insulin therapy to achieve blood glucose levels below 110 mg/dl (6.1 mm) was associated with increased mortality among medical intensive care patients who required intensive care for less than 3 days.<sup>49</sup> Lazar *et al.*<sup>59</sup> showed that tight glycemic control (defined as blood glucose  $\leq 11.1$  mm or 200 mg/dl) with glucose insulin potassium infusion improved perioperative outcome, increased survival, and decreased incidence of ischemic events and wound infection in diabetic patients undergoing coronary artery bypass graft.

Furnary *et al.*<sup>58</sup> conducted a large retrospective study involving more than 3,000 diabetic patients undergoing coronary artery bypass graft and found that patients receiving continu-

ous insulin infusion achieved tighter blood glucose control as compared with patients managed with intermittent subcutaneous insulin injections. Furthermore, the perioperative mortality was significantly lower in the continuous insulin infusion group (2.5% *vs.* 5.3%;  $P < 0.0001$ ). The decrease in mortality was primarily from a reduction in the incidence of cardiac related deaths. The authors proposed that continuous insulin infusion improves myocardial glycometabolic function by insulin-induced stimulation of pyruvate dehydrogenase activity and enhanced glycolysis that replenishes cytoplasmic adenosine triphosphate stores required for phosphorylation of extracellular glucose, stabilization of membrane function, and maintenance of cellular integrity. Enhanced glycolysis is also believed to inhibit lipolysis and mitochondrial  $\beta$  oxidation, preventing accumulation of toxic FFA metabolites.<sup>58</sup>

**Table 5. Studies Investigating the Effects of Glycemic Control (Insulin Therapy) in the Critically Ill (Including MI and CABG)**

Investigators	Study Population	Protocol and Glycemic Target, mg/dl	Outcomes
Malmberg <i>et al.</i> , <sup>41</sup> 1999	AMI in diabetics, n = 620, prospective RCT, follow-up average 3.4 yr	<i>Conventional group</i>  <i>Study group:</i> Tight glucose control (target 125–180) with insulin glucose infusion for $\geq 24$ h initially and maintained later with multidose subcutaneous injections for $\geq 3$ months	Admission glycometabolic state (glucose and HbA <sub>1c</sub> ) is an independent predictor of mortality in diabetics with AMI. No difference between the groups in short-term mortality. Reduction in long-term mortality observed in the tight glucose control group vs. conventional group (33% vs. 44%; $P = 0.011$ ). Benefits most notable in patients without history of insulin treatment and low cardiovascular risk.
van den Berghe <i>et al.</i> , <sup>40</sup> 2001	Surgical ICU, n = 1,548, 63% cardiac surgery, prospective RCT	<i>Control group:</i> Initiate insulin therapy if blood glucose $>215$ , target 180–200 <i>Study group:</i> Insulin therapy to maintain blood glucose between 80 and 100	Intensive insulin therapy (glucose $\leq 110$ ) reduced in-hospital mortality, acute renal failure, critical illness, polyneuropathy, and bloodstream infection.
van den Berghe <i>et al.</i> , <sup>50</sup> 2003	Surgical ICU, n = 1,548, prospective RCT, extension of Leuven study	<i>Control group:</i> Initiate insulin therapy if blood glucose $>215$ , target 180–200 <i>Study group:</i> Insulin therapy to maintain blood glucose between 80 and 100	Normoglycemia achieved safely within 24 h with intensive insulin therapy. Beneficial effects of intensive insulin therapy attributed to metabolic control (normoglycemia) as against insulin dose.
Krinsley, <sup>42</sup> 2004	Medical and surgical ICU, n = 1,600, comparative study	<i>Conventional therapy group</i> <i>Study group:</i> Insulin to maintain glucose $<140$ . Insulin infusion started if blood glucose $>200$ on two consecutive measurements.	Intensive glycemic management was associated with decreased mortality, organ dysfunction, transfusion requirements, and shorter duration of ICU stay without significant hypoglycemia.
van den Berghe <i>et al.</i> , <sup>49</sup> 2006	Medical ICU, n = 1,200, prospective RCT	<i>Control group:</i> Initiate insulin therapy if blood glucose $>215$ , target 180–200  <i>Study group:</i> Insulin therapy to maintain blood glucose between 80 and 100	Intensive insulin therapy significantly reduced morbidity in all patients admitted to the ICU irrespective of the duration of stay. However, reduction in mortality was observed in patients who stayed in the ICU for $\geq 3$ days.
Furnary <i>et al.</i> , <sup>58</sup> 2003	CABG in diabetics, n = 3,554, comparative	Study over 15-yr period 1st phase— <i>Subcutaneous insulin group:</i> Insulin used to maintain glucose levels $<200$ 2nd phase— <i>Continuous insulin infusion group:</i> Insulin infusion to achieve target glucose 100–150	Mortality significantly lower in the continuous insulin infusion group than in the subcutaneous insulin group (2.5% vs. 5.3%; $P < 0.0001$ ). Better glycemic control achieved in the continuous insulin infusion group.
Lazar <i>et al.</i> , <sup>59</sup> 2004	CABG in diabetics, n = 141, prospective RCT	<i>Standard therapy group:</i> Intermittent subcutaneous insulin to maintain glucose $<250$ <i>Study group:</i> Tight glycemic control with GIK to maintain glucose 120–200 Therapy started preoperatively and continued for 12 h after surgery in both groups	Glycemic control better with GIK. Tight glycemic control group had lower incidence of atrial fibrillation, shorter postoperative duration of stay, and decreased incidence of ischemic events and wound complications.
Butterworth <i>et al.</i> , <sup>69</sup> 2005	CABG in nondiabetics, n = 381, prospective RCT	Placebo vs. insulin infusion therapy  Therapy started if blood glucose $>100$ during cardiopulmonary bypass	Insulin therapy achieved better glycemic control. No significant difference with regard to neurologic morbidity and mortality (assessment at 8 days, 6 wk, and 6 mo).
Ouattara <i>et al.</i> , <sup>57</sup> 2005	Cardiac surgery, n = 200, prospective interventional	Preoperative: Subcutaneous insulin therapy Intraoperative: Intravenous insulin therapy initiated if blood glucose $\geq 180$ Postoperative: Intravenous insulin to maintain blood glucose $<140$	Poor intraoperative glycemic control ( $>200$ mg/dl) was associated with postoperative morbidity and increased odds (OR, 7.2) of worsened hospital outcome after surgery.

