Review

Pathophysiology of obesity: Focused, cause-driven approach to control the epidemic

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Obesity is a disease with serious public health and economic outcomes. It is more than simply a thermodynamic, genetic, or a metabolic problem of handling calories; it is a behavioral disorder and an inflammatory disease leading to dysregulation of metabolism and energy balance, and impairment of the neurohormonal systems, leading to accumulation of intra-abdominal fat leading to serious complications. Obesity rates as indicated by the increasing body mass index (BMI) or by abdominal girth are escalating in the United States and most industrialized countries. Approximately two-thirds of these patients develop complications that would cost billions of taxpayer dollars. However, in Asians BMI is less relevant, and the increasing abdominal girth is a better indicator that reflects accumulation of the visceral fat; the most detrimental for the health. Obesity is a multi-factorial disease for which genetics, environment, behavioral, physical and other factors contribute to its development and metabolic complications. Those who are obese, and sick and unhealthy, secondary to accumulation of excessive visceral fat are at high risk of developing complications. At the current rates, it is predicted that obesity-associated deaths are going to surpass cardiovascular deaths within the next two decades. For the majority of overweight and obese people, it is necessary to reduce only seven to ten percent of their body weight via calorie-reduced diet and increasing physical activity that would improve the metabolism and decrease potential complications and premature deaths. In addition to reasonable weight reduction programs, controlling the obesity-associated complications requires coordinated, cause-driven, and complication-centric approaches. Understanding the cause for the obesity in each patient would greatly facilitate the development of an individualized, sustainable, and successful treatment plan. Therefore, the multi-factorial nature of engender obesity needs a focused, specific, cause-driven approaches to combat. Considering the high cost of managing obesity, type 2 diabetes and their complications, prevention of obesity is the way forward that is based on controlling the causes and risk factors. This is one of the most cost-effective approaches to decrease the obesity-associated complications, morbidities and premature deaths.

Keywords: metabolism, epidemic, adipokines, body mass index (BMI), cardiovascular, morbidity, overweight

INTRODUCTION

Heightened attention to the obesity epidemic has further supported obesity as a disease that leads to serious complications. No country has adequate resources to manage or treat everyone with higher body mass index (BMI). In fact, it may not be necessary to do so, as one-third of obese, do not develop metabolic compactions.
Thus, it is important to be able to identify the two-third of the obese who would develop metabolic complications using clinical risk factors and widely available, cost-effective biochemical markers. Inclusion of clinical risk factors and the waist circumference for overall assessment would be more effective than using the BMI to identify those who need medical attention (Greenway et al., 1999; Wimalawansa, 2013). In particular, the relationship between BMI and obesity-associated complications is weak (Chan et al., 2012; Smith et al., 2007). Customarily, the body weight is categorized according to the BMI: overweight is defined as BMI $\geq 25$ kg/m$^2$; obesity, BMI $\geq 30$ kg/m$^2$; and extreme obesity, BMI $\geq 40$ kg/m$^2$ (Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults 1998; Alberti KG et al., 2006), but cutoff points for Asians are lower (Misra et al., 2006; Wimalawansa, 2013).

The key to reducing cardiometabolic risk is to reduce abdominal obesity—reducing the waist size (Smith SC et al., 2007) and reducing the underlying risk factors through elimination of causes. Controlling these causes and risk factors would not only result in improved overall health, but also would reduce complications, thus leading to decreases in morbidity and mortality. The classification of obesity as a disease (Group TOaaDW 2008) based on potential future complications, rather than BMI alone, would remove the perception that the patient has the sole responsibility for managing weight (Korner and Aronne 2003), and enhance the public-private partnerships that are needed to curb the obesity epidemic. Such a classification also would pave the way for redistribution of governmental and private resources from the acute medical care to the preventative strategies; reduction of risk factors for type 2 diabetes (T2D), cardiovascular diseases (CVD), and obesity.

