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Obesity, Metabolic Syndrome, and Cardiovascular Disease

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Obesity is rampant in the United States and is becoming increasing common worldwide. The increase in obesity prevalence is due to two major factors, plentiful supplies of inexpensive foods and sedentary jobs. Both are driven in no small part by technology. Thanks to technology, production of large quantities of cheap food is possible, and manual work is rapidly disappearing. In areas of the world in which these advances have not penetrated, obesity is not a significant public health problem. Thus, obesity is a direct result of technological advance and represents a major challenge for technological society. Obesity must also be recognized as a product of free society in which a multitude of food choices and job opportunities are available. A public health approach to the problem of obesity that restricts choice will not be acceptable to a free society. This fact puts increased responsibility on the individual to recognize the underlying causes of obesity and modify behavior to reduce the personal burden of obesity.

That obesity extracts a social cost is well recognized. The costs in physical health are less well recognized by the general public. The foremost physical consequence of obesity is atherosclerotic cardiovascular disease (ASCVD) (1). A substantial portion of the ASCVD resulting from obesity is mediated by type 2 diabetes. But obesity is accompanied by several other risk factors for ASCVD. The sum of the risk factors that predisposes to ASCVD goes by the name of metabolic syndrome. In addition, obesity is accompanied by other medical complications other than ASCVD and diabetes; these include fatty liver, cholesterol gallstones, sleep apnea, osteoarthritis, and polycystic ovary disease. These disorders are commonly found in individuals who carry the metabolic syndrome.

Obesity can be called an underlying risk factor for cardiovascular disease (ASCVD) (2). It is called this because it raises the risk for ASCVD through other risk factors. The latter include the major risk factors (hypercholesterolemia, hypertension, hyperglycemia) and emerging risk factors (atherogenic dyslipidemia, insulin resistance, proinflammatory state, prothrombotic state). The relationship of obesity to major and emerging risk factors varies, depending on the genetic and acquired characteristics of individuals. The majority of obese persons who develop ASCVD typically have a clustering of major and emerging risk factors (metabolic syndrome). The constellation of major and emerging risk factors that make up the metabolic syndrome can be called metabolic risk factors (3). This article will first examine the variable characteristics of obesity; this will be followed by an examination of the relation of obesity to the metabolic syndrome; and finally, the relation of the metabolic syndrome to ASCVD will be reviewed.

Categories of obesity

Obesity can be defined as an excess of body fat. A surrogate marker for body fat content is the body mass index (BMI), which is determined by weight (kilograms) divided by height squared (square meters). In clinical terms, a BMI of 25–29 kg/m^2 is called overweight; higher BMIs ($\geq$30 kg/m^2) are called obesity (4). A better way to define obesity would be in terms of percent total body fat (4). This can be measured by several methods (skin-fold thickness, bioelectrical impedance, underwater weighing). In terms of percent body fat, obesity can be defined as 25% or greater in men and 35% or greater in women. The measurement of percent body fat is rarely used in clinical practice, however, because of inconvenience and cost.

The best way to estimate obesity in clinical practice is to measure waist circumference. This is because an excess of abdominal fat is most tightly associated with the metabolic risk factors. In the United States, abdominal obesity is defined as a waist circumference in men of 102 cm or more and in women of 88 cm or more (4). In other countries, lesser increases in waist circumferences have been associated with metabolic risk factors, and other standards are in use.

Abdominal fat is located in two major compartments: sc and ip (visceral). The latter consists of the fat of the omentum and mesentery. The fatty acids released by visceral fat drains into the portal circulation. Some investigators (5) believe that an excess of visceral fat (visceral obesity) is more strongly related to metabolic risk factors than any other fat compartment. Subcutaneous adipose tissue nonetheless is a much larger compartment than visceral fat. The latter usually is divided into gluteofemoral and truncal sc adipose tissue. Truncal fat is more strongly related to metabolic risk factors than gluteofemoral fat (4). Moreover, truncal sc fat may have a greater impact on risk factors than does visceral fat because of its greater mass (6, 7). Several terms have been applied to

Abbreviations: apo B, Apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; HDL, high-density lipoprotein; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; NEFA, nonesterified fatty acid; PAI, plasminogen activator inhibitor; TGRLP, triglyceride-rich lipoprotein; VLDL, very LDL.

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excess fat in the trunk: abdominal obesity, truncal obesity, and upper body obesity. In fact, there is a strong correlation between waist circumference and upper body fat content. Hence because an increased girth is most readily recognized clinically, the term abdominal obesity is useful and satisfactory (2, 4).