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; GIK = glucose–insulin–potassium; HbA<sub>1c</sub> = glycosylated hemoglobin; ICU = intensive care unit; MI = myocardial infarction; OR = odds ratio; RCT = randomized controlled trial.

### Pharmacologic Agents

The IDF currently recommends treatment of individual components of metabolic syndrome in patients

where lifestyle modification alone is insufficient or the patient is at high risk of cardiovascular disease (table 6).<sup>3</sup> In clinical practice, many of the drugs used in the

**Table 6. Classification of Pharmacologic Agents Used in the Therapy of Metabolic Syndrome**

Insulin Resistance and Hyperglycemia	Atherogenic Dyslipidemia	Increased Blood Pressure
Insulin secretagogues	HMG-CoA reductase inhibitors (statins)	Inhibitors of the renin-angiotensin system
Sulfonylureas		
Nonsulfonylureas (repaglinide and nateglinide)		$\beta$ -Blockers
Insulin-sensitizing agents	PPAR- $\alpha$ ligands (fibrates)	
Biguanides (metformin)		Calcium channel antagonists
PPAR- $\gamma$ ligands (thiazolidinediones)		

HMG-CoA =  $\beta$ -hydroxy- $\beta$ -methylglutaryl coenzyme A; PPAR = peroxisome proliferator-activated receptor.

secondary intervention may have complementary effects and modulate more than one component of the syndrome.

