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Preventing Long-Term Complications of Obesity, Type 2 Diabetes, and Metabolic Syndrome: Common Sense Approach

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Abstract

During the past three decades, obesity and type 2 diabetes have become major public health problems worldwide. Together, these two are the most costly non-communicable diseases affecting most countries. Compared to the escalating management costs associated with their complications, the day-to-day management cost of these two diseases are relatively small. In addition to better management of these to diseases, the key is to not only to prevent people becoming obese and developing type 2 diabetes, but also to prevent associated complications. While implementing mass-scale public education on healthy diet and physical activities (sustainable positive lifestyle changes) on one side, patient-oriented, individualized, cause-driven, preventative approaches are essential for reducing the morbidities and mortalities associated with these two common diseases. Blindly following the standardized care of one-treatment-fits-all model is not only ineffective but also cost more in the long run, comparison to the intensive, individualize care model in preventing long-term complications and reducing management costs.

Keywords: Diabetes; obesity; BMI; metabolism; overweight

Introduction

Obesity is affecting the well-being of millions of people in industrialized as well as agricultural countries worldwide, and has become a major global public health and socioeconomic issue [1,2]. In recent years, obesity has become one of the leading cause of cancer and preventable causes of death [3-5]. Overconsumption of calories and decreased physical activity [1,6] result in increased body weight/fat. However, in addition to the environmental effects and genetic factors, epigenetics and other externalities also play roles in regulating weight, energy balance, and metabolic functions [7].

The prevalence of obesity in adults in the United States, as defined by the Body Mass Index [BMI] more than 30.0 kg/m^2, more than doubled during the past three decades; 15.0% in 1980 to 36.1% in 2010 [2,8,9], so as the world wide obesity rate [10]. Meanwhile, 68.7% of adults in America are overweight or obese [BMI over 25.0 kg/m^2] [2]. During the period between 1960 and 2000, the percentage of those who were overweight progressed obese doubled [from 13.4% to 30.9%] [11,12]. Although the childhood obesity trend is plateauing [13], the number of obese, and the persons with T2D are staggering. In addition, with less than optimism management, the complications are continue to escalate with the duration of having the disease.

Current data suggest that obesity, T2D, and metabolic syndrome are complex processes that involve an imbalance of chemicals and hormones released from the inter-related, enteric, cerebral, and neuro-intestinal systems [14]. In fact, many people who are genetically or inherently susceptible to become obese or T2D, the disease sets in during the intrauterine life [15,16]. Globally, the abundance of calorie-rich, low-cost food containing a great deal of high-fructose corn syrup and less physical activities are the prime drivers of the global obesity and T2D epidemics.

Causes Of Obesity

Factors contributing to obesity epidemic

In addition to social, cultural, and behavioral factors, education and socioeconomic status contribute in varying degrees to the obesity epidemic and type 2 diabetes [T2D] [17,18]. Despite a number of available therapeutic approaches, poor adherence to advice and therapy, prevent successful weight loss and weight maintenance. Meanwhile, the stigma of obesity hinders people seeking assistance for issues related to body weight [19].

From a physiologic standpoint and based on thermodynamic principles and the law of conservation of energy, obesity results from an imbalance between energy intake and energy expenditure [7]. When the energy intake exceeds energy expenditure over a longer period, the excess calories stored as body fat. In evolutionary terms, this is an "energy insurance" against potential future starvation [20,21]. Although the incidence and the prevalence of obesity and type 2 diabetes continue to increase in adults, cardiovascular disease [CVD] and associated mortality have decreased [2].

In addition, older people tend to accumulate more visceral fat than do younger individuals because of age-associated alterations in hormones and the ability of energy expenditure [22]. Many women during their menopausal period [23] accumulate higher amounts of body fat, in part because of relative estrogen deficiency [24].

