Endocrine, *vol. 13, no. 2, 155–165, October 2000* 0969–711X/00/13:155–165/$12.75

Metabolic Complications of Obesity

Scott M. Grundy

Center for Human Nutrition, Departments of Clinical Nutrition and Internal Medicine, University of Texas Southwestern Medical Center at Dallas, Dallas, TX

The rising prevalence of obesity is accompanied by an increasing number of patients with the metabolic complications of obesity. The major complications come under the heading of the *metabolic syndrome*. This syndrome is characterized by plasma lipid disorders (atherogenic dyslipidemia), raised blood pressure, elevated plasma glucose, and a prothrombotic state. The clinical consequences of the metabolic syndrome are coronary heart disease and stroke, type 2 diabetes and its complications, fatty liver, cholesterol gallstones, and possibly some forms of cancer. At the heart of the metabolic syndrome is *insulin resistance*, which represents a generalized derangement in metabolic processes. Obesity is the predominant factor leading to insulin resistance, although other factors play a role. The mechanistic link between insulin resistance and the metabolic syndrome is complex. The relationship is modulated by yet other factors, such as physical activity, body fat distribution, hormones, and a person's genetic polymorphic architecture. A better understanding of the molecular basis of this relationship is needed to suggest new targets for prevention and treatment of the complications of obesity. In addition, understanding at the clinical level will lead to improved management of these complications.

Key Words: Metabolic syndrome; insulin resistance; obesity; metabolic complications.

Introduction

The rising prevalence of obesity in the Unites States and worldwide will render an increase in the metabolic complications of obesity *(1)*. In the future, more and more medical resources throughout the world will have to be committed to treating these complications. Obesity contributes importantly to many of the chronic diseases that account for much of the morbidity in middle-aged and older persons. Unfortunately, medical intervention to date has a poor track record for achieving weight reduction in overweight persons. Although efforts to eliminate excess body weight in clinical practice are entirely justified *(2)*, many persons will fail to lose weight and will eventually develop metabolic complications, requiring medical intervention. This article reviews the metabolic complications of obesity and considers their pathophysiology.

Although the metabolic stress of obesity undoubtedly predisposes to several chronic diseases, these diseases typically are multifactorial in origin. There is rarely a one-to-one relationship between body fat and disease. The predisposing effects of obesity interact strongly with genetic susceptibility and with the physiologic changes of aging. Clinical evaluation of patients requires careful dissection of the contributing factors. The origins of a disease can affect selection of the appropriate therapy. For this reason, for any overweight patient who appears to have an obesity-related disorder, the question must always be asked, are there other factors involved that require separate attention?

The major metabolic abnormalities accompanying obesity are dyslipidemia, raised blood pressure, insulin resistance and glucose intolerance, a prothrombotic state, and lithogenic bile. These aberrations contribute to the development of cardiovascular disease, type 2 diabetes, fatty liver and steatohepatitis, and cholesterol gallstones. Furthermore, obesity may induce more subtle defects in cellular metabolism that increase risk for some forms of cancer.

Cardiovascular Disease

The question of whether obesity enhances risk for cardiovascular disease has a long and complex history. The clinical impression that obesity predisposes to cardiovascular disease is long-standing; objective evidence to this effect has been slow in coming. For example, early reports from the Seven Countries Study failed to demonstrate a significant correlation between body weight and incidence of coronary heart disease (CHD) *(3)*. Moreover, an international study of the pathology of atherosclerosis failed to show a significant correlation between body weight and degree of coronary or aortic atherosclerosis across a large

Received June 14, 2000; Accepted June 14, 2000.

Author to whom all correspondence and reprint requests should be addressed: Dr. Scott M. Grundy, Center for Human Nutrition, Departments of Clinical Nutrition and Internal Medicine, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Dallas, TX 75390-9052. E-mail: sgrund@mednet.swmed.edu

number of countries *(4)*. These studies led some investigators to question whether obesity plays a significant role in the causation of CHD, and possibly other forms of cardiovascular disease.

This association has more recently been reexamined in several prospective studies *(5–8)*. Some studies *(5–8)* report a positive association between body weight and the incidence of cardiovascular diseases, notably CHD. At present, most investigators hold that the association is real and not spurious. This link offers one rationale for preventing or treating obesity *per se* to reduce the risk for CHD. A positive association nonetheless raises another question: Is obesity an independent risk factor for CHD? This question can be simplified as follows: Does obesity raise the risk beyond that which is predicted by the "standard risk factors"? According to the Framingham Heart Study *(9)*, the standard risk factors are cigarette smoking, hypertension, high serum cholesterol, low levels of high-density lipoprotein (HDL) cholesterol, and diabetes. Framingham investigators *(9)* and some other researchers claim that most of CHD risk associated with obesity is subsumed under the major risk factors. Other investigators *(10)*, however, doubt that all the risk accompanying obesity is mediated through the standard risk factors. For example, what about actions of obesity to induce insulin resistance, to raise triglycerides, and to produce a prothrombotic state? Do these emerging risk factors count for nothing in CHD risk? It is doubtful.

