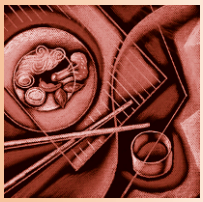

The Metabolic Syndrome

A Common Hyperinsulinemic Disorder With Severe Health Effects

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Metabolic syndrome is a recently defined medical disorder and now considered to be an epidemic. It includes several diseases stemming typically from overweight or obesity. Clinical characteristics include abnormal blood lipids, insulin resistance, abdominal obesity, high blood pressure (hypertension), and low serum high-density lipoprotein cholesterol. Individuals with this syndrome are typically not treated for any of their abnormalities until they are seriously affected by one of the diseases. Metabolic syndrome is more common in men and is becoming recognized even among children and adolescents. Metabolic syndrome arises because of altered metabolic pathways, including insulin resistance, and excessive consumption of food energy not balanced by energy expenditure in physical activities. The underlying pathophysiology is an abnormality in the metabolism of triglycerides involving fat cells, muscle cells, and other extrahepatic cells. The major diseases that result from these abnormalities are obesity, hypertension, diabetes mellitus type 2, and cardiovascular diseases (coronary heart disease and stroke). Prevention is best, but when the syndrome exists, treatment focuses on weight loss to achieve a healthy body weight. Nutr Today. 2006;41(3):115-122

A growing epidemic of metabolic syndrome, also known previously as Syndrome X, is facing our nation today. This complex disorder may be responsible for much of our chronic disease burden. It is caused primarily by excessive energy intake from all macronutrients and limited energy expenditure in daily physical activities, that is, an energy imbalance. The syndrome affects as many as 20 million adults in the United States.[1,2]

Syndrome X is a name first coined by Reaven.[3] It represents a cluster of risk factors, usually overweight or obesity, hypertension, and hyperinsulinemia, that contributes to diabetes mellitus type 2 (type 2 diabetes; DM2), cardiovascular diseases, and others with long-term latency periods and serious health consequences. This constellation of risk factors probably begins during childhood in many individuals when unhealthy eating habits may start and physical activity dwindles. Clinical criteria for diagnosing metabolic syndrome in adults are based on the Adult Treatment Panel III of the National Cholesterol Education Program[4] (Table 1). Adults, especially postmenopausal women, typically have excess body fat around the belly.

Overweight prevalence and DM2 increased in the last decade in the United States,[5,6] and these increased rates gave rise to an epidemic of this syndrome.[2] Increasing public awareness is a first step in the mounting of preventive public health campaigns to alleviate the syndrome and reduce the resulting related chronic diseases. This review provides the physiological and biochemical background for metabolic syndrome and relates its pathophysiology to the chronic diseases that represent a full-blown constellation of metabolic syndrome. Some treatment measures are also covered.

Although the focus of this review is on the excessive intake of macronutrients, metabolic syndrome may also adversely affect micronutrient status, especially through the development of DM2, and thus, it may cause more human dysfunction than previously recognized.

The deadly DROP quartet characterizes metabolic syndrome.

Table 1. Adult Clinical Criteria for the Metabolic Syndrome*

Variable	Laboratory Value	
	Men	Women
Serum triglycerides, mg/dL	≥150	≥150
HDL-C, mg/dL	<40	<50
Fasting serum glucose, mg/dL	≥100	≥100
Blood pressure, mm Hg	≥130/85	≥130/85
Waist circumference, cm	>102	>88

*Defined as at least 3 of the criteria presented above (Adult Treatment Panel III, National Cholesterol Education Program[4]).

Metabolic Syndrome Features

Metabolic syndrome commonly features 4 major risk factors, formerly referred to as "The Deadly Quartet." The acronym DROP is sometimes used to describe this deadly quartet: *d*yslipidemia or blood lipid abnormalities (increased triglycerides, low-density lipoprotein-cholesterol [LDL-C], and total cholesterol), *r*esistance to insulin or impaired glucose tolerance, *o*verweight or obesity (truncal), and increased blood *p*ressure (hypertension).[7] A fifth criterion, serum HDL-C less than 40–50 mg/dL (see Table 1), has been recently added. Similar risk factors exist for both DM2 and coronary heart disease (CHD).