Genetics and environmental effects on obesity

Genome-wide association studies have confirmed that weight gain can be associated with several genes [25-27]. Some of these genes have been considered as thrifty genes contributing to the current obesity epidemic [20,21], the abundance of cheap, calorie-dense food and drinks that are easily accessible to people in recent years [commonly through super-markets and vending machines] together with frequent snaking, prevent the physiologic utilization of stored fat as energy [7]. Thus, the unutilized stored fat gradually increase, leading to obesity. In spite of hopes, genomic studies however, have contributed little to date with reference to identifying new drug targets and generating drugs to

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prevent or treat obesity and its associated disorders [28].

Although metabolic abnormalities and the underlying pathophysiology of metabolic syndrome are not fully understood, there is a strong overlap between insulin resistance and metabolic syndrome, with cardiovascular risk factors and prediabetes [i.e., underlying impaired fasting glucose and impaired glucose tolerance]. Therefore, it is logical to categorise those with insulin resistance and other risk factors as a "metabolic risk group."

Pathobiology of Obesity

Susceptibilities for becoming obese

Because different individuals have different causes and underlying genetic susceptibilities for accumulating fat at certain sites, weight gain, and experiencing T2D and its complications [29-31], one management approach will not be effective or appropriate for everyone [32]. Therefore, for a treatment plan to be cost-effective, a management plan oriented to eliminating the root causes of weight gain [33] and identifying patients who are prone to complications is essential.

Waiting to initiate treatment till complications have developed [e.g., complication-driven approaches] is not only illogical but also unlikely to be successful or cost-effective. For successful weight loss and weight maintenance, overall treatment methods must have a focused, sustainable behavioral modification component; be affordable, culturally acceptable, and cost-effective; and be user friendly so that patients can adhere to the plan.

Role of microbiome and epigenetics in obesity

In addition to the unhealthful lifestyle changes that is occurring over the past few decades, one can also consider the worldwide occurrence of these two epidemics as inadvertent consequences of successful treatment and control of infections with the frequent [and unnecessary] use of broad-spectrum antibiotics and the widespread change to from low-fat, high-calorie diets during the past four decades [7]. Frequent and inappropriate use of antibiotics are known toinduce adverse intestinal microbiome [34], alter satiety, and alter hormone levels and metabolic functions.One can hypothesize that those who are chronically or frequently exposed to broad-spectrum antibiotics over a long period are more susceptible to permanent alterations of gut microbial flora [34]. These groups of people are more likely to experience visceral obesity, and associated inflammation-driven, long-term complications, including CVD and cancer. The situation is further aggravated by epigenetic changes, and the chronic inflammation that driven in part by potentially carcinogenic microbial inflammatory metabolites generated from the non-symbiotic gastrointestinal flora. The latter reach the liver in high concentrations through the portal circulatory system [7]. These chemicals and toxins not only interact but also initiate and aggravate hepatocellular abnormalities, including hepatic inflammation, development of non-alcoholic steatohepatitis [NASH], and a host of other metabolic abnormalities, including insulin resistance [35].

Risk factors for weight gain

In addition to the commonly recognized risk factors, each individual has additional unique risk factors [some are behavioral] that contribute to becoming overweight or obese or experiencing T2D and associated complications. Therefore, in a given individual it is important to understand and identify these risk factors so that healthcare providers can positively intervene to eliminate [or at least reduce the negative influence from] such risks in patients [7].

If such risk factors are unattended or poorly managed or only one or two components, such as hypertension, lipids, or blood sugar, are addressed, patients will continue to gain weight, worsening the metabolic syndrome [31], increasing insulin resistance, and leading to serious complications and premature death [36-38]. Therefore, a treatment approach is needed that is holistic, dealing with the reduction of all risk factors. Instead of focusing and spending resources in eliminating "one" risk factor [e.g., controlling blood pressure or lipids, elimination of smoking, etc.], that will have little effect on the outcomes.The treatment and management approach should be designed to reduce all risk factors [7]. The greater the percentage reduction of all risk factors, contributing to weight-gain, the better the outcome.