The issue of obesity as an independent risk factor goes beyond currently provisional risk factors (e.g., high triglycerides, insulin resistance, and prothrombotic state). If the latter in fact are causative risk factors, then some of the "independence" of obesity as a risk factor could be explained by these factors. Until the independent status of the provisional risk factors is resolved, it will remain unclear whether obesity exerts its effects on cardiovascular disease through them. At the same time, obesity could elicit its detrimental actions through yet-to-be-identified risk factors. For example, it has been recently proposed that obesity is a proinflammatory condition; if so, inflammatory mechanisms could promote atherogenesis *(11)*. Thus, it is possible that obesity acts as a risk factor through standard risk factors, emerging risk factors, and unidentified risk factors.

The quest to understand the mechanisms underlying the association between obesity and cardiovascular disease should not be trivialized. Uncertainty about the mechanisms provides the impetus to understand better the metabolic consequences of obesity and the pathogenic role of these consequences on the development of atherosclerosis disease. It is not enough to say that mechanisms are unimportant because the metabolic abnormalities can be reversed by weight loss. Because normalization of body weight frequently cannot be achieved in clinical practice, the mechanisms underlying the complications of obesity may themselves become targets for medical therapy.

Obesity, Insulin Resistance,and Type 2 Diabetes

Type 2 diabetes is another major chronic disease associated with obesity. No other disease has been the subject of so much metabolic research as type 2 diabetes. Thousands of investigations underlie our understanding of the metabolic basis of this disease. Adult-onset diabetes (type 2) differs fundamentally from juvenile diabetes (type 1). In contrast to the latter, type 2 diabetes has a later onset, is usually accompanied by obesity, and rarely manifests ketoacidosis. It accounts for up to 90% of diabetes in the general population. It was long assumed that patients with type 2 diabetes are deficient in insulin because insulin is required for the cellular uptake of glucose. However, when methods became available to measure plasma insulin by radioimmunoassy, insulin levels were found to be abnormally high in patients with type 2 diabetes—not reduced. This finding naturally raised the question, How can both insulin and glucose levels be elevated in the same person?

This paradox led to the concept of insulin resistance. In type 2 diabetes, tissues that utilize glucose seemingly are resistant to the actions of insulin. In some way, not understood, this resistance leads to increases in plasma insulin concentrations; the latter overcome the block in glucose uptake and restore glucose homeostasis. In some patients, insulin resistance is too severe to be overcome by compensatory hyperinsulinemia, and categorical hyperglycemia (type 2 diabetes) develops. The evolution of the concept of insulin resistance represents a major advance in our understanding of the pathogenesis of type 2 diabetes *(12)*.

Not only are patients with type 2 diabetes insulin resistant, but so are many obese persons without diabetes *(13,14)*. How then do obese persons and patients with type 2 diabetes differ? Why do some patients with insulin resistance and hyperinsulinemia have normoglycemia whereas others are hyperglycemic? Subsequent careful studies of the kinetics of glucose and insulin appear to have resolved this paradox. Patients with type 2 diabetes apparently fail to mount sufficient compensatory hyperinsulinemia to maintain normoglycemia. Even though they are able to increase the secretion of insulin in response to insulin resistance, they are not able to secrete enough to overcome the resistance to insulin action. Plasma glucose levels consequently rise to abnormally high levels *(15,16)*.

The lion's share of glucose utilization occurs in skeletal muscle; moreover, this tissue accounts for much of insulin resistance *(17)*. Some investigators believe that insulin resistance also exists in the liver *(18)*. Because insulin suppresses hepatic gluconeogenesis, insulin resistance in the liver could raise hepatic glucose production (and output) *(18)*. This response, in turn, could worsen hyperglycemia of type 2 diabetes. The quantitative contribution of increased hepatic glucose output to hyperglycemia in type 2 diabetes remains uncertain and is a topic of some dispute *(18,19)*.

The strong association between obesity and insulin resistance naturally raises the question, Why should an increase in mass of adipose tissue mass cause insulin resistance in skeletal muscle? In addition, why does insulin resistance in obese persons elicit a hyperinsulinemia response? These questions are at the heart of the search for the pathogenesis of type 2 diabetes. Perhaps the most provocative hypothesis is that of Randle *(20)*. He postulated that excess fatty acids derived from adipose tissue enters skeletal muscle, impairs the uptake and oxidation of glucose, and induces insulin resistance. The Randle hypothesis accords with many metabolic observations and deserves discussion.

Obese persons undoubtedly release an increased amount of nonesterified fatty acids (NEFA) into the circulation, and this increase could supply excess fatty acids to skeletal muscle. The Randle hypothesis has a strong rationale, engendering efforts to confirm it. To test this hypothesis specifically, investigators *(21)* infused emulsified triglycerides together with heparin into subjects with normal insulin sensitivity. Heparin infusion releases large amounts of lipoprotein lipase into the circulation; this lipoprotein lipase rapidly hydrolyzes much of the triglycerides, markedly raising NEFA levels. NEFA utilization during triglyceride/heparin infusion evokes a striking reduction in insulin sensitivity, supporting the Randle hypothesis.

