

Metabolic Syndrome and Stroke

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The metabolic syndrome is highly prevalent worldwide, and its cardiovascular toll is expected to rise with the growing obesity epidemic. Mounting evidence points to an association between metabolic syndrome and first or recurrent stroke. This article discusses the emerging data supporting a link between stroke and the metabolic syndrome and underscores the need to better understand the syndrome's pathophysiology, with a goal to appropriately and intensively limit the burden of this multiple risk factor entity.

Introduction

The probability of stroke occurrence rises with the number and severity of vascular risk factors. The vascular risk profile can identify persons at especially high risk for stroke and can help guide health care practitioners toward optimizing a multipronged stroke risk reduction strategy [1]. An emerging entity that incorporates risk stratification with the goal of mitigating vascular risk is the “metabolic syndrome.” The metabolic syndrome is a constellation of risk factors, including atherogenic dyslipidemia, hypertension, insulin resistance, and obesity, that cluster together and promote the development of atherosclerotic vascular disease. The syndrome is highly prevalent worldwide, and several studies have suggested that individuals with the metabolic syndrome are at high risk for experiencing first and recurrent stroke. Given its strong link to obesity, the prevalence of the metabolic syndrome is expected to substantially increase in the future alongside the growing obesity epidemic [2], a rise that will likely be associated with an even heavier burden of stroke on the society. Although questions persist regarding the choice of criteria and mechanistic basis for the metabolic syndrome, the scientific community agrees that it is important to identify patients with multiple risk factors to initiate lifestyle modification and, if necessary, drug treatment to prevent cardiovascular disease and stroke [3].

This article reviews the definition, diagnostic criteria, and epidemiology of the metabolic syndrome, reports on the syndrome's association with stroke risk, and discusses current and promising options for treating the syndrome.

Definition and Diagnostic Criteria

The generally accepted risk factors that cluster in metabolic syndrome include atherogenic dyslipidemia, hypertension, insulin resistance, hyperglycemia, abdominal obesity, physical inactivity, and a prothrombotic/proinflammatory state [4].

Since the metabolic syndrome was first described almost 20 years ago, several organizations, including the World Health Organization, European Group for Study of Insulin Resistance, National Cholesterol Education Program (NCEP) Adult Treatment Panel III, American Association of Endocrinologists, International Diabetes Foundation (IDF), and American Heart Association/National Heart, Lung, and Blood Institute, have proposed various diagnostic criteria mostly based on similar components. A meta-analysis of more than 40 studies with 172,573 individuals found that no matter which diagnostic criteria were used, the metabolic syndrome was associated with greater cardiovascular risk [5•].

The revised NCEP [4] and IDF criteria [6] are the two broadly recognized definitions at this time. The two criteria are similar and will likely identify many of the same individuals as having the metabolic syndrome. There are three significant differences between the revised NCEP and IDF criteria: 1) IDF requires the presence of abdominal obesity, whereas revised NCEP does not; 2) IDF has lower thresholds for abdominal obesity; and 3) IDF uses geographic-specific cut points for waist circumference.

Epidemiology

The metabolic syndrome is highly prevalent; data from the NHANES (National Health and Nutrition Examination Survey) estimate that more than 47 million individuals in the United States have it [7]. The prevalence of metabolic syndrome increases with age, from 6.7% among individuals aged 20 to 29 to 43.5% among individuals aged 60 to 69 [7]. Hispanics are more likely to have metabolic syndrome than whites or blacks. There are no significant gender differences in prevalence rates of metabolic syndrome among whites; however, among blacks and

Hispanics, women are more likely to have metabolic syndrome than men [7].

Each component of the metabolic syndrome independently increases the risk of cardiovascular disease and stroke. Atherogenic dyslipidemia is an aggregation of lipoprotein abnormalities, including 1) reduced high-density lipoprotein cholesterol (HDL); 2) elevated serum triglycerides; 3) elevated apolipoprotein B (apoB)-containing lipoproteins; and 4) elevated small low-density lipoproteins (LDL) particles. Whereas elevated triglycerides, apoB-containing lipoproteins, and small LDL particles are associated with an increased risk for cardiovascular disease and stroke [8], HDL levels are inversely associated with a risk of ischemic stroke [9].