**Obesity is the most rapidly spreading disease**

The health repercussions and associated economic costs of the obesity epidemic are overwhelming (Forster et al., 2011). The causes of obesity fall into two general categories: genetic and environmental; the current epidemic is most likely a combination of the two. The World Health Organization estimates that 300 million people worldwide are obese and another 750 million are overweight (MSNB. Obesity mars boomer health gains). Thus, more than 1.0 billion people worldwide are at risk of overweight-associated morbidities, including CVD, T2D, hypertension, and certain cancers. In the United States alone, there are more than 115 million overweight and obese adults (NIH, Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults 1998), and these numbers continue to increase (Bank, W). As illustrated in figure 1, obesity is a complex, multi-factorial disease.

In most Western countries, the evolution of the obesogenic environment has been both rapid and multifactorial, and has led to the current epidemics of T2D and obesity—diabesity. In industrialized countries, there is an increasing access to high-fat and/or energy-concentrated food. At the same time, there has been a trend of decline in the amount of physical activity engaged by individuals in affluent countries. Meanwhile, in many other countries food in general and specifically nutritious food is becoming scarce. According to the National Institutes of Health, obesity is the second leading cause of preventable death in the United States (second to tobacco use), with an estimated 300,000 deaths per year (NIH, Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults 1998) and those numbers seem to be increasing. (DHHS, Overweight and obesity: a major public health issue 2001);

Globally, the distribution of obesity epidemic is not uniform. The prevalence of obesity in the United States is predicted to increase from 114 million in 2011 to 125 million in 2015, and to 165 million in 2020 (Bank W). Meanwhile the incidence of obesity is estimated to double within the next three decades in China and in certain parts in south Asian countries (Cherian et al., 2012; Wang et al., 2012; Zhang and Wang 2012; Ying-Xiu and Shu-Rong 2012; Singh and Kirchengast 2011) (Bank, Forster et al., 2011; NIH, Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults 1998; NIH, Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults 1998; NIH, Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults 1998).

**Causes leading to obesity**

**Historical aspects of excess calorie intake and glycemic load**

The major contributor for excess accumulation of body fat in all ages is the excess consumption of food that contains refined sugar, carbohydrates, and excess fatty acids. Our ancestors are thought to have eaten less than one-quarter pound of sugar per year (Cordain et al., 2005), whereas today, some people consume more than that amount within a week. During the past five decades, sugar consumption has increased from ten pounds to more than fifty pounds per person per year. Moreover, the calories consumed from sugar that comes from high-fructose corn syrup have increased from 10% to 65% during the last three decades (Wimalawansa 2013). The latter is mostly consumed in the form of liquid calories from soft drinks and sweetened beverages. However high-fructose corn syrup is widely used in bakery...
products and other processed foods, worldwide. Nevertheless, the impact on obesity from the liquid calories consumed from soft drinks and sweetened beverages is greater than that from solid foods (Ludwig et al., 2001).

Glycemic load and nutrient density in food are controlled in part by the fiber content of food. Thus, fiber is an important ingredient in human food. Higher the fiber content in the diet, lower the glucose and insulin peaks in the blood; both are beneficial outcomes. However, in recent years the fiber consumption has decreased from 100 grams a day to less than 10 grams per day, per person (Eaton and Konner 1985). Inadequate dietary fiber leads to a surge of sugar and insulin levels in the circulation, which promotes insulin resistance, T2D, obesity, increase vascular atheroma formation and thus acceleration of heart disease, and perhaps colon cancer (Chandalia et al., 2000). Healthy meal adaptation, such as consumption of modest 50 grams of fiber per day, has been shown to lower hemoglobin A1c as effectively as does the use of anti-diabetic medications (Chandalia et al., 2000).

**Neutrogenomics and caloric/nutrient imbalances**

Nutrigenomics, phytonutrients, macro- and micro-nutrients, as well as lipemic and glycemic loads can modify human gene expressions and thus, modify the downstream energy metabolism and storage (Cordain et al., 2005; Eaton and Konner, 1985). Changes in physical activity and dietary patterns often are the result of environmental and societal changes including the "westernization" of societies, ineffective legislation, and inadequate supportive governmental policies. Particularly in the areas of preventative health, education, agriculture, transportation, urban planning, the environment, and food regulations. The latter includes, processing, storage, distribution, advertising, and marketing of food (Trivedi et al., 2012).

