Series Editor: A. Maziar Zafari, MD, PhD, FACC

Stress Response and the Metabolic Syndrome

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The metabolic syndrome, characterized by abdominal obesity, elevated serum triglycerides, high blood pressure, and increased fasting glucose levels and low concentrations of high-density lipoprotein (HDL) cholesterol, has an estimated prevalence of almost 25% in the US population.[1] The underlying abnormality causing these conditions to cluster together is thought to be insulin resistance. Recently, the metabolic syndrome has been recognized as an important risk factor for cardiovascular disease and all-cause mortality,[2–5] and it was listed as a secondary target of therapy in the National Cholesterol Education Program's Third Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).[6]

Although genetic and biological factors play a major role in the development of obesity, hypertension, insulin resistance, and diabetes, these common disorders that are part of the metabolic syndrome are probably influenced by other factors. Evidence suggests that these disorders are mediated by a complex interplay between genetics, biology, and the environment (**Figure 1**). Stress, whether related to depression,[7] environmental stressors,[8] or perceived stress,[9] is associated with increased release of corticosteroids and other neurohormonal factors that may predispose to abdominal obesity, insulin resistance, and the other features of the metabolic syndrome.[9–20] This article is the second in a series on the metabolic syndrome. Its goal is to review the literature linking stress and the neurohormonal stress response to the metabolic syndrome and to discuss the pathophysiological mechanisms that are involved in these relationships.

TAKE HOME POINTS

- Stress, whether related to depression, environmental stressors, or perceived stress, is associated with increased release of neurohormonal factors that predispose to abdominal obesity, insulin resistance, and other features of the metabolic syndrome.
- Abnormalities in the neuroendocrine and autonomic responses typical of chronic stress appear to be a characteristic feature of the metabolic syndrome.
- Stimulation of the hypothalamic-pituitary-adrenal axi, with increased cortisol production, causes accumulation of visceral adipose tissue.
- Catecholamines stimulate the production of inflammatory cytokines in adipose and other tissues, which contribute to the development of insulin resistance.
- Stress reduction techniques and other psychosocial interventions have been shown to reduce blood pressure, body weight, and lipid levels as well as improve eating habits and exercise.

CURRENT CONCEPTS ON STRESS

The stress system coordinates adaptive responses of the organism to stressors.[21] Two main components mediate the neurohormonal response to stress: the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). This stress-responsive system is regulated by centers in the hypothalamus and the brainstem. These regulatory centers include neurons in the paraventricular nucleus (PVN) of the hypothalamus, which secrete corticotropin-releasing hormone (CRH) and arginine-vasopressin, and the noradrenergic neurons of the locus ceruleus of the brain stem, which secrete norepinephrine

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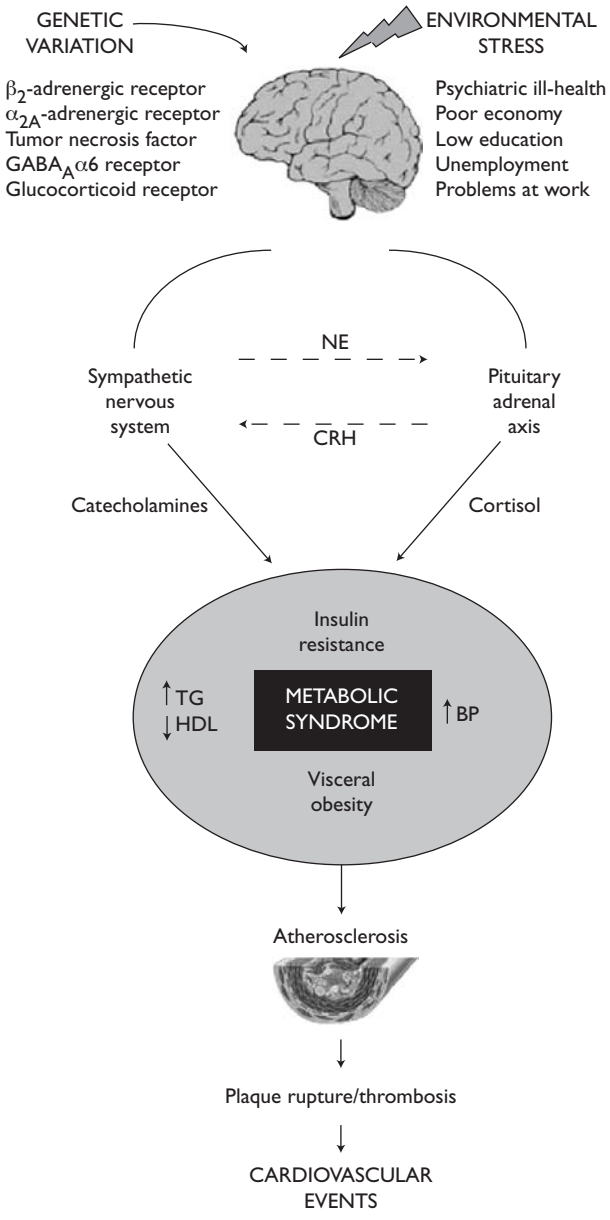

