Stress and the Metabolic Syndrome
An Interesting but Enigmatic Association

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Modern society has brought with it profound changes in lifestyle and an increased incidence of atherosclerotic vascular disease. Body weights are on the rise, diets are becoming less healthy, and people are becoming increasingly sedentary, resulting in elevations of blood pressure and metabolic alterations that increase atherothrombotic risk. In fact, obesity, insulin resistance, and diabetes are becoming a public health problem of epidemic proportions.\(^1,2\) In addition, modern society imposes demands on many that lead to difficulties in coping with their situations and more chronic “stress.” Stress engages the central nervous system and activates behavioral and physiological response patterns, such as the “defense” and “defeat” reactions, which have been beneficial for the survival of the individual and the species but may become maladaptive when stress is chronic.\(^3\) The concepts of “allostasis,” ie, adaptation to physiological states and the environment, and “allostatic load” are helpful in understanding how responses to stress may become maladaptive and damaging.\(^5\)

Stress activates the sympathoadrenal system and the hypothalamic-pituitary-adrenocortical (HPA) axis. Defense reactions involve catecholamine release, vagal withdrawal, cortisol secretion, and activation of the renin-angiotensin system; the less well characterized defeat reaction is a stimulus for cortisol production.\(^3,4\) These mediators subserve functions that help the individual during short-term stress. When stress is frequent, adaptation (coping) is lacking, the ability to shut off the stress response is deficient, or the responses to stress are inadequate and compensatory mechanisms are activated, the allostatic load may become overwhelming and the adaptive processes become maladaptive.\(^5\) Stress is involved in the pathophysiology of cardiovascular disease, as nicely demonstrated in animal experiments,\(^3,4\) but human research in this area is complicated. Thus, it is difficult to extrapolate from the laboratory environment to everyday life, to quantitate and categorize stress over time in the individual, and to pinpoint the role of stress in multifactorial cardiovascular diseases. Epidemiological studies have, nonetheless, shown associations between psychosocial factors and cardiovascular disease.\(^6\) The study by Brunner and coworkers\(^7\) in this issue of Circulation examines the role of neuroendocrine activation in the metabolic syndrome and discusses the role of psychosocial factors and stress in this context.

The “metabolic syndrome” (also referred to as “syndrome X” or the “insulin resistance syndrome”) has emerged as an important cluster of risk factors for atherosclerotic disease, the exact definition of which is less than fully agreed on.\(^8\) Common features are central (abdominal) obesity, insulin resistance/hyperinsulinemia, hypertension, and dyslipidemia (high triglycerides, low high-density lipoprotein cholesterol, and small atherogenic low-density lipoprotein particles). The metabolic syndrome is based on continuous rather than dichotomous variables, and diagnostic criteria or cut-off values vary between studies and recommendations. Insulin resistance is a key feature, and there are interesting parallels between the metabolic syndrome and type 2 diabetes.\(^10\) Abdominal obesity is associated with insulin resistance and hypertension.\(^11\) Hypertension is frequently associated with insulin resistance and other features of the metabolic syndrome, but non-obese hypertensives may also be insulin resistant.\(^11,12\) There are indications that neurohormonal activity may be causally involved in all of these conditions.\(^11,13\) Finally, obesity, insulin resistance, and diabetes are associated with a proinflammatory state, which is associated with increased cardiovascular risk.\(^2,10,14\) Important questions are if and how the different manifestations of the metabolic syndrome share underlying causes that may be causal targets for prevention or therapy, or if they merely represent a clustering of risk factors that must be dealt with one by one.

Brunner and coworkers\(^7\) performed a nested case-control study among working men aged 45 to 63 in the Whitehall II cohort to investigate associations between markers of neurohormonal and inflammatory activity and presence (or previous presence) of the metabolic syndrome. The authors applied two definitions of the metabolic syndrome to their material, and obtained similar results with the two sets of criteria. Main findings are that cases had elevated urinary excretion of cortisol metabolites and normetanephrine (a marker for sympathetic activity), lower heart rate variability (HRV), and elevated levels of interleukin-6 (IL-6) and C-reactive protein, but not of other markers of inflammatory activity (serum amyloid A and plasma fibrinogen). In multifactorial statistical analyses, psychosocial factors were found to account for 5% to 37% of the various differences between cases and controls, the interactions being strongest for normetanephrine. In addition, obesity (BMI), a diagnostic feature of the syndrome, accounted for a large part of the differences in outcome.
variables. Previous studies in the Whitehall II cohort have demonstrated an association between lower social position, which is associated with increased (dis)stress, and the metabolic syndrome. The authors conclude that neuroendocrine stress axes are activated in the metabolic syndrome and that chronic stress may be a causal factor in its development.