Associated Diseases

Typical overweight or obesity is the condition that triggers the development of other diseases. Body mass index (BMI) standard is 25 to 29.9 for overweight and 30 or above for obesity. The android or abdominal distribution of fat (as shown by a waist-to-hip ratio of ≥1.0 in men or ≥0.8 in women) relates more strongly to this syndrome than does the typical gynoid (buttocks and hips) distribution of fat (low waist-to-hip ratio). Localization of fat in central stores likely plays a role in this syndrome.

Metabolic syndrome–associated diseases include obesity, DM2, hypertension, and cardiovascular diseases, including CHD and stroke. Nonalcoholic steatohepatitis (NASH) is a condition resulting from excessive fat accumulation in the liver resulting from too great a consumption of energy as part of metabolic syndrome. In addition, colon cancer, polycystic ovary syndrome (PCOS), and chronic kidney disease may also be potentiated by obesity and hyperinsulinemia. Figure 1 shows that overweight or obesity generates hyperinsulinemia, and it, in turn, serves primarily as the trigger for the many potential adverse effects of metabolic syndrome.

Overweight/Obesity

There is an obesity epidemic here and abroad.[8] Approximately 64% of adults are overweight (body mass index between 25 and <30) or obese (body mass index of ≥30), and this percentage has been increasing since the early 1990s. Greater rates of overweight and obesity occur in Hispanic and African American subpopulations in the United States, reaching well over 50% overweight and approaching 50% obesity among older women in these 2 groups; the rates for white women are also high.[5,6] Obese people of lower social economic status and with less education are less likely to be advised by healthcare professionals to lose weight.[9,10]

The pathophysiology of overweight/obesity is caused by excess triglyceride (triacylglycerol or TAG) accumulation in fat tissues scattered throughout the body. Patients with an android distribution of fat, that is, abdominal fat, have more insulin resistance than do those with gynoid distribution of fat in the buttocks and thighs. Whether this differential fat distribution results from the intrinsic properties of the 2 locations of fat or to other metabolic factors is not clearly established.[11] It is clear, however, that insulin resistance results from the excessive android fat distribution.

Whole-body insulin resistance in overweight and obesity is caused partly by the inability of insulin to appropriately enhance glucose uptake in skeletal muscle. The Randle hypothesis, originally proposed by its namesake in 1963, can be broadly interpreted to mean that an increase in the availability of fatty acids or TAGs as a fuel leads to the rejection of glucose as a fuel in skeletal muscle, that is, to insulin resistance. In such

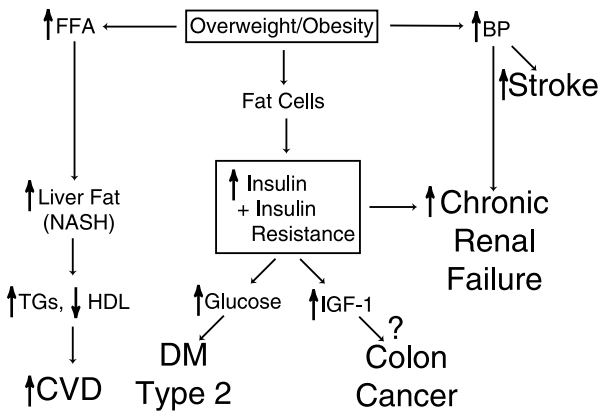

Figure 1. Metabolic syndrome and its consequential diseases. Start with overweight/obesity and follow the arrows across and down. An increase in insulin and then an increase in insulin resistance are central elements of this syndrome. BP indicates blood pressure; FFA, free fatty acids; NASH, nonalcoholic steatohepatitis; TGs, triglycerides or triacylglycerols; IGF-1, insulin-like growth factor-1; CVD, cardiovascular disease.

broad terms, the Randle hypothesis continues to be valid, although its explanation, originally cast in terms of enzyme regulation, has been updated to involve long-chain fatty acid and TAG accumulation in muscle cells (myocytes) in addition to fat tissue, as well as changes in intracellular signaling pathways and transcriptional regulation.[12] Metabolic inflexibility is an impaired ability of the biochemical pathways of muscle cells to respond appropriately to changing serum insulin concentrations by shifting from fatty acid oxidation in the postabsorptive state to glucose oxidation in the absorptive (postprandial) state.[13] The end result of insulin resistance in both adipocytes and muscle cells is decreased uptake of glucose from the blood. Limited uptake results because of the reduced translocation and distribution of glucose membrane transporters, especially the GLUT-4 porter, into the plasma membrane; as a consequence, glucose and insulin concentrations gradually increase over time.[14,15]

