



A Comprehensive Analysis of Obesity Part 1. Overview of Obesity

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Preface

Due to the extent of this subject, the resultant research was developed into seven distinct, but interconnected papers entitled as follows: Part 1. Overview of Obesity, Part 2. Causation and Pathophysiology of Obesity, Part 3. Metabolic Syndrome, Part 4. The Obesity Epidemic in Public Health, Part 5. An Algorithm for Obesity, Part 6. The Role of Primary Care and Pharmacological Interventions in Obesity, and Part 7. Bullet Points of Obesity. Each paper stands independent from the others and can be read and appreciated separately. However, it is recommended to read the articles sequentially from the first paper to the last to enhance the reading experience and to better grasp and assimilate the interrelated information and concepts.

Keywords: Central Obesity; Comorbidity; Diabetes Mellitus; Epidemic; Evidence-Based; Hypertension; Neuromodulation; Obese; Overweight; Public Health; Syndrome X; Weight Management; Zero Hunger

Abbreviations

AACE	:	American Association of Clinical Endocrinologists
ACE	:	American College of Endocrinology
ADA	:	American Diabetic Association
AHA	:	American Heart Association
AMA	:	American Medical Association
BMI	:	Body Mass Index
BP	:	Blood Pressure
CDC	:	Center for Disease Control and Prevention
CCO	:	Consensus Conference on Obesity
CO	:	Central Obesity
CVD	:	Cardiovascular Disease
DM	:	Diabetes Mellitus;
EASD	:	European Association on the Study of Diabetes

EGIR	:	European Group for the Study of Insulin Resistance
FBG	:	Fasting Blood Glucose
FDA	:	U.S. Food and Drug Administration
HDL-C	:	High Density Lipoprotein Cholesterol
Hs-CRP	:	High Sensitivity C Reactive Protein
HTN	:	Hypertension
IDF	:	International Diabetic Federation
IR	:	insulin resistance
LDL-C	:	Low Density Lipoprotein Cholesterol
MS	:	Metabolic Syndrome
NCEP/ATP III:	:	National Cholesterol Education Program-Adult Treatment Panel III
PCE	:	Practicing Clinicians Exchange
RAAS	:	Renin Angiotensin Aldosterone System
SNS	:	Sympathetic Nervous System
tDCS	:	transcranial direct current stimulation
TG	:	Triglyceride
WHO	:	World Health Organization

Prologue

According to the Obesity Medicine Association, obesity is defined as “A chronic, relapsing, multi-factorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass resulting in adverse metabolic, biomechanical, and psychosocial health consequences”.

Introduction

The global incidence of overweight and obese individuals has grown exponentially in the last three decades resulting in a health epidemic morphing into a pandemic. Adult obesity is now considered a chronic disease. Chronic disease management should

be a collaborative effort between patients and healthcare providers to determine the most effective treatment that addresses excess weight. Healthcare professionals have a responsibility to consider therapeutic strategies that are patient-specific ensuring safety with an evidence-based approach [1-3]. The past prevention efforts addressing this public health concern have evolved and developed evidence-based strategies of obesity management.

The World Health Organization (WHO) defines overweight and obesity as an accumulation of fat in excess that presents a health risk. The primary measurement for evaluating the general population is calculating the Body Mass Index (BMI). This calculation is a person's weight (in kilograms) divided by the individual's height (in meters) squared. An individual with a BMI equal to or more than 25 is considered overweight and at 30 or more is considered obese [1,4].

In 2013, the American Medical Association (AMA) classified obesity as a disease. The expanding American waistline refers to the dramatic increase in rates of obesity as a significant health problem. There were debates in 2013 between committees that said that "medicalizing" obesity would include one-third of all Americans as being ill and could lead to more reliance on costly drugs and surgery. The AMA had concerns that there may be an excess treatment of the patients in the overweight classification who could otherwise utilize lifestyle modifications instead of medical treatments [5,6]. Despite the patients who fall on the border of potential treatment guidelines, there was a mandate to utilize an evidence-based obesity algorithm for weight loss in patient care [2,3].