An important issue in epidemiological studies is whether statistical associations are causally related, and what the direction of this causality is (i.e., the “hen-and-egg” problem). Cross-sectional studies cannot establish temporal relationships between alterations that are observed, whereas longitudinal studies may establish sequences of events that indicate the direction of the putative causality. Interventions to reduce the impact of the implicated causative factor (e.g., weight reduction in obese individuals) are of considerable importance in the analysis of cause and effect in pathophysiological research.

Brunner and coworkers' attempt to shed light on the problem of causality by comparing ex-cases (defined as having had the metabolic syndrome 5 years previously) with current cases and controls. The authors believe the results support the hypothesis that psychosocial stress and neuroendocrine activation contribute causatively to the metabolic syndrome. The outcome variables, however, were very similar in ex-cases and current cases. IL-6 levels tended \( P=0.08 \) to be lower in ex-cases; several other variables show somewhat smaller differences compared with controls, but no significant differences compared with cases. The study is underpowered for the purpose of showing differences between ex-cases and cases (having fewer than 30 subjects in each group in this comparison), and thus is not conclusive. More importantly, however, there are no measurements of the ex-cases from when they were cases, and no information on what possibly made them become ex-cases (weight reduction? improved psychosocial conditions? treatment of other risk factors recognized 5 years previously?). Regression toward the mean must also be considered when subjects are reclassified at different points in time. Among the 30 current cases, 23 were also cases 5 years previously, indicating that most of them had stable alterations. The time courses for improvement of ex-cases, and recruitment of new cases are not known. In addition, the differences between cases and ex-cases are not convincing, and I fully agree with the authors that prospective studies are needed to clarify these relationships. Such studies should preferably also be interventional.

The hypothesis that neurohormonal activation is involved in the metabolic syndrome is supported by the Whitehall II data,7 as normetanephrine excretion was elevated and HRV was reduced among metabolic syndrome cases and ex-cases. Psychosocial factors contributed to both differences, but their influence was strongest for normetanephrine. Health-related behavior (diet, exercise, and smoking) influenced HRV more than normetanephrine. Interestingly, there was no trend toward any difference between cases and ex-cases for the autonomic variables. If they were of etiologic importance, other modifying factors must have accounted for the improvement of diagnostic criteria in ex-cases.

Sympathoadrenal activity is frequently evaluated by measurements of catecholamines in various ways that reflect local or systemic conditions. Sympathetic nerve activity is differentiated, and the contributions of various organs to norepinephrine levels in mixed venous or arterial plasma depend on organ size and innervation, as well as the pattern of nerve activity, which differs at rest and during mental or physical activity.15 In addition, the neuroanatomical conditions in the organ (the tightness of neuroeffector junctions, which influence the removal of norepinephrine by reuptake and/or extraneuronal metabolism), blood flow, and capillary diffusibility influence norepinephrine spillover into plasma. Thus, the factors determining norepinephrine levels in plasma are complex, and variable analytical precision adds to the complexity.15 Urinary catecholamines reflect their levels in arterial plasma (overall sympathetic activity and epinephrine secretion), but renal function may influence catecholamine excretion, and the completeness of 24-hour urine sampling is often a problem. Thus, it is advantageous to relate catecholamine excretion to creatinine excretion. Brunner et al7 measured the 24-hour urinary excretions of the extraneurally formed (O-methylated) catecholamine metabolites normetanephrine and metanephrine; the method used and the robustness of relationships between the O-methylated metabolites and their parent compounds are not indicated. It is possible that the relationship between norepinephrine and normetanephrine changes with increasing obesity. Previous studies, however, indicate that sympathetic activity (norepinephrine turnover) is increased in obesity.11

Increased peripheral sympathetic nerve activity may contribute to several aspects of the metabolic syndrome.11,12 Reduced nutritive blood flow to skeletal muscle will attenuate glucose uptake and thus reduce insulin sensitivity. Sympathetically mediated lipolysis will increase free fatty acids and glycerol and thereby increase gluconeogenesis. Increased skeletal muscle sympathetic activity may also reduce the accessibility of lipoprotein lipase in skeletal muscle via decreased nutritive flow, and thus contribute to the dyslipidemia. Insulin has direct vasodilator effects, but may also increase sympathetic nerve activity via a central mechanism of action, thereby providing another link between the metabolic syndrome and sympathetic nerve activity. The hemodynamic model of insulin resistance and findings that nonbese hypertensives may also be insulin resistant suggest that increased sympathetic nerve activity may be causative rather than adaptive.11,12 Furthermore, increased sympathetic nerve activity may contribute to the development of hypertension in other, nonmetabolic ways.12 Thus, the findings of elevated normetanephrine as a statistically independent factor in metabolic syndrome cases in the Whitehall study7 are in agreement with, but do not prove, an etiologic role for the sympathetic nervous system.