Insulin resistance causes a loss of suppression of fatty acid release from adipose tissue stores into the blood. These fatty acids are transported to the liver in the unesterified ("free") state bound to albumin. In the liver, these fatty acids are re-esterified to become TAGs. Hyperinsulinemia supports the hepatic production of triglyceride-rich very low density lipoproteins, which become increased in blood and in turn deliver the excess fatty acids as TAGs back to adipocytes,[16] and creates a vicious cycle. The shuttling of fatty acids between the liver and fat cells is another indicator of altered fat metabolism and glucose intolerance.[17] Excessive dietary energy, whether from fats, carbohydrates, proteins, or alcohol, contributes to this abnormality in fat metabolism. The resultant increase in TAGs is a key indicator for metabolic syndrome.

In obesity, adipocytes do not respond normally, and insulin can no longer suppress fat (TAG) degradation and mobilization nor can insulin augment fat storage. Serum TAGs are increased because of increased hepatic production and reduced uptake in adipose tissue. As a result, TAGs are deposited in other tissues, such as the skeletal muscle and hepatic tissue (NASH). Obesity therefore affects insulin resistance and increases the risk for development of metabolic syndrome involving other organ systems, especially cardiovascular tissues.

In summary, obesity is a critical antecedent in the development of insulin resistance, dyslipidemia, and hypertension and, therefore, in metabolic syndrome. The interplay of obesity and genetic susceptibility with these metabolic and hemodynamic abnormalities determines the likelihood of developing the clustering pattern of disorders of metabolic syndrome. As yet, the molecular mechanisms and the specific gene culprits that may explain the link between the environment and heritable factors that result in the progression from obesity to CVD and other chronic diseases[17] are unknown.

Obesity and type 2 diabetes are both present in epidemic proportions.

Hyperinsulinemia, Impaired Glucose Tolerance, and DM2

In 2002, diabetes mellitus was the sixth leading cause of death by disease in the United States and is present in epidemic proportions. Of the almost 20 million people with diabetes in the United States (7% of the population), an estimated 25% are unaware that they have it; 90% to 95% of individuals with diabetes have DM2.[18] The age-adjusted prevalence of diagnosed diabetes increased by 19% between 1980 and 1996, and this is closely linked to the increase in rates of obesity. The rate of increase in the prevalence of DM2 was highest among black men (50% increase) and lowest among white women (10% increase).[19]

Type 2 diabetes is the leading cause of blindness in adults in the United States aged 20 to 74 years. In 2002, approximately 44% of new cases of chronic kidney disease had DM2.[18] Unfortunately, the trend is only worsening. Having diabetes also greatly increases the risk of non-traumatic leg amputation, and 60% of these amputations occur in patients with DM2. African Americans and Hispanic Americans are almost twice as likely to develop DM2 as whites do, and the Native American population also has a high prevalence, that is, 12.8% versus 7.0% in the general population. Prevalence is highest in American Indians living in southern Arizona (27.6%) and in the southern states (26.7%), whereas the lowest rate is for Alaskan Native Americans (8.1%).[18]

Cardiovascular diseases of one type or another are found in 65% of deaths due to diabetes. People with this disease are 2 to 4 times more likely to suffer from heart disease or stroke.[18] The atherosclerotic process is accelerated in metabolic syndrome and in DM2 because of the presence of multiple metabolic abnormalities. In insulin resistance, atherosclerotic plaque formation may be accelerated.[20]

The development of DM2 typically begins with insulin resistance, which is later compounded by the inability of pancreatic beta (β or B) cells to maintain high insulin secretory rates. Insulin resistance alone, however, has been linked with an increased risk for the development of CVD. People with increased insulin levels have higher

levels of small, dense LDL-C, which is more atherogenic than larger, less dense LDL-C. Hyperinsulinemia also results in damage to the endothelial lining of arteries and arterioles, which impairs vasodilation and blood flow, and permits an increase in clot formation.[21,22] Thus, a number of potential mechanisms exist by which increased blood insulin concentrations contribute to the development of CVD, an important component of metabolic syndrome.