**Insulin Secretagogues: Sulfonylureas and Glinides.** Sulfonylureas close adenosine triphosphate-sensitive potassium ( $K_{ATP}$ ) channels on the pancreatic  $\beta$  cells depolarizing the cell and consequently releasing insulin.  $K_{ATP}$  channels are tetradimeric molecules that exhibit adenosine triphosphatase activity.  $K_{ATP}$  channel isoforms that differ in the composition of the individual subunits are also found on the cell membranes of cardiomyocytes and vascular myocytes, among others, as well as the inner mitochondrial membrane (mito  $K_{ATP}$  channels). Sulfonylureas differ in their selectivity for the pancreatic and cardiovascular isoforms of  $K_{ATP}$  channels, with glibenclamide being one of the least selective (table 7).<sup>70-72</sup> Newer sulfonylureas, such as glimepiride, exhibit greater selectivity to the pancreatic  $K_{ATP}$  channels.<sup>73</sup>

The  $K_{ATP}$  channels in the cardiac sarcolemma and the mitochondria are now believed to play a central role in the phenomenon of ischemic preconditioning—a phenomenon whereby brief periods of ischemia and reperfusion before prolonged ischemia protects the myocardium from the consequent deleterious effects.<sup>74</sup> These  $K_{ATP}$  channels are also believed to mediate a similar phenomenon, called anesthetic preconditioning, whereby volatile anesthetics protect the myocardium against the effects of ischemia.<sup>75</sup>

The effects of sulfonylurea use on both animal and human myocardium have been extensively researched, and the compound most often studied is glyburide (also known as glibenclamide). An increase in vascular tone, decreased tolerance to ischemic injury mediated by an inhibition of ischemic preconditioning, and an antiarrhythmic effect, among others, have been reported.<sup>71</sup> However, the clinical significance of these effects is uncertain. Besides, the proposed subtype selectivity of sulfonylureas has also not been addressed. Sulfonylureas

may also adversely affect anesthetic preconditioning. Glibenclamide has been shown to prevent isoflurane-induced anesthetic preconditioning during cardiac surgery in diabetic subjects. Further, preoperative use of insulin instead of glibenclamide seemed to restore the protective effect of anesthetic preconditioning.<sup>76</sup> Sulfonylureas may thus not be appropriate agents in an acute care setting considering the potentially harmful myocardial effects of sulfonylureas, their inability to achieve metabolic control due to stress-induced insulin resistance after an acute illness, and the potential benefits of tight glycemic control with insulin.<sup>41</sup>

The University Group Diabetes Program study, a placebo-controlled, multicenter, clinical trial, reported in 1970 an increased risk of cardiovascular mortality in patients with type II diabetes treated with tolbutamide.<sup>77</sup> The findings resulted in the termination of the tolbutamide arm of the study and the publication of a US Food and Drug Administration warning.<sup>71</sup> These findings have been criticized because a subsequent analysis showed that the excess cardiovascular mortality purportedly related to tolbutamide was in fact restricted to a group with poorly controlled diabetes.<sup>78</sup> The United Kingdom Prospective Diabetes Study (UKPDS), a large prospective study of newly diagnosed type II diabetics, restored confidence in sulfonylureas, showing no increase in cardiovascular mortality. They further reported that intensive glycemic control either with sulfonylureas or insulin reduced microvascular but not macrovascular disease among type II diabetics.<sup>79</sup> Apart from the side effects of weight gain and hypoglycemia, sulfonylureas do not influence other components of metabolic syndrome.<sup>73</sup>

Another class of insulin secretagogues introduced recently are the glinides. These molecules resemble the nonsulfonylurea portion of glibenclamide and have a similar mechanism of action. They differ from sulfonylureas in their poor protein binding and shorter duration

**Table 7. Selectivity of Sulfonylureas for Different Types of Adenosine Triphosphate-sensitive  $K^+$  Channels<sup>70-72</sup>**

	Tolbutamide	Glibenclamide	Gliclazide	Nateglinide	Repaglinide
Pancreatic $K_{ATP}$ ( <i>SUR1/Kir6.2</i> )	4,900–10,500	0.13–4.2	50	800	5.6–21
Cardiac $K_{ATP}$ ( <i>SUR2A/Kir6.2</i> )	85,000	27–45	100,000		2.2
$\beta$ -Cell selectivity	High	Moderate	High	High	Nonselective

$K_{ATP}$  = adenosine triphosphate-sensitive  $K^+$ ; Kir = inward rectifying  $K^+$  channel; SUR = sulfonylurea receptor.

of action. Their role in clinical management of diabetes is yet to be established.<sup>70,73</sup>