Body fat and metabolic syndrome

The metabolic syndrome is a constellation of metabolic risk factors that consist of the following (2):

- Atherogenic dyslipidemia [serum elevations of triglycerides, apolipoprotein B (apo B), and small low-density lipoprotein (LDL) particles plus low high-density lipoprotein (HDL) cholesterol]
- Elevated blood pressure
- Elevated glucose associated with insulin resistance
- Prothrombotic state
- Proinflammatory state

Many of these factors can be identified through special testing but are not measured in clinical practice. Recently the National Cholesterol Education Program Adult Treatment Panel III report (2) proposed a simple scheme for the routine diagnosis of metabolic syndrome. According to this scheme, a diagnosis of metabolic syndrome can be made if a person has three of the following five features:

- Increased waist circumference (≥102 cm in men and ≥ 88 cm in women)
- Elevated triglycerides (≥150 mg/dl)
- Reduced HDL cholesterol (<40 mg/dl in men and < 50 mg/dl in women)
- Elevated blood pressure (≥130/85 mm Hg or on treatment for hypertension)
- Elevated glucose (≥100 mg/dl)

When the waist circumference is 102 cm or more in men or 88 cm or more in women, the term abdominal obesity can be applied. The advantage of measuring waist circumference is that an excess abdominal fat is correlated more closely with the presence of metabolic risk factors than total body fat. The cut points for defining abdominal obesity are arbitrary. For susceptible individuals, lesser accumulations of abdominal fat can precipitate or aggravate metabolic risk factors. This is particularly so in certain populations; for example, in Asian populations lower waist circumference cut points have been identified to define abdominal obesity.

Patients with diabetes (fasting glucose ≥ 126 mg/dl) are said to have the metabolic syndrome if two other features are present. If a person qualifies for the metabolic syndrome under Adult Treatment Panel III criteria, measurement of a 2-h postprandial glucose may uncover a diagnosis of diabetes (2-h glucose ≥ 200 mg/dl) or impaired glucose tolerance (IGT) (2-h glucose 140–199 mg/dl) (1). The presence of IGT indicates an increased risk for type 2 diabetes (8). Additional testing can provide confirmation of the metabolic syndrome. Confirmatory biomarkers for this syndrome include high levels of fasting insulin, 2-h postprandial insulin, apo B, increased small LDL particles, C-reactive protein (CRP), fibrinogen, and plasminogen activator inhibitor (PAI)-1. The clinical utility of detecting these additional abnormalities beyond confirmation of the syndrome is uncertain, although investigations are underway to evaluate potential utility. For example, the presence of elevated CRP may indicate a greater risk for acute coronary syndromes (9).

A disputed area in the relation of obesity and metabolic syndrome concerns the role of insulin resistance. Most persons with multiple metabolic risk factors are insulin resistant. This observation led to the concept that insulin resistance is the cause of the metabolic syndrome (10). This concept in turn generated an alternative term for the metabolic syndrome, namely the insulin resistance syndrome (10). Various pathogenic schemes have been proposed to explain the connection between insulin resistance and metabolic risk factors. There is no doubt that insulin resistance is a risk factor for IGT and type 2 diabetes. A causal relationship between insulin resistance and other metabolic risk factors is less certain. Moreover, the interaction between obesity and defects in insulin signaling is so complex that it is so far not possible to disentangle the two. For example, obesity causes insulin resistance, whereas insulin resistance seemingly exacerbates the adverse effects of obesity. A strong case can be made for a role of genetic forms of insulin resistance being a contributor to the metabolic syndrome in the general population. On the other hand, there is little doubt that increasing prevalence of overweight/obesity is mainly responsible to the rising prevalence of the metabolic syndrome in the United States and worldwide (11).

Our understanding of the relation between obesity and metabolic risk factors is growing rapidly. This understanding is based on the discovery of multiple products released from adipocytes. In the presence of obesity, these products are released in abnormal amounts. Each of these products has been implicated in the causation of one or another of the metabolic risk factors. The following is a list of the factors most implicated in the development of metabolic syndrome (12):

- Nonesterified fatty acids (NEFAs)
- Inflammatory cytokines
- PAI-1
- Adiponectin
- Leptin
- Resistin

Current concepts of the relation of each of these products to metabolic risk factors can be reviewed.

