Multifactorial causation of obesity: implications for prevention1,2

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ABSTRACT  Obesity threatens to become the foremost cause of chronic disease in the world. Being obese can induce multiple metabolic abnormalities that contribute to cardiovascular disease, diabetes mellitus, and other chronic disorders. Unfortunately, prevalence of obesity is increasing both in the United States and worldwide. Reasons for the rising prevalence include urbanization of the world’s population, increased availability of food supplies, and reduction of physical activity. Although severe obesity has received much attention in the clinical setting, most obesity in the general public is only moderate. Even so, moderate obesity can elicit several metabolic abnormalities that are precursors to chronic disease. Therefore, for the population as a whole, moderate obesity is responsible for most obesity-related disorders. Moderate obesity is undoubtedly multifactorial in origin, and acquired influences probably exceed genetic factors in its causation. These acquired causes thus deserve greater attention in the development of a public health strategy for the control of overweight in the general population. A major public health effort is urgently needed to counter the increasing frequency of moderate obesity in the United States and throughout the world. Am J Clin Nutr 1998; 67(suppl):563S–72S

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INTRODUCTION

Obesity threatens to become the 21st century’s leading health problem. As more nations become industrialized and urbanized, the prevalence of obesity will inevitably rise. The cause of this increasing prevalence is twofold: food is more available to everyone, and the physical activity of workers is reduced with increasing urbanization. Recent breakthroughs leading toward understanding of the genetic basis of obesity in laboratory animals have focused attention on the endogenous causes of weight gain, but powerful socioeconomic forces are at work that can largely account for the alarming increase in the worldwide prevalence of obesity. In the future, the medical complications of obesity will impose a heavier burden on the already fragile health-care systems of many nations. Although the complications of obesity are not as dramatic as those of HIV and other infectious diseases, these complications will affect more people and will demand more long-term care for affected persons than will those of infectious disease. Consequently, obesity-induced diseases will increasingly compete with infectious diseases for health-care resources in the next century.

COMPLICATIONS OF OBESITY

Obesity and metabolic syndrome

The metabolic abnormalities engendered by obesity occur in the cardiovascular system. These abnormalities can be called risk factors because they raise the likelihood for cardiovascular disease. The major metabolic risk factors resulting from obesity are as follows: 1) atherogenic dyslipidemia (borderline-high total cholesterol concentrations, raised triacylglycerol concentrations, small LDL particles, and low HDL concentrations), 2) raised blood pressure, 3) insulin resistance and glucose intolerance, and 4) abnormalities in the coagulation system (procoagulant state) (1). This constellation of risk factors is particularly common in persons who develop premature coronary heart disease (CHD), ie, CHD before age 65 y (2, 3). Some investigators believe that insulin resistance is the root cause of this group of risk factors; hence, they favor the term insulin resistance syndrome (4–6). A reduction in insulin sensitivity, however, may be but one of several abnormalities resulting from a generalized metabolic derangement induced by obesity. Thus, a more generic term for the syndrome of multiple metabolic risk factors, metabolic syndrome (1), seems more appropriate and will be used in this article to denote the constellation of risk factors commonly associated with obesity.

The mechanisms whereby obesity predisposes one to metabolic syndrome are not fully understood. Ideally, an energy imbalance leading to energy overload would result in excess fat being stored inertly in adipose tissue. In some overweight persons, this ideal state may pertain. In many others, however, energy overload is not adequately contained by adipose tissue and several tissues are exposed to excessive nutrient substrates. Some of this tissue overload can occur during disposal of nutrients in the postprandial state. However, even in the fasting state a large release of nonesterified fatty acids from adipose tissue accentuates the overload (7–9).

Several tissues bear the brunt of high fasting concentrations of nonesterified fatty acids in obesity. Skeletal muscle, the major site of nonesterified fatty acid utilization (5), is one target. According to Randle et al (10), increased muscle uptake of nonesterified fatty acids in obese persons shifts energy utilization...
from carbohydrates to fatty acids. This shift leads to resistance to the action of insulin in muscle (11, 12), which creates a tendency for hyperglycemia requiring multiple metabolic adjustments.

Another target for fatty acid overload is the pancreatic β-cell. Peripheral insulin resistance engendered by obesity is accompanied by hyperinsulinemia (13, 14). Impaired glucose uptake by skeletal muscle possibly signals pancreatic β-cells to secrete more insulin. Moreover, high nonesterified fatty acid concentrations may act directly on β-cells to prime them for enhanced insulin secretion in response to any given serum glucose concentration (15). Prolonged overstimulation of insulin secretion by β-cells may eventually impair β-cell function, thereby reducing insulin secretion and leading to type 2 diabetes (16, 17).

