Focused Perspectives

Metabolic Syndrome and Vascular Disease
Is Nature or Nurture Leading the New Epidemic of Cardiovascular Disease?
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Whereas the previous epidemic of coronary heart disease (CHD) between 1910 and the 1960s was largely attributed to increased intake of saturated fat, it is quite plausible that the current epidemic of obesity and metabolic syndrome (MS) will lead the new epidemic of CHD, not only in the United States but throughout the world. During the previous epidemic, the populations of the Western and industrialized nations were those predominantly affected; however, on the basis of the fact that obesity is reaching epidemic proportions in most parts of the world, the new epidemic of CHD related to obesity and MS is likely to impose an unprecedented global burden of cardiovascular (CV) disease (CVD). Although the precise reason for the global epidemic of obesity and MS has not been established, there is general agreement that environmental factors and changes in lifestyle are major contributors. It is thought that common changes in people’s behavior, which lead to consumption of high-calorie, refined food in association with decreased levels of physical activity, are largely responsible for obesity and MS. Because of their strong association with CVD, both obesity and MS are major public health problems.

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Because MS is associated with increased risk of CHD, it has also been called the “Deadly Quartet” or cardiovascular dysmetabolic syndrome.1,2 MS comprises a cluster of abnormalities that occur as a result of perturbations in multiple metabolic pathways, leading to hyperinsulinemia, insulin resistance (IR), hyperglycemia, atherogenic dyslipidemia, and hypertension. Recent findings also suggest that MS is a proinflammatory condition, as characterized by elevations of serum high-sensitivity C-reactive protein.3,4 There is now evidence that several atherothrombotic factors also are increased in MS; these include increased levels of plasminogen activator inhibitor-1, serum fibrinogen, von Willebrand factor, factor VII, and thrombin, as well as increased platelet activation and aggregation.5 All of these abnormalities lead to increased risk of CVD, especially CHD. Several recent studies have demonstrated that the presence of MS is associated with significant increases in the risk of CV events and cardiac mortality.6–8 The article by Ninomiya et al6 in the present issue of Circulation provides further evidence to support the strong association between MS and CVD.

MS and CVD
In their study, Ninomiya et al6 have evaluated the association between MS and history of myocardial infarction (MI) and/or stroke among the participants in the Third National Health and Nutrition Examination Survey (NHANES III). On the basis of participants’ self-reported histories, they found that the presence of MS was associated with increased risk of MI, stroke, and MI/stroke.6 These findings give further credence to the prevailing thinking that the presence of MS identifies a cohort of the population that is at substantial risk of CVD.

There are several important findings in the article by Ninomiya et al6 that deserve mention. First, it is important to note that the strong association reported in their study is based on self-reported history and, as the authors point out, it is likely that the exact incidence of MI was higher.6 This is quite likely as fatal events were obviously not included, and silent MIs were not detected because of the lack of available ECG data.6 It is also important to note that in this study, the comparison of various components of MS between those with and those without MI/stroke revealed the strongest association of CV events with high triglyceride levels, especially in women. These findings are of clinical relevance because of the fact that, despite available data supporting its role, hypertriglyceridemia is not always regarded as a major contributor for the risk of CHD.6 It is also important because the prevalence of MS is significantly higher in women of certain minority subgroups, such as Hispanics and South Asian immigrants, in whom there is the strongest association between hypertriglyceridemia and CHD. These findings are important because hypertriglyceridemia can be one of the earliest abnormalities (even before hyperglycemia) present in subjects with MS. The clinician should consider paying closer attention to levels of serum triglyceride in susceptible individuals. Another important finding of the present study is the similar risk of MI/stroke in MS subjects with or without a history of diabetes, which emphasizes the point that risk of CV events is increased regardless of incident hyperglycemia.