In summary, the current trend of increasing frequency of obesity and sedentary lifestyles in the US population makes it probable that diabetes will continue to be a major healthcare problem among all people in future decades. Although preventing the development of diabetes is optimal, treatment of the disease once it develops is critical. Because DM2 can result to heart, kidney, and neural diseases, and retinal damage, experts think that the better serum glucose levels are controlled, the less likely these complications will develop. Improvement of blood glucose control significantly reduced an aggregate end point of any diabetes-related complication and a combined end point of clinical retinopathy and nephropathy complications in the United Kingdom Prospective Diabetes Study.[23] By simply lowering blood sugar, the risks of retinopathy and nephropathy (renal damage) may be greatly reduced, and neuropathy, although not examined in this study, may also be lowered.[23]

Hypertension and stroke are also very common.

Hypertension and Stroke

Hypertension is directly responsible for almost 50,000 deaths in the United States and contributes to over 200,000 deaths from other morbidities. Almost 25% of all adults have high blood pressure, and many of these individuals are unaware of their condition. Since 1989, the mortality rate from hypertension has increased more than 20%. This condition is more prevalent among people of lower socioeconomic status. Adult African American men have a 4-fold greater rate of hypertension than do white adults. In elderly people, more than 75% of women and 64% of men older than 75 years are hypertensive. Hypertension results in 17.2 million office visits each year[24] and more than 1 million visits to hospital outpatient departments in 2002.[25] Because overweight and obesity directly contribute to increases in blood pressure, this factor alone has become a major contributor to hypertension.

Although insulin resistance is considered an early event in the development of metabolic syndrome, uncertainty remains over whether it contributes to hypertension. A study of Atherosclerosis Risk in Communities found a significant association between increased fasting insulin and hypertension in white Americans of European heritage, but not in African Americans.[26] Body mass index and waist circumference only partly explained the correlation. However, increased fasting insulin was more closely associated with hypertension, as part of metabolic syndrome, than hypertension alone. These findings may help explain why previous studies have yielded inconclusive results.[26]

The mechanisms linking insulin resistance to hypertension include sympathetic nervous system activity, endothelial damage, and other altered functions. An increase in sympathetic nervous system activity[27–30] may contribute to cardiovascular risk in approximately 30% of hypertensive individuals who have increased sympathetic tone.[29] Stimulation of the sympathetic nervous system, in turn, increases the responses of the renin-angiotensin-aldosterone system, which initiates renal sodium reabsorption and increases heart rate, stroke volume, and peripheral vascular disease. Cardiac and vascular hypertrophy both occur, which is significant because left ventricle hypertrophy alone is strongly associated with death from CVD. Because blood pressure is a function of cardiac output and peripheral resistance, the development of hypertension is accelerated.

The diseases of affluence in modern societies are tied to overnutrition and to factors such as psychosocial stress, socioeconomic hardships, and physical inactivity. The hypothesis put forth by Bjorntorp et al[30] is that the physical and psychological stresses of modern life serve to continuously engage limbic-hypothalamic centers, resulting in hypertension and metabolic syndrome. Individual differences in incidence could perhaps be explained by genetic susceptibility. Many of the blood-flow–related abnormalities that cluster in hypertensive subjects are triggered by overactivity of the sympathetic nervous system.[31] The pathogenesis of hypertension includes overreaction to psychosocial stimuli by the hypothalamic and sympathohormonal centers.

In summary, adiposity is a complicating factor when attempting to tease out the contribution of hypertension to metabolic syndrome. Obesity increases sympathetic nervous system activity, increases serum concentrations of insulin and other hormones or factors, and decreases vasodilation. All of these contribute to the development of hypertension, but body weight itself remains a major factor in the increase in blood pressure. Mechanistic explanations for the development of hypertension remain uncertain.

Altered Blood Lipids and CHD

Major changes in blood lipids and lipoproteins accompany the development of metabolic syndrome in most adults and, to a lesser extent, in children. The classic modifications occurring in most individuals with significant weight gain are an increase in serum TAGs and a decline in HDL-C. Low-density lipoprotein particles may also become smaller and denser, but age, sex, race, and ethnicity may reduce the risk of these modifications. Hypertriglyceridemia may be the initial perturbation that leads to other lipoprotein abnormalities via the exchange of triglyceride for cholesteryl ester in HDL and LDL particles, and subsequent action of hepatic lipase on HDL and LDL.[14] High blood triglyceride, low HDL, and small LDL particles have all been associated with increased cardiovascular risk.[20] In general, an increase in carotid intimal-medial wall thickness is associated with diagnoses of both CHD and metabolic syndrome.[32] Furthermore, a substantial percentage of US participants 50 years of age and older in the NHANES III survey, who were predominantly overweight, also had CHD, DM2, and, therefore, metabolic syndrome.[33]

The prevention of CHD in metabolic syndrome has recently been reviewed.[34,35] The prevention of CHD includes restriction of energy intake to satisfy energy expenditures in activity, reduction of total fat and saturated fat intake but increase in unsaturated fat intake, and increase in intake of fruits, vegetables, and whole grains. These same general dietary recommendations also serve for metabolic syndrome.