A third major target of nutrient overload is the liver. High concentrations of circulating nonesterified fatty acids, both in fasting and postprandial states, promote hepatic uptake of nonesterified fatty acids, enhance hepatic synthesis rates of triacylglycerol and cholesterol, and increase secretion rates of VLDLs (18–21). Many of the abnormalities in serum lipoprotein characteristics in atherogenic dyslipidemia apparently derive from the hepatic oversecretion of VLDLs. The increased VLDL particles entering the bloodstream raise both plasma triacylglycerol and cholesterol concentrations (18, 19). The higher triacylglycerol concentrations in turn engender smaller LDL particles (22, 23) and decrease concentrations of HDL cholesterol (24). In addition, obesity apparently increases the activity of hepatic triacylglycerol lipase (25, 26); this change also may reduce LDL particle size (27) and lower HDL cholesterol concentrations (28, 29).

It has been proposed that hepatic overproduction of VLDL due to high nonesterified fatty acid concentrations in obese persons is accentuated by elevated serum insulin concentrations (30). Insulin stimulates the synthesis of malonyl CoA (31), an inhibitor of fatty acid oxidation. Thus, high insulin concentrations could inhibit fatty acid oxidation by enhancing synthesis of malonyl CoA; consequently, more fatty acids would be available for VLDL-triacylglycerol synthesis (30). Finally, the combination of high plasma concentrations of both nonesterified fatty acids and insulin, which is characteristic of obese patients, may enhance the synthesis of coagulation proteins, giving rise to a procoagulant state (32–34).

A fourth target of the obese state is the cardiovascular system. Obesity is commonly accompanied by elevated blood pressure. High insulin concentrations may modify the function of the autonomic nervous system or raise arteriolar tone (35). Whether the hypertension associated with obesity is secondary to hyperinsulinemia per se or a more generalized metabolic disorder characteristic of the insulin-resistant state remains to be elucidated.

It must be noted that the ability of adipose tissue to keep nonesterified fatty acids out of the bloodstream varies from person to person. Release of nonesterified fatty acids is required to ensure an energy source in the fasting state, but excessive release leads to tissue lipid overload. Various adipose tissue disorders are responsible for abnormally high nonesterified fatty acid concentrations, tissue lipid overload, or both. Normally, nonesterified fatty acid secretion is appropriately regulated physiologically by insulin. However, in simple obesity per se, nonesterified fatty acid release escapes the normal insulin regulation and leads to high nonesterified fatty acid concentrations. This is accentuated when most fat is located in the trunk, ie, when a person has truncal obesity (8). Finally, in more extreme forms of adipose tissue disorders, eg, partial lipodystrophy and generalized lipodystrophy, nonesterified fatty acid release is disrupted even more, leading to severe tissue lipid overload.

Although obesity and related adipose tissue disorders are major contributing causes of metabolic syndrome, other factors undoubtedly augment metabolic risk factors. For instance, physical inactivity can worsen insulin resistance and promote development of metabolic abnormalities (36). In the general population, therefore, physical inactivity and obesity go hand in hand in causation of metabolic syndrome. In addition, the composition of the diet may play a role. A diet high in animal fat will enrich the nonesterified fatty acid pool with saturated fatty acids and thereby raise serum LDL cholesterol concentrations (37); furthermore, excessive intakes of carbohydrate will raise serum triacylglycerol and reduce HDL cholesterol concentrations (38). Aging is another factor because the risk factors of metabolic syndrome are well known to worsen with increasing age. Finally, genetic factors frequently influence the severity of the risk factors that develop under the stress of the other causative factors (1). As will be discussed later, some populations seem to be genetically prone to developing particular patterns of risk factors.

Relation of obesity-induced risk factors to CHD

A topic of great importance and complexity is the mechanistic explanation of metabolic syndrome whereby different risk factors, which are worsened by obesity, increase the risk for CHD. It may be conceptually useful to juxtapose metabolic syndrome with elevated serum concentrations of LDLs. The past decade has witnessed growing evidence that high LDL cholesterol concentrations are a prerequisite cause of coronary atherosclerosis. High serum LDL concentrations initiate atherogenesis by inducing fatty streaks in the coronary arteries (39, 40); moreover, with severe LDL elevations, full-blown coronary atherosclerosis and premature CHD often occur in the absence of other risk factors (41). Findings from clinical trials showing that a marked lowering of serum LDL concentrations is accompanied by a dramatic reduction of acute coronary events (42–44) confirm that high LDL concentrations play a major role in atherogenesis even in late stages, including the end-stage changes leading to clinical events. The mechanisms whereby elevated serum LDL concentrations lead to unstable coronary plaques and acute coronary events are a subject of growing interest (45, 46). The designation of high LDL cholesterol as the essential risk factor of CHD does not downplay the importance of the other risk factors, but it does emphasize that the adverse effects of the other risk factors are greatly enhanced by a rising LDL concentration. Moreover, in populations in which LDL cholesterol concentrations are low, CHD rarely develops even when the prevalence of other risk factors is high. In contrast, when metabolic syndrome exists in the presence of high LDL concentrations, risk for CHD is greatly accentuated.