Discussion

Obesity has reached epidemic portions and is on the rise. Nearly 900 million people around the world are undernourished, while 1.9 billion are overweight [7]. Worldwide obesity has more than doubled since 1980. Over 600 million people out of this sector were obese. These numbers represent 39% and 13% respectively [8]. It is ironic to note how the current worldview finds these numbers in conflict as many nations are attempting to implement governmental policies of "Zero Hunger" while the global population reaches record levels of obesity [9].

In the 1960s, prisoner-feeding experiments conducted by a University of Vermont physician researcher Ethan Sims addressed the concept of metabolic homeostasis. In 1967, Sims fed inmates at the Vermont State Prison upwards of 10,000 kcal per day. Over 200 days on this overfeeding regimen, 20 inmates gained an average of 20 to 25 pounds.

The metabolic rates of these previously normal-weight subjects sped up in response to their increased caloric consumption as if to defend their initial, lower weights. Once their calorie intake returned to normal, the men had difficulty maintaining the weight gained and lost all the weight they had gained relatively quickly. The exceptions were two inmates who gained weight swiftly and effortlessly but then struggled to lose that weight even after caloric consumption was reduced. Both of these men had family histories of obesity which added empirical support to the belief that an overweight condition could be heritable [10].

The Epidemic of Obesity

In 2001, obesity was labeled a health "epidemic" according to

the U.S. Surgeon General's "Call to Action" policy to prevent and reduce overweight and obesity. Traditionally, the label "epidemic" has been used in public health referring to an outbreak or an increase in the disease. However, health professionals concluded that "epidemic" was an appropriate label for obesity because of its growing prevalence in America and its threat to overall health with its associated comorbidities [11].

Obesity is the most significant public health issue in the developed world affecting all socioeconomic backgrounds and ethnicities [12]. "No discrimination" means obesity can affect anyone without mercy, chronically, deleteriously, and overwhelmingly; and to compound the issue, obesity requires a sophisticated understanding of the health-disease process [9]. The WHO organized prevalence in Figure 1 (below) with the United States having the highest prevalence of overweight adults in a group of English-speaking countries which share common roots in British culture (i.e., Anglosphere) and history [13].

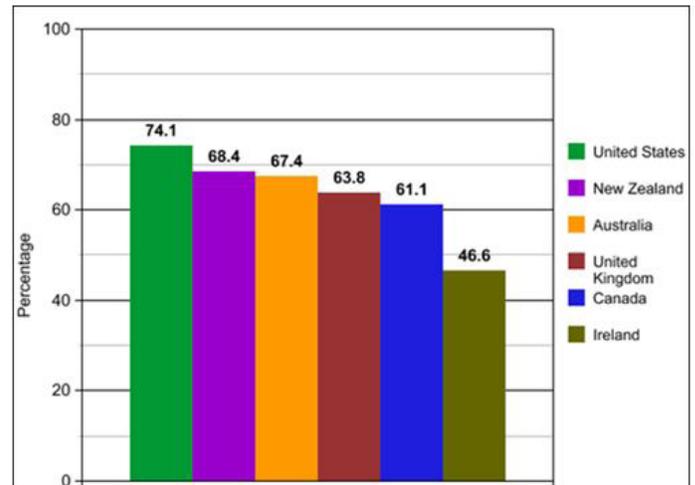


Figure 1: Prevalence of Overweight People in the Anglosphere [8].

In the United States, the prevalence of obesity currently exceeds a third of the adult population and is associated with a fivefold increase in diabetes mellitus (DM) and threefold increase in cardiovascular disease (CVD) risk [14]. Obesity is not a new epidemic or pandemic. In 2003, obesity was the second only to smoking as the leading cause of preventable death [15].