Nutrient-poor, calorie-dense diets promote a society of overfed, yet malnourished, people. Thus, in many patients obesity is associated with malnutrition. These can be deficiencies of macronutrients or micronutrients, but predominantly, deficiencies of micronutrients and vitamins, including clinical or subclinical deficiencies of minerals and vitamins B, C, and D. Individuals who are overweight, obese, and/or have T2D are usually seems there is an extra-space here deficient in a number of key nutrients important to the prevention of such conditions, including vitamin D (Reis et al., 2009; Wimalawansa 2012), omega 3 fatty acids, chromium, biotin, magnesium, zinc, and a variety of antioxidants, such as lutein and alpha-lipoic acid (Poh and Goh, 2009). Many of

Figure 1. Obesity is a complicated and a multi-factorial disease. Genetics, inflammation, individual behavior, and environmental influences are the three most important factors leading to obesity. Therefore, solutions need to address each of these modifiable issues.
the micronutrients work as co-factors in metabolism and have effect on gene expression, regulate hormones and enzymes that control glucose and lipid metabolism, endothelial cell functions, hormone and insulin secretion (Kelly, 2000).

Because during food processing of and the use of newer methods of large-scale food-growing and harvesting methodologies alter nutritious value of food, it can have a negative (or at some times, positive) effect on the balance and quality of the diet. Therefore, nutrient and food supplementation is becoming even more important, especially among vulnerable people methodologies, such as children under the age of five, pregnant and lactating mothers, and the elderly (Review, 2008). Shifting from a nutrient-poor diet to a nutrient-dense diet that is abundant in fiber-rich, plant foods such as fresh whole fruits, vegetables, nuts, seeds, beans, and whole grains improves health and bodily functions, and decreases morbidity (Hyman, 2006). Artificial sweeteners do not provide calories, yet promote obesity by increasing appetite and thus, the quantity of food consumed, as well as reducing thermogenesis and body temperature (Wimalawansa, 2013).

**Chronic inflammation is a causative factor for obesity**

A number of causes such as chronic stress, certain medications, sedentary lifestyles, chronic infections, inhaled or ingested toxins, food intolerance, allergies, and chronically imbalanced unhealthy diets lead to generalized chronic inflammation. Dietary sugars and refined carbohydrates, hyperinsulinemia, hyperlipidemia, and dysmetabolism also exacerbate inflammation (Tzanavari et al., 2010). Unhealthy diets containing deficient fiber and high proinflammatory dietary components including refined sugar, free fatty acids, trans fat, and a high ratio of omega-6 to omega-3 fatty acids (Gomez et al., 2011; Simopoulos 2008) facilitate and maintain a low-grade chronic systemic inflammation (Esposito et al., 2003). Therefore, in appropriate patients, correcting ongoing chronic inflammation is an important and reasonable approach to weight loss and reducing complications associated with obesity (Goran and Alderete, 2012).

Inflammation from any source (allergen, viral, bacterial or parasitic infections; toxin, poor diet, stress) contributes not only to obesity but also to several other chronic diseases, including diabetes, CVD, cancer, autoimmune diseases, osteoporosis, and Alzheimer’s disease (Schmidt and Duncan, 2003). Elevated C-reactive protein is broader marker of inflammation, and is a reasonable indicator of underlying pathological issue that may lead to the development of several chronic diseases, including CVD, T2D and obesity (Pradhan et al., 2001; Selvin et al., 2007). The excess visceral adipocytes perpetuates a vicious cycle of inflammation via production of inflammatory adipokines (Yudkin et al., 2004; Fain et al., 2004), further aggravating adiposity.

Chronic infections also lead to chronic inflammation, which can contribute to weight gain or weight loss via tumor necrosis factor alpha (TNF-α) (Tzanavari et al., 2010; Fain et al., 2004). Infections with adenovirus have been linked to insulin resistance and obesity (Atkinson 2007). Similarly, the increased load of organic pollutants such as polychlorinated biphenyl (Trasande et al., 2012), pesticides and herbicides, and heavy metals such as cadmium, arsenic, mercury, and lead (known water pollutants), increase the production of inflammatory cytokines and enhance insulin resistance, obesity, and development of T2D (Jones et al., 2008), and chronic renal failure.

