Autonomic Dysregulation and the Metabolic Syndrome: Pathologic Partners in an Emerging Global Pandemic

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This review will examine the importance of the autonomic nervous system both in the pathophysiology and complications of the metabolic syndrome. Metabolic syndrome refers to a constellation of risk factors related to insulin resistance and obesity with a pattern of central fat distribution. While the insulin resistance syndrome has been attracting attention over the last three decades, the metabolic syndrome achieved heightened prominence after the publication and review of the World Health Organization (WHO) Expert Committee Report on the diagnosis and classification of diabetes mellitus, in 1998, and the National Cholesterol Education Program guidelines (Adult Treatment Panel [ATP] III) in 2001, in the United states1-3. Although definitions provided differ somewhat, both anticipate a significant increase in the risk of coronary heart disease and cardiovascular disease in general4-6.

The metabolic syndrome affects a substantial proportion of adults in societies characterized by excessive calorie intake, use of labor-saving devices, and passive leisure activities. This syndrome is liable to become a pandemic, because obesity has been growing dramatically as the world’s population ages7. Its costs, both in health and financial terms, are extremely high and can be more devastating than the largest armed conflict.

This review focuses primarily on the role of the sympathetic nervous system in the metabolic syndrome, providing a gamut of information and directing its efforts rationally to prevent and treat the health consequences of this increasingly prevalent condition effectively.

Metabolic syndrome

Definition

The WHO and ATP-III definitions of the metabolic syndrome are not similar1-3 (Tab. 1).

Associated risk factors

This syndrome is associated with postprandial hyperinsulinemia, insulin resistance with reduced glucose and fatty acids, higher levels of denser LDL-cholesterol particles8, low HDL-cholesterol levels and smaller HDL-cholesterol particles. Obesity and the metabolic syndrome are related to high levels of inflammatory markers/factors, including interleukins, tumor necrosis factor-α (TNF-α), C-reactive protein9, and abnormal fibrinolysis, such as higher plasminogen activator inhibitor-
Obesity prevalence, trends and associated health risks. Obesity risks, including hypertension, diabetes, and increased cardiovascular and renal disease risks, have been described for more than 80 years. Subsequent studies have shown that obesity, particularly central or abdominal obesity, is associated with hypertension, fast heart rate, hyperinsulinemia, and insulin resistance with abnormal carbohydrate and lipid metabolism. This syndrome is associated with premature cardiovascular morbidity and mortality, including sudden death. Despite the recent information explosion on risks associated with overweight, the overweight (BMI between 25-30 kg/m²) and obesity (BMI > 30 kg/m²) epidemic remains expanding at an unpredictable rate.

Prevalence: WHO definition
Criteria established by WHO for the metabolic syndrome were applied to eight different European cohorts, and its prevalence was determined for men and women from 40 to 55 years old and also for those older than 55. Prevalence according to age and gender is summarized in Table 2.

NCEP/ATP III definition
Metabolic syndrome age-adjusted prevalence based on data from the United States’ Third National Health and Nutrition Examination Survey (NHANES III), covering 1988–1994, using ATP III criteria, was 23.7%, or approximately 47,000,000 adults. Although ATP III did not use the body mass index (BMI, kg/m²) to define the metabolic syndrome, this condition is strongly related do BMI in men and women alike, as shown in Table 3.

Future trends in prevalence
The metabolic syndrome has reached epidemic proportions and is likely to become endemic in the coming years, owing to rapid increase in obesity prevalence magnified by two strong demographic trends:

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Age-adjusted prevalence of obesity in the United States rose from 22.9% in the 1988-1994 survey to 30.5% in the 1999-2000 survey. Overweight prevalence rose from 55.9% to 64.5% between 1994 and 2000. A recent US survey suggests that obesity prevalence increased more in 2001 than in 2000. This rapid increase in obesity rate has also been found in developing countries, such as Brazil. The presence of obesity in individuals with neither risk for nor cardiovascular disease is associated with overweight, the overweight (BMI between 25-30 kg/m²) and obesity (BMI > 30 kg/m²) epidemic remains expanding at an unpredictable rate.

