The Metabolic Syndrome and Stroke: Potential Treatment Approaches

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The metabolic syndrome (MetS) consists of a constellation of vascular risk factors and metabolic abnormalities comprising (1) centrally distributed obesity; (2) atherogenic dyslipidemia, characterized mainly by elevated triglycerides and decreased high-density lipoproteins; (3) high blood pressure; and (4) hyperglycemia. This cluster of highly interrelated factors appears to increase the individual’s risk of vascular disease by promoting the development of atherosclerotic vascular disease and type II diabetes mellitus.

It is important to recognize that the MetS is a syndrome and not a defined uniform entity. In the effort to introduce the MetS into clinical practice, diverse organizations have used different diagnostic criteria, which may respond to 2 main different conceptual approaches to the syndrome (Table). The first approach focuses on the pathogenesis of MetS and considers insulin resistance as the common physiological abnormality that can lead to the clustering of the mentioned metabolic risk factors and therefore as a main therapeutic target. The second approach responds to a more pragmatic view and has the purpose of identifying people at higher long-term risk for atherosclerotic vascular disease who may deserve clinical intervention to reduce vascular risk. These distinct conceptual views of the MetS have probably contributed to a lack of certainty regarding its pathogenesis and value as a cardiovascular disease risk marker. Therefore, for now, we will attempt to follow a comprehensive and pathogenesis-based approach to MetS to make our exposition more intelligible.

Insulin Resistance: A Proposed Common Underlying Pathophysiological Mechanism

Insulin resistance is a metabolic disorder characterized by diminished tissue sensitivity to insulin that originates from the effect of a sedentary lifestyle and central obesity, among other environmental factors, in individuals with a significant genetic predisposition. This defect in insulin action may lead to (1) abnormalities of glucose metabolism; (2) impaired handling of plasma triglycerides and free fatty acids, giving place to an atherogenic dyslipidemia; (3) elevation of blood pressure; (4) abnormalities in vascular reactivity; (5) endothelial dysfunction; (6) chronic subclinical inflammation; and (7) a prothrombotic phenotype. Therefore, insulin resistance appears as a pivotal pathophysiological contributor to the development of vascular risk factors.

It has been demonstrated that a high proportion of individuals with MetS has insulin resistance. However, there is division of opinions regarding the role of insulin resistance in the MetS. First, the definitions stated by the World Health Organization, by the European Group for Study of Insulin Resistance, by the American Association of Clinical Endocrinologists, and by the International Diabetes Foundation defend the preeminent role of insulin resistance as the common underlying pathophysiological mechanism of the MetS and consider insulin resistance as the only physiological abnormality that can lead to the clustering of metabolic alterations that conform the MetS. Second, the definitions published by the National Cholesterol Education Program Adult Treatment Panel III and by the American Heart Association/National Heart, Lung and Blood Institute Scientific Statement consider its 5 diagnostic criteria, including insulin resistance, as hierarchically equal. Despite this existing confusion, there is an increasing consensus to focus on defining and treating insulin resistance more specifically given the potential impact of therapies aimed to target insulin resistance on both cardiovascular and type II diabetes mellitus risk. In accordance with this notion, the most recent MetS definitions (International Diabetes Foundation and American Heart Association 2005) have lowered to 100 mg/dL the cutoff value for high fasting glucose, which is the MetS criterion with the greatest positive predictive value to detect insulin resistance. Given their capacity to identify insulin-resistant individuals, we suggest that these 2 definitions may be preferable for the diagnosis of MetS in patients with stroke.
Prevalence of the Metabolic Syndrome: A Global Epidemic

The prevalence of MetS worldwide is high and continuously increasing. Following the National Cholesterol Education Program Adult Treatment Panel III definition,6 the age-adjusted prevalence of the MetS among US adults in the National Health and Nutrition Examination Survey reports reached 24.1% between 1988 and 1994 and 34.5% between 1999 and 2002.14,15 Diverse studies performed in other countries have yielded similar frequencies of MetS worldwide. In addition, when the new International Diabetes Foundation definition is applied,5 the proportion of the population affected by the MetS dramatically raises to 39% to 46% in every ethnic and age group.16 Finally, the high prevalence of MetS among US adolescents seems especially worrisome.17

The previously mentioned data support the idea that the MetS is becoming an important public health concern.15 The constant modern changes in the human environment, behavior, and lifestyle may have contributed decisively to confer epidemic dimensions to the problem of MetS. More importantly, the subsequent increase in the future risk of cardiovascular disease and type II diabetes mellitus associated with the high current prevalence of MetS is now recognized as one of the major threats to human health in the 21st century.