Gluten intolerance or celiac disease is another relatively common condition that triggers chronic systemic inflammation. It is associated with increased incidences of autoimmune diseases, cancer, and CVD mortality (Rubio-Tapia et al., 2009). In fact, the presence of gluten sensitivity, even in the absence of positive intestinal biopsy, increases inflammation and lead to premature death, mostly through CVD and cancer (Ludvigsson et al., 2009). However, the combination of chronic inflammation (Goran and Alderete, 2012) and impaired gastrointestinal tract permeability, overuse of antibiotics and nonsteroidal anti-inflammatory agents, proton pump inhibitors, or H₂ blockers, together with low-fiber and high-sugar diets and dysfunctional gliadin proteins (Silano et al., 2008) are some of the potential triggering factors for the excess morbidity and mortality in patients with celiac disease.

**Immunomodulation and weight gain**

Adipose tissues are involved in energy metabolism and storage, and thus the regulation of food intake; these are interconnected. Meanwhile a healthy balance of these are necessary for healthy survival. Once the adipocytes become overloaded with fat and oxidative products, these cells begin constantly release, excessive amounts of inflammatory cytokines (Esposito et al., 2003), which contribute to the development of insulin resistance, T2D, CVD, and cancer. These prolonged imbalances can lead to chronic ill health—obesity or even cachexia.

Fat cells and tissue macrophage cells secrete immunomodulatory cytokines including interleukin-6 (IL-6), which is a potent stimulus for the synthesis of C-reactive protein (Selvin et al., 2007). IL-6 generated from the visceral adipocytes drains directly to the liver via the portal vein and further enhances hepatic inflammation. IL-6 also interferes with the insulin-receptor signaling transduction and thus, leads to further insulin resistance. Adipocytes also secrete the protective cytokine adiponectin, which inversely correlates with the degree of obesity (Belalcazar et al., 2012) and the percentage of fat
in fat cells (Cnop et al., 2003). Adiponectin is also a hepatic insulin sensitizer and an anti-inflammatory cytokine that provides cytoprotection.

**Alterations of gut microflora, toxins, and the development of obesity**

Recent research indicates that insulin resistance and metabolic dysfunction are also linked to derangement in the intestinal microenvironment, including microbial flora (Tsai and Coyle 2009). Human microbiome consists of a microbial community that includes bacteria, eukaryotes, and viruses (Zoetendal et al., 2004). It consists of about 100 trillion microbial cells, which in fact outnumber human cells 10 to 1 (Savage DC 1977). Shifting from a traditional, healthy balanced diet to a diet of convenience consisting of processed and high-sugar, high-saturated fat, low-fiber containing foods and overindulgence in antibiotics not only has a marked negative influence on glycemic index, food absorption, and (mal)nutrition, but also alters gut microflora, unfavorably. This alteration in intestinal microflora not only generates a plethora of harmful chemicals, but also changes the beneficial symbiosis to dysbiosis—a harmful interaction between microflora and the human host.

In healthy individuals, the microbiota provides a wide range of symbiotic metabolic functions that humans’ lack (Gill et al., 2006), therefore, it is not surprising that a major alterations in gut microflora significantly affecting human physiology. These altered floras create potential metabolic endotoxemia through an increased production and absorption of bacterial chemicals—endotoxins and lipopolysaccharides (LPS), which bind to immune cells, including lymphocytes. Consequently, these release proinflammatory cytokines, including TNF-α with its deleterious systemic effects (Romanatto et al., 2007), such as blocking the peroxisome proliferator activated receptor (PPAR) family of nuclear receptors that control inflammation, insulin sensitivity, and impairment of mitochondrial-energy metabolism (Jacobi et al., 2012). As a result, a cycle of inflammation, insulin resistance, and accumulation of fat ensues, and weight gain escalates (Cani et al., 2007). Improving the quality of the diet, normalizing gut flora with healthful natural food including yogurt and probiotics, and avoiding the use of broad-spectrum antibiotics facilitates the reduction of ongoing systemic inflammation.