Epidemicobesity strikes young adults and children not only in developed countries, but also in emerging economies all over the world. In fact, epidemic obesity is growing rapidly in these new targets (emerging countries).

Given the strong relationship between obesity, the metabolic syndrome (Table 2), and the development of cardiovascular risk factors and events over the next decade among overweight and obese adults with no risk disease or risk for it, the magnitude of the metabolic syndrome and its related health problems will reach catastrophic proportions.
Among adult Americans in the age group between 20 and 29, around 7% meet ATP III criteria for the metabolic syndrome. This prevalence rises to 40% or more among those who are 60 or older. Thus, between 2000 and 2022, the absolute number of adult Americans with the metabolic syndrome is likely to increase more than 12 million individuals due to increasing age alone.

**Ethnic trends** - Obesity, the major controller of the metabolic syndrome, occurs more often among Hispanics and Africans than among Caucasians in the United States. These demographic differences extend to children, and obesity and its associated health problems are nearly doubling the rate in these high-risk populations, compared with Caucasians. Considering the rapid growth of ethnic minorities in the United States, prevalence of the metabolic syndrome and its complications is likely to increase dramatically in the following years unless effective, culturally-appropriate, and population-based strategies are implemented to promote health.

**Clinical significance** - Impact on coronary artery disease (CAD), cardiovascular disease (CVD), and overall mortality. The clinical significance of the metabolic syndrome is not defined by its prevalence, but rather by its impact on health outcomes and costs. Metabolic syndrome, defined by WHO and ATP III in Table I, is associated with significantly higher mortality from CAD and CVD, as well as with overall mortality. When the WHO and ATP III criteria were applied to a Finnish male population followed up on from 1989 to 1998, an important positive relationship was found with mortality from CAD, CVD, and overall mortality (Table 5).

### Economic impact

The cost of obesity alone in the United States was estimated in 46 to 68 billion dollars in 1990, rose to 99 billion dollars in 1995 and is likely to have exceeded this amount annually. While obesity hastens degenerative joint diseases and increases breast, uterus, prostate, and spine cancer rates, most of the high cost associated to obesity is generated by cardiovascular risk factors and events, that is, it is related to the metabolic syndrome.

Given prevalence, future trends, clinical impact, and economic burden of the metabolic syndrome, this disorder currently constitutes a major health problem and is still on the rise. Further efforts to identify the mechanisms and consequences involved in sympathetic dysfunction may provide insights into therapeutic advances to reduce cardiovascular risk and its consequences. Now, we are going to explore the literature relating sympathetic nervous system, obesity, and metabolic syndrome.

### Overweight, obesity, plus insulin action and dynamics

Body mass index and insulin action and dynamics are interrelated. For example, among Italians, hyperinsulinemia and insulin resistance affect only 10% of subjects with BMI < 25 kg/m², but 60% or more of subjects with BMI ≥ 35 kg/m². In some ethnic groups, such as Asians and Afro-americans, the risk for insulin resistance and several features of the metabolic syndrome starts when the BMI is below 25 kg/m².

Although physicians and scientists have only recently recognized health hazards posed by obesity, its adverse impact has been known for at least 80 years. The acknowledgement of obesity epidemics worldwide over the last decades has led to an explosion of scientific interest and discoveries. Insight gained from intensified investigations include from clinical epidemiology observations to experiments in the areas of cell and molecular biology. A similar range of scientific research has furth ered our understanding of the role of the sympathetic nervous system in the metabolic syndrome, also called insulin resistance syndrome.

This review intends to summarize information from community to bedside and laboratory bench in order to shed new light on the underlying sympathetic activation involved in the pathogenesis of this condition, as well on metabolic and cardiovascular consequences among individuals with the insulin resistance syndrome. Evidence suggests that abnormalities in neurogenic regulation are partly directed to several aspects of the syndrome and that enhanced sympathetic tone may contribute to the dimension of the metabolic syndrome and the complications associated with target organs. Therefore, further understanding of the causes and consequences of sympathetic hyperactivity in the metabolic syndrome may intensity efforts to more effective prevention and better management of this condition and its complications. We will start this discussion by providing a brief, general overview of obesity and insulin resistance epidemiology.