Randle et al. *(22,23)* performed many studies on the molecular mechanisms whereby excess fatty acids in skeletal muscle impair glucose uptake and utilization. They postulate that excess fatty acids in cells impair glucose oxidation by inactivating pyruvate dehydroglucose (PDH) complex, a key regulator of glucose oxidation. They contend that products of fatty acid oxidation activate PDH kinase, which phosphorylates PDH and inactivates the complex. This molecular mechanism has never been fully confirmed, but the fundamental hypothesis that excess circulating NEFA induces insulin resistance in muscle seems sound.

Recently, some workers *(24,25)* have suggested that the interplay of fat and carbohydrate at the molecular level is more complex than envisioned by Randle et al. *(22,23)* and have proposed alternate biochemical mechanisms. Excess fatty acids, for example, could directly interfere with the insulin-signaling cascade, which causes insulin resistance.

Insulin action is initiated by the binding of insulin to the insulin receptor. This receptor is a transmembrane glycoprotein having protein tyrosine kinase activity. Binding of insulin causes autophosphorylation and phosphorylation of other proteins, notably the "docking proteins", insulin receptor substrate-1 (IRS-1) and IRS-2. After phosphorylation, IRS-1 associates with other signaling molecules, phosphatidylinositol-3 kinase (PI-3 kinase), and Ras protein. Progressive phosphorylation causes a spread of activation through signaling cascades that is responsible for the pleiotropic actions of insulin. One consequence of insulin action is enhanced cellular uptake of glucose. This response depends on the activation of PI-3 kinase. The latter stimulates the recruitment of vesicles containing a glucose transporter, GLUT-4, or recruits GLUT-4 from unique intracellular locations *(26–29)*. GLUT-4 moves to the cell membrane and facilitates the uptake of glucose. Various steps in this chain of reactions could be blocked by excess fatty acids, causing insulin resistance.

Recent investigations further show that adipocytes produce tumor necrosis factor-α (TNF-α). This cytokine seemingly interferes with insulin action *(30,31)*; it enhances the activity of protein kinase C, which impairs insulin action by phosphorylating the serine residues of the insulin receptor *(32,33)*. In the presence of obesity, TNF-α may be released in excessive amounts from adipose tissue, and this overproduction also could impair insulin action.

Some investigators have speculated that obesity induces insulin resistance by stimulating an excess of insulin secretion. The mechanisms responsible for hyperinsulinemia in obese subjects have never been adequately explained. Recent research indicates that high levels of circulating NEFA overload pancreatic β-cells with lipid, which, in turn, appears to overstimulate the production of insulin *(34–37)*. Excess insulin production, leading to hyperinsulinemia, could downregulate insulin receptors causing insulin resistance in skeletal muscle. Although this mechanism has never received much attention, it is plausible and worthy of more serious investigation.

Excessive secretion of NEFA by an expanded pool of adipose tissue remains an attractive mechanism for the insulin resistance of obesity. This hypothesis receives additional support from the relation between distribution of body fat and insulin resistance. There is a marked difference in insulin sensitivity in skeletal muscle depending on whether fat is located predominantly in the trunk of the body or mainly in peripheral tissues, particularly the gluteofemoral region. Insulin resistance is highest when weight gain occurs predominantly in the trunk *(13,14)*. The latter has been called abdominal obesity because excess fat in the trunk is most noticeable in the abdomen. In fact, when the abdomen is overloaded with fat, excess adipose tissue usually occurs in the sc fat over the entire trunk *(14)*. For this reason, this form of obesity might better be called upper body obesity. It contrasts to lower body obesity (or gluteofemoral obesity).

There appears to be a fundamental difference in the metabolism of adipose tissue depending on whether it is located in the upper or lower body. The triglycerides of upper body fat turn over more rapidly than does fat in the lower body *(38–41)*. Consequently, plasma NEFA rises to higher levels with upper body obesity than with lower body obesity. Seemingly, upper body fat is more insulin resistant than lower body fat, which accounts for differences in NEFA release. The molecular basis for regional differences in the metabolic activity of adipose tissue has not been elucidated.

One hypothesis holds that most of the metabolic consequences of upper body obesity result from increased visceral fat. Visceral adipose tissue drains its NEFA directly into the portal circulation and thus could overload the liver with lipids *(42,43)*. According to this theory most of insulin resistance in muscle is secondary to metabolic changes in the liver, perhaps hepatic glucose overproduction. This is an attractive hypothesis that may hold some truth. There are caveats, however. Subcutaneous adipose tissue in the upper body exceeds visceral adipose tissue in mass by three-to-four-fold *(14)*; the former also is metabolically overactive compared to sc gluteofemoral fat *(44,45)*. Glucose clamp studies show that whole-body insulin sensitivity is more highly correlated with sc adipose-tissue mass in the trunk than with visceral fat (*14*). Thus, the high turnover rate of fatty acids by subcutaneous tissue in the trunk may well be the major factor producing insulin resistance when upper body obesity is present. If so, excess NEFA presumably would act more directly on skeletal muscle than on the liver.