Toxins promote obesity through multiple mechanisms (Hyman 2007). Many environmental toxins are PPAR antagonists, and thus impair insulin sensitivity and mitochondrial activity, and augment inflammation (Yudkin et al., 2004; Remillard et al., 2002). Prevention and elimination of environmental pollution, particularly from fossil fuels, petrochemicals, and water contamination with agrochemicals and heavy metals (some of these are fat-soluble and thus difficult for the human body to eliminate), are likely to improve human health.

**Chronic stress and obesity**

Stress promotes central obesity, insulin resistance, and diabetes through chronic elevations of cortisol (Meyer and Badenhoop 2003), insulin, and inflammatory cytokines (Hunte and Williams 2009). Therefore, stress management choices, including relaxation therapies, meditation (Wimalawansa 2012), breathing exercises, yoga (Kristal et al., 2005), group support, biofeedback, exercise, dancing, and laughing are likely to reduce stress-associated chemical imbalances and normalize the neuroendocrine and hormonal signaling and biochemical response. Moreover, depression, diabetes, and obesity are linked, and likely to be interactive (Holt et al., 2009). Thus, as a part of the treatment plan, a detailed psychospiritual approach to obesity warrants investigation.

One cannot ignore the negative effects of chronic unmanaged stress, depression, and anxiety for sustaining chronic inflammation (Munhoz et al., 2008). A certain amount of physical activity is physiological and necessary for human’s well-being. Lack of exercise is unphysiological (consider exposure to microgravity, or a bedridden patients) and leads to inherent low-grade inflammation (Smith et al., 1999), as does excessive physical activity. Thus, as with the food, one need to strike the right balance with physical activities (taking the Middle-Path). Some evidence suggests that malnutrition (consists of both under-nutrition and over-nutrition) and antioxidant deficiencies also promote inflammation (Wintergerst et al., 2007). In this regard, studies have shown that consumption of a multivitamin and mineral supplements could effectively lower inflammatory markers, as good as with HMG-CoA reductase (statin) medications (Church et al., 2003). However, this may not be applicable to people who consume imbalanced diets.

**The role of mitochondria in obesity**

In addition to toxins and chemicals, the long-term ingestion of calorie-rich, sugar-dense, poor quality foods may lead to impaired mitochondrial function and pathologically enhanced oxidative stresses (Petersen et al., 2004). Hypoxia secondary to sleep apnea chronic lung diseases or, infections, accentuate inflammatory damage to mitochondria, and impair mitochondrial functions through escalating the oxidative stress. These further exacerbate insulin resistance.

Some antioxidant compounds, including resveratrol which is present in red grapes (Yao et al., 2010), are known to improve mitochondrial dysfunction (Hampton T 2004). Resveratrol affects mitochondrial health through its effects on the sirtuins gene, which facilitates restoring
mitochondrial function and thereby improving mitochondrial enzymatic efficiency and insulin sensitivity (Sadrudin, 2009). In addition, weight loss and calorie restriction restore physiological mitochondrial functions (Fontana, 2009).

Healthy living, including a healthy lifestyle and physical activities (Kristal AR et al., 2005; Balagopal P et al., 2005), eating a nutrient-dense balanced diet, and the appropriate use of dietary supplements enhances the mitochondrial function, reduces oxidative stress, and decreases diabesity (Ames BN, 2003). Genetic or acquired, defects in mitochondrial function can lead to impaired energy metabolism and oxidative stress (Ceriello and Motz, 2004), insulin resistance, diabetes, and obesity (Hampton, 2004), leading to the development of CVD.