### Sympathetic function in obesity

Obesity is not a homogeneous disorder. Both in animals and humans, evidence of sympathetic hypofunction and hyperfunction has already been demonstrated. Collectively, the available literature strongly suggests sympathetic hyperactivation in a substantial subgroup of subjects. Several studies provide clues to the pathogenesis and consequences of sympathetic hyperactivity in obesity (Fig. 1).

In a subgroup of obese subjects, sympathetic tone is found to be heightened in key organs, such as the kidney, skeletal muscle, and peripheral vessels. Evidence of increased sympathetic tone to the heart in humans is not as strong, especially in normotensive obese patients. Impaired autonomic control of heart rate variability, including decreased vagal tone, with or without increased sympathetic tone, is well documented. Sympathetic activation in many target sites seems to play an important role in the pathogenesis of
insulin resistance related to obesity, hypertension, renin-angiotensin system activation, and sudden death. Now we will explore evidence from several animal and human studies documenting that sympathetic nervous system activity is activated in obesity and insulin resistance.

**Evidence of sympathetic activation in obesity and insulin resistance**

Animal studies

Evidence of sympathetic hypofunction and hyperfunction has already been demonstrated in animal obesity models. In fact, sympathetic hypofunction seems to be related to low metabolic rates, which contribute to obesity in rodents. In healthy animals, obesity induced by excessive intake of food is associated with sympathetic activation and hypertension. Sympathetic activation is prematurely induced by overeating and reverted with weight loss. Apparently, the onset of diet-induced sympathetic alterations both precedes and triggers changes in the renin-angiotensin system activity. In some of these models, hypertension is prevented or reverted either by central α-2 receptor agonists or a combined α-1 and β-adrenergic blockade. Findings from experimental studies have provided information on the mechanisms whereby obesity and insulin resistance activate the sympathetic nervous system and thus contribute to cardiovascular disease risk. Results from these studies indicate that the relationship between obesity, insulin resistance, and sympathetic function is complex and appears to be modified by genetic and environmental factors.

In normotensive rats, a high-sucrose diet, even in the absence of weight gain, induces insulin resistance and hypertension, which is attenuated by centrally acting α-2 adrenergic agonists. In rats and dogs, hypertension induced by high sucrose or fat diets is abolished by clonidine, whereas hyperinsulinemia is affected variably.

**Human studies**

Plasma and urinary catecholamines, systemic or regional norepinephrine turnover, and direct nerve recording (microneurography) are used to measure sympathetic activity in humans. All these methods have provided evidence for sympathetic hyperfunction among obese subjects with metabolic syndrome.

**Plasma catecholamines** – A number of studies identified higher plasma catecholamine levels in obese subjects, particularly those with high blood pressure. Moreover, weight loss is associated with a relatively rapid reduction in plasma norepinephrine, which is correlated to a drop in blood pressure that accompanies the negative balance of calories. Studies have demonstrated that plasma norepinephrine is elevated in obese children with high blood pressure, and that this is a predictor of the blood pressure drop that occurs with salt restriction.

These data suggest that sympathetic hyperactivity contributes to sodium retention and increased blood pressure in obese children, which is consistent with evidence from studies on regional catecholamine turnover in obese adults.
Muscle sympathetic nerve activity has been reported to be higher in men than in women. In studies focused on evaluating this gender-related difference, Jones et al examined the relationship between body fat and MSNA in men and women and found that it was more strongly correlated with central fat than with peripheral fat. Central fat, or the male fat distribution pattern, is associated with a greater degree of hyperinsulinemia, insulin resistance, hypertension, diabetes, and coronary artery disease than peripheral fat, or the female fat distribution pattern. The marked sexual dimorphism in fat distribution is present in young adults and decreases as women gain weight and show a centripetal distribution of fat with age. Moreover, overweight is more strongly related to hypertension in men than in women older than 45. These findings reported in the literature relating MSNA with obesity strengthen the possibility that enhanced sympathetic activation among subjects with abdominal obesity contributes to their tendency to hypertension, insulin resistance, and diabetes.