**Biguanides.** Metformin, the only drug among the biguanide class in clinical use, decreases blood glucose levels by sensitizing target tissues to insulin, especially the liver, inhibiting hepatic glucose production and increasing peripheral glucose uptake. It has good oral bioavailability and negligible protein binding and is almost exclusively excreted unchanged by the kidneys.<sup>80</sup> It has modest effects on lipid metabolism, including decreasing triglycerides and LDL cholesterol, increasing HDL cholesterol, and promoting weight loss.<sup>80</sup> It may also improve endothelial dysfunction.<sup>73</sup>

The United Kingdom Prospective Diabetes Study (UKPDS 34) showed that addition of metformin to diet-controlled overweight type II diabetics significantly reduced microvascular and macrovascular disease. Metformin did not induce weight gain and was also associated with fewer episodes of hypoglycemia. The additional benefits observed with metformin monotherapy could not be accounted for by the improvement in glycemic control alone but were suggested to be due to decreases in plasminogen activator inhibitor 1 and enhanced fibrinolysis.<sup>81</sup> A population based retrospective study showed that metformin use either alone or in addition to sulfonylureas in newly treated diabetics reduced all-cause and cardiovascular mortality in comparison to sulfonylurea monotherapy.<sup>82</sup> Combinations of metformin with other oral hypoglycemic and insulin-sensitizing agents have also been shown to be safe and effective.<sup>80,83</sup> Adjuvant metformin therapy in type I diabetes improves insulin sensitivity, diabetic control, body composition, and patient well-being.<sup>84</sup>

A retrospective investigation of diabetic patients undergoing cardiac surgery reported that allowing metformin therapy until the night before surgery and early resumption postoperatively did not increase cardiac morbidity (odds ratio [OR], 0.3; 95% confidence interval [CI], 0.1-1.7), neurologic morbidity (OR, 0.9; 95% CI, 0.3-2.6), or in-hospital mortality (OR, 0.5; 95% CI, 0.1-2.0) as compared with other oral hypoglycemic agents. Metformin-treated patients, however, required a shorter course of tracheal intubation and had lower infection-related morbidity (OR, 0.2; 95% CI, 0.1-0.7) and overall morbidity (OR, 0.4; 95% CI, 0.2-0.8).<sup>85</sup>

**Thiazolidinediones.** Thiazolidinediones are insulin-sensitizing agents that bind to the nuclear  $\gamma$  isoform of peroxisome proliferator-activated receptor (PPAR- $\gamma$ ). These receptors are primarily expressed in adipose tissues but also find expression in the skeletal myocytes, hepatocytes, and vascular endothelial and smooth muscle cells. PPAR- $\gamma$  activation results in the transcription of several genes encoding various insulin-sensitive proteins, including lipoprotein lipase and GLUT4. They have a slow onset, requiring up to 12 weeks to reach maximum effect.<sup>73</sup> Thiazolidinediones enhance insulin sensi-

tivity in adipose tissue, skeletal muscle, and the liver. They are highly protein bound and undergo extensive hepatic metabolism, in the case of pioglitazone to active metabolites.<sup>80</sup>

Thiazolidinediones also increase expression of genes that encode proteins that enhance adipogenesis in the subcutaneous adipose tissue. The net result is believed to be a redistribution of fat stores from the muscle and visceral adipose tissue resulting in a decreased visceral-to-subcutaneous adipose tissue ratio.<sup>80</sup> Thiazolidinediones differ in their effects on the lipid profile. Whereas pioglitazone alters the profile favorably by decreasing triglycerides, rosiglitazone was associated with an increase in LDL cholesterol and total plasma cholesterol. The mechanism of this differential alteration in lipid profile and its clinical significance are as yet unclear.<sup>86</sup>

Thiazolidinediones have favorable effects on markers of atherosclerosis.<sup>80</sup> They decrease thrombotic risk especially on atherosclerotic areas by inhibiting plasminogen activator inhibitor 1. Further, they decrease the serum high-sensitivity C-reactive protein, tumor necrosis factor- $\alpha$ , and interleukin-6 levels. While some of the antiatherogenic effects could be associated with improvement of glucose metabolism, thiazolidinediones seem to prevent progression of atherosclerosis independent of their effects on glucose metabolism. Nitric oxide, an important regulator of vascular endothelial function, is inactivated by superoxide ( $O_2^-$ ) free radicals. PPAR- $\gamma$  agonists are believed to promote endothelial function by suppression of NADPH oxidase, a major superoxide generating enzyme while inducing the superoxide scavenging cytosolic superoxide dismutase.<sup>87</sup> The antioxidant properties of PPAR- $\gamma$  agonists may also restore the function of  $K_{ATP}$  channels that are impaired by high glucose concentrations.<sup>88</sup>