Consequences of Obesity

The obesity epidemic parallels the rising incidence of T2D [17,39,40]. In addition to the commonly associated complications, these two diseases are directly correlate with prevalence of cardiovascular diseases [CVD]; such as hypertension, myocardial infarctions, and strokes. Moreover, a variety of other complications, including arthritis, sleep apnea, cognitive impairment, and certain cancers also manifest in susceptible individuals [6,41]. The combination of aforementioned and the underlying metabolic derangements, enhance the morbidity, mortality, and overall associated costs.

Nevertheless, not all obese patients are at risk for complications such as T2D, CVD, and stroke [18,42]. The long term metabolic health risks associated with obesity are markedly influenced by the type of distribution of body fat: the intra-abdominal [visceral] fat versus subcutaneous fat [7]. In this regard, people who are obese but with normal amounts of visceral fat could be relatively healthy [43] and less likely to experience obesity-associated major complications [29]. In parallel, even those with normal BMI but with increased accumulation of visceral fat as is in the case for many South Asians, are more likely to have or develop significant metabolic abnormalities and are at increased risk for developing complications, including premature death. .

Visceral fat and morbidities

Abdominal obesity represents a collection of enlarged and inflamed adipocytes in visceral fatty tissues, which synthesize and release many harmful adipokines/ infokines [44-46]. Most of these cytokines liberated from the hyperactive, enlarge fat cells are inflammatogenic, promoting insulin resistance, inflammation, and atherosclerosis [47-49]. In persons with visceral obesity, the synthesis and secretion of protective cytokines such as leptin and adiponectin are significantly reduced [14,50,51]. Thus, having excess visceral fat (i.e., abdominal obesity) leads to a perpetual vicious cycle of generalized inflammation, and metabolic syndrome, leading to serious complications, and premature death [44-46].

Excess visceral adiposity is positively correlated with insulin resistance, T2D, and premature deaths [52,53]. Those who are genetically susceptible to metabolic syndrome are more vulnerable to develop glucose intolerance, T2D, and a number of associated complications [51,54]. The latter is particularly important in the presence of chronic stress, increased (uncontrolled) caloric intake, and less-than-appropriate physical activities [i.e., adverse environmental influences] [39,40,55]. Moreover, metabolic syndrome is the underlying driver common to complications developing in persons with obesity and T2D [17,55,56].

Excessive inflammatory cytokines deriving from visceral fat cause insulin resistance and a series of metabolic dysfunctions, which further

increase the severity of metabolic syndrome [57,58]. These together, drives the longer term complications associated with obesity and T2D [59,60]. The higher the percentage of visceral adipose tissue mass as a percentage of body weight, the greater the risk for insulin resistance, hyper-insulinemia, comorbidities, and complications [61,62].

The role of Adipocytokines

The pro-inflammatory chemicals and cytokines released from visceral adipose tissues, in part due to the chemicals derived from the intestinal microbiome, further interfere and derange the metabolic pathways [45,46,48,49]. Nevertheless, the hyperlipolytic state of visceral fat alone cannot explain all abnormalities observed in persons with metabolic syndrome, T2D, and CVD [31,63-65].

For example, in many patients, bypassing the stomach and duodenum via bariatric surgery could significantly ameliorate insulin resistance, metabolic syndrome, and T2D in a relatively short period, occurring even before a significant weight loss is achieved [57,66]. Therefore, abdominal fat *per se* may not be the sole cause of metabolic abnormalities [67-69]. Meanwhile, the roles of several other issues, such as contribution form the environment, stress, and hormonal abnormalities, are not understood [14,51].

Visceral adipose tissue is an endocrine organ; it is a key site of production of (mostly) harmful inflammatory adipokines/ cytokines and certain hormones that activate a pathological, metabolic vicious cycle [53,70]. Visceral adipocytes are hyperlipolytic and are more resistant to insulin than is subcutaneous fat [48,49,71]. Nevertheless, the hyperlipolytic state of visceral fat alone cannot explain all metabolic abnormalities [T2D and CVD] observed in persons with metabolic syndrome [63-65]. Secretions from enlarged fat cells also affect the satiety and cravings, and activate a pathological, metabolic vicious cycle [45,46,70]. In addition, because the venous blood from the visceral [omental] fat drains directly to the liver via the portal vein, the liver is constantly exposed to high concentrations of inflammatory cytokines and free fatty acids. This enhances hepatic inflammation [as reflected by increased levels of C-reactive proteins], formation of fatty liver, and NASH [35,72].