Interpreting the Body Mass Index

According to the WHO, the definition of overweight and obese are generally defined as an excessive fat accumulation that may impair health. BMI is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m^2). The WHO definitions are as follows:

- BMI higher than or equal to 25 is overweight;
- BMI higher than or equal to 30 is obesity.

BMI provides the most useful population-level measure of overweight and obesity as it is the same for both sexes and all ages of adults. However, it should be considered a rough guide because

it may not correspond to the same degree of fatness in different individuals [4]. In 2013, the AMA classified obesity as a disease [16]. The classification can be broken down further as shown in Table 1 (below).

Ethnic Specific Values for Waist Circumference: International Diabetes Federation Consensus World Wide Definition of Metabolic Syndrome www.idf.org		
Population	Male	Female
United States	≥ 102 cm or 40 in	≥ 88 cm or 35 in
Europids (Caucasians)	≥ 94 cm or 37 in	≥ 80 cm or 31 in
South Asians, Chinese, Japanese	≥ 90 cm or 35 in	≥ 80 cm or 31 in
South and Central Americans	Use South Asian criteria until more specific data are available	
Sub-Saharan Africans, Eastern Mediterranean and Middle East (Arab)	Use Europid criteria until more specific data are available	

Table 1: AMA Obesity Classification [6].

Asian and Hispanic populations develop negative health consequences at a lower BMI than Caucasians. The Japanese define obesity as a BMI higher than 25kg/m², with China selecting 28 kg/m² [17].

The data in Figure 2 (below) illustrates overweight and obesity increasing exponentially from less than 10 percent to greater than 30 percent. Since 2010, leadership in government has recognized obesity as a chronic disease and put strategies in place for reduction and cessation. The Center for Disease Control and Prevention (CDC) has publicized fact sheets. The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) convened a Consensus Conference on Obesity (CCO) in 2014 to develop an algorithm from evidence-based medicine as well as for implementing evidence-based strategies [6].

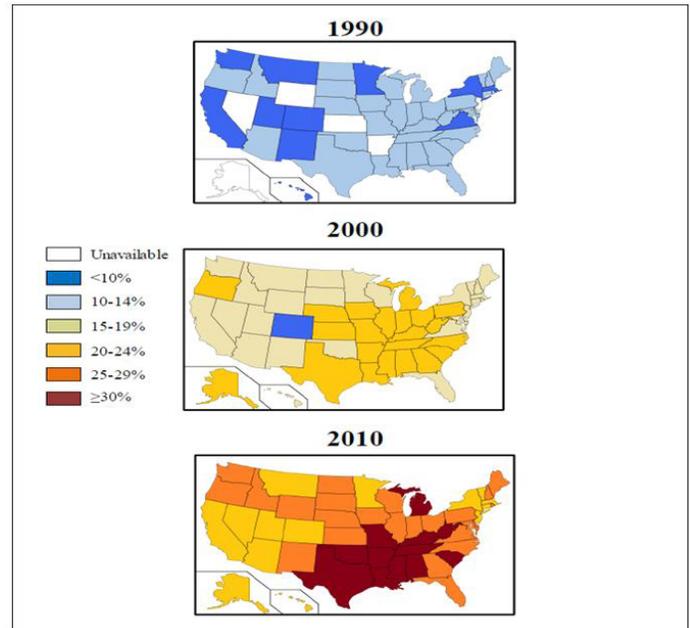


Figure 2: Behavioral Risk Factor Surveillance System: BMI ≥30, or about 30 lbs. overweight for 5'4'' person. Obesity Trends Among U.S. Adults. BRFSS, 1990, 2000, 2010 [2].

Comorbidities of Obesity

DM and CVD are the top two comorbidities associated with excess weight. Historically, obesity was considered a problem only in high-income countries, but, currently, there has been a dramatic rise in obesity in the low- and middle-income countries, especially in urban settings [1]. Primary care providers must engage in pathways of disease prevention for all patients since there is now an equalization of socioeconomic status and the disease process [18,19].