HRV was reduced, and heart rates were elevated in metabolic syndrome cases and ex-cases, indicating an altered autonomic balance regulating the sinus node.7 This is in agreement with previous findings that were also based on short-term recordings of HRV at rest.16 The relative roles of vagal withdrawal and cardiac sympathetic activation are, however, difficult to evaluate because vagal activity influences all components of HRV. The high frequency (HF) component is governed by vagal activity, but the low/very low frequency components (LF and VLF) are also influenced
by vagal activity (for references, see 17). The LF/HF ratio is sometimes taken as an index of cardiac sympathetic activity, but this is uncertain. In the Whitehall study, all HRV indices except the LF/HF ratio were affected, which might point to a predominantly vagal alteration. In our experience, however, ambulatory HRV and simultaneously determined urinary norepinephrine excretion were correlated for all frequency domains of HRV but not for the LF/HF ratio. Prognostic implications were also found among patients with stable angina pectoris for all frequency domains of HRV, but not for the LF/HF ratio or for catecholamines in urine or plasma, and there was no prognostic advantage of metoprolol compared with verapamil treatment. Thus, the HRV findings in the present7 and previous studies may mainly reflect alterations of cardiac vagal activity. Vagal withdrawal is involved in the defense reaction pattern of physiological responses, and it would be interesting to also evaluate ambulatory HRV to assess the degrees of arousal (stress) in the everyday life of subjects with the metabolic syndrome compared with controls.

Urinary cortisol metabolite excretion was increased in metabolic syndrome cases, whereas salivary cortisol measurements in the afternoon and evening revealed no difference between cases and controls.7 Previous studies,13 however, indicate that morning and mid-day salivary measurements should be performed to reveal altered cortisol secretion and changes in cortisol reactivity to stress and meals in the metabolic syndrome. These investigators also found a subgroup of individuals with central obesity and depressed function of the HPA axis, having low cortisol secretion and impaired suppressibility by dexamethasone, and speculate that some individuals with the metabolic syndrome may have “burned-out” function of the HPA axis due to chronic stress.13 Interestingly, there is also genetic variation in the glucocorticoid receptors mediating central feedback in the HPA axis that is related to abdominal obesity.14 The studies of Björntorp and Rosmond13 reveal complex relationships between HPA axis function, obesity, and metabolic parameters that are compatible with an etiologic role for stress-induced glucocorticoid secretion in the metabolic syndrome; however, further proof of the theory is needed.15 The complexity of this field of research is underscored by findings of altered glucocorticoid metabolism in obesity and local generation of cortisol in visceral adipose tissue.19 The elevation of cortisol metabolite excretion among Whitehall cases is in line with previous findings,13 and there are interesting associations between psychosocial factors, stress, and the HPA axis that may well be of etiologic importance in the metabolic syndrome.

The metabolic syndrome is complex, and a unifying concept with one treatable cause may not emerge. Underlying contributors may be identified by factor analyses in large cohorts. Factor analyses have given the overall impression that 3 to 4 underlying phenotypes may explain the metabolic syndrome, including obesity-hyperinsulinemia, dyslipidemia, impaired glucose tolerance, and hypertension.20 Hypertension is more loosely associated than other dimensions of the metabolic syndrome.20 How psychosocial factors fit into this overall picture is not entirely clear, but the Whitehall studies6,7 may provide valuable clues. There is a need for longitudinal and interventional studies to further clarify relationships between psychosocial factors, neuroendocrine activation, and the various features of the metabolic syndrome.

Nonpharmacological prevention and therapy (weight loss, exercise, dietary intervention) are obviously an attractive way to deal with the metabolic syndrome, especially in view of its large and growing prevalence. The need for multiple-drug treatment to correct each of the components of the metabolic syndrome should be reduced to a minimum, but drugs will still be needed. Psychosocial interventions to reduce stress and improve working conditions (to reduce inappropriate demands and improve control and job satisfaction) and social support are, of course, also on the “wish list,” but this is easier said than done. Society faces a tough challenge regarding the metabolic syndrome and its medical consequences in the future.

References


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