Once we have tried to introduce a global view of the MetS, we will focus on the relationship between MetS and cerebrovascular disease. This review attempts to condense the existing scientific evidence regarding the following issues: (1) MetS as an independent risk factor for first-ever and recurrent ischemic stroke; (2) influence of MetS on the prognosis of stroke underlying etiologic diseases; (3) impact of MetS on acute ischemic stroke outcome; (4) molecular mechanisms of MetS and possible therapeutic targets; and (5) potential treatment approaches.

Metabolic Syndrome and Stroke Risk

The Increased Prevalence of the Metabolic Syndrome Among Patients With Stroke

The presence of MetS has been associated with an increased risk of prevalent stroke in the existing literature. In the National Health and Nutrition Examination Survey among 10,357 subjects,18 the prevalence of MetS was significantly higher in persons with a self-reported history of stroke (43.5%) than in subjects with no history of vascular disease (22.8%). MetS was independently associated with stroke history in all ethnic groups and in both sexes (OR, 2.16; 95% CI, 1.48 to 3.16). The association between MetS and stroke has been confirmed in other populations integrated by elderly subjects, and the frequency of MetS has been reported to be
The Metabolic Syndrome as a Predictor of Future Cerebral Ischemic Events
Long-term follow-up population-based studies have demonstrated that healthy individuals with the MetS are at a markedly increased risk for major cardiovascular events, including stroke, and cardiovascular mortality. Adjusted risk ratios for incident ischemic stroke associated with MetS in prospective studies range between 2.1 and 2.47, and a hazard ratio as high as 5.15 has been reported. This predictive capacity appears not to be influenced by the MetS definition used and shows no significant variation across the studied sex, age, or ethnic groups. Moreover, the risk for incident ischemic stroke seems to augment with the increasing number of components of the MetS, all of which have been individually associated with an increased risk for future cerebral ischemic events.

Considerations for Stroke Prevention: Targeting Insulin Resistance
The notion that the MetS is associated with an increased risk for future stroke reaffirms the need to develop preventive strategies directed to control the syndrome and each of its component conditions. In fact, the recognition and management of the MetS have been recently included in stroke prevention international guidelines. However, there is still controversy regarding whether the individual components of MetS are equivalent or even better predictors of incident cardiovascular disease than the MetS itself and whether the MetS is really more useful than validated risk factor scales in the stratification of subjects who are at an increased risk of experiencing a stroke.

Metabolic Syndrome and Cerebral Atherosclerosis
The increase in the risk for incident cerebral ischemic events observed in patients with MetS may derive in a great part from the potential capacity of MetS to enhance the development and progress of atherosclerotic lesions affecting brain-supplying large arteries. In this setting, insulin resistance may represent a crucial factor underlying the association of MetS with atherosclerosis, because it is known to cause multiple proatherothrombotic effects both on the fibrinolytic system and on the vascular endothelium.

Metabolic Syndrome and Carotid Atherosclerosis
The prevalence of increased carotid intima-media thickness and of asymptomatic carotid atherosclerotic plaques has been consistently shown to be higher in individuals with the MetS. Subjects with the MetS are also at increased risk for progressive carotid atherosclerosis, although the question whether the metabolic risk factors that compound the MetS synergize to produce carotid atherosclerosis beyond what is expected from their individual effects remains unclear. Insulin resistance may have a deleterious role in all the stages of carotid atherosclerosis, from endothelial dysfunction to plaque growth; therefore, interventions targeting insulin resistance may reduce carotid atherosclerosis development in patients with MetS and type 2 diabetes.

Metabolic Syndrome and Intracranial Atherosclerosis
The importance of the relationship between MetS and intracranial atherosclerosis has been first stressed by 2 recent studies. The MetS is present in approximately half of the patients with symptomatic intracranial atherosclerosis and may be burdened with an excess risk for recurrent ischemic events. The fact that intracranial arteries show a proneness to be affected by the MetS may reflect the existence of relevant topographic variations in the vessel sensitivity to the metabolic abnormalities associated with MetS such as oxidative stress. Finally, the association between type 2 diabetes mellitus and a higher number of intracranial atherostenoses, observed in European-Mediterranean patients with intracranial atherosclerosis, suggests that insulin resistance might play a prominent role in the development of this disease.