The major life habit that causes elevated LDL cholesterol concentrations is high intake of saturated fatty acids and cholesterol. In addition, increasing obesity contributes to rising serum concentrations of LDL cholesterol (47, 48). The other lipid-related risk factors—high VLDL concentrations (49), small LDL particles (50), and low HDL concentrations (51, 52)—are also induced by obesity (53), and these risk factors apparently augment the atherogenicity of elevated serum LDL (1). There is growing evidence that each of these other lipid risk factors is independently atherogenic. Some forms of VLDL, especially smaller VLDL particles, probably rival LDL in atherogenic...
potential. High serum VLDL concentrations may augment atherogenesis in other ways as well, notably by generating smaller LDL particles and by reducing serum HDL concentrations (54). Many reports indicate that combining these other lipid risk factors with an elevated serum LDL concentration enhances CHD risk more than high serum LDL alone (49–52).

The nonlipid risk factors engendered by obesity—hypertension, insulin resistance, glucose intolerance, and a procoagulant state—further accelerate atherogenesis, increase risk of CHD, or both. Despite years of research, much has yet to be learned about mechanisms whereby each of these factors exert their adverse effects. Hypertension may produce endothelial damage, force more LDL into the arterial intima, and promote smooth muscle cell proliferation. Insulin resistance, hyperinsulinemia, or both may directly and adversely affect arterial walls (55). When type 2 diabetes develops, the resulting hyperglycemia may promote glycation of lipoproteins and cause accumulation of advanced glycation products, and both changes probably attract macrophages into the arterial wall (56). A procoagulant state in conjunction with obesity could lead to CHD in several ways (57, 58): it could induce endothelial dysfunction and precipitate microthrombi, which could accelerate atherogenesis, or it could enhance the size of a thrombus occurring in response to a plaque rupture, which could worsen the severity of acute coronary syndrome, if present. Future studies in vascular biology should yield important information on the mechanisms whereby nonlipid risk factors enhance atherogenesis in the presence of the lipid-related risk factors induced by obesity.

PATTERNS OF WEIGHT GAIN WITH AGING

The current trend of body weight gain in the United States is part of a changing pattern of body fat content worldwide; however, this trend seems to be accentuated in the American public. Obesity stands out as being increasingly prevalent, and there is a disproportionate increase in the number of severely overweight people (59). A general impression holds that Europeans are less obese than Americans; but even so, many European countries are experiencing a rise in the prevalence of obesity (60–63). In Eastern Europe and Russia, obesity is already commonplace and is undoubtedly contributing to an alarming increase in cardiovascular diseases in these regions. In both Eastern and subcontinental Asia, the prevalence of obesity lags behind that in the United States, but is rising (64, 65). Industrialization and adoption of Western lifestyle habits clearly predispose these populations to weight gain and metabolic syndrome. In Africa and the Middle East, a similar picture is emerging (66, 67). Although famine and malnutrition may be highlighted by the media, the reality in most of these countries is a trend in the opposite direction, toward an increased prevalence of obesity.

The estimated prevalence of obesity in a particular country depends on how obesity is defined. Governmental agencies in the United States have defined overweight as a body mass index (BMI in kg/m²) > 27.8 for men and > 27.3 for women (59). These values correspond with the 85th percentile for the adult population of the United States from 1978 to 1980, as determined by the second National Health and Nutritional Examination Survey (NHANES II) (68). According to these definitions, 24% of adult men and 28% of adult women in the United States were overweight from 1978 to 1980 (68). In 1988 and 1991, these percentages rose to 31% and 34%, respectively (59, 69). The prevalence of obesity is particularly high among black women and Hispanic men and women (59, 69).

These definitions of overweight are conservative and do not take into account the fact that lesser degrees of overweight can have significant untoward effects (70). For this reason, a different definition of overweight that takes the metabolic consequences of overweight into account more accurately should probably be used. Accordingly, a BMI in the range of 25–26.9 should be defined as borderline (moderate) obesity; the range of 27–30.9, obesity; and ≥ 31, marked obesity. BMIs are valuable for defining degrees of obesity in populations. For individuals, however, BMIs as used to estimate body fat content do not always apply. A more direct clinical assessment of body fat and fat distribution may be required.