In animal models, thiazolidinediones seems to limit infarct size and attenuate postinfarct left ventricular remodeling and failure.<sup>89,90</sup> In comparison with other oral hypoglycemic agents, thiazolidinediones significantly reduces microalbuminuria. However, it remains unclear whether this is mediated primarily *via* improvement in glycemic control, insulin sensitivity, or endothelial dysfunction or is independent *via* its the blood pressure-decreasing effect.<sup>91</sup> A prospective study to assess the ability of rosiglitazone to reduce the incidence of diabetes mellitus in subjects with impaired fasting glucose and/or impaired glucose tolerance reported an absolute risk reduction of 14.4% (number needed to treat = 7) at the end of a median follow-up period of 3 yr. That the study reported 70-80% increased likelihood of return to normoglycemia may suggest that thiazolidinediones treat dysglycemia as well as prevent diabetes.<sup>92</sup>

The PROactive study, a large European multicenter study involving 5,238 patients, showed no significant reduction in the composite primary endpoints with pioglitazone. However, the study found a significant reduc-

tion in the secondary endpoints of all-cause mortality, MI, or stroke. This improvement, observed in a group of high-risk patients, was in addition to that with their normal medical care, including antihyperglycemic, antiplatelet, antihypertensive, and lipid-lowering therapies. Glycemic control and lipid profile was better with pioglitazone compared with placebo, despite an increased use of metformin and insulin in the placebo group. They also had a better blood pressure profile at the end of the study than at the beginning.<sup>93</sup> However, considerable controversy surrounds the methodology and statistical analysis of the PROactive study. It is suggested that the results need to be confirmed and that they are seen as hypothesis-generating only.<sup>94</sup>

A meta-analysis of 22 trials that randomly assigned approximately 6,200 people to pioglitazone therapy for at least 24 weeks showed no evidence of benefit with respect to patient-oriented outcomes such as mortality, morbidity, adverse effects, cost, and health-related quality of life. Further, metabolic control (hemoglobin A<sub>1c</sub>) was found to be no better when compared with other oral antidiabetic drugs. However, the analysis reported a higher incidence of edema with pioglitazone and concluded that the risk-benefit ratio was unclear until further results were available. It also highlighted the different prescribing indications by the US Food and Drug Administration and the European Medicines Agency.<sup>94</sup> Common side effects reported with thiazolidinediones include weight gain (up to 4 kg), fluid retention, and heart failure.<sup>86,92-94</sup> They are contraindicated in New York Heart Association class III or IV heart failure, and the American Heart Association recommends that patients and physicians be aware of the risk of heart failure associated with their use in type II diabetes patients.<sup>95</sup>

**Statins.** Statins are inhibitors of  $\beta$ -hydroxy- $\beta$ -methylglutaryl coenzyme A reductase, the rate-limiting enzyme in the synthesis of cholesterol. They interrupt cholesterol synthesis in the liver and activate hepatocyte LDL receptors and decrease LDL.

Statins have proved beneficial in primary and secondary prevention of adverse cardiovascular events.<sup>96,97</sup> Furthermore, intensive decreasing of LDL cholesterol with high-dose atorvastatin therapy (80 mg) has also been shown to significantly reduce adverse vascular events in high-risk patients with both coronary heart disease and metabolic syndrome.<sup>13</sup> They are recommended in the early treatment of patients with unstable angina and MI.<sup>98</sup>