Future Research: Impact of Metabolic Syndrome on Acute Stroke Outcome
Most of the research about the MetS and cerebrovascular disease has been restricted to the field of stroke prevention. To our knowledge, the impact of MetS per se on acute stroke prognosis has not been evaluated. However, some of the metabolic abnormalities and risk factors that integrate the MetS have been associated with a worsening of stroke outcomes. In this context, MetS-related alterations comprise impairment in the endogenous fibrinolytic capacity, hyperglycemia, endothelial dysfunction, chronic endothelial damage, and a proinflammatory state, all of which may contribute to amplify cerebral ischemic damage and to hamper arterial recanalization. Future research should clarify whether MetS may be associated with an aggravation of acute ischemic stroke prognosis.

Molecular Mechanisms of Metabolic Syndrome and Possible Therapeutic Targets
The search for intra- and intercellular signaling pathways in MetS has shown the involvement of multiple factors that might serve as potential therapeutic targets for its treatment and prevention.

Inflammation: Cytokines and Transcription Factors
It was not until recent years when it was postulated that the activation of a proinflammatory state could underlie insulin resistance induced by obesity. Dysregulation of the secretion of adipose tissue-derived factors in obese individuals participates in a chronic inflammatory condition associated with obesity. These factors include adipokines such as leptin, adiponectin, resistin, retinol-binding protein 4 and visfatin as well as classical chemokines and cytokines such as tumor...
necrosis factor-α. Some of these factors derive not only from adipocytes, but also from macrophages, showing that there is a strikingly high degree of overlapping features between the metabolic and immune responses. Activation of the innate immunity through the Toll-like receptors, caused by increased levels of nutritional fatty acids, also leads to inflammation. In this context, Toll-like receptor-4-deficient animals are partially protected against high fat diet-induced insulin resistance, possibly attributed to reduced inflammatory gene expression in liver and fat.

Obesity intervenes in the inflammatory pathways leading to insulin resistance by activating serine kinases involved in the action of transcription factors such as IκB kinase-β and Jun kinase-1, a Jun kinase isoform (Figure 1). Several stimuli account for the activation of these factors, either through specific membrane receptors such as proinflammatory cytokines, Toll-like receptors, and receptors for the advanced glycation end products or by nonreceptor pathways such as those triggered by oxidative stress. The increased hepatic activity of the IκB kinase-β target, the transcription factor NF-κB, causes insulin resistance in obesity-associated liver steatosis, likely attributed to increased gene expression of the cytokines interleukin-6, tumor necrosis factor-α, and interleukin-1β. In addition, insulin resistance frequently results from phosphorylation of the insulin receptor substrate-1, a process which can be catalyzed by Jun kinase-1. In the case of IκB kinase-β, a similar phosphorylating mechanism has been reported, but other transcriptional effects mediated by NF-κB are involved.

**Mitochondrial Activity**

Defects in mitochondrial activity can lead to insulin resistance as demonstrated recently in the elderly and in children of patients with type 2 diabetes. Similarly, it has been shown that impairment of mitochondrial function might link reduced fitness to cardiovascular and metabolic disease.

**Activation of Peroxisome Proliferator-Activated Receptor γ Receptors as a Therapeutic Target in Insulin Resistance**

The existing convergent pathways among the molecular mechanisms involved in metabolic syndrome appear as the most suitable therapeutic target. In this context, the nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ) is an important transcriptional regulator, the activity of which can be modulated by binding of specific agonists such as the thiazolidinediones.

Genetic studies indicated the role of PPARγ in glucose homeostasis. In humans, the Pro12Ala polymorphism in the
PPARγ gene is associated with enhanced glucose homeostasis, whereas dominant-negative mutations lead to severe insulin resistance.\textsuperscript{55,56} In animals, mice lacking PPARγ are prone to develop insulin resistance, whereas a mutation that increases PPARγ activity protects from obesity-induced insulin resistance.\textsuperscript{57–59} PPARγ agonists improve insulin action, by 2 major mechanisms, in which activation of lipid metabolism and reduction of inflammatory mediators are involved. Regarding metabolic actions, PPARγ agonists improve insulin sensitivity by inducing the expression of genes involved in adipocyte differentiation, lipid and glucose uptake, and fatty acid storage.\textsuperscript{60} In addition, PPARγ agonists exert other indirect effects by regulating several target genes such as adiponectin, an insulin-sensitizing factor, or the insulin resistance inducer resistin, which are increased or decreased, respectively, by PPARγ activation (Figure 2).\textsuperscript{61,62}

Figure 2. Activation of PPARγ receptors acts on several metabolic and inflammatory signaling pathways in metabolic syndrome. PPARγ regulates the expression of target genes for lipid metabolism and adipokines such as adiponectin, resistin, and RPB4. In addition, PPARγ inhibits the induction of inflammatory mediators by interfering in the activity of transcription factors such as nuclear factor κB or AP-1. These factors are activated by kinases such as Jun kinase and IkappaB kinase, which thus participate in direct or indirect impairment of insulin receptor. PPARγ also causes mitochondrial remodeling and increased energy expenditure. (For other details, see Figure 1.)