NEFA. Obese persons release increased amounts of NEFAs into the circulation (13). NEFAs are derived by lipolysis of adipose tissue triglycerides. The greater the amount of fat in adipose tissue, the more the amounts of NEFAs released will be. This greater release of NEFAs proceeds despite the higher insulin levels that are present in obese persons. Even though high insulin levels suppress adipose tissue lipolysis, they cannot reduce NEFA release to normal in obesity. NEFAs are the primary source of nutrient energy in the fasting state. With obesity, however, NEFA flux exceeds tissue needs, and defense mechanisms must come into play. The consequences of these defense mechanisms undoubtedly contribute to metabolic risk factors.

Excessive influx of NEFAs into muscle leads to insulin resistance. The mechanisms whereby increased fatty acids in muscle cause insulin resistance have not been fully eluci-

dated. Randle *et al.* (14) early postulated that excess fatty acids inhibit glucose oxidation (glucose-fatty acid cycle). Recent research (15) suggests that muscle levels of diacylglycerol are raised, which stimulates the serine phosphorylation of the insulin receptors and thereby inhibits normal insulin signaling. Other mechanisms have been proposed and may play a role (16). The resulting insulin resistance in muscle predisposes to hyperglycemia; the latter becomes clinically manifest in those persons to acquire a defect in insulin secretory capacity.

Influx of excess NEFAs into the liver increases the triglyceride content of the liver (fatty liver) (17). Fat accumulation in the liver seemingly produces insulin resistance as it does in muscle. Reduction in insulin action in liver allows for enhanced glyconeogenesis and increased hepatic glucose output; this will accentuate hyperglycemia in those patients who have reduced insulin secretory capacity. Increased fat in the liver also promotes development of atherogenic dyslipidemia. It provides a stimulus for increased formation and secretion of very LDL (VLDL) particles. The result is higher serum levels of triglyceride, apo B, and small LDL particles. High serum triglycerides reduce HDL-cholesterol concentrations through exchange of VLDL triglycerides with HDL cholesterol esters. HDL-cholesterol lowering is accentuated by an increase in synthesis of hepatic lipase that occurs in people with obesity-induced fatty liver; lipase degrades HDL particles, converting large HDL into small HDL.

An important but unresolved question is whether high NEFA levels contribute to higher blood pressure or a proinflammatory state. Hypotheses have been developed to link higher NEFA levels to higher blood pressures (18). Whether the link is causal remains to be determined. Moreover, accumulation of fat in the liver has been reported to be associated with increased hepatic synthesis of PAI-1, fibrinogen, and inflammatory cytokines, the key mediators of the prothrombotic and proinflammatory states (19).

Inflammatory cytokines. Adipose tissue synthesizes and secretes TNFα, IL-6, and other cytokines. The production of these cytokines is increased in obese persons. This increased synthesis may interfere with the action of insulin to suppress lipolysis; if so, this would represent insulin resistance of adipose tissue. Obese persons in addition have elevated circulating cytokines; so far, it is uncertain whether these circulating cytokines have systemic effects, *i.e.* promoting insulin resistance in muscle (15), increased synthesis of acute-phase reactants in the liver (CRP and fibrinogen), or activation of macrophages in atheromatous plaques (20). It is possible increased release of acute-phase reactants from liver may be the result entirely of lipid accumulation in this organ.

PAI-1. Adipose tissue synthesizes PAI-1, too. Reports suggest that abdominal adipose tissue is more active in PAI-1 synthesis than lower-body adipose tissue (21). A fatty liver may be another source of PAI-1. The resulting high PAI-1 levels in obese persons together with the high plasma fibrinogen observed in such persons contributes to a prothrombotic state.

Other adipose tissue products. Several other products of adipose tissue may influence development of the metabolic syndrome. Their precise role, however, remains to be fully determined. Adiponectin is one potentially important product (22). This substance has been reported to have antiinflammatory and antiatherogenic properties. Obese persons generally have low levels of adiponectin and hence may be deprived of its protective effects against the metabolic syndrome. Leptin also may play a systemic role beyond being an adipose tissue-derived appetite suppressant. Whether the systemic effects of leptin are direct or secondary to its action on the central nervous system is currently being debated. Regardless, this hormone has been reported to have a beneficial effect on the liver to protect against fatty liver (23). Its mechanism may be to enhance fatty acid oxidation in the liver. Finally, resistin is an adipose tissue-derived hormone that seemingly opposes the action of insulin (24). Whether it has a physiological role in humans has not yet been determined.