Genetic basis of obesity

In certain patients, there is genetic basis for obesity. Examples include defects in the gene coding for leptin, which is involved in appetite regulation, and abnormalities in the enzyme prohormone convertase, which converts hormone proopiomelanocortin (POMC) into neuropeptides that regulates appetite, which can dysregulate energy metabolism. The conversion of POMC is necessary for the proper response of leptin. These novel findings are intriguing and offer a glimpse into the future directions for obesity-related genetic research that could lead to the development of a new class of drug. Nevertheless, these defects are rather uncommon and are not found in the vast majority of persons at risk for or with obesity (http://www.weight.com/causes/causes.html).

Studies of persons adopted at birth have shown no relationship between adult weights or adiposity with their adoptive parents. Instead, the adoptee's weights related to the weights of their biological mothers and fathers (http://www.grammashouse.net/obesity4.htm), which strengthens the genetic hypothesis of the development of obesity. Data suggest that for biologic mothers who are heavy in their adulthood, there is a 75% chance that their children will be heavy, even if the children do not live with the biological mother. Another study reported that maternal weight accounts for most of the positive correlation between the higher birth weight and the excess weight in the adulthood of the offspring (Law, 2001). These data provide further strength to the notion of a genetic component in the development of obesity, an area that may not be possible to intervene.

Neurohormones and obesity

Adipose tissues are involved in energy metabolism and storage, and the regulation of energy balance and food; these are interconnected and essential for survival (Kershaw and Flier 2004; Ahima and Flier 2000). However, once adipocytes become overloaded with fat and fat-oxidation products, these will continue to release excessive amounts of harmful and inflammatory cytokines (Esposito K et al., 2003; Friedrich MJ 2012; Dandona P et al., 2003). These contribute extensively to the development of insulin resistance, T2D, CVD, and cancer. Consequently, these imbalances can lead to extremes of ill health – obesity or cachexia, and premature death.

Obesity could result from neurohormonal or immune dysregulation (Golden, 2007). Impairment in insulin sensitivity, hypothryoidism, adrenal dysfunction, imbalances in sex-hormones (thus, infertility and a higher incidence of miscarriages) or the neuroendocrine system, and appetite dysregulation are common features in diabesity (Maratou E et al., 2009). Undiagnosed or undertreated hypothryoidism could worsen insulin resistance (Maratou et al., 2009), whereas insulin resistance causes thyroid dysfunctions (Ayturk et al., 2009).

Chronically elevated serum glucocorticoids promote insulin resistance, central adiposity, dyslipidemia, depression, and even dementia (Golden, 2007). Such levels also promote visceral adiposity, muscle wasting, bone loss, interferes with thyroid and growth hormone functions, and disrupts sleep and sexual functions (Kolotkin et al., 2006). Abnormality in sleep also promote obesity; sleep deprivation, impaired sleep pattern, or sleep apnea increases appetite, promotes erratic eating behavior (including cravings for sugar, pastry, and refined carbohydrates), and nocturnal binging. For example, in healthy young men deprived of 2 hours of sleep a day increased their serum ghrelin levels and decreased PYY, which increased appetite (Van Cauter et al., 2007). Figure 2 illustrates the interlinked nature of key metabolic diseases, the environment, and the individual's behavior affecting CVDs.

A number of neurohormones are involved in the regulation of appetite and body weight, including insulin, glucagon, leptin, ghrelin, and serotonin. Leptin is predominantly secreted by adipocytes, and circulatory levels indirectly reflect the lipid contents of fat cells. Leptin acts on the hypothalamus to reduce hunger and stimulate energy expenditure. It also regulates a number of other physiological processes (Romanatto et al., 2007), including inhibiting food intake and enhancing metabolic rate.

Obese individuals have higher leptin levels, but obesity causes relative leptin resistance in the hypothalamus. Thus, in obese individuals the leptin signal does not reduce the appetite. The endocannabinoid (CB) system also plays an important role on satiety. Excessive stimulation of its hypothalamic receptors (CB1 and CB2) is associated with weight gain (Aronne et al., 2008). In the nucleus accumbens, stimulation of endocannabinoid CB1-R releases dopamine, thus
Figure 2. A simplified version of the interlinked nature of key metabolic–endocrine disorders that initiate or/worsen cardiovascular diseases (CVDs). Each disorder potentially exacerbates the others. Therefore, it is necessary to decrease the severity of each of these conditions to decrease the morbidity and mortality secondary to CVDs.

increasing appetite (Bellocchio et al., 2007). In obese people, the endocannabinoid system is chronically up-regulated, leading to excessive (or at times, compulsive) eating.

