An integrative view of obesity[1–4]

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ABSTRACT

Obesity is the result of the accumulation of excess body fat and not simply excess weight that can be muscle or fat. Adipocytes function in the adaptation to starvation, in exercise energetics, and in the immune defense against pathogens. Sustained positive energy balance results in excessive accumulation of adipocytes, which, in the abdomen, leads to chronic inflammation. Although informative studies have been performed with cultured adipocytes, an integrative approach to the regulation of abdominal adipose tissue involves feedback from autocrine and paracrine effectors secreted by adipocytes, the immune system, and blood flow through adipose tissue. Numerous adipokines, chemokines, and cytokines feed back to other bodily systems to regulate both energy balance and immune function. Studies of the interactions of the gastrointestinal tract and the central nervous system, as well as psychophysiological considerations of reward circuitry in the central nervous system, have shown a general adaptation to starvation that is opposed to those strategies being proposed for the prevention and treatment of obesity, ie, food restriction and increased physical activity. The obesogenic environment of highly palatable foods with hidden fats and sugars can promote metabolic syndrome and obesity, whereas fruit and vegetables with anti-inflammatory phytochemicals can counteract metabolic syndrome. Therefore, a plant-based diet and the seamless integration of increased physical activity and social support to alter modern diets and lifestyles hold out the greatest hope for the solution of the obesity epidemic. Both public health and medical nutrition approaches can benefit from this integrative view of obesity. *Am J Clin Nutr* 2010;91(suppl):280S–3S.

INTRODUCTION

Public health, governmental, public, private, and medical institutions interested in stemming the global epidemic of obesity and chronic disease must take into consideration the interface of physiology, human behavior, and the obesogenic environment of modern industrialized societies. Over the last 50,000 y, humans have benefited from an ability to store fat, and this has been identified as a key survival adaptation mediated through so-called thrifty genes (1). Over the last 200 y, changes in the human diet and lifestyle have outstripped the ability of the genome to adjust to a changing environment, and billions of people around the world are now overfat as a result (2–8).

Although studies show that hunter-gatherers ate >800 varieties of plant foods (9), Americans eat only ≈3 servings of fruit and vegetables/d, which fail to provide enough of the naturally occurring antioxidants, phytochemicals, vitamins, and minerals that are essential to good health. Highly processed foods with refined starches, sugars, fats, and oils often fail to contain the essential nutrients that are found in nutrient-dense foods (10). At the same time, labor-saving devices of all kinds and advances in transportation have made a highly sedentary lifestyle possible over the last 30 y (11).

A global epidemic of obesity and chronic disease, which is underestimated if one uses the body mass index (BMI) alone, is sweeping the globe as industrialization and improved standards of living are spreading to urban centers. Certain ethnic groups including Asians, Asian Indians, Latinos, and Native Americans are genetically susceptible to metabolic syndrome [due to the accumulation of visceral fat that results in inflammation in the absence of marked increases in BMI (12)]. It is estimated that within the next 10 y, the majority of all heart disease will be associated with type 2 diabetes, with significant increases in incidence projected in China, India, Southeast Asia, Mexico, and Latin America (13).

VALUE AND SHORTCOMINGS OF THE BMI

The BMI (weight divided by height squared) is used in epidemiologic surveys to track an increase in the overall global incidence of obesity, because most overweight individuals in any population are also overfat (14). However, ethnic differences in body fat distribution have already undercut the generalizability of BMI in Southeast Asia, requiring new BMI limits for the definition of obesity (15). Men and women with athletic builds often have greater-than-average muscle mass contributing to their excess body weight (hypermuscular obesity), whereas asthenic individuals (including young women who voluntarily restrict their intake to reach societally defined desirable body shapes) can have normal body weight with reduced muscle mass but excess body fat (sarcopenic obesity or normal-weight obesity) (16). Sarcopenia has been shown to be a determinant of chemotherapy toxicity and time-to-progression in women with metastatic breast cancer (17). Therefore, subtypes of obesity can have significant implications for approaches to weight management in prevention and treatment of chronic disease. Sarcopenic obesity raises issues related to the relative importance of diet and exercise in weight

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maintenance and in the proper amount of dietary protein to be provided in a hypocaloric diet.