Obesity and Disease Clusters

Obesity leads to a cluster of diseases that comprises metabolic syndrome (MS) and, as such, has been advocated as a simple clinical tool for predicting DM and CVD. It also forms a conceptual basis for understanding some of the pathophysiological links between metabolic risks, DM, and CVD as depicted in Figure 3 (below). Obesity is positioned as the only central and reversible

CVD disease risk factor that directly influences all of the other associated factors comprised of the following: high-density lipoprotein cholesterol (HDL-C), high-sensitivity C-reactive protein (hs-CRP), hypertension (HTN), low-density lipoprotein cholesterol (LDL-C), renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), and triglycerides (TGs) [14].

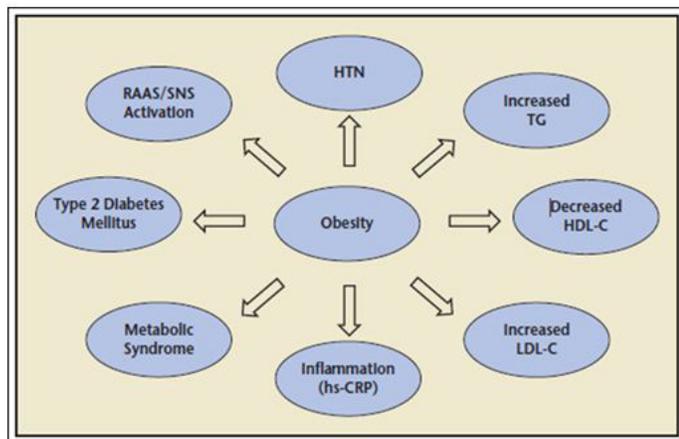


Figure 3: Pathophysiological Links between Metabolic Risks [14].

The clustering of metabolic syndromes as direct, contributory risks in DM and CVD has been recognized for more than 80 years, but the modern concept of MS began when Gerald M. Reaven, M.D. proposed a conceptual framework which established links between biological events in a single pathophysiological construct with emphasis on insulin resistance (IR) [20]. Reaven's construct suggested that IR provides common mechanisms underlying the associated abnormalities, such as BP, lipid abnormalities, and glucose intolerance. In 1947, Jean Vague, a physician from Marseilles, observed that upper body obesity was significantly associated with DM, atherosclerosis, gout, and calculi; all these conditions were improved by consuming a low carbohydrate diet [20-22].

In 1977, Haller described metabolic syndrome as being associated with obesity, diabetes mellitus, hyperlipoproteinemia, hyperuricemia, and hepatic stenosis. In the same year, Singer added that hypertension and gout could also be associated with the syndrome [14,23]. Later, in 1988, Reaven proposed that IR was the underlying factor for metabolic syndrome, and also termed the disease syndrome X. Reaven did not include obesity as one of the factors in the syndrome as earlier researchers had done. However, obesity-in particular, central obesity (CO)-was later recognized as one of the critical underlying factors involved in MS [20].

Metabolic Syndrome

The terms metabolic syndrome, insulin resistance syndrome or syndrome X were used to define the clustering of factors that increase the risk for DM and CVD. There has been much debate about whether MS should be considered a syndrome at all. By definition, a syndrome is described as a group of signs and symptoms with a common underlying pathology; but the exact pathology of MS is still not yet fully known [21]. Some authors

argue that, although the symptoms of MS often appear together, they may reflect diverse disease processes. Kahn argued that the risks of MS are real even if the terminology is questionable. He proposed using metabolic risk or cardio metabolic risk as a better way to describe the syndrome. He summarized by saying that it is useful as a concept rather than using the term "Syndrome" [22,24].