Obesity-induced metabolic syndrome as a multidimensional risk factor for ASCVD and type 2 diabetes

Several recent reports (25–28) indicate that the presence of the metabolic syndrome is associated with increased risk for both ASCVD and type 2 diabetes. Persons with the metabolic syndrome have at least a 2-fold increase in risk for ASCVD, compared with those without (1). Risk for type 2 diabetes in both men and women is increased about 5-fold (1). The risk for diabetes is highest in those with impaired fasting glucose or IGT. Once a patient develops type 2 diabetes, risk for ASCVD is enhanced. Not only is relative risk for coronary heart disease (CHD) raised by 2- to 3-fold, but once CHD becomes manifest in a patient with diabetes, the prognosis for survival is greatly reduced (2). In addition, diabetes is accompanied by microvascular disease, which is a common cause of chronic renal failure. The relationship between the metabolic risk factors and development of ASCVD is complex and certainly not well understood. Nonetheless, a brief review of hypothesized mechanisms may be of interest.

Atherogenic dyslipidemia. This condition is characterized by an increase in elevated triglycerides (and increased VLDL particle number), increased small LDL particles, and low HDL cholesterol (2). It is commonly present in obese persons. The increased number of VLDL and LDL particles accounts for the increased level of total apo B usually observed with atherogenic dyslipidemia. The atherogenic potential of each lipoprotein abnormality has long been a topic of great interest but one that is not fully resolved.

For many years triglyceride-rich lipoproteins (TGRLPs) were thought not to be atherogenic. Nonetheless, there is growing evidence that smaller TGRLP (remnant lipoproteins) are in fact atherogenic (29). This evidence comes from studies in laboratory animals, patients with genetic disorders causing remnant accumulation, metaanalysis of epidemiological studies, and clinical trials (1). TGRLPs as a class are a mixture of lipoproteins, and it has been difficult to differentiate between atherogenic and nonatherogenic forms of TGRLPs. Nonetheless, there is a growing consensus among investigators that TGRLP fraction definitely contains atherogenic lipoproteins.

The LDL particles associated with the metabolic syndrome

and atherogenic dyslipidemia tend to be small and dense. A theory widely held is that smaller LDL particles are more atherogenic than larger LDLs (30). Smaller LDLs may filter more readily into the arterial wall. They further may be more prone to atherogenic modification. Even so, not all investigations are convinced that small LDL particles are unusually atherogenic, compared with other apo B-containing lipoproteins. Nonetheless, when small LDLs are present, the total number of lipoprotein particles in the LDL fraction usually is increased (31). Most researchers will agree that the higher the number of LDL particles present, the higher will be the atherogenic potential. In other words, small LDL particles are often a surrogate for an increased LDL particle number (31).

A simple strategy for assessing the sum of atherogenic particles is measurement of either LDL+VLDL cholesterol (non-HDL cholesterol) or total apo B (2). In persons with metabolic syndrome and atherogenic dyslipidemia, both LDL+VLDL cholesterol and total apo B typically are elevated. These measurements should be used increasingly both in risk assessment and as targets of therapy in persons with the metabolic syndrome (32).

A low HDL level is another characteristic of atherogenic dyslipidemia (2). As a risk predictor, a low HDL rivals an elevated total apo B (or VLDL+LDL cholesterol). This fact has led to the concept that HDL is intimately involved in the atherogenic process. The theories abound as to the mechanisms whereby HDL is antiatherogenic, *e.g.* enhanced reverse cholesterol transport, antiinflammatory properties, ability to protect against LDL modification, among others. Although HDL in fact may be directly antiatherogenic, it also is a marker for the presence of other lipid and nonlipid risk factors. Obesity itself reduces HDL levels (4), and obese patients with metabolic syndrome and atherogenic dyslipidemia almost always have low HDL levels. Thus, the association between low HDL and ASCVD risk is complex (2), and the various components of this association are difficult to differentiate. Regardless of mechanism, however, the presence of a low HDL level carries strong predictive power for development of ASCVD.

Elevated blood pressure. Obese persons have a higher prevalence of elevated blood pressure than lean persons. Moreover, a higher blood pressure is a strong risk factor for cardiovascular disease (CVD) (33). Well-known complication of hypertension are CHD, stroke, left ventricular hypertrophy, heart failure, and chronic renal failure. Yet some reports (34, 35) suggest that the elevated blood pressure accompanying obesity is less likely to produce CVD than when it occurs in lean persons. The implication is that obesity-induced hypertension is not particularly dangerous to the cardiovascular system. This concept generally is not accepted by the hypertension community, nor was it supported by the Framingham Heart Study (36).