A BMI-centric view of obesity, and the referral of the severely obese to specialists after the fact, can lead to overutilization of expensive pharmacologic and surgical approaches to obesity and an underemphasis on prevention and research regarding less-expensive medical nutrition and public health approaches to the worldwide obesity epidemic. Alternatively, an understanding of the physiologic regulation of body weight and food intake, along with an appreciation for the central role of the adipocyte in human physiology, can improve preventive approaches based on weight reduction and improvement of the quality of the diet. For example, inflammation-associated insulin resistance in susceptible individuals may be improved by increasing their dietary intake of fruit and vegetables (which have lower energy density and are a source of antiinflammatory phytochemicals).

THE FAT CELL IS MORE THAN A BAG OF FAT

Although the fat cell has been referred to simply as a signet-ring cell with a thin layer of cytoplasm surrounding a large fat droplet, this thin layer of cytoplasm is actually a highly complex endocrine, inflammatory, and metabolic tissue. It regulates the storage and breakdown of fat, communicates with the central nervous system and gastrointestinal tract, and plays an important role in the inflammatory response (18).

The location of body fat also has significant implications for the health risks associated with obesity, and abdominal fat cells accumulated during rapid weight gain can outgrow their blood supply and interact with monocytes attracted from the bone marrow. Studies by Cancello et al (19) and Cinti et al (20) have shown that the number of macrophages is increased in obese subjects compared with nonobese subjects. Furthermore, several studies have shown that macrophages form crownlike structures (21–23) that surround perilipin-negative necrotic adipocytes (20). Perilipin, a protein involved in the regulation of lipolysis, is located at the interface between the cytosol and the triacylglycerol droplets of adipocytes (24). Cinti et al (20), by applying electron microscopy, found negative perilipin staining in adipocytes, the membranes of which were observed to be disrupted and engulfed by macrophages. Therefore, it appears that negative perilipin staining is a marker of adipocyte death, which explains why the number of crownlike structures found in abdominal fat is increased in both obese mice and humans.

Fat cell size correlates with obesity (25) and with the degree of macrophage infiltration into adipose tissue (21). Cell death correlates with mean adipocyte size in abdominal fat (18). In hormone-sensitive lipase transgenic knockout mice ($HSL^{-/-}$), adipocyte cell size is markedly increased but body fat mass is similar to that of wild-type mice. In these $HSL^{-/-}$ mice, adipose tissue was infiltrated with macrophages, implying that increased cell size rather than overall obesity is the trigger to macrophage infiltration (20).

In a recent study by Kolak et al (26), subcutaneous adipose tissue biopsies were obtained from healthy women both with and without increased liver fat (LFAT) (2.3 ± 0.3% compared with 14.4 ± 2.9%, respectively) with similar BMIs and percentage body fat. Expression of cytokines and chemokines that include CD68, CCL2 (monocyte chemoattractant protein 1), CCL3 (MIP-1α), and PAI-1 were significantly increased, whereas peroxisome proliferator-activated receptor γ and adiponectin were significantly decreased in women with high measures of LFAT compared with women with normal measures of LFAT, even though subcutaneous fat cell size, BMI, and percentage body fat were similar. Furthermore, CD68 expression, which correlated with the number of macrophages and crownlike structures and concentrations of 154 lipid species that were determined by using lipidomic methods in adipose tissue, revealed several key differences between the groups. The most striking differences were increased concentrations of triacylglycerols (particularly long-chain) and ceramides [specifically Cer(d18:1/24:1), $P = 0.01$] in the high LFAT group. Expression of sphingomyelinases SMPD1 and SMPD3 were also significantly increased in the high, compared with normal, LFAT group. Changes found in adipose tissue in terms of ceramides are similar to those found in atherosclerotic plaques and again incriminate systemic inflammation in the comorbidities associated with abdominal obesity.