The reasons for differences in body fat distribution are not known. Steroid hormones almost certainly affect body fat distribution. Men are more prone to upper body obesity than women, which suggests that androgens are involved. That androgens may favor upper body obesity is supported by the presence of this type of obesity in women with polycystic ovary syndrome—a condition characterized by hyperandrogenemia *(46,47)*. Of interest, however, androgens administered to older men seemingly cause fat mobilization and even loss of visceral adipose tissue *(48)*. This finding still does not rule out an action to favor upper body fat when excess fat accumulates. Corticosteroids and growth hormones also influence body fat distribution; both hormones apparently promote the uptake of fatty acids into adipose tissue of the upper body *(49)*. Genetic factors also may affect sites of fat accumulation *(50,51)*.

Because upper body obesity and insulin are associated, an intriguing question must be asked: Which comes first? The insulin resistance in South Asians in particular calls forth this question. Their level of insulin resistance exceeds their degree of obesity *(52)*; but, they accumulate most of their excess adipose tissue in the upper body *(53)*. These observations raise the possibility that insulin resistance precedes accumulation of upper body fat. Furthermore, patients with Cushing disease and other forms of hypercorticoidism apparently have insulin resistance on the basis of excess corticoid, and they too develop upper body obesity. Regardless of which comes first, obesity is an integral part of the insulin resistance syndrome; in most persons with very low body fat, insulin resistance is rare.

Reaven *(54)* suggests that much of insulin resistance in the U.S. population has a genetic basis. Without question a portion of insulin resistance is genetically determined. This is shown by the fact that the degree of insulin resistance can vary considerably at any given amount of body fat. Even so, within a particular ethnic group, genetic factors probably do not account for more than 50% of the variation in insulin sensitivity within that population; obesity still seems to be the dominant contributor *(13,14)*.

Another important factor affecting insulin sensitivity is level of physical activity. Exercise improves insulin sensitivity, i.e., reduces insulin resistance. Recent investigations *(55–57)* show that physical activity promotes expression of GLUT-4 in skeletal muscle. This action may enhance glucose uptake into muscle. Moreover, physical activity undoubtedly promotes the oxidation of fatty acids by muscle, which also should induce insulin resistance. The ability of regular exercise to decrease insulin resistance is considerable *(58)*. Thus, in "insulin-resistant" populations, it is difficult to tease apart the relative contributions of excess body fat and insufficient exercise.

Undoubtedly a person's genetic architecture affects the metabolism of both glucose and fatty acids. South Asians as a group seem highly susceptible to insulin resistance even in the presence of mild obesity; presumably genetic factors promoting insulin resistance aggregate in this population. At the other extreme, some obese persons from other ethnic groups maintain a moderately high insulin sensitivity. Thus, the genetic contributions to insulin resistance can be viewed in two ways. Among different racial populations, the baseline level of insulin sensitivity differs depending on genetic factors. For example, South Asians undoubtedly have a greater genetic predisposition to insulin sensitivity than do Caucasians. On the other hand, within a genetically homogeneous population, the major factors affecting the variability in insulin resistance are life habits, especially total energy balance and exercise habits.

It might be asked, Is severe insulin resistance alone enough to produce type 2 diabetes? The current paradigm holds that two metabolic aberrations are required to develop categorical hyperglycemia: insulin resistance and a deficient insulin secretion. This view is supported by the fact that hyperglycemia typically makes its appearance only after many years of insulin resistance. Gradually, over the years, the ability of pancreatic β-cells to mount a hyperinsulinemic response abates, and at some point the insulin response is insufficient to maintain normoglycemia. Moreover, the usual course of type 2 diabetes is one of progressive worsening of hyperglycemia; this worsening reflects a progressive decline in insulin secretion. Its causes have not been determined, but there probably is a genetic component. Genetic differences in β-cell function thus may well explain why some obese persons develop type 2 diabetes whereas others do not. A long-standing question is, Does prolonged hyperinsulinemia owing to insulin resistance contribute to the decline in insulin secretion ("insulin exhaustion")? This question remains unanswered.

The mechanisms whereby the hyperglycemia of type 2 diabetes predisposes to cardiovascular and neurologic complications are beyond the scope of this paper. Cardiovascu-

lar disease, including CHD, stroke, heart failure, and renal failure, represents the foremost cause of death in patients with type 2 diabetes. Peripheral neuropathies also are common. Poorly controlled hyperglycemia undoubtedly contributes directly to multiple complications. Prevention of these complications presents a major challenge to clinicians who care for patients with diabetes.

Obesity, Fatty Liver, Dyslipidemia, and Cholesterol Gallstones

A major target organ for the obese state is the liver. The full impact of obesity and hepatic metabolism is complex and incompletely understood. Two influences nonetheless come to the fore. One is a high level of plasma NEFA, and the other is an elevated plasma insulin. Both apparently alter hepatic metabolism. Other factors released by adipose tissue also may change hepatic function. Examples are leptin and TNF-α. The actions of insulin on the liver in obese persons has been the subject of an ongoing debate. One school of thought holds that high insulin levels overstimulate metabolic processes in the liver; if so, this overstimulation could be responsible for many of the metabolic complications of obesity. By contrast, another view maintains that obesity makes the liver resistant to insulin; if so, metabolic complications derive from the failure of insulin to suppress influential pathways. Moreover, the actions of obesity on lipoproteins that are secreted and removed by the liver are of special interest. For this reason, the relation between obesity and dyslipidemia must be considered in some detail.