Insulin resistance has only recently emerged as an important risk factor for stroke. Insulin resistance is a state in which defective muscle glycogen synthesis and glucose transport result in a subnormal response to insulin. Almost all patients with type 2 diabetes mellitus exhibit insulin resistance. Insulin resistance is also commonly seen in elderly individuals, blacks, and in individuals with essential hypertension, obesity, lipoprotein abnormalities, coronary artery disease, carotid artery disease, family history of diabetes, and physical deconditioning. Up to 50% of patients with a recent transient ischemic attack or stroke display insulin resistance [10]. Four case-control studies and five prospective observational cohort studies have demonstrated an association between insulin resistance and stroke risk [11]. The adjusted RR for stroke is 1.5 to 2.6 for nondiabetic patients in the highest 20th to 30th percentile of insulin resistance [11]. Five studies have shown the link between insulin resistance and carotid atherosclerosis [12–16]. Results of clinical trials in patients with diabetes mellitus suggest that reducing insulin resistance can prevent carotid atherosclerosis and stroke [17–19].

Abdominal obesity correlates strongly with insulin resistance [4]. Individuals with abdominal obesity have an unusually high release of nonesterified fatty acids from adipose tissue, leading to lipid accumulation in sites other than adipose tissue. Ectopic lipid accumulation in muscle and liver predisposes individuals to insulin resistance and dyslipidemia. The adipose tissue in obese individuals exhibits abnormalities in producing adipokines that affect insulin resistance. The Northern Manhattan Stroke Study found those with a waist-to-hip ratio of greater than the median had an overall OR of 3.0 (95% CI, 2.1–4.2) for ischemic stroke even after adjustment for other risk factors and body mass index, concluding that abdominal obesity is a potent independent risk factor for ischemic stroke [20].

Metabolic syndrome is associated with chronic, low-grade inflammation. In the setting of obesity, adipose tissue produces inflammatory cytokines. These inflammatory cytokines induce insulin resistance in adipose tissue and muscle, exacerbating the syndrome. A proinflammatory

state marked with increased inflammatory markers denotes a higher risk for acute cardiovascular syndromes [21,22].

A critique of the metabolic syndrome concept has been that it should not be considered as a separate disease because it may not be clear that the syndrome itself is a vascular risk factor above and beyond its recognized individual risk factors. Although several questions remain, a recently published large systematic review not only found a significantly increased risk of cardiovascular events and death in people with the metabolic syndrome, but also noted that after simultaneously adjusting for the metabolic syndrome and its components, the metabolic syndrome remained an independent predictor of vascular risk (RR 1.54, 95% CI, 1.32–1.79) [5•].

Stroke Risk

Surrogate end points

Metabolic syndrome is associated with intracranial and extracranial atherosclerotic disease. Individuals with metabolic syndrome have an increased prevalence of carotid intima-media thickness and asymptomatic carotid atherosclerotic plaques [23–25]. Metabolic syndrome is also significantly associated with leukoaraiosis in healthy individuals [26].

Retrospective studies

In the third NHANES study, the metabolic syndrome conferred an OR of 2.2 (95% CI, 1.5–3.2) for ischemic stroke [27]. A retrospective analysis of 243 patients with diabetes mellitus and first-ever stroke revealed that lacunar stroke incidence was significantly higher than cortical stroke incidence in patients with and without the metabolic syndrome [28]. A post hoc analysis of the Warfarin-Aspirin Symptomatic Intracranial Disease trial revealed that the metabolic syndrome was present in about half of individuals with symptomatic intracranial atherosclerotic disease and was associated with a substantially higher risk of vascular events [29•].

Prospective studies

In recent years, several prospective studies have validated the link between metabolic syndrome and stroke. Two studies of patients with ischemic stroke revealed that metabolic syndrome was more prevalent in patients with intracranial rather than extracranial large artery atherosclerosis and was independently associated with intracranial atherosclerosis [23,30]. Table 1 summarizes studies with prospectively collected data that have demonstrated an increased risk of stroke in the presence of metabolic syndrome.

Risk Assessment

Per the NCEP, the first step in managing individuals with metabolic syndrome is assessing their absolute 10-year risk [8]. Individuals with any clinical form of atherosclerotic

Table 1. Studies with prospectively collected data assessing stroke risk in the presence of metabolic syndrome

Study	Study population and methodology	Location	Stroke in the presence of metabolic syndrome, risk or HR (95% CI)
Boden-Albala [33•]	3398 stroke-free adults in an urban community	United States	1.57 (1.12–2.21)
Takahashi et al. [34]	1493 stroke-free adults over age 55 in voluntary health screening exercise, observed 6.4 ± 3.8 years	Japan	Women: 23.1 (2.7–196)
Wannamethee et al. [35•]	5128 stroke-free men aged 40–59 drawn from general practices, observed over 20 years	United Kingdom	1.61 (1.26–2.06)
Najarian et al. [36•]	2097 stroke-free adults aged 50–81, observed over 14 years	United States	2.10 (1.37–3.22)
McNeill et al. [37•]	12089 stroke-free adults aged 45–64, observed over mean of 11 years	United States	Women: 1.96 (1.28–3.00); men: 1.42 (0.96–2.11)
Ovbiagele et al. [29•]	476 patients with symptomatic intracranial atherosclerosis enrolled in clinical trial, mean follow-up of 1.8 years	United States and Canada	1.7 (1.1–2.6)