Obesity and hypertension have separate and additional effects in MSNA. In studies conducted by Grassi et al, MSNA was similarly elevated (around 40% to 50%) in lean hypertensive and obese normotensive subjects, compared to lean normotensive subjects. In obese hypertensive subjects, MSNA was almost twice as high as that of lean normotensive subjects, suggesting that obesity and hypertension in MSNA were approximately additive. These investigators showed that reflex modifications in MSNA secondary to blood pressure changes were impaired in obese normotensive subjects, compared to lean normotensive and lean hypertensive subjects. Baroreflex impairments mediated by MSNA changes were greater in obese hypertensive than in obese normotensive subjects. These findings indicate that obesity is associated with increased MSNA, as well as worse MSNA regulation by baroreceptors. These abnormalities related to MSNA in obese subjects are magnified in the presence of concomitant hypertension.

Spectral analysis – Obese patients are more likely to experience ventricular arrhythmias and sudden death than lean subjects. It is noteworthy that changes in the sympathetic and parasympathetic control of heart rate are greater in women with visceral obesity than in those with lower-body obesity. Furthermore, weight loss from caloric restriction improves parasympathetic tone to the heart at night and reduces heart sympathetic/parasympathetic tone ratio during the day without changing resting heart rate. Although this review focuses primarily on the sympathetic nervous system, obesity is associated with abnormalities in the parasympathetic function that may be clinically relevant. Many autonomic changes associated with obesity improve with weight loss.

Potential mechanisms that may contribute to sympathetic activation in obesity

Several factors involved in the sympathetic activation that occurs in obesity are mentioned in the literature. Since obesity is a heterogeneous condition, relative contribution of these factors may vary depending on changes in other biological, genetic, and environmental factors. Now we are going to analyze the evidence for several factors that can increase...
sympathetic activity in obesity. The following list is not meant to be exclusive, and there may be other factors.

**Insulin** – Extensive literature on animals and humans indicates that elevated plasma insulin levels, even within the physiological range, activate the sympathetic nervous system. In fact, theories linking hyperinsulinemia and insulin resistance with hypertension are based on the assumption that potential pressor effects of insulin are maintained (e.g. sympathetic activation and renal sodium retention), while some potential depressor effects are reduced (e.g. vasodilation), an argument that is beyond the scope of this review.

A series of experiments conducted by Anderson et al at the University of Iowa has shown that euglycemic hyperinsulinemia increases the MSNA in healthy young and elderly subjects, as well as in subjects with borderline hypertension. In spite of differences in terms of insulin action and peripheral vasodilatation, no short-term increase in blood pressure occurs in these groups. In other studies, the MSNA is more strongly correlated with BMI ($n = 37$, $r = 0.67$, $p < 0.001$) and total body fat ($r = 0.64$, $p < 0.001$) and less strongly correlated with plasma insulin ($r = 0.34$, $p < 0.04$). These data suggest that hyperinsulinemia may account solely for a small part of the sympathetic activation found in obesity. However, contrary to reports from other investigators, this group observed that obese subjects are resistant to insulin’s action to increase MSNA, but are equally responsive to other stimuli that increase MSNA. Collectively, evidence suggests that insulin contributes to, yet may not fully explain, the sympathetic activation that occurs in obesity.