In 2005, the American Diabetic Association (ADA) and European Association on the Study of Diabetes (EASD) pointed out specific controversies in the diagnosis of the metabolic syndrome [25]. For instance, the value of including DM in the definition was questioned. Also, the use of IR as the unifying etiology was considered uncertain. The ADA/EASD committee also pointed out that there was not a clear basis for including or excluding CVD risk factors in the diagnosis of MS [25]. There are several existing criteria for defining MS being used by the American Heart Association (AHA), European Group for the Study of Insulin Resistance (EGIR), National Cholesterol Education Program-Adult Treatment Panel III (NCEP/ATP III), WHO, and International Diabetic Federation (IDF). The most commonly used definition of MS was described by the WHO and NCEP/ATP III criteria [25]. Regardless of the existing controversies in definition and diagnosis, MS is still considered to be a useful diagnostic tool in primary care prevention. The label allows for early patient identification, and subsequent education regarding behavioral changes implicated in the prevention of DM, CVD, and HTN which are critical factors in MS [26].

Patient Education

Patients should be educated early about the connection between their lifestyle, health risks, and medical outcomes. For instance, the NCEP/ATP III identifies MS as an indication for compelling lifestyle intervention. Effective interventions include diet, exercise, and judicious use of pharmacologic agents to address specific risk factors [17, 27]. Weight loss will dramatically improve all aspects of MS [18]. An increase in physical activity and a decrease in caloric intake (by reducing portion sizes) have been found to improve MS, even in the absence of weight loss. Specific dietary changes that are appropriate for addressing different aspects of the syndrome include reducing saturated fat intake to lower TG levels, reducing sodium intake to lower BP, and reducing high-glycemic-index carbohydrate intake to lessen the potential development of IR [6,17].

Typical physical activity (lack thereof) and poor dietary habits of an average American adult have been shown to increase BMI approximately five percent each decade. The life expectancy, in 2012, was 79 years old with approximately 35 percent of that population segment being overweight or obese. Studies show that in older individuals, an increase in weight is due to sedentarism. Obesity in the general population is the result of a lifestyle which is sedentary with a reduction in everyday physical activity. It can be hypothesized that the combination of aging and obesity further promotes sedentary lifestyles in baby boomers and older adults [2,3,23].

Weight Management in Primary Care

Excess body fat and other associated health risks such as DM and CVD are well-documented and provide the rationale for the management of obesity [17]. Other comorbidities follow. BMI

and waist circumference are key screening tools used to identify overweight and obese patients. Implementing a systematic and practical approach to manage these patients will reduce the factors that comprise MS. A reduction in these clinical markers will improve patients' overall health and wellness. Improvement has been shown with five percent weight loss [27,28]. The CCO has prepared a definitive obesity algorithm for primary care providers, and others formulated on evidence-based medical practice. Permanent weight loss can be achieved through behavioral reductions in food intake and increases in energy expenditure. Most patients find weight loss difficult as restricting food intake and finding the time for increasing exercise (along with a possible dysfunctional hormonal system) is challenging to many [6].

A developing field of study, neuromodulation, may help in restricting food intake and the type of food consumed. The brain circuitry influences taste and can be a neural gateway to hedonic pathways. Transcranial Direct Current Stimulation (tDCS) involves the non-invasive placement of electrodes usually to the dorsolateral prefrontal cortex [29]. The research regarding tDCS is focused primarily on its effect on food cravings. However, according to researcher Miguel Alonso-Alonso "Anodal tDCS applied over the motor cortex promotes brain energy consumption and causes systemic glucose uptake" [30]. The intensity of stimulation and the number of sessions are still under investigation to determine a therapeutic endpoint.

Pharmacological Interventions in Obesity

There are four new medications introduced in the past few years that have received U.S. Food and Drug Administration (FDA) approval for weight loss, adding to an older one, Orlistat, that was approved in 1999. Orlistat is currently labeled under Xenical as 120 mg dose by prescription, whereas the over-the-counter version, Alli, is sold as a 60 mg dose. These medications promote weight loss by decreasing the absorption of fat through the intestines [4,27].