Perhaps the most disturbing finding of the present study is the lack of association between waist circumference (WC) and risk of MI/stroke. Because truncal obesity (indicating increased visceral adipose tissue) is considered to be a central and hallmark abnormality in MS and previous studies have shown strong correlations, such lack of association raises several possibilities and questions. First, it is conceivable that WC is a better predictor in younger individuals and, because the patients with
The prevalence of MS is increasing globally, it is critical to design large prospective studies to examine the relationship between the components of MS and risk of diabetes. During the 5-year observational period, the risk of incident CVD was found to increase with the number of components of MS and increased by >5-fold in those with 4 or more components compared with those with only 1 component. These data are clinically important; they emphasize that the risk of CVD is increased in incremental fashion with various components of MS and give credence to the requirement of ≥3 components (as stated in the ATP III definition) for establishing diagnosis of MS. However, the strong association between MS and CVD might not be universal. It is known that, although black men have higher prevalence of MS, their risk of MI is not proportionally increased. The recent data from the Strong Heart study in nondiabetic American Indians with MS and IR shed further light in this area. Of the total 2283 American Indian nondiabetic subjects free of CVD at baseline, 798 (35%) had MS, and 181 (7.9%) developed CVD over an ≈8-year follow-up period. IR was assessed by using the homeostasis model assessment (HOMA-IR). Although various components of MS and risk of diabetes increased across the tertiles of HOMA-IR, the risk of CVD did not increase either as a function of HOMA-IR or MS. The results of this study emphasize the importance of assessing the risk attributes of MS in various populations, as the risk might be inordinately higher in some (eg, South Asian Indians), whereas it might not be affected in others, such as the one observed in the Strong Heart study. Because the overall prevalence of MS is increasing globally, it is critical to design large prospective studies to examine the relationship between MS and CVD in various ethnic subgroups and different populations across the world.

Pathophysiological Considerations

The association between MS and CVD raises important questions about the underlying pathophysiological process(es), especially for designing targeted therapeutic interventions. It is generally accepted that IR is the primary underlying abnormality that precedes and contributes to most metabolic and other perturbations seen in MS. Although obesity in general and truncal obesity in particular are thought to be main predisposing factors for MS, how they relate to IR is not precisely established, because not all obese people develop IR and not all MS patients are obese. It also has been proposed that IR and MS occur as a result of lipotoxicity in various organs, including pancreas, skeletal muscle, and myocardium. There is also emerging evidence that suggests that adipocytes secrete and/or influence actions of a variety of cytokines, including adiponectin, leptin, tissue factor, angiotensinogen, lipoprotein lipase, interleukin-6, plasminogen activator inhibitor-1, and many others. Thus, it is conceivable that the increased visceral adiposity (truncal obesity) is responsible for IR by lipotoxicity due to release of free fatty acids in the portal circulation, as well as by the actions of various cytokines released or modulated by adipocytes. It also has been shown that there is significant increase in vascular oxidative stress in MS, and many subjects with MS have evidence of endothelial dysfunction at an early stage of the process. Several studies also have emphasized that MS is a proinflammatory condition. This is largely based on the elevated levels of high-sensitivity C-reactive protein; however, the precise mechanism by which this occurs has not been elucidated. Because many of the abnormalities associated with MS can themselves cause inflammatory reaction at the vascular level, it is conceivable that it is an indirect effect, or it is also possible that IR and MS themselves may occur as a result of inflammatory reactions. Whatever the underlying precise mechanism for MS might be, it is reasonable to emphasize that IR is a major contributor for various components of MS.

MS and Obesity Epidemic: Is It Nature or Nurture?

It is fairly clear that the prevalence of MS goes hand in hand with the prevalence of obesity. As evidenced by the data from NHANES III, both the prevalence of obesity and MS have significantly increased in the US population. During the past 20 years, the prevalence of obesity has been constantly increasing and has now reached epidemic proportions. It is estimated that >60% of adults (20 to 74 years of age) in the United States are either obese or overweight (27% obese, 34% overweight). There is an alarming increase in the prevalence of overweight/obesity among children in the United States. During the past 2 decades, the prevalence of obesity has nearly doubled in children and tripled in adolescents. This increase has been more dramatic in black and Hispanic children and adolescents. These figures are alarming and should alert public health authorities to the health impact of these trends 20 to 30 years down the road, as it is known that 70% of obese adolescents remain obese as adults, and many will develop MS and diabetes mellitus. The data from NHANES III have revealed a parallel increase in the prevalence of MS. The overall prevalence of MS is 24% in adults and progressively increases with age, reaching nearly 45% for those >60 years of age. The importance of these figures is highlighted by the most recent data from Human Health Services, which announced that, between 1997 and 2002, the number of Americans with diabetes has increased by 27%. The greatest increase was in young adults. A recent article by the US
Centers for Disease Control and Prevention estimated that children born in 2000 will have a 53% to 39% lifetime risk of developing diabetes and emphasized that the highest risk will be for Hispanic females, who will have an ~53% lifetime risk (ie, 1 of every 2 persons). These data are alarming not only because of the risk of diabetes but also because of the obvious impact of epidemic proportions on the incidence of CVD.6–8