The hypothalamus regulates appetite and energy metabolism and thus, the body weight. Hypothalamic nuclei, including POMC neurons, also regulate the metabolic rate, energy expenditure, and the appetite. These neurohormone receptors, including leptin and serotonin, are key targets for appetite-regulating hormones and thus have been targets for the development of new drugs to combat obesity.

Ghrelin is secreted by the stomach and stimulates hypothalamic neurons, increasing appetite and food intake (Keen-Rhinehart and Bartness 2005). Circulatory ghrelin increases with fasting, peaks just before meals, and rapidly decreases after a meal (Garcia-Unzueta et al., 2005). One of the key reasons for difficulty with weight loss by following a diet plan is that dieting decreases the leptin and increases ghrelin levels, leading to reduced metabolism and increased appetite; perhaps, an evolutionary survival mechanism.

Glucagon-like peptide produced by the L-cells in the intestine, on the other hand, has an important positive effect on the pancreatic beta cells. It enhances glucose-induced insulin secretion, suppresses the release of glucagon from the alpha cells, and reduces food intake. Insulin enhances glucose uptake in muscle and fat cells and suppresses glucose release from the liver. Its effects on the cerebral neurons facilitating the regulation of whole-body glucose homeostasis and thermoregulation. Insulin also has a paracrine effect on alpha cells in the pancreas, suppressing the release of glucagon; thus, a reduction in insulin production enhancing glucagon release, worsening hyperglycemia and glucotoxicity.

Lifestyle modification

Lifestyle modification is the foundation of obesity treatment. The effective lifestyle modifications lead to significant reduction of cardiometabolic risks, including T2D (Gavin, et al., 2009). Recent studies have addressed the cause-driven risk reduction in patients with T2D, focused on a weight-reduction target of 7% of starting weight through a healthy low-calorie, low-fat diet and regular physical activity of moderate intensity, totaling approximately 150 minutes per week (Forster et al., 2011; Elmahgoub et al., 2009). Prevention of obesity and T2D in individuals who have become overweight is important in minimizing their future health hazards; this can be achieved through healthful lifestyle changes. Irrespective of the BMI, weight, age or ethnicity, adequate regular physical activity decrease insulin resistance.

Weight loss and exercise can also prevent T2D. Therefore, patients who are obese or having prediabetes or T2D would be markedly benefitted by engaging in regular physical activities. In this regards, the Look Ahead (Action for Health in Diabetes) study investigated a population of obese individuals with type 2 diabetes...
and the utility of intensive lifestyle interventions with the addition of portion-controlled food items, compared with a control group that received group diabetes support and education sessions (Look et al., 2006; Wadden et al., 2011).

In the Look Ahead trial, 5145 adults with type 2 diabetes with BMI > 25 were randomly assigned to the intensive lifestyle arm or the diabetes support and education arm (Look et al., 2006). Subjects allocated to the intensive lifestyle arm experienced a 5.0% reduction and maintenance of their body weight over the study period (Neiberg et al., 2012). This modest weight loss improves some surrogate marker-end points, such as sleep apnea urinary incontinence, renal functions, and so forth. However, it did not demonstrate any benefit in macro-vascular outcomes (Wadden et al., 2011; Wadden et al., 2011).

Sensible diet with increased physical activity decrease insulin resistance and T2D in part via reducing the visceral adiposity, and thus, reducing the waist circumference (Janiszewski and Ross 2007). This decrease of health risks occur independent of body weight changes (Janiszewski and Ross, 2007). With the downward trend in body weight and the abdominal girth, the health-related quality of life, mobility, co-morbidities will also improve (Kolotkin et al., 2001; Kolotkin et al., 2001). In addition, long-term studies suggest that weight loss may not be the only factor involved in improving the quality of life and reducing health risks. In a 24-month period of behavioral-weight loss intervention, health-related quality of life improved irrespective of the weight loss that was achieved and maintained (Blissmer et al., 2006). Therefore at every patient encounter, clinicians should encourage healthful lifestyle changes for their patients, in terms of improving diet and physical activities, and regularizing their sleep pattern.