Obesity and Fatty Liver

Obesity predisposes to fatty liver. The prevalence of obesity in the United States is rising and has brought greater attention to the problem of fatty liver. For many years, most cases of fatty liver were attributed to alcohol abuse. The mechanisms underlying alcohol-induced fatty liver are instructive for the pathogenesis of fatty liver in general. One route to elevated hepatic triglyceride is through increased synthesis of fatty acids in the liver. Another is through inhibition of assembly and secretion of triglyceride-rich lipoproteins (TGRLPs); failure to normally secrete TGRLPs leads to a retention of triglycerides in the liver. A third mechanism is defective oxidation of fatty acids. Alcohol-induced fatty liver seemingly results from all three mechanisms *(59,60)*; among them, reduced oxidation of fatty acids may be the most important. The latter results from a shift of the $[NAD^+]/[NADH]$ ratio to reduction *(59)*. Also, alcohol and its oxidative products may directly injure the mitochondria where fatty acids are oxidized, thus inhibiting fatty acid oxidation.

Whether accumulation of fat in the liver *per se* can cause cirrhosis is a disputed issue. Excess liver triglyceride could be toxic to liver cells, and if so, necrosis of liver cells could be a precursor to cirrhosis. A newly emerging pathologic condition is nonalcoholic hepatosteotosis (NASH). This form of fatty liver, whose cause is unknown, can result in cirrhosis in some patients. Fatty liver in NASH, of course, could be an epiphenomenon of an underlying process that itself produces cirrhosis. The packing of fat in liver cells nonetheless could be toxic, and in some obese patients with NASH, the fatty liver itself may be responsible for cirrhosis *(61–63)*. The possibility that triglyceride accumulation is hepatotoxic is supported by the observation that many patients with obesity manifest abnormalities in liver function tests (raised transaminases), even when cirrhosis is not present *(62)*. More and more, obesity is competing with alcohol abuse as a cause of fatty liver. The growing recognition of the common association of obesity and fatty liver in fact has led to a renewed interest in the causes of fatty liver. Obesity seems to provide an example of a fundamentally different mechanism for the development of fatty liver. All the metabolic changes induced by alcohol that produce fatty liver appear to occur directly in the liver. By contrast, the fatty liver of obesity seemingly has its origins in adipose tissue, outside the liver.

The primary cause of the fatty liver of obesity appears to be an increased plasma level of NEFA resulting from excess adipose tissue. The liver seemingly "sops up" excess NEFA; that is, it removes NEFA that were not taken up by skeletal muscle and other tissues. It might be theorized that excess plasma NEFA would just return to adipose tissue for reesterification; but, in fact, this pathway appears to be trivial. Instead, the liver serves as a transit mechanism for excess NEFA. Some of the excess fatty acids in the liver probably are oxidized. Even in the normal state, fatty acids probably are a major source of fuel for the liver. Limited evidence suggests that fatty acid oxidation by the liver is raised in obese persons *(64,65)*; enhanced oxidation will get rid of some excess fatty acids. The fatty acids that are not oxidized are reesterified into triglycerides and are incorporated into TGRLPs. The latter are secreted into plasma, and after lipolysis of their triglycerides by adipose tissue lipoprotein lipase, the locally released fatty acids enter adipose tissue, where they undergo reesterification into triglyceride. The liver thus serves as a necessary intermediate site in the cycling of excess fatty acids from adipose tissue back to adipose tissue.

In most nonobese persons, the influx of NEFA into the liver is low enough that fatty acids can be oxidized and/or resecreted (as TGRLP-triglyceride) without appreciable triglyceride accumulation. In the presence of obesity, however, the influx of NEFA exceeds the liver's ability to dispose of them, and triglycerides accumulate. This basic mechanism accounts for the fatty liver of obesity. Even so, the amount of triglycerides that accumulate in the liver of obese persons vary depending on several factors. The magnitude of the plasma NEFA flux undoubtedly is one. Persons with upper body obesity are more prone to fatty liver

than are those with lower body obesity. The former likewise has a higher flux of NEFA than does the latter. The excess visceral adipose tissue accompanying upper body obesity likely accentuates the amount of NEFA entering the liver. If an increased influx of NEFA coexists with a defect in fatty oxidation in the liver, triglyceride accumulation will be accentuated; excess NEFA thus may not be the only factor responsible for fatty liver in obese persons. Minor genetic defects in fatty acid oxidation may be relatively common and could contribute to fatty liver, as could an excess consumption of alcohol.

Obesity and Dyslipidemia

An increase in hepatic triglyceride content in obese persons sets the stage for the development of dyslipidemia. The most commonly recognized relation between obesity and serum lipids is an elevation in triglycerides. An elevation of serum triglycerides is a compensatory response to hepatic triglyceride overload. The incorporation of hepatic triglycerides into very low-density lipoprotein (VLDL) is necessary to complete the return of excess fatty acids back to adipose tissue. Isotope kinetic studies indicate that an increased secretion of VLDL triglycerides accompanies obesity *(66)*. Clearly, serum triglycerides vary from one obese person to another *(67)*. Secretion rates of VLDL thus are not the only factor determining serum levels of VLDL triglycerides; serum concentrations are affected both by hepatic secretion rates of VLDL and the efficiency of the lipolytic process. Rates of lipolysis of VLDL-triglyceride also are important; when lipolysis is sluggish, serum triglycerides will be raised *(67)*. Genetic factors affecting lipolytic processes almost certainly account for some of the variability in serum triglycerides in obese persons.