Other Potential Diseases of the Metabolic Syndrome

Some investigators have suggested that colon cancer, chronic renal disease, and others may result from the alterations of fat and carbohydrate metabolism or other pathways relating to energy regulation. Similar pathophysiologic changes in fat metabolism are speculated to occur in the cells of these tissues as in the liver and fat cells.

Nonalcoholic Steatohepatitis

Steatohepatitis, or fat accumulation by liver cells, typically occurs when an excess of dietary energy, not simply fat, is consumed. This form of fatty liver, that is, NASH, is not associated with alcohol consumption. Hepatocytes store newly synthesized triglycerides in cytoplasmic droplets, which continue to increase in number and size if excess energy intake continues. If energy intake declines over time, the droplets will decrease in both size and number over time. The pattern of fat accumulation in liver tissue is a concomitant of the overweight- and hyperinsulinemia-driven metabolic syndrome.[36] The mechanism for increased stores may relate both to insulin resistance, which leads to the steatohepatitis and to oxidative stress, and its subsequent inflammatory responses.[37,38]

Colon Cancer

At least 1 recent report has speculated that colon cancer is associated with metabolic syndrome.[39] An increase in insulin-like growth factor-1 has been identified as an important contributor to cancer in individuals who have excess body fat. Mechanisms remain poorly understood, but insulin resistance seems to be the critical variable that triggers loss of regulation of cell division. Colonic epithelial cells may undergo some of same steps of dysregulation as other cell types in response to hyperinsulinemia and active insulin-like growth factor-1.[40]

Chronic Kidney Disease

Many cases of end-stage renal disease are now considered to result from renal abnormalities of metabolic syndrome, especially from hyperinsulinemia and hypertension.[41,42] Almost 8 million people in the United States have the potential to develop chronic kidney disease because of significantly reduced renal function. Mechanisms are speculated to include damage to the glomeruli and to the cluster of distal tubular cells that secrete renin and initiate the increase in aldosterone production and, hence, sodium and water retention. Insulin resistance may therefore trigger the abnormal cellular events in the renal tubules that lead to hypertension.

Polycystic Ovary Syndrome

The epidemic of polycystic ovary has remained unexplained until recently. Polycystic ovary syndrome is characterized by insulin resistance, dyslipidemia, and truncal obesity.[43] Weight loss helps reduce the severity of these factors and may also reduce the prevalence of the syndrome. Both DM2 and CHD are higher in women with these characteristics than in women without them.[44] Most women with PCOS are overweight or obese, insulin resistant, and have or are going to have metabolic syndrome.[45] A case of an adolescent girl with PCOS and the onset of metabolic syndrome was recently reported.[46]

Dietary Treatment of the Metabolic Syndrome

Many people are overweight or obese,[6] and this, along with excess abdominal fat, has been associated with several disease and metabolic abnormalities, including metabolic syndrome.[47] Treatment is weight reduction through dietary interventions and other lifestyle

Table 2. Dietary Treatment Recommendations for the Metabolic Syndrome

Balance energy intake and expenditure in physical activities
Increase intake of foods high in fiber, especially viscous fiber
Decrease intake of highly refined and processed foods
Decrease intake of high-glycemic-index foods
Decrease intake of saturated fats and *trans*-fats and substitute monounsaturated fats and omega-3 polyunsaturated fats
Include plant stanols/sterols in the diet
Avoid or limit alcohol if triglycerides high

modifications such as exercise.[47,48] Referral to a registered dietitian or other qualified nutrition professional may be helpful.

Modest weight loss of 5% to 10% of the initial body weight helps to decrease insulin resistance, improves glycemic control in individuals with DM2, decreases blood pressure, and decreases serum triglycerides and total cholesterol.[49] Engaging in a regular pattern of physical activity can aid in weight reduction and plays an important role in the maintenance of weight loss.[49] An energy intake greater than energy expenditure is a predictor of weight gain, and thus, some reduction in energy intake is usually needed. Implementation of an appropriate diet and exercise program may require several months to become well established and to generate beneficial results. Lifestyle changes should be introduced gradually and maintained over extended periods for long-term health benefits.