The often subtle nature of obesity is revealed by the tendency for gradual weight gain with increasing age. For example, the average American adult gains ≈10 kg between age 20 and 50 y (71). This weight gain is not accompanied by more muscle mass in most cases; in fact, muscle mass usually declines with aging (72). Most of the increment in weight thus occurs in adipose tissue (72). Moreover, if muscle mass decreases with aging, the increment in adipose tissue mass may actually exceed absolute weight gain. When adipose tissue mass increases, not all of the gain is in the form of fat (triacylglycerol) per se. Adipose tissue itself contains a component of lean body mass; ≈25% of the increment in weight occurs in the lean portion of adipose tissue (73).

When young adults gain weight, extra muscle mass may develop to support the increased adipose tissue weight (74), but because aging itself is usually accompanied by loss of muscle mass, body fat probably accounts for most of the weight gained with aging.

If the weight gain of ≈10 kg with aging is the average, many Americans obviously will gain even more, and they will be in even greater danger of experiencing the metabolic consequences of obesity. Although many Americans will gain <10 kg, a detrimental effect from lesser weight gain can still occur. Even modest gains in weight can produce adverse metabolic effects in susceptible persons, such as those with a predisposition to truncal obesity. The risk of cardiovascular disease will be accentuated when weight gain accompanies reduced physical activity and high intakes of saturated fatty acids. Some people are resistant to the potentially adverse effects of weight gain and do not develop coronary risk factors or type 2 diabetes. Many others, however, are genetically susceptible to the development of risk factors; in them, any weight gain can bring one or more risk factors to the fore (75). Genetic susceptibility dictates that some persons will acquire dyslipidemia with weight gain, others will become hypertensive, and still others will eventually develop type 2 diabetes. This interaction between weight gain and a genetic susceptibility to risk factors represents fertile ground for future investigation. Perhaps the most striking example of an adverse response to moderate weight gain is found in subcontinental Asia, where people traditionally lived in rural areas, engaged in heavy physical labor, and subsisted on limited food resources. For this population, these life habits resulted in a low percentage of body fat. Under such conditions, the adverse consequences observed in states of nutrient overload are virtually nonexistent. In recent years, however, the life habits of many subcontinental Asians have changed. Their societies are becoming more urbanized and industrialized. The food supply is growing, and physical activity is declining. The result is weight gain in the population (76). So far, weight gain in subcontinental Asians has not
been marked compared with that in the populations of many Western nations, but even with moderate overweight, metabolic abnormalities and disease complications are occurring with increasing frequency. Of particular note, serum LDL cholesterol concentrations, insulin resistance, and glucose intolerance are rising in subcontinental Asians. This multiplication of risk factors underlies a striking rise in the frequency of CHD (77).

Changes in life habits and the prevalence of risk factors are particularly evident in subcontinental Asians who migrate to various industrialized countries. In their new countries, overeating and physical inactivity are becoming a way of life. As migrating Asians lapse into these habits, their risk for CHD increases disproportionately (78–85). Subcontinental Asians almost certainly are genetically susceptible to acquiring risk factors. No single risk factor consistently stands out above the others, except perhaps a state of insulin resistance and a tendency to develop type 2 diabetes (85, 86). Commonly, several metabolic risk factors cluster in milder forms in a single person. The coexistence of these multiple risk factors probably accounts for unusually high rates of CHD in persons migrating from the subcontinent.

Although a high proportion of subcontinental Asians are susceptible to developing multiple metabolic risk factors with small gains in weight, persons from other populations are genetically susceptible to more severe forms of one or another risk factor. For instance in the United States, African Americans are known to be unusually prone to hypertension, European Americans to dyslipidemia, and Hispanic Americans and Native Americans to type 2 diabetes (87, 88). Despite these generalizations, some people in each of these populations will manifest multiple risk factors, similar to subcontinental Asians, and hence will be unusually susceptible to premature CHD.

CAUSES OF WEIGHT GAIN WITH AGING

The causes of weight gain with aging undoubtedly are multifactorial. Efforts to identify these causes seem worthwhile because each could be a target for public health intervention. The discussion to follow will speculate on these causes, with the aim of fostering the development of a public health strategy for the prevention and control of obesity in the general population. Because weight gain typically occurs slowly over decades, from age 20 to 50 y (71), most causes of weight gain must be insidious. Certainly in some persons the gain can occur in sizable, short-term increments followed by stable periods. Many people probably are unaware of gradual accumulation of body fat, or may view it as innocuous and inevitable, even as a sign of maturity. Efforts to prevent slow weight gain are often lessened by a lack of immediate adverse consequences. Regardless of causative factors, prevention will require a change in life habits brought about by some mental effort, often going against the grain of social pressures. There probably are many reasons why weight control is rarely given a high priority in young adulthood and early middle age. We should not dismiss the possibility, however, that one important reason is that the factors causing weight gain are not well understood. An effort should be made to identify them and to define their contribution more precisely.