Cryptogenic cirrhosis is a common cause of liver-related morbidity and mortality in the United States. Nonalcoholic fatty liver disease (NAFLD) is now recognized as the most common cause of cryptogenic cirrhosis (27). Accumulating evidence supports an association between NAFLD and metabolic syndrome, diabetes, and obesity. The epidemiology, pathogenesis, and approach to treatment of NAFLD follow the same trends as these other metabolic disorders, and insulin resistance is the key event linking NAFLD to these diseases. The impairment in fat and glucose metabolism that ensues from the onset of insulin resistance leads to similar biochemical and clinical abnormalities in patients with NAFLD. Many recent studies that have investigated the cellular and genetic basis of these diseases have led to a better understanding of their pathogenesis and insight into treatment and management. The most effective treatment thus far is weight loss and the use of insulin-modulating pharmacologic agents. A few additional treatment strategies include the use of lipid-lowering, antioxidant, or cytoprotective agents, but there is no single therapeutic approach that is effective for managing NAFLD. Future therapies may combine drugs that target specific pathways involved in NAFLD pathogenesis. The prevalence of steatosis is estimated to be >50% among overweight and obese individuals.

The systemic inflammation associated with obesity can also contribute to the pathogenesis of heart disease, diabetes, neurodegenerative diseases, and common forms of cancer. Metabolic syndrome has emerged as an important cluster of risk factors for atherosclerotic disease. Common features are central (abdominal) obesity, insulin resistance, hypertension, and dyslipidemia, with high triglycerides and low HDL cholesterol. According to the clinical criteria developed by the third report of the Adult Treatment Panel, it has been estimated that ≈1 of every 4 adults living in the United States merits the diagnosis. The presence of metabolic syndrome is highly prognostic of future cardiovascular events.

Chronic inflammation may represent a triggering factor in the origin of metabolic syndrome: stimuli such as overnutrition, physical inactivity, and aging would result in cytokine hypersecretion and eventually lead to insulin resistance and diabetes in genetically or metabolically predisposed individuals. Alternatively, resistance to the antiinflammatory actions of insulin would result in enhanced circulating concentrations of proinflammatory

cytokines, which would result in persistent low-grade inflammation. A generally enhanced adipose tissue–derived cytokine expression may be another plausible mechanism for the inflammation/metabolic syndrome relation. The role of adipose tissue as an endocrine organ capable of secreting a number of adipose tissue–specific or enriched hormones, known as adipokines, may play a pathogenic role in metabolic syndrome. Although the precise role of adipokines in metabolic syndrome is still debated, an imbalance between increased inflammatory stimuli and decreased antiinflammatory mechanisms may be an intriguing working hypothesis. The chronic inflammatory state that accompanies metabolic syndrome is associated with both insulin resistance and endothelial dysfunction, which provides a connection between inflammation and metabolic processes that is highly deleterious for vascular function. However, small amounts of weight loss, which relieve the pressure for abdominal adipocytes to proliferate, have been shown to reduce inflammation in patients with type 2 diabetes (28) and have been shown in 2 large trials to reduce the incidence of new cases of diabetes over 5 y by 58% in individuals with glucose intolerance and insulin resistance (29).