Markers of MS include elevated BP, dyslipidemia (elevated TGs, lowered HDL-C), elevated Fasting Blood Glucose (FBG), and Central Obesity (CO); these markers were monitored for 52, 56, or 102 weeks using one of four distinct drugs or drug combinations: Lorcaserin, Phentermine/Topiramate, Naltrexone/Bupropion, and Liraglutide. Results indicated all patient groups lost weight (3.3 to 6.6 pounds) with a corresponding decrease in the following: waist circumference (2.5 to 5.2 inches), plasma TG (4.8 to 13.3 mg/dl), systolic BP (0.7 to 2.8 mmHg) and diastolic BP (0.8 to 7.9 mmHg), and FBG (0.8 to 7.9 mg/dl). The highest weight loss was seen with Phentermine/Topiramate combination after 52-102 weeks of treatment. These results indicate that long-term administration of weight loss medications can be a safe and effective regimen for weight control.

Key Factors Affecting Successful Weight Management Programs

A key component to successful weight management is public awareness and reimbursement for the physician in a primary care setting. With the launch of these drugs, there have been many symposiums in the last few years discussing the options for patients who suffer from chronic obesity. The algorithm constructed in 2014 recommends different modalities depending upon the

patient's history, health status, and current comorbidities [14]. There are symposiums held nationally where Practicing Clinicians Exchange (PCE) dedicates lectures on this topic for primary care providers. PCE conducts a brief analysis via a questionnaire after each lecture as well as a six-week electronic follow up. The focus of the lectures is on the level of commitment for changing practice guidelines in the primary care clinic.

Conclusion

Obesity is one of the most severe public health issues in the developed world affecting all socioeconomic backgrounds and ethnicities [12]. "No discrimination" means obesity can affect anyone. Obesity is a complex condition [9]. The global incidence of overweight and obese individuals has grown exponentially in the last two to three decades resulting in an epidemic escalating into a pandemic. Currently, adult obesity is considered a chronic disease. Chronic disease management should be a collaborative effort between patient and healthcare providers to determine the most effective treatment for addressing excess weight. Healthcare professionals have a responsibility to consider therapeutic strategies that are patient-specific while ensuring safety with an evidence-based approach [1-3].

According to the WHO, the definition of overweight and obese is commonly defined as an excessive fat accumulation that may impair health. In 2013, the AMA classified obesity as a disease [15]. Obesity leads to a cluster of diseases which constitutes MS; and, as such, has been advocated as a clinical tool for predicting DM and CVD. The CCO has prepared a definitive obesity algorithm for primary care providers that is formulated on evidence-based practice medicine. Bureaucratic measures have been focused on solving morbid obesity; however, past bureaucratic efforts have been ineffective and burdensome to put into practice. Useful preventative care guidelines need to be feasible for widespread use and compliance. Mechanisms for comprehensive care need to be put into place [28].

Excess body fat and other associated health risks, such as DM and CVD, are well-documented and provide the rationale for the management of obesity [17]. Many other comorbidities follow obesity. BMI and waist circumference are key screening tools to identify overweight and obese patients. Patients should be educated early about the connection between their lifestyle, health risks, and medical outcomes.

The algorithm constructed in 2014 recommends different modalities depending upon the patient's history, health status, and current comorbidities [14]. Four new medications have been introduced (with FDA approval) for weight loss in addition to an older medicine, Orlistat. The clinician today has an armamentarium for the care and treatment of obese patients. The least expensive and most efficacious method is behavioral change through a healthy diet and consistent exercise program. This non-pharmacological and non-surgical intervention is successful for some. The next modality of care is pharmaceutical management. A treatment option for moderate to severe obesity (BMI 35-40+) is bariatric surgery. If proven effective, the future of obesity treatment may include tDCS to modify hedonic pathways. Successful weight management involves public awareness and reimbursement to the

physician in the primary care setting. Primary health care workers could be more effective in helping patients to change their lifestyle behaviors by assessing each patient for the presence of specific risk factors, communicating these risk factors to patients, identifying appropriate interventions to address specific risks, and assisting patients in identifying barriers to behavior change [6,18].

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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