An important question is, Does excess hepatic triglyceride modify the number of VLDL particles produced in the liver? One theory holds that a fixed number of rudimentary VLDL particles are preformed, and triglycerides are inserted in the core of lipoprotein particles as the last step before secretion. If this mechanism pertains, obesity merely overloads VLDL particles with triglycerides, and the number of VLDL particles secreted by the liver is not changed in the obese state. An alternate theory contends that accumulated triglycerides in the liver recruit a greater number of lipoprotein particles to carry more triglycerides in the circulation. Studies in cellular systems support this second mechanism *(68)*, as do isotope kinetic investigations in humans *(69,70)*. Research in laboratory animals gives equivocal results *(71)*. This is an important issue because the serum concentrations of lipoprotein particles are determined in part by the number of particles secreted into the circulation. The number of circulating lipoproteins is identified by the serum concentration of apolipoprotein B-100 (apo B). The apo B–containing lipoproteins distribute between VLDL and low-density lipoprotein (LDL). Available evidence suggests that overweight patients tend to have abnormally high levels of apo B. These high levels are consistent with findings that obesity stimulates an overproduction of apo B–containing lipoproteins by the liver.

It might be expected that a high serum level of LDL–apo B would be reflected by an increase in LDL cholesterol. The relation between obesity and LDL-cholesterol levels, however, remains a topic of some debate. Nevertheless, cross-sectional data suggest that obesity produces higher LDL-cholesterol concentrations *(72,73)*. Support for a positive relationship comes from the well-described rise in serum LDL cholesterol with aging. This rise appears to be closely associated with the weight gain that occurs with aging; in population surveys, at any given age range, higher body mass indexes are accompanied by higher LDL-cholesterol concentrations *(74)*. On the other hand, weight reduction in humans does not consistently reduce LDL-cholesterol levels *(75)*. The latter finding, however, may be confounded by an increase in particle size of LDL with weight loss. In the obese state, a higher serum LDL–apo B level may not be accompanied by a higher LDL-cholesterol level because LDL particles are small, dense, and partially depleted of cholesterol. Small, dense LDL in fact is characteristic of obese persons and seems to be the result of higher triglyceride levels and possibly higher activities of hepatic lipase. With weight loss, LDL particles become larger because of enrichment with cholesterol. Thus, with weight loss, the concentration of LDL particles may fall even though the LDL-cholesterol level does not decline. In overweight persons, the serum level of LDL–apo B thus may be a better indicator of the influence of obesity on LDL metabolism than is the LDL-cholesterol level.

Recent research highlights yet another factor that modulates lipoprotein metabolism and may be affected by obesity: apo CIII, an apolipoprotein that both inhibits lipoprotein lipase and retards removal of VLDL remnants via LDL receptors. One report indicates that the gene for apo CIII has an insulin-response element *(76)*; if so, the synthesis of apo CIII may be increased in overweight persons. Apo CIII inhibition of VLDL catabolism could raise serum triglycerides over that caused by an overproduction of VLDL triglycerides.

Another lipoprotein modulator that is affected by obesity is hepatic lipase. This enzyme promotes the catabolism of HDL and may favor the formation of small, dense LDL *(77)*. In obese subjects, the activity of hepatic lipase typically is high *(78)*. This higher hepatic lipase undoubtedly contributes to lower HDL-cholesterol levels, which are commonly observed in overweight persons.

It is unlikely that the only role of the liver in obesity is to serve as a conduit for excess fatty acids. An increased input of fatty acids into the liver almost certainly modifies other pathways of hepatic metabolism. This likelihood

remains to be fully explored. High concentrations of fatty acids in the liver seemingly drive an increased oxidation of fatty acids. The increase in high energy bonds produced by a high fatty acid oxidation thus could stimulate various metabolic processes, such as protein synthesis. Increased syntheses of hepatic lipase and apo CIII could be responses to increased fatty acid oxidation. In addition, Randle et al. *(23)* postulate that the fatty acid–glucose cycle operates in the liver; if so, obesity may shift hepatic fuel toward fatty acids and away from carbohydrate. This possibility raises the question, Could a shift in fuel source to fat induce insulin resistance in the liver?

Let us therefore return to the significance of hyperinsulinemia vis-à-vis hepatic metabolism in obese persons. If the liver is "insulin resistant" in overweight persons, the action of insulin in this organ will be impaired, and, consequently, insulin will fail to inhibit gluconeogenesis and reduce hepatic glucose output. Moreover, there would be a failure to promote glycogen synthesis; to suppress fatty acid oxidation and ketogenesis; and to inhibit the formation of apo B, apo CIII, and hepatic lipase. On the other hand, should the liver respond appropriately to a high plasma insulin, there would be an inhibition of fatty acid oxidation and diversion of fatty acids into TGRLP. Elucidation of the effects of insulin on the liver in obese persons is complicated by the fact that insulin modifies the substrate supply to the liver by inhibiting NEFA release from adipose tissue and by inhibiting production of gluconeogenic precursors by muscle. In the presence of a generalized insulin resistance, hepatic metabolism thus is altered by an increased influx of fatty acids and gluconeogenic substrate. Although the liver seemingly responds to an increased influx of NEFA in obese persons by becoming insulin resistant, the full impact of obesity on hepatic metabolism remains to be elucidated.