INTEGRATIVE SOLUTIONS

In view of the above discussion, it is clear that integrative solutions to the obesity epidemic are likely to include approaches at a public health and medical level that accomplish the following: First, subjects will require a rebalancing of energy intake and expenditure to reduce the physiologic accumulation of abdominal fat through the use of portion control and daily physical activity. Second, subjects will require a rebalancing of dietary calories to achieve an increased intake of fruit, vegetables, whole grains, and tree nuts, which should also result in a better proportion of omega-6 and omega-3 fatty acids than is found in the modern American diet, with a commensurate reduction in inflammation-associated insulin resistance. Recent studies (30) have shown that supplementation of an obesogenic high-fat diet with whole blueberry powder in male mice protects against adipose tissue inflammation and insulin resistance. Blueberry powder supplementation at 2.7% of total energy did not affect high-fat diet–associated alterations in energy intake, metabolic rate, body weight, or adiposity, but gene expression in the adipose tissue of mice fed the high-fat diet without the blueberry powder showed a shift toward global up-regulation of inflammatory genes that included tumor necrosis factor-α, interleukin-6, monocyte chemoattractant protein 1, inducible nitric oxide synthase, increased M1-polarized adipose tissue resident macrophages ($CD11c^+$), and reduced glutathione peroxidase 3. This shift was attenuated or nonexistent in mice fed a high-fat diet with the blueberry powder. Furthermore, mice fed these diets were protected from insulin resistance and hyperglycemia coincident with reductions in adipocyte death. These effects of blueberry powder may be shared by many antioxidant polyphenols found in colorful fruit and vegetables via effects on adipocyte physiology and gene expression altering mitogen-activated protein kinase and nuclear transcription factor-κB stress-signaling pathways, which regulate cell fate and inflammatory genes. These results suggest that cytoprotective and antiinflammatory actions of dietary polyphenols from fruit and vegetables can provide metabolic benefits to combat obesity-associated pathology. There are also some studies in humans that support this concept. In a study of 4601 participants (aged 45–84 y) in the Multi-Ethnic Study of Atherosclerosis who were free of clinical cardiovascular disease, the associations of dietary patterns with metabolic syndrome, left-ventricular mass, and function were examined to identify dietary patterns that maximally explained the variation in metabolic syndrome components by using reduced-rank regression (31). Left-ventricular mass, stroke volume, and ejection fraction were measured by magnetic resonance imaging. In this study, the primary reduced-rank regression dietary pattern score was positively correlated with high-glycemic-index food intake (high-fat meats, cheeses, and processed foods) and negatively correlated with a low intake of low-glycemic-index foods (vegetables, soy, fruit, green and black tea, low-fat dairy desserts, seeds and nuts, and fish)—ie, highly influenced by metabolic syndrome variables that suggest an influence of a phytochemical-rich dietary pattern.

In addition, a clinical study also provides evidence supporting these concepts. A randomized controlled outpatient trial conducted in 116 patients with metabolic syndrome showed the benefits of the fruit and vegetable–rich Dietary Approaches to Stop Hypertension Trial (DASH) eating plan on metabolic risks in patients with metabolic syndrome in comparison with a matched control diet and weight-reducing diets over a period of 6 mo (32). In comparison with the usual weight reduction diet, patients adhering to the DASH diet reduced their energy intake and increased their consumption of fruit, vegetables, low-fat dairy, and whole grains, resulting in a lowered intake of saturated fat, total fat, and cholesterol. Relative to the control diet, adherence to the DASH diet resulted in higher HDL cholesterol and lower triglycerides, systolic blood pressure, diastolic blood pressure, and fasting blood glucose among men and women. The DASH diet reduced most of the metabolic risks in both men and women that are known to be associated with insulin resistance and metabolic syndrome.

Finally, we need to recognize that these well-intentioned approaches are fighting natural human tendencies to eat more and exercise less (33). Potential solutions that emphasize social support networks and innovative methods of integrating a balanced diet and healthy active lifestyle, in ways that are personally rewarding based on financial or social incentives, are urgently needed (34). For those persons who do not respond to these approaches, medical and surgical alternatives remain important options. However, the application of such intensive approaches to the entire population of obese individuals would bankrupt the health care system. Therefore, continued attention to an integrative view of the prevention and treatment of obesity is required. (Other articles in this supplement to the Journal include references 35–37.)

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