Figure 1. Multifactorial model for the etiology of the metabolic syndrome and central role of the stress system. BP = blood pressure; CRH = corticotropin-releasing hormone; GABA = gamma-aminobutyric acid; HDL = high-density lipoprotein; NE = norepinephrine; TG = triglycerides. (Adapted from Rosmond R. Role of stress in the pathogenesis of the metabolic syndrome. Psychoneuroendocrinology 2005;30:7. Copyright © 2005 with permission from Elsevier.)

centrally in the brain.[21] The different components of the stress system innervate and stimulate each other and have unique basal and stress-related patterns of activity. In individual subjects, the secretion of the end-product of the HPA axis, cortisol, is maintained within a quite stable and narrow range by a tightly regulated feedback system that prevents excessive and prolonged cortisol secretion that would be detrimental to the organism.[22]

In addition to affecting the HPA axis and the autonomic nervous system, activation of the stress system produces a variety of other effects, including influences on brain functions involved in emotion, cognitive function, and behavior as well as the reproductive system, the endocrine system, and immune function. In general, these behavioral and biological changes are meant to improve the ability of the organism to effectively counteract the stressor. Repeated or chronic activation of the stress system or a malfunctioning stress system characterized by sustained hyperactivity or hypoactivity may contribute to various pathophysiological abnormalities across a wide range of organ systems, potentially resulting in endocrine, inflammatory, and psychiatric disorders.[21]

Selye[23] provided one of the first comprehensive descriptions of the stress response, including how the organism responds to stressors and the role of stress in physical disease. Chrousos[21] introduced the concept of stress-related disorders, highlighting the role of stress in leading to maladaptive physiological responses that could predispose to physical conditions. Following a similar paradigm, Sterling and Eyer[24] coined the term *allostasis*, defined as the ability of the body to increase or decrease vital functions in response to changing demands. Subsequently, McEwen[25] introduced the term *allostatic load* to define the long-term effects of repeated disruptions of the homeostatic system due to stress, resulting in a drift of the equilibrium toward levels that can predispose to disease.

Following these concepts, *stress* can be defined as a state of threatened homeostasis, and *chronic stress* is associated with long-term repeated disruption of a homeostatic system that results in wear and tear on a number of bodily functions and therefore predisposes to disease.[25,26] One of the initiating events is thought to be a disruption of HPA axis regulation, a phenomenon noted after intense or protracted exposure to psychological stress.[25,27,28] Normal HPA response to stress is characterized by increased cortisol secretion but maintained central regulation, circadian variation, and feedback control. Disrupted HPA axis response, however, is characterized by downregulation of the hippocampal and pituitary glucocorticoid receptors, resulting in increased corticotropin and cortisol responses to stress with poor feedback regulation and flattening of the normal diurnal cortisol rhythm. These changes result

from chronic hypersecretion of CRH with a reset of the HPA axis. Eventually, with more protracted disruption of the HPA central control system, there will be a net reduction in cortisol output and a loss of the diurnal secretory pattern.[29] The altered daily cortisol secretion pattern is thought to produce somatic sequelae similar to chronic hypercortisolism because suppression of the normal morning cortisol surge may not adequately compensate the evening excess of cortisol production.[22] Indeed, similar HPA axis abnormalities are found in persons with metabolic syndrome, as described below.