Hepatic inflammation also impairs uptake of insulin, in the liver exacerbates hyperinsulinemia, and increases gluconeogenesis [73]. This negative vicious cycle promotes impairment of liver function, increases hepatic glucose production, and leads to excessive production of glucose, free fatty acids, and apolipoprotein B-containing, triglyceride-rich lipoproteins [14]. Thus, the metabolic derangement present in insulin resistance [visceral obesity, T2D, and metabolic syndrome] causes many metabolic disturbances These include, hyperinsulinemia, hyperglycemia, hypertriglyceridemia, and increased apolipoprotein B, leading to glucotoxicity and lipotoxicity in target tissues [36,60,74].

Treatment Strategies

An effective treatment and interventional strategy needs to include identifying the causes of overweight/obesity and metabolic syndrome in a given patient. The goal is to prevent individuals from becoming overweight or obese. Generally, this is achieved through education and monitoring appropriate lifestyle changes, motivating patients to adhere to advice and therapy to prevent gaining or regaining weight, and if necessary, prescribing medications [7,39,40,55]. However, for the intervention to be effective, clinicians should be able to motivate the patient to enhance his or her adherence to lifestyle changes and treatment [75]. This is best achieved through an individualized care and treatment plan. Generic approaches to the treatment of obesity and T2D are unlikely to be successful for patients [7].

Lack of cost-effective diagnostic modality to identify high-risk patients

Despite the escalating incidence of obesity and T2D, no clear cut and cost-effective way of identify who is vulnerable to develop serious complications exists. In addition, there are no specific, sensitive, and cost-effective markers or tests available for differentiating those who are likely to experience complications from those who are not [7]. Currently available biochemical and molecular methodologies are not specific enough to identify those who are at high risk for serious complications at an early stage so that complications can be effectively prevented. These lack of advancements and hiatus of knowledge significantly contributes to the escalating costs of managing obesity and T2D. Attempts to fill this gap by medications is unlikely to be successful.

Moreover, expensive, high-tech testing via imaging is available for quantifying visceral fat to identify those who are at risk of CVD. However, because of the lack of cost-effectiveness, it is hard to justify the use of such imaging techniques, biopsies, or high-tech methods for routine investigation of obesity weight maintenance, and assessment of future cardiovascular risk. Therefore, a simple anthropometric measurement, such as waist circumference or waist-to-hip ratio, together with family and personal history and basic blood lipid profiles are adequate in most obese persons for assessing future risks in a cost-effective manner [32,76]. Measurement of abdominal girth is one of the easiest and the most cost-effective ways to identify and monitor overweight and obese persons, to assess their future CVD risks [7].

Sustainable positive lifestyle changes are the key to weight loss and maintenance

Lifestyle changes are the fundamentals of managing overweight, obesity, T2D, and the metabolic syndrome [77,78]. Such changes include healthy eating and increasing physical activity [39,55]. However, the adherence to such plans is limited. Lifestyle changes are equally important for obese persons who opt to have pharmacotherapy or bariatric surgery because such sustainable changes are crucial for weight maintenance [33,79]. In selected patients, medications and bariatric surgery can be effective, but they are not the first line of treatment options. Neither would they work alone well, in the absence of adhering to lifestyle changes [75]. Even when such treatments are offered, they must be complementary to compliance with lifestyle and behavioral changes [80].

Relative inactivity and sedentary lifestyles lead to increased caloric intake, reduced energy metabolism, and the accumulation of body fat [39,55,75]. Although metabolic abnormalities and the underlying pathophysiology of insulin resistance are ill understood, in metabolically high-risk patients, there is a strong correlation between insulin resistance and CVD [7,31,47].