In summary, obesity underlies a pattern of dyslipidemia called atherogenic dyslipidemia *(79)*. It is so named because it commonly associates with premature CHD. This pattern includes raised triglycerides, small LDL particles, low HDL cholesterol, and increased total apo B *(79)*. Nonetheless, the specific distribution of lipoprotein abnormalities in patients with atherogenic dyslipidemia varies, and this variation likely reflects genetic variability. Differences in the expression of atherogenic dyslipidemia serve as a prime example of the interaction between obesity and genetics and also illustrate how the adverse metabolic consequences of obesity are moderated by genetic influences.

Obesity and Cholesterol Gallstones

Obese persons carry increased risk for cholesterol gallstones *(80)*. They often have lithogenic bile, i.e., containing more cholesterol than can be held in solution by the solubilizing lipids (bile acids and phospholipids) *(81)*. Obese women secrete lithogenic bile more often than men and thus develop gallstones more readily. In addition, some racial groups are genetically predisposed to cholesterol gallstones, including Native Americans in both North and South America, Hispanics with Native American genes, and Scandinavian women. Conversely, African Americans have a lower propensity to gallstones than do Caucasian Americans. Most genetic differences in susceptibility for cholesterol gallstones appear to be owing to differences in the prevalence of lithogenic bile.

The primary cause of lithogenic bile in obese persons is an excessive synthesis of cholesterol *(82)*. Most of this excess synthesis presumably occurs in the liver, but other tissues may produce too much cholesterol as well. Overproduction of cholesterol raises the secretion of cholesterol into bile *(83,84)*. Obese persons tend to compensate by synthesizing more bile acids and phospholipids in the liver, but the excess of biliary cholesterol often exceeds the solubilizing capacity of these other lipids. When this occurs, lithogenic bile is the result. With lithogenic bile, cholesterol tends to spontaneously form cholesterol crystals, which can aggregate an initiate formation of cholesterol gallstones *(81)*.

Native Americans have two defects in sterol metabolism that confer extreme susceptibility for gallstone formation. Besides an overproduction of cholesterol owing to obesity, they have a defective synthesis of bile acids *(83)*. Consequently, the bile becomes highly lithogenic, and gallstone formation is unusually common. Presumably a similar combined defect is responsible for a high prevalence of cholesterol gallstones in the Hispanic population. Even in Caucasian premenopausal women, estrogens also may disturb bile acid synthesis and predispose to gallstone formation when they become obese.

Effects of Obesity on Blood Pressure and Cardiovascular-Renal Function

Although hypertension is a well-recognized component of the metabolic syndrome, the mechanistic relation between obesity and hypertension remains unknown. No single mechanism has been identified to explain why obesity raises blood pressure (BP). Causation most likely is multifactorial. Moreover, obesity has adverse effects on cardiovascular and renal functions that go beyond higher BP.

Many obese patients do not have categorical hypertension. Hence, some investigators doubt that obesity has allpervasive effects on BP. However, Hall et al. *(85)* have pointed out that persons who have a relatively low baseline of BP may not demonstrate a rise in pressure to categorical hypertension despite a significant increase. This is a critical insight. The positive relationship between BP and cardiovascular disease holds over a broad range of BP levels. A rise in pressure from low normal to high normal therefore

can increase the risk for cardiovascular disease, especially when it occurs in the setting of other components of the metabolic syndrome.

Although obesity undoubtedly raises BP, much of the research on hypertension in recent years has shifted to its "genetic component" *(86,87)*. This shift is not surprising because of a growing emphasis on molecular biology. So far, several instances of monogenic disorders causing hypertension have been identified *(88)*. These, however, cannot account for most cases of hypertension. Instead, hypertension represents what human geneticists call a "complex genetic disorder." BP regulation is achieved by the interactions of multiple tightly interrelated systems. Genetic modification in any of these systems could, and probably does, affect baseline BP levels. Obesity likely affects these same systems. In overweight persons, therefore, the interplay of obesity and genetic variation acting together on several different regulatory systems probably combines to produce hypertension. BP also is known to rise with advancing age. Some of this rise almost certainly can be explained by the weight gain with aging. Nonetheless, the aging process itself likely represents another factor that determines BP in middle-aged and older persons. The influence of obesity on BP, like that of genetics, probably is multifactorial. A single mechanism has not been identified to account for the effects of obesity on BP. Research, however, has uncovered several possible links, which are reviewed briefly in the following sections.