Psychosocial Risk Factors and the Metabolic Syndrome

The metabolic syndrome has been linked to psychosocial stress in a number of studies. The Whitehall II study, a population study of British civil servants, described a close relationship between lower social position and increased probability of having the metabolic syndrome, an association that was little affected by differences in health behaviors.[30] Whitehall II investigators also demonstrated disturbances in neuroendocrine and cardiac autonomic activity, compatible with activation of the neuroendocrine stress axes in subjects with metabolic syndrome compared with controls.[14] Notably, psychosocial factors (socioeconomic status and job-related stress) explained a large portion of the association between adrenal/autonomic disturbances and metabolic syndrome, while again health behaviors had a modest impact. A strong association has also been reported between depression and the metabolic syndrome in population studies: clinical depression or depressive symptoms predicted insulin resistance, metabolic syndrome, or diabetes in both cross-sectional[31,32] and longitudinal studies.[32,33] Other psychosocial risk factors that have been linked to the development of the metabolic syndrome include anger[32] and hostility.[34]

Role of the Sympathetic Nervous System

Given the function of the SNS in the regulation of blood pressure,[11,35] a role of the sympathoadrenal system in the etiology of hypertension has long been suspected. Animal and human experimental studies have shown that repeated stress-induced activation of the sympathoadrenal system results in cardiovascular adjustments leading to increased blood pressure.[36] More recently, these effects on blood pressure have been thought to be mediated by insulin resistance, which is etiologically linked to essential hypertension.[11] Consistent with this view, several if not all of the other components of the metabolic syndrome have been associated with SNS and autonomic disturbances.[11,12,14,19,20] Hyperinsulinemia typical of insulin-resistant states, on the other hand, stimulates SNS by acting on hypothalamic regulatory centers,[11] thereby further worsening insulin resistance and metabolic syndrome risk factors. Decreased heart rate variability, a measure of autonomic dysfunction, also has been linked to insulin resistance.[12,14] This fact further highlights the connection between the autonomic nervous system and the metabolic syndrome. On the whole, current evidence strongly suggests that altered autonomic and noradrenergic function, characteristic of the stress response, is a feature of the metabolic syndrome.

Role of the HPA Axis

Cortisol has well-established actions in the regulation and distribution of adipose tissue. Clinical observations have long suggested a connection between Cushing syndrome, characterized by excess endogenous or exogenous cortisol, and visceral obesity as well as other features of the metabolic syndrome, including insulin resistance, dyslipidemia, dyscoagulation, and hypertension. These facts have stimulated extensive research on cortisol metabolism in obesity.[37] This research has shown a clear relationship between neurohormonal stress response, visceral fat, and insulin resistance,[9,17–20] including HPA dysregulation in obesity that is reminiscent of exposure to chronic stress.[9]

In primates other than humans, exposure to psychosocial stress results in features similar to hypercortisolemia, including diminished feedback regulation of cortisol secretion, visceral obesity, insulin resistance, dyslipidemia, hypertension, and coronary atherosclerosis.[38] Similarly, humans exposed to psychosocial stressors or socioeconomic subordination have more visceral obesity and show perturbations in the HPA axis consistent with chronic stress, such as blunted dexamethasone suppression (indicator of diminished feedback regulation of cortisol on the HPA axis), elevated stress-induced cortisol secretion, and disruption of the normal cortisol circadian pattern.[9,39] In addition to perceived stress and low social status, many other psychosocial factors have been linked to visceral obesity or intraabdominal fat in humans, including depression, "vital exhaustion," anxiety, anger, and hostility.[20,40–43]

FROM NEUROHORMONAL STRESS RESPONSE TO METABOLIC SYNDROME: BIOLOGICAL PATHWAYS

Metabolic Effects

Catecholamines and cortisol have similar metabolic effects. They stimulate glycogenolysis and gluconeogenesis in the liver and inhibit insulin sensitivity and glucose uptake in the skeletal muscle (**Table**). These effects lead to impaired glucose tolerance and insulin

Table. Physiological Effects of Stress System Activation That Might Contribute to the Development of the Metabolic Syndrome*