The important and obvious questions are, "Why is there such an unprecedented increase in obesity and MS? Is it nature (genetic) or nurture (environmental influences)?" Although the precise answer to this question is not known, it seems that it is probably both, to some extent; however, there is clearly a much bigger and unquestionable contribution of environmental factors. A lot of effort has been directed toward defining the precise genetic abnormalities related to obesity and MS.13 Several candidate genes have been proposed and include genes regulating peroxisome proliferators–activated receptor γ, leptin, adiponectin, glucocorticoids, lipoprotein lipase, CD-36, sterol regulatory element–binding protein 1C, and 11β-hydroxysterol dehydrogenase type 1 gene.13 There is also the prevailing concept of the “thrifty-gene” hypothesis. No single gene has been incriminated as the most important one, and it is likely to be polygenic abnormalities that still require environmental influences to manifest.13 Thus, the role of environmental influences seems to be a dominant factor. It is clear that the epidemic of obesity is related to present lifestyles that emphasize consumption of high-caloric food and is further complicated by the ever-popular mega-sizing of fast-food items and high-carb drinks. This is exacerbated by the lack of physical activity that results from television, Nintendo, and computer infatuation, especially in the younger generation. These lifestyle patterns lead to energy imbalance in the body due to caloric intake far in excess of caloric expenditure, which leads to adiposity and obesity. Public health trends and lifestyle patterns clearly suggest that nurture is the biggest contributor to the epidemic, and serious attention and public health measures are needed to curb this epidemic of obesity, MS, and CVD.

**Therapeutic Interventions**

Clearly, the first step in curbing the epidemic of MS and the subsequent risk of CVD would be to identify individuals at the earliest possible stage of the syndrome. This can be done by simple physical examination and assessment of routine laboratory findings, which should include measurement of fasting glucose and lipid profile.14 Once a person is identified as having MS, it is important to emphasize the significance of MS to the individual, particularly highlighting the risk of developing diabetes and CVD.

The most important therapeutic intervention effective in MS subjects is lifestyle change, with the focus on modest weight reduction and regular leisure-time physical activities. The Diabetes Prevention Programs in the United States and the Finnish diabetes prevention study have both shown that as little as a 10% reduction in weight and regular physical activity can reduce the risk of developing diabetes by nearly 50%.15,16 These measures would also reduce the risk of CVD in the future. Some patients would require the aid of pharmacological therapy, such as insulin-sensitizing agents. The results of ongoing trials should be able to identify the most effective pharmacological interventions; however, until then, public health measures should be directed toward promoting therapeutic lifestyle changes. This would be a much more cost-effective strategy than to pay for all the cardiac procedures and interventions that will be required in the future for a majority of those with obesity, MS, and diabetes.

**A Call for Action**

It is well established that obesity and MS are truly affecting the US population in epidemic proportions. There is a need to allot more research funds, as currently only 1% of the National Institutes of Health budget is spent on obesity and related research programs. There is an urgent need to institute serious and focused public health measures designed to curb this epidemic with the hope of preventing the lurking epidemic of CVD on the horizon. It is important to emphasize that the government should take serious steps toward public education, weight reduction programs, and exercise facilities. This should be a matter of urgent attention. Because of the potential serious public health impact, there should be national plans (to curb obesity) that are given as much importance as the plans on terrorism and homeland security. It is most appropriate to remember here that an ounce of prevention is better than a pound of cure.

**References**

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