**Leptin** – Many studies have documented that leptin induces sympathetic activation both in animals and humans. Leptin, like insulin, has actions that are potentially pressor and others that are depressor. For example, leptin acts directly on the kidney by increasing renal sodium excretion and nitric oxide production, which may result in a drop in blood pressure. Leptin also increases sympathetic tone in the heart, kidneys, and adrenals, which may raise blood pressure. While short-term infusion of leptin in animals usually does not raise blood pressure, long-term leptin infusion has a pressor effect. Short-term leptin infusions are natriuretic, whereas long-term infusions reduce renal blood flow, thus enhancing sodium retention, and increase renal vascular resistance. Other evidence also implicates leptin in some models of hypertension associated with obesity. Although both insulin and leptin may activate the sympathetic nervous system, regional patterns of sympathetic activation differ with these peptides. Additionally, in humans, the multivariate analysis shows that MSNA seems to be more related to plasma leptin than to insulin.

**Non-esterified fatty acids (NEFAs)** – Non-esterified fatty acids or free fatty acids are usually elevated in metabolic syndrome subjects and are less responsive to suppression by insulin. Elevated plasma fatty acids are strongly correlated to abnormalities in the glucose and lipid metabolism that follows insulin resistance. Until the last decade, abnormalities in NEFAs metabolism were not related to sympathetic activation and cardiovascular regulation.

In minipigs, an increase in NEFA plasma levels through infusion of Intralipid, a source of triglyceride, and heparin, which activates lipoprotein lipase and accelerates hydrolysis of fatty acids from triglyceride, induces vasoconstriction and raises blood pressure. In normotensive rats, the portal venous infusion of oleate solution induces sympathetic activation and raises blood pressure. The pressor response induced by oleate is blocked by α1-adrenoceptor antagonists. In dogs, oleate infusion failed to induce sympathetic activation or pressor response. In humans, the two-fold increase in non-esterified fatty acids during Intralipid and heparin infusion raised blood pressure in 12–14/6–8 mmHg in a four-hour period. Despite blood pressure elevation, heart rate increased –8 bpm, consisting in neurogenic activation. In other study, Intralipid and heparin infusion also impaired endothelium-dependent vasodilation and enhanced α1-adrenoceptor-mediated pressor reactivity. These two effects may be linked, because nitric oxide appears to attenuate α1-adrenergic receptor-mediated vasodilatation. One or more NEFA effects may explain their independent association as predictors of hypertension in the Paris Prospective Study.

Raising plasma fatty acids in humans also reduces baroreflex sensitivity; however, sympathetic control improves and parasympathetic control of heart rate variability decreases. Since lower heart rate variability is associated with higher mortality rate, these findings may provide a potential mechanism linking higher fatty acid levels with sudden death in the Paris Prospective Study.

**Cytokines** – The relationship between cytokines and sympathetic activation in obesity is speculative. Nevertheless, adipocytes produce a variety of inflammatory cytokines in proportion to their volume (Fig. 2). Obesity is associated with an increase in several of these pro-inflammatory peptides. Patients with heart failure or sleep apnea have increased cytokine levels and sympathetic activity, implying an association but not necessarily a causal relationship.

**Triiodothyronine** – The active T3/reverse T3 ratio is associated with calorie intake, especially carbohydrate. This ratio increases rapidly with overeating and drops with fasting. Similarly, overeating is associated with increased deprivation of calories and decreased sympathetic activity, as described previously. Although this association increases the possibility of a causal relationship, some evidence links excess thyroid hormone (T4) levels with sympathetic activation while other evidence suggests sympathetic inhibition with hyperthyroidism. Further studies are needed to determine whether T4 and T3 effects on autonomic function are similar.

**Eicosanoids** – Adipose tissue secretes several peptides and other molecules that may be augmented among obese individuals. Eicosanoid products modulate autonomic activity in a clinically significant manner. Therefore, abnormal eicosanoid metabolism in obesity may potentially impair sympathetic activation and inhibition.

**Nitric oxide** – Nitric oxide is a neurotransmitter and a local autoduct that modulates central sympathetic activity and peripheral neurogenic vasconstriction. Leptin increases nitric oxide and sympathetic tone. Nitric oxide inhibition during exogenous leptin infusion enhances sympathetic tone significantly, especially to the heart.