Decline in resting metabolic rate

Several reports note that the resting metabolic rate (RMR) declines with age (72, 89–92). The major reason is probably an age-related reduction in muscle mass. Muscle metabolism contributes importantly to RMR, and its decline with aging leads to a proportional decrease in RMR. If energy intake does not fall in parallel with loss of muscle mass, body fat will increase. Some studies, however, suggest that the decline in RMR with aging cannot be explained entirely by a decrease in muscle mass (71–73). Seemingly, less metabolic energy is wasted in older people, possibly due to a reduction in futile metabolic cycling. This latter possibility deserves more research, whereas efforts to maintain muscle mass through physical activity must also receive a high public health priority.

Decline in physical activity

Many people become progressively more sedentary as they pass through adulthood. Adolescents and young adults commonly engage in sports and other physical activities; older people tend to give these up. Frequently, sports-related injuries enforce physical inactivity. As family responsibilities mount, more time goes toward earning a living or caring for children, and less time is available for physically active recreation. Nowadays most work is sedentary in nature. Even the physical work of manual jobs is reduced by machines that do the work. Energy expenditure through physical activity thus is at a new low in the United States (93).

To make matters worse, physical activity in childhood and adolescence appears to be on the decline (94). Watching television and playing computer games cuts into time formerly spent in outdoor play. Urban decay and crime make playgrounds unavailable after school. For safety’s sake, children often go home immediately after school and lock themselves indoors. Parents at work cannot oversee their children’s activities. Children frequently spend their late afternoons watching television and snacking. An alarming increase in obesity in children and adolescents can be explained partly by these changes in society and culture (95). This obesity is usually carried into adulthood.

Increase in food intake with aging

Although much of the weight gain with aging is probably related to declining energy expenditure, food intake may actually increase after age 20 y. Food supplies are abundant in the United States and many other countries. With marriage often comes new pressures to eat more from families and friends. Meals become more regular, more frequent, and often more generous. Extra eating and drinking after dinner can become a regular habit. Food may be used to express or elicit affection; when so, it is often rich in energy. Working couples eat out more, and restaurants compete with one another by providing larger and more tempting meals. More leisure time is available, thus increasing the opportunities for socialization—and eating is typically a prominent part of social gatherings.

Another cause of overeating and weight gain can be the stress of adult life. With modern life comes greater competition and challenge, compounding the usual stresses of social and family responsibilities. A common pattern of response is to fall back on pleasurable escapes. All too common examples are smoking, drinking, and eating. Those resorting to eating for pleasure and relief of nervous tension often manifest excessive weight gain. A common pattern in overweight, middle-aged adults includes periods of weight gain while under stress followed by efforts at weight control at other times; often, weight gain wins out over control. Thus, the gain of weight with aging, seen with greater frequency, may be partly the result of overeating, in response to social trends and stresses of modern, urbanized society.
High-fat diets

Some investigators contend that diets high in fat account for much of the obesity in industrialized societies (96–99). The fat content of the diet generally does not increase with aging, however, so it cannot be the major cause of weight gain. According to one view, nonetheless, excess nutrient energy is consumed more readily when the diet contains a high percentage of fat because of the high energy density of fat. In other words, if all other eating behavior is equal, more weight should be gained in persons consuming high-fat diets than in those consuming low-fat diets. This phenomenon definitely occurs in laboratory animals. Many species of mice and rats fed ad libitum with high-fat diets gain more weight than those fed low-fat diets (99). To the extent that body weight in humans is unconsciously determined, the ingestion of high-fat diets over a period of many years could produce gradual weight gain.

It has been suggested that high-fat diets will cause weight gain relative to low-fat diets even when the diets are isoenergetic. A notion advanced is that thermal and metabolic energies of fats and carbohydrates are not equivalent, and that fats contain a higher metabolic energy than do carbohydrates. However, this concept is probably not valid: long-term studies in humans comparing high-fat and high-carbohydrate diets under controlled conditions fail to show differential effects on body weight (100).