Overall management of obesity and T2D

The combination of sustainable lifestyle changes and pharmacotherapy or bariatric surgery in selected patients can be effective in weight reduction and maintenance, and minimizing long-term complications of T2D and obesity [77,81]. Combined approaches described above are effective in reducing insulin resistance [82], and decreasing CVD, heart failure, stroke, cancer, diabetes, and all-cause mortality [83-85]. However, because of poor compliance, unwillingness to accept obesity as a disease, and associated social stigma [19], the overall effectiveness of therapies for weight loss and metabolic syndrome is imperfect. Meanwhile, others have suggested a complication-centric

management for the control of obesity [86], for which the outcomes are has not been established.

In high-risk populations, timely and effective interventions to achieve 5% to 10% weight loss and subsequent weight maintenance significantly improve insulin resistance and morbidities and reduce future complications [57,86]. Extra weight loss may be beneficial for improving mechanical loading on joints hypersomnolence, obstructive sleep apnea, depression [87,88], and for cosmetic reasons. However, managing obesity, T2D, and metabolic syndrome requires prioritization of resources and combined, "cause-driven" approaches [32,33]. It is easier to prevent obesity than to lose weight after weight gain; thus, one needs to identify risk factors in individual patients at peril for weight gain at the earliest possible time and intervene [7].

Future perspectives

Obesity is not just a lifestyle issue; it also is not solely a thermodynamic, genetic, or metabolic problem of handling calories [7]. It is an inflammatory and endocrine disorder, with a behavioral component. The combination leads to dysregulation of metabolism and energy balance, which results in the accumulation of visceral fat; it has multiple pathologic etiologies and sinister outcome, unless intervened early. Thus, treatments must be holistic and cannot rely on to reduce future risks, solely on prescribing expensive weight loss medications or surgery.

While there are only a handful of approved medical therapies for obesity, many new molecules are currently under development to tackle the obesity epidemic using novel therapeutic targets. Currently approved anti-obesity drugs are costly, and have limited effectiveness and associated with significant adverse effects [89]. There are several molecules known for a while, that are currently under investigation, including leptin analogues, oxyntomodulin, tesofensine, melanocortin-4 receptor agonists, peptide-YY, neuropeptide Y analogues, and various combination therapies are currently under investigation.

To get into the next level of anti-obesity medications, not only the efficacy but also specificity must be improve to decrease adverse effects. Both the new targets and new paradigm as well as combination approaches need exploring. The latter includes the usage of lower doses of multiple agents targeting different pathways and combination using peptides/antisense molecules, and designer-small molecules worth exploring.

There are several bariatric surgical approaches already exists as obesity therapy, including various types of gastric bypass surgery, gastric banding and balloons, and sleeve gastrectomy [90,91]. Novel approached that are currently under investigation includes, stem-cell therapy and adipose tissue transplantation, the use of circadian rhythm to enhance therapeutic efficacy [90,91], and using brown adipose tissue as a target for treatment [92].

Conclusions

Those with visceral obesity, metabolic syndrome, and T2D also have significant impairment of the neurohormonal systems. Thus, addressing the weight loss alone to resolve obesity, metabolic syndrome, or T2D without paying attention to inflammatory and neurohormonal abnormalities is unlikely to establish a sustainable program of weight weight maintenance and reducing long-term risks and complications. Even if patients lose weight initially, neglecting the holistic approach will lead to most people regaining weight.

The cost-effectiveness of the focused, individualized treatment would materialized from the back end, through the prevention of complications associated with obesity and T2D. Although somewhat cumbersome and time consuming to follow patients with individualized approaches and customizing treatment for these two common diseases, billions of dollars will be saved in the long-run by such targeted treatment programs.

In addition to employing reasonable weight reduction programs, clinicians seeking to prevent obesity-associated complications in their patients must use coordinated, individualized, cause-driven approach that would reduce future complications [33,79]. Understanding the cause of obesity in individual patient would greatly facilitate the development of an individualized, acceptable, and sustainable treatment plan with successful health outcomes. Managing with the best options for those who are already overweight or obese and implementing obesity prevention strategies and methods are the most cost-effective ways to move forward in reducing future complications and curtailing escalating costs.

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