HPA/Cortisol	SNS/Catecholamines
Increased blood pressure	
+ Vasoconstriction	+ Vasoconstriction
+ Catecholamines	+ Angiotensin II
	+ Angiotensin II → endothelin
– Vasodilation	
– Kallikrein/prostacyclin	
– Nitric oxide synthase	
+ Sodium and fluid retention	+ Sodium and fluid retention
+ Sodium reabsorption → + angiotensinogen → angiotensin II → aldosterone	+ Angiotensin II → aldosterone
	+ Angiotensin II → vasopressin
Metabolism	
+ Carbohydrate intolerance	+ Carbohydrate intolerance
+ Gluconeogenesis	+ Gluconeogenesis
+ Glycogenolysis	+ Glycogenolysis
+ Glucagon secretion	+ Glucagon secretion
– Glucose utilization/insulin sensitivity	– Glucose utilization/insulin sensitivity
+ Lipolysis → free fatty acids → insulin resistance	+ Lipolysis → free fatty acids → insulin resistance
+ Visceral fat cell growth and function	– Downregulation of insulin receptor
+ Small, dense LDL, VLDL, triglycerides	+ Small, dense LDL, VLDL, triglycerides
– HDL	– HDL
+ Coagulation	+ IL-6 (α-adrenergic effect)
	+ Angiotensin II → inflammatory cytokines
	+ Coagulation

+ = stimulation; – = inhibition; HDL = high-density lipoprotein; HPA = hypothalamic-pituitary-adrenal; IL = interleukin; LDL = low-density lipoprotein; SNS = sympathetic nervous system; VLDL = very low-density lipoprotein. (Adapted with permission from Chrousos GP. The role of stress and the hypothalamic-pituitary-adrenal axis in the pathogenesis of the metabolic syndrome: neuro-endocrine and target tissue-related causes. Int J Obes Relat Metab Disord 2000;24:S50–55. Copyright 2005, Macmillan Publishers Ltd.)

*Only the principal actions are listed; because the HPA system and the SNS stimulate each other, they act synergistically.

resistance. In addition, β-adrenergic stimulation induces a rapid downregulation of insulin receptors in isolated adipocytes.[44] Catecholamines and cortisol also stimulate the breakdown of stored triglycerides in the adipose tissue, resulting in an increase in plasma free fatty acids. A higher level of free fatty acids inhibits the release of insulin from the pancreas in response to glucose, further worsening glucose intolerance and insulin resistance. In addition, the hepatic synthesis of triglycerides from free fatty acids, and the formation of very-low-density lipoprotein particles, is enhanced. Insulin-resistant states are characterized by increased lipolysis in adipocytes, with elevation of free fatty acid levels and related lipoprotein effects.[45]

Inflammation and Oxidative Stress

A major mechanism linking psychosocial stress, neurohormonal abnormalities, and the metabolic syndrome is stress-mediated production of inflammatory cytokines in the adipose tissue, which in turn can induce insulin resistance. Several studies have documented alterations in immune function and increased inflammation due to psychosocial stress[46–51] or depression.[52–58] In other studies,[59–61] psychological stress has been associated with

production of reactive oxygen species, which in turn stimulate the expression of inflammatory cytokines.

Chronic, low-grade systemic inflammation is a consistent feature of the metabolic syndrome, which is now considered an inflammatory disorder.[62] Enhanced inflammation in the metabolic syndrome is due primarily to production of inflammatory cytokines in the adipose tissue, such as interleukin (IL)-6, IL-1, and tumor necrosis factor-α (TNF-α). Indeed, the level of circulating inflammatory markers is highly correlated with the degree of obesity and insulin resistance.[62–65] These markers also predict the development of diabetes.[66–68] Inflammatory cytokines are currently thought to play an important role in the pathogenesis of insulin resistance through a variety of mechanisms, including phosphorylation of the insulin receptor and inhibition of the production of adiponectin, which increases insulin sensitivity.[51,62,69]

There are several pathophysiological mechanisms that may link psychosocial stress and metabolic syndrome by increasing inflammation and oxidative stress:[14,29,51,70] (1) glucocorticoid-mediated accumulation of abdominal adipose tissue, which provides a substrate for cytokine production; (2) catecholamine-mediated stimulation of cytokine production in the adipose tissue and other tissues; (3) SNS–mediated activation of the renin-angiotensin system which, through the type 1 angiotensin II receptor (AT_1), leads to increased blood pressure and production of reactive oxygen species and inflammatory mediators;[71,72] (4) increased systemic IL-6 concentrations mediated by catecholamines through β_2-adrenergic receptors;[73] and (5) cortisol-mediated inhibition of nitric oxide synthase (NOS) activity,[74,75] with consequent stimulation of the production of cytokines and reactive oxygen species.