Experiments showing that high-fat diets promote weight gain in animals lead us to ask whether body weight is regulated through conscious or unconscious mechanisms. We can assume that rodents are unaware of the relation between food intake and body weight, and that they do not care what they weigh. To the extent that the same is true of humans, diets of high nutrient energy density, such as high-fat diets, may support weight gain over prolonged periods. However, diets high in carbohydrate and low in fat are no sure defense against the development of obesity. In the United States, low-fat food items are increasingly available and are eaten in response to national recommendations to reduce dietary fat. National surveys further indicate that the percentage of total nutrient energy consumed as fat is declining (101). However, there is no evidence that body weight is declining in response to decreasing fat intake; in fact, according to data from several surveys (59, 62, 68, 69, 102), average body weight is rising. Moreover, in many European countries where obesity is less prevalent than in the United States, the percentage of nutrient energy in the form of fat is higher than in the United States. Thus, there is a growing realization among many investigators that decreasing the percentage of total nutrient energy from fat is not the solution to worsening obesity in the United States. With little doubt, a reduction in nutrient energy intake with aging will be required as one component of a program to prevent age-related weight gain, along with a decrease in fat intake. But weight gain cannot be prevented simply by substituting carbohydrates for fat (98, 100). To achieve this aim, carbohydrate intake must either remain the same, that is, not replace removed fat, or decrease as well.

Social and cultural factors

Personal attitudes toward body weight and fatness vary considerably among different social and cultural groups. Differences in attitude undoubtedly affect prevalence rates of obesity in various social and ethnic groups. In some developing countries, obesity is a symbol of affluence, and thus is to be desired; the most affluent therefore are the most obese. In the United States and Western Europe, in contrast, affluent people usually shun obesity. In these countries, social standing views obesity as undesirable. In the upper socioeconomic strata in these countries, social pressures mount against obesity in adolescence and against weight gain with aging. Indeed, the high prevalence of eating disorders (anorexia nervosa and bulimia) among adolescents in the affluent subpopulations may be due to social pressures. Eating disorders could be worsened by the fear of social rejection should obesity occur because of over-consumption of foods. In contrast, the high prevalence of obesity among older African American and Hispanic women appears to be more acceptable, perhaps a symbol of motherhood and dignity. Regardless, the differences in prevalence of obesity among ethnic groups and between more and less affluent populations in the United States point to the powerful influence of social and cultural factors in the causation of obesity.

Genetic factors

Studies in identical twins strongly imply that body weight in humans is under genetic control (103). Moreover, findings in genetic epidemiology suggest that between one-fourth and one-half of the variability in body weight in the general population can be explained by genetic factors (104). Whereas external influences undoubtedly create a pressure for development of obesity, genetic factors seemingly affect the response to external factors and influence the ultimate body weight of an individual. The nature of these genetic influences is largely unknown. They could affect amount of food ingested, the rate of energy expenditure, or both.

Models of obesity in mice suggest that an appetite drive plays a critical role in determining food intake. The discovery of leptin, a satiety factor, requires us to ask whether appetite drive in humans is likewise under genetic control (105). Several recent studies failed to show a deficiency of leptin in most obese humans (106–108); nonetheless, it is still possible that appetite drive in humans is variable and under genetic control. People having more intense appetites may be those more likely to develop obesity, especially severe obesity. The observation that some antidepressant drugs can induce weight gain illustrates that biochemical regulation of appetite drive can influence total food consumption in humans.

Another point of genetic control could be the regulation of energy expenditure. RMR varies from one person to another. Genetic factors could affect RMR and thus energy expenditure. Much remains to be learned about the process of energy expenditure in humans. Some expenditure produces useful metabolic work; some is wasted in various futile cycles. Genetic factors could affect the distribution between these two pathways. Energy-efficient persons may be prone to obesity. The finding that heredity influences body weight in animals led to renewed interest in the causes of obesity in humans. A role for heredity is implied by studies in twins and in genetic epidemiology. These latter investigations suggest that some people are particularly susceptible to obesity. Some variation in body weight undoubtedly derives from differences in social, cultural, psychologic, and educational factors. Genetic variations in appetite drive and energy expenditure probably contribute to population variability in weight as well.

Summary

The above considerations indicate that multiple factors contribute to weight gain with aging. For the purpose of simplicity,
these causes can be divided into three categories: unconscious, subconscious, and conscious. The different causes discussed act at one or more of these levels. For example, factors affecting appetite drive, RMR, and the thermal effect of food are essentially unconscious. Hidden nutrient energy high-fat diets or other energy-dense foods belong in this category too, as shown by weight gain in animals fed such diets. In contrast, eating habits acquired early in life that are under family and cultural influences probably reside in the subconscious mind. In many people, subconscious factors apparently predominate over conscious factors in determining how much and what kinds of foods are consumed. If a child grows up in a family where overeating is encouraged, the habit of eating to excess will probably be acquired, and these habits will be recalcitrant later in life when less nutrient energy is needed. Finally, in everyone, food intake is controlled to some extent by conscious factors. When persons become more aware of the link between eating habits and body weight, and how weight gain can increase risk for disease, eating patterns should become increasingly under conscious control.