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PPARγ activation is also known to exert major antiinflammatory actions in several systems.\textsuperscript{63} This is also important in the setting of the MetS, because ligands of PPARγ have been shown to reduce not only the production of inflammatory mediators as tumor necrosis factor-α, but also the subsequent tumor necrosis factor-α induced signaling in obesity.\textsuperscript{64,65} More importantly, antiinflammatory actions of PPARγ ligands appear to be mediated by transrepression of NF-κB signaling with the subsequent decrease in inflammatory gene expression.\textsuperscript{64} Additionally, LXR, a different member of the nuclear receptor superfamily, is known to be a PPARγ target gene.\textsuperscript{65} LXR ligands have been shown to improve glucose metabolism in animals, an effect that may contribute to the PPARγ-mediated improvement on insulin sensitivity.\textsuperscript{66}

Potential Treatment Approaches in Metabolic Syndrome

Glitazones, Insulin Resistance, and Stroke Prevention

Specific therapies targeting insulin resistance (insulin sensitizers) may offer additional benefit in stroke prevention beyond the risk reduction achieved by treating the individual components of the MetS. Thiazolidinediones, also known as glitazones, improve insulin sensitivity and lower blood glucose in type 2 diabetes and in nondiabetic patients with a recent transient ischemic attack or stroke and impaired insulin sensitivity.\textsuperscript{61,67,68} The best known mechanism of action of glitazones is their capacity to act as agonists of the receptor PPARγ, resulting in activation of lipid metabolism, glucose uptake, and antiinflammatory actions. The reduction in blood glucose is often accompanied by reductions in circulating insulin, inflammatory markers, and triglycerides. In addition, glitazones have beneficial effects on the cardiovascular system independently of its effect on glycemic control such as antiatherogenic and antihypertensive effects.\textsuperscript{35,69,70} Therefore, the overall pattern of changes induced by glitazones suggests
a general improvement in various risk factors that might reduce cardiovascular morbidity and mortality.

Recently, pioglitazone has been shown to reduce the combined secondary end point of all-cause mortality, myocardial infarction, and stroke compared with placebo on top of glucose-lowering, antiplatelet, antihypertensive, and lipid-altering therapies in 5238 patients with type 2 diabetes who had a high risk of macrovascular events (hazard ratio, 0.84; 95% CI, 0.72 to 0.98).\textsuperscript{70} The effect was consistent across all the individual components of the composite end point. The pioglitazone-treated group had a better metabolic profile in terms of glucose, high-density lipoprotein cholesterol, and triglyceride concentrations and a better blood-pressure profile at the end of the study. However, thiazolidinediones are hampered by adverse effects related to increased weight gain, fluid overload, and congestive heart failure, so the role of glitazones in prevention of cardiovascular diseases is not fully defined.\textsuperscript{71,72}

**Novel Cytoprotective Effects of Glitazones in Acute Cerebral Ischemia**

Recent experimental findings suggest that glitazones could have cytoprotective effects in acute cerebral ischemia. Glitazones have been described to decrease infarct size in experimental models after middle cerebral artery occlusion through different mechanisms that include decreased activation of microglia and macrophages, reduced excitotoxic-mediated brain ischemic damage, decreased expression of inflammatory mediators such as interleukin-1β, cyclooxygenase-2, and iNOS as well as the increase in the antioxidant enzyme Cu,Zn-SOD.\textsuperscript{73–77} Interestingly, other nonthiazolidine PPARγ agonists such as the endogenous cyclopentenone prostanoid 15-delta\textsuperscript{12,14}-prostaglandin J2 (15d-PGJ2) share these neuroprotective effects of glitazones in experimental models of ischemic stroke or intracerebral hemorrhage.\textsuperscript{77–79} Importantly, high plasma levels of 15d-PGJ2 have been associated with good neurological outcome and smaller infarct volume in patients with an acute atherothrombotic stroke,\textsuperscript{80} and recent preliminary data suggest that current treatment with glitazones may improve functional recovery after stroke.\textsuperscript{81} Taken together, these novel actions of glitazones and other PPARγ agonists could offer some protection against the potentially enhanced damage of brain ischemia in patients with MetS and may open new exciting lines of investigation on stroke treatment.

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None.

**References**


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