Diet

An additional potential mechanism linking psychosocial stress to obesity and the remaining features of the metabolic syndrome is overfeeding. In laboratory animals, food intake, particularly carbohydrate and fat, increases SNS activity, while fasting decreases it; similar dietary-induced changes in SNS activity occur in humans.[11] These changes in sympathetic outflow are mediated by insulin, which stimulates the uptake and metabolism of glucose in regulatory centers in the hypothalamus. Glucose metabolism in these neurons suppresses an inhibitory pathway to the SNS centers in the brainstem, thereby resulting in increased sympathetic activity. The latter increases the metabolic rate (dietary thermogenesis), with the purpose of increasing energy expenditure and restoring energy balance.[11] The insulin-mediated increase in SNS activity, however, also contributes to hypertension, insulin resistance, and enhanced inflammation and oxidative stress, which in turn may worsen insulin resistance as described above (**Figure 2**). Therefore, while stress-mediated SNS activation contributes to insulin resistance and leads to hyperinsulinemia, the latter activates the SNS, therefore worsening insulin resistance in a feedback-forward fashion.

Genetic Predisposition

Recent data indicate that genetic predisposition may modulate the effects of sympathetic and HPA activity on the metabolic syndrome. Genetic background may also interact with stress exposure by increasing the likelihood of insulin resistance in carriers of specific genotypes. Consistent with this notion, a number of polymorphisms of genes involved in the regulation of catecholamines (eg, genes encoding α- and β-adrenergic receptors) alter sympathetic effects and may modify individual susceptibility to insulin resistance.[76] Similarly, several polymorphisms of the glucocorticoid receptor gene, which may affect cortisol sensitivity and the development of insulin resistance, have been reported.[77] For example, the BclI polymorphism has been associated with visceral obesity, hypertension, insulin resistance, increased atherogenic profile, and dysregulation of the HPA axis.[77,78] Many other polymorphisms of factors involved in the modulation of HPA function (eg, neurotransmitters and cytokines) have also been associated with obesity, blood pressure, and abnormalities in HPA function.[26,76]

PSYCHOSOCIAL STRESS AND THE METABOLIC SYNDROME: WHICH COMES FIRST?

Although the evidence presented above suggests a causal role of psychosocial stress in the etiology of the metabolic syndrome, it is also clear that obesity and other features of this syndrome predispose to psychosocial risk factors. In a longitudinal study, Raikkonen et al[32] found that depression, tension, and anger at baseline predicted the development of the metabolic syndrome during follow-up, but having the metabolic syndrome at baseline also predicted increasing anger and anxiety in the following years.

Since excess body weight is a key feature of the metabolic syndrome, psychosocial stress may arise from the social stigma associated with obesity. However, emotional problems in obese persons may also derive from cytokine production in the adipose tissue. The latter recently has been recognized as an active secretory organ that produces a variety of molecules known as adipocytokines.[62] These include inflammatory cytokines such as IL-6, IL-1, and TNF-α as well as other factors such