PREVENTION OF WEIGHT GAIN WITH AGING

Weight gain could theoretically be prevented in either of two ways: 1) by changing daily habits, such as amount of food ingested and physical activity, or 2) by pharmacologic control. Although the development of drugs for weight control is currently a topic of growing interest, drug therapy almost certainly will not be a practical way to prevent age-related weight gain for the whole population. Only a therapeutic breakthrough leading to completely safe, highly effective, and inexpensive drugs would make pharmacologic prevention of obesity feasible. This is unlikely to occur in the near future. A more realistic strategy is to bring about a change in eating behavior and exercise habits for the general population. The lower prevalence of obesity among some socioeconomic groups of Americans strongly implies that prevention of weight gain can be learned if the motivation is strong. Public health efforts in the past have focused mainly on dietary saturated fats and cholesterol. These efforts have been moderately successful: in the United States, intakes of cholesterol and saturated fats are declining, as are serum cholesterol concentrations (109). Fewer public health efforts have addressed the problem of obesity. This may in part account for the fact that body weight in the general population is going up. Many investigators are pessimistic about a public health approach to modulating energy balance to reduce the overall prevalence of obesity (59). It is true that short-term efforts at weight control are largely ineffective for producing sustained weight loss; long-term efforts, on the other hand, could be more effective. Consideration therefore should be given to developing a long-term strategy.

Degree of energy imbalance leading to obesity

A critical piece of information needed for preventing weight gain is that a relatively small energy imbalance underlies most moderate obesity in the general population. From standard estimates of energy requirements per kilogram of body weight, it can be calculated that \( \leq 1255 \text{ kJ/d (300 kcal)} \) maintains \( \approx 10 \text{ kg (22 lb)} \) of excess weight. Thus, the middle-aged person who has gained 10 kg of excess weight since age 25 y has only 1255 kJ/d of energy imbalance. By the same token, only \( \leq 2510 \text{ kJ/d (600 kcal)} \) sustains \( \approx 20 \text{ kg of excess weight} \). Most overweight people in America carry \( < 20 \text{ extra kilograms of weight} \). Thus, the reduction in nutrient energy intake needed to restore desirable weight will be relatively small for most people. This fact should introduce a note of optimism and encouragement to the public. Persons having moderate obesity should be taught that weight control is not as daunting as generally believed. Major changes in eating and exercise habits will not be needed to eliminate excess weight for most persons. Instead, a decrease of only 10–20% in total nutrient energy intake is all that is required. Diets very low in nutrient energy are not necessary to obtain and sustain acceptable body weights. If anything, such diets are doomed to failure.

Raising subconscious habits to consciousness

Most middle-aged adults with moderate obesity probably give little thought to their body weights, and when they do, they usually do not link body weight with increased risk of chronic disease. A critical goal for a successful public health strategy for preventing (or eliminating) overweight therefore is to bring awareness of eating behavior and exercise habits out of subconsciousness and into consciousness. Weight control should be given a higher priority in the daily lives of the public. This change will require several steps of learning. First, a better understanding of the medical dangers of weight gain should enhance conscious motivation. The fact that cardiovascular risk factors can develop with only mild gains in weight should be emphasized. Second, the public should be brought to recognize that moderate obesity is not difficult to prevent or eliminate. Certainly persons having severe obesity fall into a different category; they often are recalcitrant to educational and other therapeutic efforts. But moderate obesity, which is much more common, should be much less resistant to correction. Much of the pessimism about the possibility of effective weight control derives from failed attempts at weight reduction in severely obese people. The fact that those having only moderate obesity do not become severely obese implies a degree of self-control in most people. The public health goal of prevention is to expand each person’s inherent ability to learn and exert self-control.

Dealing with animal fats

Because the atherogenicity of all the risk factors accompanying metabolic syndrome is proportional to the degree of elevation of LDL cholesterol, the first goal of dietary modification should be to reduce LDL-raising nutrients. Foremost among these nutrients are animal fats that contain cholesterol and cholesterol-raising saturated fatty acids. The American diet currently contains \( \approx 35\% \) of total nutrient energy as fat and \( \approx 12\% \) of total nutrient energy as saturated fatty acids. A reasonable first goal for the general public is to reduce saturated fatty acids to \( \approx 8\% \). This can be easily achieved for most persons by removing obvious sources of animal fats from the diet. If these fats are not replaced, total energy intake will fall, inducing weight loss. In practical terms, saturated fats can be reduced by use of products that are lower in animal fat and dairy fat. A critical point of note is that in overweight persons any animal fats removed from the diet must not be replaced by other energy sources; otherwise, total energy will not decline.