**Endorphins** – Endorphins act centrally as modulators of the sympathetic nervous system, appetite, and glucocorticoid
function (hypothalamic-pituitary-adrenal axis)\(^{91-95}\). In fact, endorphins seem to mediate the sympatholitic effects of \(\alpha-2\) and imidazoline receptor agonists\(^{96}\). In short-term human studies, opioid antagonists are potent modulators of sympathetic activity\(^{97}\). The endorphin/opioid effects on sympathetic function are not consistent and may depend on specific sites of action and on the subtype of activated receptor\(^{98}\). Albeit speculative, abnormalities in endorphins may contribute to changes in energy intake relative to expenditure, both in the hypothalamic-pituitary-adrenal axis and autonomic functions described in obesity.

**Neuropeptide Y** – Neuropeptide Y (NPY) acts on the hypothalamus reducing the appetite and sympathetic flow, while improving sympathetic function peripherally\(^{99}\). As with endorphins, there are several subtypes of NPY receptors to mediate specific effects on tissues. While NPY levels seem to be normal in obesity, changes in central and/or peripheral levels, as well as central NPY actions, may also contribute to impaired autonomic drive and tone.

**Sleep apnea** – Sleep apnea, unlike the aforementioned factors that may participate in neurogenic activation in obesity, is a medical condition rather than a peptide or lipid signaling molecule. It is a common yet underrecognized condition associated with obesity that might be present in about 50% of the hypertensive patients\(^{85,100}\). Sleep apnea is associated with multiple changes, including insulin resistance, hyperleptinemia, hypercytokinemia, and sympathetic activation\(^{101}\). Several factors already discussed may contribute to adrenergic activation in patients with this condition. Furthermore, hypoxemia through activation of peripheral chemoreceptors and/or central effectors, for example, C1 and catecholamine-containing neurons in the medulla, may play the primary role in the sympathetic activation that occurs in sleep apnea\(^{102}\). It must be emphasized that imidazolines, including clonidine, inhibit sympathetic activation by acting on C1 neurons\(^{103}\). Thus, activation of these receptors by hypoxia may potentially contribute to neurogenic hypertension in obese patients with sleep apnea.

**Conclusion**

Obesity has emerged as a worldwide epidemic, and health problems related to the metabolic syndrome have accompanied it. It is no exaggeration at all to say that this global epidemic is likely to become a pandemic in coming years. The clinical significance of the metabolic syndrome is highlighted by an association with a two- to four-fold increase in coronary heart disease, general cardiovascular diseases, and global mortality. The rapid increase in obesity prevalence, along with an aging population and increased proportion of high-risk ethnic groups, make it more important to implement effective strategies for primary prevention of the metabolic syndrome. Obesity is associated with several health risks that may have structural and functional impact on the body as a whole. Obesity is a heterogeneous condition modulated by a variety of genetic, environmental and developmental factors. Literature indicates that the
sympathetic nervous system is activated in a substantial subgroup of subjects and seems to play a key role in insulin resistance, hypertension, tachycardia, complications in target organs, and sudden death which occur prematurely and more often in obese patients. Evidence implicates leptin and hyperinsulinemia in the sympathetic activation related to obesity. Hypothetically, other factors, such as fatty acids, neuropeptide Y, eicosanoids, and endorphins may participate in this sympathetic activation. It is speculated that cytokines and triiodothyronine can activate or cause the development of sympathetic activation in obesity. Sleep apnea, a frequent yet unrecognized complication of obesity, may trigger enhanced sympathetic activity through several mechanisms.

Although not discussed in this review, behavioral factors, such as suppressed anger and hostility, might potentially contribute to autonomic changes in obese subjects\(^{104}\).

This review focused on examining sympathetic activation causes and consequences in the metabolic syndrome. Hopefully, it contributes to a better understanding of those factors that induce sympathetic activation and its health consequences in subjects with insulin resistance. Scientific discoveries and understanding are critical to the development of new therapeutic interventions to reduce, at least in part, the devastating consequences of the metabolic syndrome both in health and economic terms, and current evidence indicates several promising research fields.

References