Insulin Resistance, Hyperinsulinemia, and Hypertension

The strong association between obesity and BP naturally raises the question, Is the insulin resistance of obesity a linking factor? Research on this question focused first on the causative role of the two factors: hyperinsulinemia and insulin resistance. Two possible mechanisms whereby an elevation in plasma insulin might raise BP were postulated from earlier studies in small animals: increased activity of the sympathetic nervous system and/or retention of sodium by the kidney *(89,90)*. Recent investigations, however, have failed to confirm a hypertensive effect of hyperinsulinemia *(91)*. Thus, if hyperinsulinemia itself does not directly raise BP, could the more generalized disorder, insulin resistance, produce metabolic changes that will raise BP? This is an exceedingly difficult question to answer. Because the actions of insulin are pleotropic, an impairment in the responsiveness to insulin could affect many pathways, some of which could influence BP. As of yet, specific metabolic pathways whereby the cascades of intracellular action of insulin modify BP have not been identified. Nonetheless, some of the pathways stimulated by insulin could affect BP; if so, insulin resistance could raise BP. This possibility awaits further investigation.

Cardiac Output and Regional Blood Flow

Obesity seemingly leads to volume expansion and increased cardiac output. Abnormalities in regional blood flow to the kidneys, gastrointestinal tract, and skeletal muscle also have been reported *(92)*. These various changes could raise BP. The impact of obesity on cardiac hemodynamics probably is greater than revealed by usual investigations. For example, recent studies suggest that obesity accentuates cardiac hypertrophy at any level of BP *(93,94)*. An increased resting heart rate in an obese person also may be owing to autonomic dysregulation somehow induced by the obese state *(95)*. These changes could predispose to cardiovascular disease independently of obesity.

Renal Function

In some obese persons, renal-pressure natriuresis seemingly is impaired, leading to sodium retention. This retention of sodium likely contributes to the volume expansion. Hall et al. *(85)* speculate that four factors may impair pressure natriuresis: insulin resistance, activation of the renin-angiotensin system, increased activity of the sympathetic nervous system, and compression of the renal medulla by excess adipose tissue. Various lines of experimental evidence support each of these mechanisms; in truth, all may be involved.

In summary, obesity appears to adversely affect renal function, leading to volume expansion and increased cardiac output. In addition, obesity may induce abnormalities in the autonomic nervous system, raising the heart rate and increasing peripheral insulin resistance. In some persons, the action of obesity to raise BP is only moderate, and categorical hypertension may not develop. In others, who are genetically predisposed to high BP, frank hypertension usually will develop. Moreover, the natural tendency of BP to rise with aging will be accentuated in older patients if they are obese. The prevalence of hypertension is already high in the United States and will increase even more as the average age of the population increases and as obesity becomes more common. It must be recognized as well that obesity contributes importantly to high-normal BP, which is a common component of the metabolic syndrome. The impact of obesity on cardiovascular risk therefore is mediated in no small part through its influence on the BP.

Obesity and a Prothrombotic State

One of the emerging risk factors for cardiovascular disease is a prothrombotic state. Some of the factors listed in the prothrombotic state are plasminogen activator inhibitor-1 (PAI-1), fibrinogen, von Willebrand factor, and factor 7 activity *(96,97)*. The mechanistic link between elevations in these factors and the development of CHD remains to be determined. Speculation nonetheless centers on three mechanisms. First, high plasma levels of pro-

thrombotic factors could impair endothelial function, which may promote atherogenesis. Second, if atherogenesis proceeds by a process of microscopic plaque ruptures, as some researchers believe, an excess of coagulation factors should increase the size of microthrombosis with each rupture. Organization of these microthrombi will enlarge the atherosclerotic lesion. Finally, if a macroscopic plaque rupture occurs, a prothrombotic state will produce a larger thrombi, causing more severe clinical sequelae (unstable angina and myocardial infarction).

All the aforementioned coagulation factors have been reported to be increased in patients with obesity *(98–101)*. Among these, PAI-1 seemingly can be synthesized by adipose tissue *(101–106)*. An excess of adipose tissue thus may be one source of the high plasma levels of PAI-1 reported in patients with upper body obesity. Although adipose tissue may contribute to excess coagulation factors, the liver could be another source. Regardless, high plasma levels of coagulation factors including PAI-1 leading to a prothrombotic state could be one mechanism whereby obesity raises the risk for CHD.

Obesity and Cancer

The relationship between nutrition and cancer is extremely complex. Many lines of research point to nutritional factors influencing susceptibility to various forms of cancer. One of these factors appears to be energy balance. The presence of obesity is one indicator of nutritional imbalance. At the least its presence reflects the ingestion of more nutrient energy than required to maintain a desirable weight. Many studies report that obese persons are more susceptible to different forms of cancer, especially colon, breast, and prostate cancers, than are people of desirable weight *(107–111)*. The mechanisms underlying this increased susceptibility remain unknown. Some researchers evoke endocrine alterations induced by obesity. Others speculate that the presence of obesity reflects the overconsumption of tumor-promoting nutrients. Alternatively, the release of proinflammatory factors by adipose tissue could modify cell replication. Because so little is known about the pathogenesis of common tumors, particularly the role of external influences, it is difficult to do more than speculate about the nature of the association between obesity and cancer. Regardless of mechanism, obesity appears to be a susceptibility factor for cancer, and this association provides an additional rationale for efforts to avoid or mitigate excess body weight.

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