Several dietary recommendations are emphasized in the treatment of metabolic syndrome. Assessment of an individual's current energy intake and nutrient composition, together with usual physical activity, is needed. This information enables the setting of a realistic weight reduction goal and recommendations for an appropriate dietary and exercise regimen. The diet should include high-fiber foods such as whole grains, fruits, legumes, and other vegetables. Viscous (soluble) fiber (10–25 g/d) is especially recommended.[4] On the other hand, consumption of highly refined and processed foods, such as instant products and sugar beverages, should be limited. The use of low-glycemic foods may be beneficial in helping to lower the body's glucose and insulin response.[50] The glycemic index classifies foods according to their glycemic effect. The rise in blood glucose levels after ingestion of equal amounts of foods is ranked relative to a standard, such as glucose or white bread. Postprandial hyperglycemia seems to be a strong independent risk factor for cardiovascular disease, and a regular diet of high-glycemic-index foods may also increase risk for obesity and DM2.[50] Low-glycemic foods, on the other hand, may reduce these risks; these foods include milk and plain yogurt, legumes, nonstarchy vegetables, some bran cereals, and certain fruits like berries, peaches, plums, and cherries. "Heart-healthy" monounsaturated fatty acids and omega-3 polyunsaturated fatty acids in the diet should be substituted for some of the "heart-unhealthy" saturated fatty acids and *trans*-fats.[4] Monounsaturated fatty acids include olive, canola, and peanut oils. Omega-3 polyunsaturated fatty acids include canola oil, fish oils (from "fatty" fish such as sardines, herring, mackerel, and salmon), and flaxseed oil. Saturated fatty acids come mainly from animal sources and include butter, lard, and full-fat cheese. Tropical oils, such as coconut and palm oils, are also classified as saturated fatty acids. *Trans*-fatty acids exist in certain margarines and commercial baked goods that contain hydrogenated or partially hydrogenated vegetable oils. Plant stanols/sterols (2 g/d) can be included in the diet to help decrease LDL-C.[4] The addition of soy protein to the diet may also provide cardioprotective benefits. In 1999, the Food and Drug Administration authorized claims that 25 g of soy protein a day may help reduce the risk of heart disease when used with a low-fat diet. Regular consumption of large amounts of alcohol (3 or more drinks per day) may contribute to metabolic syndrome, including alcohol-induced fatty liver, although smaller amounts may have health benefits.[7] Increased alcohol intake can also aggravate hypertriglyceridemia.[51] Table 2 lists the major dietary recommendations for individuals with metabolic syndrome. Table 3 gives the specific dietary recommendations for the Therapeutic Lifestyle Change Diet,[4] which is being recommended by the National Cholesterol Education Program of the National Institutes of Health.

Table 3. Therapeutic Lifestyle Change Diet of the National Cholesterol Education Program (Adult Treatment Panel III[4])

Nutrient	Recommended Intake
Saturated fat	<7% of total energy
Polyunsaturated fat	Up to 10% of energy
Monounsaturated fat	Up to 20% of energy
Total fat	25–35% of total energy
Carbohydrate	50–60% of total energy
Fiber	20–30 g/d
Protein	About 15% of total energy
Cholesterol	<200 mg/d
Total energy	To maintain desirable weight

The Next Chronic Disease Epidemic

In the future, there is likely to be an increase in the rate of DM2 and possibly also an increase in death rates for CHD and stroke. The "couch potato" generation of the 1970s and 1980s is being succeeded by the "computer and video" generation of the last decade of the 20th century and the first decade of the new one. Activity levels of children and adolescents are woefully inadequate, and the substitute activities are largely sedentary. Almost 30% of current US adolescents who are overweight or obese also qualify as having metabolic syndrome.[52] Hence, as a society, we can only anticipate greater percentages of overweight and relatively unhealthy youth. The increase in their body weight may not be accompanied by a proportionate increase in muscle mass and bone mass. This low bone mass makes the obese adolescents more susceptible to fractures, as recently reported in a study from New Zealand.[53]

Conclusions

Metabolic syndrome is rearing its head like a hydra-headed monster in our society, with severe and even deadly consequences caused by the chronic diseases that it spawns. Its epidemic proportions make it imperative that new and more effective public health measures be initiated and implemented.

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