Elevated plasma glucose. There is no question that persons with diabetes are at increased risk for ASCVD. In epidemiological studies, the onset of diabetes is accompanied by increased risk for ASCVD, suggesting that hyperglycemia *per se* is atherogenic. Limited data that directly address the question of whether hyperglycemia accelerates the development of atherosclerosis are available. Nonetheless, one recent study (37) indicated that intensive diabetes therapy in type 1 diabetes is accompanied by a reduction in intima-media thickness of carotid arteries. Although this finding is consistent with epidemiology, it generally has not been possible to demonstrate an atherogenic potential of hyperglycemia in animal models. Moreover, whether the hyperglycemia of type 1 diabetes promotes atherogenesis has been uncertain. The major cause of death in persons with type 1 diabetes is CVD; even so, it is possible that most atherosclerotic disease develops later in the course of the disease after development of chronic renal failure and hypertension.

A variety of mechanisms have been proposed whereby hyperglycemia might promote atherosclerosis (38). Examples include nonenzymatic glycosylation of lipids and proteins, pathogenic effects of advanced glycation products, increased oxidative stress, activation of protein kinase C, and microvascular disease of the vasa vasorum of the coronary arteries. All of these potential mechanisms are of interest, but so far, none has been shown to play a direct role in atherogenesis; most likely all are involved in one way or another. But a fundamental question remains to be answered, namely whether hyperglycemia is directly atherogenic.

Another possibility is that insulin resistance *per se* is independently atherogenic. In prospective studies, the presence of insulin resistance is associated with increased ASCVD risk (39). But in persons with insulin resistance, confounding by other known risk factors makes it difficult to be certain that insulin resistance (or resulting hyperinsulinemia) is directly atherogenic (39). If so, the mechanisms for such an effect are entirely speculative at this time.

Prothrombotic state. Obesity is accompanied by a large number of coagulation and fibrinolytic abnormalities (40). This suggests that obesity induces a prothrombotic state. What is not known at present is how a prothrombotic state will either promote the development of atherosclerosis or participate in the development of acute ASCVD events. Perhaps the most attractive candidate for enhanced atherogenicity associated with coagulation and fibrinolytic abnormalities is endothelial dysfunction. It is believed by many workers that endothelial dysfunction is somehow involved in the atherogenic process (41). Several pathways have been proposed; so far, however, none of these have been substantiated. Perhaps more likely, the obesity-induced procoagulant and antifibrinolytic factors contribute to a worsening of acute coronary syndromes. Thrombosis occurring with plaque rupture or erosion is a key element in determining the severity of the syndrome. If normal coagulation and fibrinolysis are impaired at the time of plaque rupture or erosion, then a larger thrombus should form. An attractive hypothesis is that acute plaque disruption is common, but only when thrombosis is large is there a significant acute coronary syndrome. If so, such could make the presence of a prothrombotic state important for determining the clinical outcome.

Proinflammatory state. The cardiovascular field has recently shown great interest in the role of inflammation in the development of ASCVD. The basic concept is that atherogenesis represents a state of chronic inflammation. It is charac-

terized by lipid-induced injury that initiates invasion of macrophages followed by proliferation of smooth muscle cells. All of these processes are classic features of chronic inflammation albeit occurring at a very slow rate. The finding that elevations of serum CRP carry predictive power for the development of major cardiovascular events led to the concept that advanced and unstable atherosclerotic plaques are in an even higher state of inflammation than stable plaques (9). It is of interest that obese persons (42) and particularly those with the metabolic syndrome (43) also have elevated levels of CRP. This finding has suggested that obesity is a proinflammatory state and is somehow connected with the development of unstable atherosclerotic plaques. So far, however, a mechanistic connection has not been made. The associations are suggestive, but how elevations of CRP associated with obesity could promote or precipitate major cardiovascular events is not clear. This lack of identified mechanism does not rule out a causative connection. But so far the connection has not been uncovered.

Summary

Obesity is a major underlying risk factor for ASCVD. It is associated with multiple ASCVD risk factors, and it also is a risk factor for type 2 diabetes. Diabetes itself is a cardiovascular risk factor. Despite the strong association between obesity and ASCVD, the mechanisms underlying this relationship are not well understood. Our understanding of the connection between obesity and vascular disease is complicated by a plethora of possibilities. Obesity acts on so many metabolic pathways, producing so many potential risk factors, that it is virtually impossible to differentiate between the more important and less important. The possibilities for confounding variables are enormous. This complexity provides a great challenge for basic and clinical research. It also raises the possibility for new targets of therapy for the metabolic syndrome. With this said, the fundamental challenge is how to intervene at the public health level to reduce the high prevalence of obesity in the general population. This approach offers the greatest possibility for reducing the cardiovascular risk that accompanies obesity.

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