CONCLUSIONS

The majority of public health recommendations are directed toward maintaining a healthy weight and maintaining health in non-overweight healthy people. Etiologies for obesity include consumption of poor-quality and unhealthful processed food, leading to nutritional deficiencies; chronic inflammation and infections; hormonal dysfunctions; ingestion of food allergens, contaminants, environmental toxins, and endotoxins; chronic stress and oxidative stress; and defects in energy metabolism and mitochondrial function. Most obese patients have one or more of these factors, leading to insulin resistance and obesity. Understanding the causative factors in a given individual would greatly facilitate his or her clinical management. Therefore, it is important that physicians systematically focus on the underlying causative factors in each obese patient, within a complex network of metabolic dysfunction; corrective actions of these causative factors will result in favorable gene expressions and successful clinical outcomes.

Obesity is not only associated with other diseases, but also could be the cause of other disorders (Malterud and Ulriksen, 2011). Examples of the latter include sleep apnea, hypertension, and dyslipidemia, which further increase cardiovascular risks. Thus, one of the key focuses of management of obesity should be to minimize the associated complications.

However, not every obese person experiences CVD and other complications. People with less visceral fat but higher amounts of peripheral subcutaneous fat, even those with high BMI, can be healthy (Brothers et al., 2012) and may not develop obesity-associated complications. Thus, a clear definition and distinction of metabolically healthy obesity is necessary to facilitate targeting those who are vulnerable to develop obesity-associated complications.

This would allow cost-effective weight loss interventions focusing on the high risk patients. Evidence-based research on lifestyle interventions has demonstrated the effectiveness of such interventions in reducing insulin resistance, CVD, heart failure, stroke, cancer, diabetes, and premature deaths from all causes (Cordain et al., 2005; Eaton and Konner 1985; Kelly, 2000).

There is no doubt that policies and practices affect behavioral and lifestyle changes and thus, patients health and weight. Such policies and practices relate to education, technology, advertising, production, agriculture, transportation, the environment, the food industry, and appropriate allocation of health care resources—curative (acute) medicine versus preventive medicine.

Implementing public health measures must include increased access to affordable good quality, nutritious food, and prevention of environmental pollution. Regardless of the patient's age, the number of hours of television watched or time spent using computers, iPods, etc., is linearly related to obesity (Hu et al., 2003). Meanwhile, there are a large number of environmental pollutants and toxins that promote obesity, but this is a neglected area of research (Hyman, 2007). Consumers generally tend to consume convenience foods (mostly processed food) outside their homes rather than eating naturally grown healthful foods. In addition, tightly built offices and centers along with today's effort-sparing technology, such as elevators and electronic communication devices, and abundant sedentary entertainment options further decreases the necessity of physical activity, thus contributing to the obesity epidemic.

Obesity is a complex metabolic disorder with a background genetic component. Once the conditions are favorable for accumulation of energy, obesity sets in; equally affecting people live in both industrialized and agricultural countries. Due to the (un)availability and the
affordability of nutritious food, and the eating habits, in most countries, the ethnic minorities are affected the most. However, preventative and management strategies are applicable and relevant to the entire population. A coherent cause-and risk-factor-driven strategy is necessary for the successful and cost-effective management of obese patients. Recently proposed complication-centric approach by the American Association of Clinical Endocrinologists is another cost-effective way of managing patients who are prone to develop metabolic complications associated with obesity (Garvey, W. T. (2013) New tools for weight-loss therapy enable a more robust medical model for obesity treatment: rationale for a complications-centric approach, 19 (5): 864-74). It is unwise to wait for anyone to develop metabolic complications of obesity prior to start him or her on a medical regimen. Overall, the cause-driven approach to prevent and treat obesity is much more cost-effective than treating any of the obesity-associated complications at a later stage.

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