Evidence suggests that statins, besides their effects on lipids, reduce endothelial dysfunction, inhibit inflammatory responses, stabilize atherosclerotic plaques, and modulate procoagulant activity and platelet function, the so-called pleiotropic effects.<sup>99</sup> Statins may reduce the risk of severe sepsis and infection-related mortality independent of their lipid-lowering effect.<sup>100</sup> The effect of withdrawal of chronic statin therapy during acute coro-

nary syndromes has been studied prospectively. Statin therapy was associated with a reduced rate of nonfatal MI or death at the end of 30 days. Requirement for revascularization procedures was reduced, as was hospital stay. However, among patients whose chronic statin therapy was withdrawn after hospital admission, the incidence of death and nonfatal MI increased when compared not only with patients whose statin therapy was continued, but also with patients who did not receive any statin therapy at all.<sup>101</sup> It is hence suggested that statins should be continued uninterrupted in acute coronary syndrome and intensive care patients to maintain their beneficial pleiotropic effects.<sup>102</sup>

A large observational study based on administrative data found that preoperative lipid-lowering therapy primarily with statins reduced the odds of in-hospital mortality after major noncardiac surgery by 38%. The study also reported that the number needed to treat to prevent a postoperative death was 30 among patients with a higher cardiac risk.<sup>103</sup> A recent meta-analysis of perioperative statin therapy concluded that while statins may confer a survival benefit, their effect of postoperative cardiovascular morbidity was inconclusive. The paucity of prospective data and heterogeneity of retrospective data were also highlighted. The authors suggest that with current data preoperative statin therapy be restarted as early as possible postoperatively.<sup>104</sup>

**Fibrates.** Fibrates are lipid-modulating drugs that act as ligands to the  $\alpha$  isoform of PPAR nuclear receptors that activates the transcription genes encoding for proteins involved in lipoprotein metabolism. Fibrates induce synthesis of the major HDL apolipoproteins (apoA-I and apoA-II). By inducing lipoprotein lipase, fibrates stimulate lipolysis and decrease triglyceride synthesis and very-low-density lipoprotein secretion.<sup>105</sup> Gemfibrozil has been shown to reduce the risk of major cardiovascular events in middle-aged men with dyslipidemia.<sup>106</sup> But the FIELD study investigating the effects of fenofibrate on cardiovascular events in type II diabetes showed only a weak reduction in cardiovascular risk. However, it did show that fibrates were associated with less albuminuria progression and retinopathy and a significant reduction in incidence of nonfatal MI in low-risk patients.<sup>107</sup> Fibrates are associated with a 5.5-fold increase in the risk of rhabdomyolysis when compared with statin monotherapy. When combined with fibrates, statins further double this risk.<sup>108</sup> The IDF recommends fibrates as an option in the management of atherogenic dyslipidemia but highlights the risk of complications when combined with statins.<sup>3</sup>

**Antihypertensive Therapy.** Intensive treatment of diastolic hypertension has been shown to reduce the incidence of adverse cardiovascular events, with diabetic patients deriving most benefit.<sup>109</sup> The IDF recommends that antihypertensive therapy be introduced early and at much lower blood pressure ( $\geq 130/\geq 80$  mmHg)

in diabetic patients as compared with nondiabetic patients ( $\geq 140/\geq 90$  mmHg).<sup>3</sup> Tight blood pressure control with either angiotensin-converting enzyme inhibitors or  $\beta$ -blockers has been associated with reduced incidence of microvascular and macrovascular complications in diabetic patients.<sup>110</sup>

No particular agent has been identified as being preferable for hypertensive patients with metabolic syndrome. Instead, current data suggest that the benefits associated with antihypertensive therapy are largely due to their blood pressure-decreasing effect rather than the drug type.<sup>3,110</sup> However, it has recently been suggested that drugs that block the renin-angiotensin system may prevent or delay the development of diabetes and thus confer cardiovascular benefit.<sup>111-113</sup>

#### *Exercise and Mobilization*

Increased physical activity has been recommended in the primary management of metabolic syndrome because of its beneficial effects on the various components of the syndrome.<sup>2,3</sup> Exercise induces the insertion of glucose transporters that do not depend on insulin into the skeletal muscle membrane.<sup>31</sup> Immobilization may thus induce insulin resistance with reduction in skeletal muscle glucose uptake and glycogen synthesis. In diabetic patients, physical rehabilitation and exercise may improve insulin sensitivity and glucose control.<sup>2</sup> Early postoperative mobilization as part of an enhanced recovery protocol has been shown to be associated with minimal postoperative insulin resistance.<sup>114</sup>