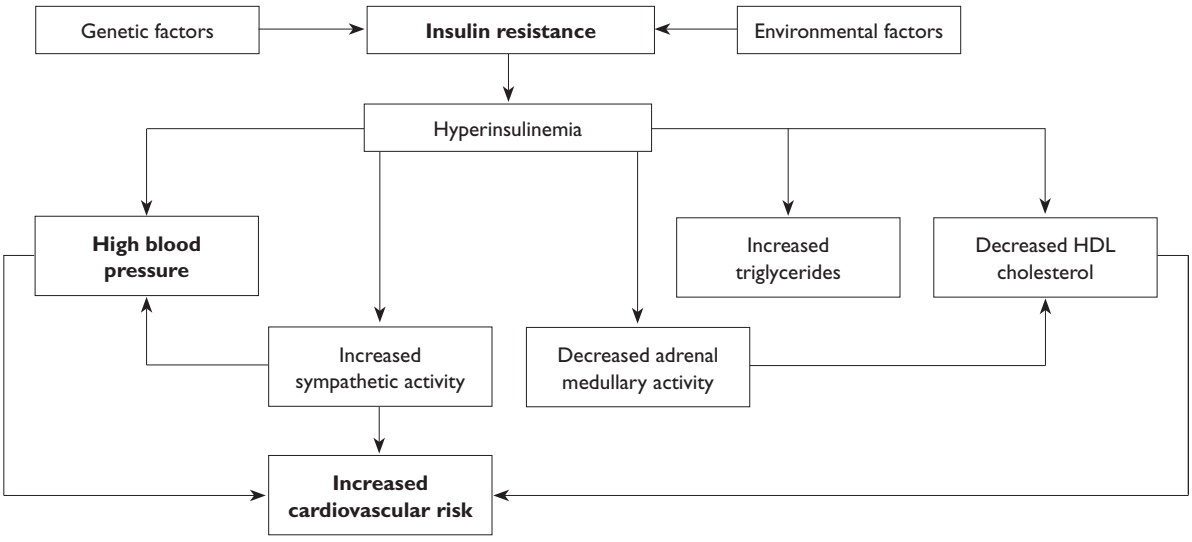

Figure 2. Postulated relationships among insulin resistance, hypertension, and increased cardiovascular risk. The sympathetic nervous system and adrenal medulla are the effector links between insulin resistance, metabolic syndrome risk factors, and cardiovascular disease. HDL = high-density lipoprotein. (Adapted with permission from Reaven GM, Lithell H, Landsberg L. Hypertension and associated metabolic abnormalities: the role of insulin resistance and the sympathoadrenal system. N Engl J Med 1996;334:379. Copyright © 1996, Massachusetts Medical Society. All rights reserved.)

as leptin, adiponectin, resistin, and components of the renin-angiotensin system. The production of some of these factors in the fat tissue is substantial. For example, adipose tissue production accounts for approximately 30% of circulating IL-6 levels in humans. Some of these factors, such as leptin and IL-6, act in the central nervous system to inhibit food intake and increase energy expenditure, thereby attempting to correct excess body weight and achieve negative energy balance.[62] Others, particularly TNF-α, contribute to the development of insulin resistance through phosphorylation of the insulin receptor and other mechanisms, as described earlier.

Another key action of inflammatory cytokines, which has been well-described during acute and chronic inflammatory diseases, is activation of the HPA axis.[73] In turn, HPA axis activation may determine emotional disturbances characteristic of hypercortisolism, such as those seen in patients with Cushing syndrome.[22] Therefore, inflammatory cytokines released in the context of the metabolic syndrome could be the cause, rather than the consequence, of mood and other emotional problems, and thus may contribute to the high rates of depression and other emotional disturbances observed in these subjects. In accordance with this view, inflammatory cytokines released during tissue damage or treatment with interferon-α, a potent cytokine inducer, have been found to alter neurotransmitter function and produce behavioral and emotional changes similar to major depression.[79]

As described above, hyperinsulinemia may activate the SNS by acting on hypothalamic centers, which represents yet another mechanism through which the metabolic syndrome may predispose to behavioral and emotional problems. Thus, while there are several possible mechanisms through which psychosocial stress might contribute to the etiology of the metabolic syndrome, there are also several pathways in the opposite direction (ie, making the metabolic syndrome a risk factor for psychosocial stress). No matter what the predominant direction is, it is important to recognize that behavioral/emotional problems and the metabolic syndrome are interconnected and enhance each other in a feed-forward pattern.

STRESS-REDUCTION INTERVENTIONS AND THE METABOLIC SYNDROME

Stress reduction techniques and other psychosocial interventions have been shown to reduce blood pressure, body weight, and lipid levels as well as improve health behaviors (eating habits, smoking, exercise) and reduce morbidity and mortality in patients with a diagnosis of coronary heart disease.[80,81] Stress-reduction interventions appear particularly effective in reducing blood pressure in hypertensive as well as normotensive subjects,[82,83] in adults or older

patients,[84] and in children or adolescents.[82,83] Controlled trials of stress reduction to lower blood pressure have used a number of techniques, including progressive muscle relaxation,[85] transcendental meditation,[82,84] or simple breathing techniques.[83] All of these methods appear effective, although transcendental meditation may achieve larger reductions in blood pressure than other techniques: about 10 mm Hg systolic blood pressure and 6 mm Hg diastolic blood pressure, an order of magnitude comparable to drug treatment.[86,87] In addition to lowering blood pressure, stress-reduction programs decrease sympathetic arousal, improve health behaviors (eg, cease cigarette use and excessive alcohol consumption), and decrease anxiety and depression.[88–91]