The net effect of removing excess animal fat from the diet in overweight persons is as follows. Because animal fats contain unsaturated as well as saturated fatty acids, their elimination will considerably reduce total fat intake. Take for example the effects of removing 1255 kJ/d (300 kcal) of animal fats. Total fat intake will decline from 35% to \( \approx 27\% \) of total energy; saturated fatty acids will fall from 12% to 8%. Depending on the kind of animal
fat removed, cholesterol intakes should decrease by 40–70 mg/d. Because 1255 kJ/d sustains 10 kg of excess weight, this change alone will reduce body weight by 10 kg over the period of a year. If a greater decrease in nutrient energy is needed to achieve a desirable body weight, other energy sources must be targeted. But priority should first be given to eliminating fats containing saturated fatty acids because of their cholesterol-raising potential. Importantly, removal of animal fat need not require eliminating animal protein. Many sources of low-fat (or nonfat) animal protein are available.

If a person is at a desirable weight, removal of animal fat is still indicated; in this case, animal fats can be replaced by unsaturated fats of vegetable origin. Polyunsaturated fatty acids probably should not exceed 7% of total nutrient energy, but monounsaturated fatty acids can be allowed to reach 15–20% of energy (110). Any saturated fatty acids should come from vegetable fats, as some saturated fatty acids from vegetable sources will be stearic acid, which does not raise cholesterol concentrations (111). There is a growing concern about use of trans fatty acids contained in hydrogenated vegetable oils. This concern follows recent observations that trans fatty acids raise LDL cholesterol concentrations (112–114). Thus, new processes are needed to reduce the need for hydrogenation in preparation of margarines and shortenings. In the meantime, however, sources of trans fatty acids should be eliminated to further promote weight control.

**Long-term weight control**

Prevention of weight gain with aging must be a long-term effort, extending over many years. In the past, most attempts at weight control have been short-term. “Crash diets” are commonly used in commercial weight-control programs. Experience shows, however, that crash diets are almost always unsuccessful: recidivism rates approach 100%. A new way of thinking about weight control thus is necessary. Foremost is the need for long-term changes in eating habits. Weight loss in the short term is of little value. To avoid weight gain with age, fundamental modifications in eating and exercise habits will be required as young adults progress toward middle age. More emphasis must be given to education and to taking personal responsibility. Professional guidance likely will be less effective than support structures built around family, friends, and work. Even if educational efforts at weight control in families fail in the first generation, they may succeed in the second or third generation. In the United States, there is a trend toward increased personal awareness of health issues and the need for taking responsibility for one’s own health. This trend must be encouraged. The public health goal to avoid development of obesity in young adulthood and early middle age should be high on the list of the nation’s health priorities.

**New public health approaches to weight control**

The United States and most other nations have not developed systematic approaches to the prevention of obesity through public education. Most previous efforts have relied heavily on the media to heighten the public’s awareness of obesity-related health problems. Effective use of the media has been made by the National High Blood Pressure Education Program and the National Cholesterol Education Program (3). The public’s awareness of blood pressure and cholesterol as personal health issues has risen over the past two decades. The results have been favorable: healthier life habits have been adopted by many people. Use of the media is unfortunately becoming an increasingly unreliable means of educating the public. A variety of conflicting messages under the guise of news are reaching the public. Some of the previous advances in public awareness appear to have been eroded by a profusion of conflicting reports related to health and nutrition. Consequently, new approaches to public education are needed.

This is especially the case for prevention of obesity. There is no systematic national effort to make the public aware of the dangers of obesity. Little information is available on the need to prevent weight gain or how to maintain a desirable body weight. The media no longer can be depended on to provide consistent information to the public. Because obesity is of concern to many different health agencies (eg, those committed to preventing heart disease, stroke, diabetes, and cancer), a coordinated effort should be made. Innovative joint approaches are needed. These can begin with giving obesity a higher priority on the public health agenda.

**CONCLUSIONS**

Obesity will probably replace cigarette smoking as the major killer of Americans in the next century. In addition, unless the trend toward weight gain is halted, a high prevalence of obesity will develop worldwide. This high prevalence derives from a fundamental change in the world’s social structure. It results from urbanization, an increasing availability of food, and a reduction in physical activity. Most of the obesity resulting from weight gain with age will be moderate, not severe. But, even this degree of obesity produces significant metabolic consequences in many persons. Moderate obesity is the driving force behind metabolic syndrome, a major cause of premature CHD. Some population groups, such as subcontinental Asians, seem unusually prone to the atherogenic effects of metabolic syndrome. In almost all populations, however, weight gain with aging and long-term obesity have substantial health consequences. The solution to this problem must be found at the public health level.

Pharmacologic approaches may be helpful for some severely obese people, but will not be applicable for prevention of moderate obesity for the whole population. Instead, systematic public education is needed instead to increase awareness of the dangers of moderate obesity and to provide the public with effective ways of avoiding weight gain with aging.

**REFERENCES**

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