HR—hazard ratio.

cardiovascular disease (ASCVD) or diabetes are considered high risk. Individuals without ASCVD or diabetes should have Framingham risk scoring to determine 10-year risk of coronary heart disease. This assessment triages patients into three risk categories based on 10-year risk. At this time, the metabolic syndrome is not considered an adequate tool for optimally assessing risk of coronary heart disease or stroke, but most agree that its presence places individuals at high risk for future development of diabetes mellitus; as such, it should be treated whenever identified.

Treatment

The primary goal of therapy in metabolic syndrome is to address the modifiable underlying risk factors—obesity, physical inactivity, and atherogenic diet—through lifestyle changes to prevent or delay the onset of ASCVD and diabetes mellitus [4]. Weight reduction through reduced caloric intake and increased physical activity reduces the severity of most or all of the metabolic risk factors [4]. Individuals with metabolic syndrome are encouraged to reduce their body weight by 7% to 10% over the course of 6 to 12 months [4]. Current recommendations for physical activity include at least 30 minutes of moderate-intensity exercise on most, if not all, days. The diet should be low in saturated fats, trans fats, cholesterol, sugars, and simple sugars [8].

If ASCVD or diabetes is present, or if an individual is high risk by Framingham criteria, drug therapies targeting the metabolic syndrome's individual components may also be required [4]. The treatment of atherogenic dyslipidemia should only be targeted after the goal for LDL cholesterol has been attained [8]. In individuals without diabetes or chronic kidney disease, the goal for antihy-

pertensive therapy is a blood pressure of less than 140/90 mm Hg; however, in those with diabetes or chronic kidney disease, the goal is less than 130/80 mm Hg [31]. Mild blood pressure elevations can be treated with the Dietary Approaches to Stop Hypertension diet; however, drug therapy is frequently necessary to prevent long-term adverse effects of hypertension [31].

In individuals with metabolic syndrome with elevated fasting glucose, physical activity and weight reduction can delay or prevent the onset of type 2 diabetes mellitus [4]. Metformin and thiazolidinediones have been shown to lower the risk for type 2 diabetes mellitus in individuals with impaired fasting glucose (Table 2) [32]. Other generally familiar compounds have shown preliminary promise in targeting a number of risk factors within the metabolic syndrome cluster (Table 2). Nonetheless, it appears that drugs' efficacy is markedly improved with concomitant lifestyle modification. Although individuals with metabolic syndrome typically manifest a prothrombotic state, clinical trials have not addressed treating these parameters. Currently, the long-term approach to countering their contribution to arterial thrombosis is antiplatelet agents [4].

Conclusions

The metabolic syndrome is, unfortunately, a rampant condition that threatens to increasingly plague society in the years to come. This burden in the form of symptomatic vascular disease appears to also include stroke, a leading cause of morbidity and mortality in the United States. At its worst, diagnosing the metabolic syndrome could serve as a simple clinical algorithm to help predict

Table 2. Promising pharmacologic options requiring further study in treating risk factors for metabolic syndrome

Study	Therapy	Postulated mechanism of action
Despres et al. [38], Pi-Sunyer et al. [39], and Van Gaal et al. [40]•	Rimonabant	Blocks cannabinoid-1 receptor
Orchard et al. [41]	Metformin	Stimulates the hepatic enzyme AMP-activated protein kinase*
He et al. [42]	Magnesium	Cofactor in glucose metabolism and insulin homeostasis
Szapary et al. [43]	Pioglitazone	Modulates PPAR- γ receptor
Vitale et al. [44]	Telmisartan	Partially modulates PPAR- γ modulator
Thoenes et al. [45]	Niacin	Decreases free fatty acids from adipose tissue, raises adiponectin*
Wilding et al. [46]	Topiramate	Antagonizes AMPA/kainite subtype of the glutamate receptor

*Among other postulated actions.
AMP—adenosine 5'-monophosphate; AMPA— α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid; PPAR- γ —peroxisome proliferator-activated receptor- γ .

diabetes and possibly vascular risk, as well as reinforce the need for prompt attention to lifestyle modification or counseling by patients and physicians alike. At its best, the syndrome may represent an independent risk factor above and beyond its components that will necessitate aggressive behavioral and possibly pharmacologic management geared at averting future cardiovascular events, including stroke. Further study is warranted.

Disclosures

Neither of the authors has any possible conflict of interest, financial or otherwise.

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