#### *Nutrition*

Fasting represents an extreme state of nutritional stress, and its adverse effects include depletion of glycogen stores and breakdown of proteins and fat to provide energy. It also impairs mononuclear phagocytic system, increases bacterial translocation, and enhances oxidative stress injury.<sup>115,116</sup> Studies in experimental animal models have shown that feeding before acute injury preserves energy stores, maintains bacterial homeostasis in the gut, and aids endotoxin clearance.<sup>116</sup> Therefore, the issue of preoperative fasting must be addressed from a metabolic perspective. Preoperative intake of carbohydrate-rich beverage has been shown to maintain insulin sensitivity in surgical patients.<sup>117</sup> Improvement in insulin sensitivity with preoperative carbohydrate treatment may also decrease nitrogen losses and promotes protein synthesis.<sup>118</sup> However, the effects of preoperative carbohydrate loading on postoperative morbidity and mortality have not been evaluated.

#### *Anesthesia and Analgesia*

Volatile anesthetics protect the myocardium against the effects of ischemia, a phenomenon closely resembling ischemic preconditioning. This phenomenon, called anesthetic preconditioning, is also believed to be

mediated by  $K_{ATP}$  channels in the myocardial sarcolemma and the mitochondrial membrane.<sup>75</sup> Hyperglycemia is believed to adversely affect preconditioning. High blood glucose concentrations have been shown to attenuate the protective effects of ischemic and anesthetic preconditioning in both diabetic and nondiabetic animal models.<sup>119,120</sup> In doses used for anesthesia, intravenous induction agents have no effect on circulating metabolite and hormone concentrations, except for etomidate, which has been shown to inhibit cortisol synthesis.<sup>121</sup>

In healthy volunteers, acute pain has been shown to induce insulin resistance and decrease nonoxidative glucose disposal.<sup>122</sup> Therefore, it seems logical that effective analgesia may potentially attenuate insulin resistance. High-dose opioids have been shown to attenuate the stress response to surgery, but this response lasts only till the high levels are maintained.<sup>123</sup> Epidural anesthesia has been shown to attenuate stress response, prevent intraoperative hyperglycemia, and reduce protein breakdown, which also lasts only for the duration of continuous blockade.<sup>124,125</sup> The effect of neuraxial blockade on sympathetic efferents to the liver, adrenals, and pancreas may mediate these effects. Decreased hepatic sympathetic efferent tone may reduce glucose output from the liver, whereas a reduced sympathetic stimulation of the adrenals attenuates release of catecholamines and cortisol, promoting peripheral glucose clearance.<sup>39</sup> Neuraxial blockade may also reduce hepatic perfusion and hence the supply of gluconeogenic precursors to the liver.<sup>125</sup> Furthermore, effective analgesia provided by neuraxial blockade may attenuate reduction in pain-mediated insulin resistance.<sup>123</sup> Children demonstrate similar responses to surgical stress that is attenuated by epidural blockade.<sup>126</sup> Continuous neural blockade has also been shown to improve insulin sensitivity after major joint surgery in subjects previously known to be insulin resistant.<sup>127</sup> Whether effective neuraxial blockade in patients with metabolic syndrome impacts perioperative morbidity or mortality is as yet unknown.

## **Conclusions**

Metabolic syndrome, a rapidly growing global epidemic, is a cluster of cardiovascular risk factors that is associated with a heightened risk of morbidity and mortality. Lifestyle modification and pharmacotherapy targeting individual components of the syndrome have been recommended as primary and secondary prevention strategies. Insulin resistance and central obesity are increasingly recognized as being central to the pathogenesis of metabolic syndrome. Insulin resistance commonly manifests as hyperglycemia during acute illness and in the perioperative period. Management of insulin resistance to achieve glycemic control improves outcome. It is suggested that preoperative statins be con-

tinued uninterrupted or at least reinstated as soon as feasible to harness the benefits derived from its pleiotropic effects. Early postoperative mobilization and exercise have shown some promise, but their role must be defined clearly. Modulation of the other components of the syndrome in the acute phase of illness and in the perioperative period needs further evaluation. Perioperative physicians must identify patients at risk of insulin resistance and metabolic syndrome, and strategies aimed at modulating the altered metabolic milieu should be identified.

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