The efficacy of these interventions in reducing blood pressure and other coronary heart disease risk factors confirms the importance of stress in the etiology of these conditions. No studies, however, have specifically examined the effects of stress reduction techniques in reducing insulin resistance and improving the metabolic syndrome as a whole, pointing out the need for further investigation in this area.

Behavioral Approach to Reducing Stress

The behavioral approach to the metabolic syndrome patient should be multifaceted. It should address stress-related factors that might contribute to the development of the metabolic syndrome as well as modification of behavioral risk factors, including eating habits, smoking, and exercise. Several approaches have been developed to reduce stress, all of which may have useful applications to the metabolic syndrome. These approaches can be utilized by patients with the aid of self-help books on anxiety that can be purchased in any book store. The first step is to reduce feelings of increased arousal. Patients can visualize a peaceful place, like a favorite beach or being on a mountain top, and feel themselves floating or falling. Another technique is deep breathing with muscle relaxation. The patients breath deeply for several minutes, then while they hold a breath, tighten and then relax different groups of muscles, starting from their head down to their toes. Meditation is another method of reducing stress, as discussed above. Various methods of meditation use different techniques, such as transcendental meditation, mindfulness meditation, and yoga therapy. Specific meditation training programs are available in the community.

Patients may also benefit from therapeutic help. Cognitive behavioral therapies have been shown to be useful for stress reduction.[92] Cognitive therapy usually involves a combination of exposure to distressing or upsetting images with cognitive restructuring, or improving distorted ways of thinking about things ("It is my fault; if I hadn't done things in this way, things wouldn't turn out that way."). Patients are asked to rate their feelings of distress while they imagine a stressful or upsetting experience. With repeated sessions, the stress feelings are reduced.

Finally, drug treatment may be helpful in ameliorating emotional distress in selected patients (eg, those meeting clinical criteria for depression or posttraumatic stress disorder). Medications that have proven useful for stress reduction and treatment of depression include the serotonin reuptake inhibitors paroxetine and sertraline. Given the relationship between stress, depression, and the metabolic syndrome, these medications may be helpful in improving insulin resistance and related metabolic abnormalities, although they have not been tested in this capacity.

Treatment should also be directed at the behaviors that predispose to the metabolic syndrome, such as overeating and lack of exercise. Specific behavioral programs aimed at modifying these patterns of behavior are widely available and should be useful to the metabolic syndrome patient.

CONCLUSION

There are clear bidirectional pathways linking psychosocial stress, neurohormonal abnormalities, inflammation, and the metabolic syndrome. Abnormalities in the neuroendocrine and autonomic responses typical of chronic stress appear to be a characteristic feature of this syndrome. Reduction in the level of psychosocial stress may help prevent the metabolic syndrome and may also improve the quality of life of patients with this condition.

SUMMARY

Several psychosocial factors, including depression, lower socioeconomic status, anger, and hostility, are associated with the metabolic syndrome. Patients with the metabolic syndrome show neuroendocrine abnormalities compatible with chronic stress. Psychosocial stress may contribute to the etiology of the metabolic syndrome through mechanisms involving both the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis, which mediate the neuroendocrine response to stress. Stimulation of the HPA axis, with increased cortisol production, causes accumulation of intra-abdominal adipose tissue. Catecholamines, released during SNS activation, and cortisol, resulting from HPA axis activation, have

many effects on glucose and lipid metabolism leading to impaired glucose tolerance and insulin resistance. Catecholamines stimulate the production of inflammatory cytokines in the adipose tissue and other tissues. Inflammatory cytokines, in turn, contribute to the development of insulin resistance. Psychosocial stress is a risk factor for the metabolic syndrome, but the metabolic syndrome is also a risk factor for psychosocial stress. Psychosocial interventions, particularly stress-reduction interventions, have shown efficacy in reducing blood pressure and other coronary risk factors. **HP**

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