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Is Obesity/Adiposity-Based Chronic Disease Curable: The Set Point Theory, the Environment, and Second Generation Medications

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Short Title: Body Weight Set Point in ABCD

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Abstract

Adiposity-Based Chronic Disease (ABCD) is a chronic disease and requires life-long treatment and follow-up. Obesity protects obesity through altered regulation of caloric intake and set point mechanisms that maintains a high equilibrium body weight. Lifestyle interventions and obesity medications do not permanently alter the set point which often makes weight loss achieved by lifestyle short-lived and operates to drive weight regain once medications are discontinued. Bariatric surgery procedures can alter appetite and lower the “set point” for equilibrium body weight via unknown mechanisms. However, few patients attain ideal body weight following surgery, many regain weight, and all require long-term follow-up for the disease. The excess adiposity of ABCD gives rise to complications that impair health and confer morbidity and mortality; however, the genetic risks and potential interactions between genes and environment that give rise to complications also cannot be eliminated. The equilibrium body weight around which set point mechanisms operate can be modified by environment, which underscores the importance of a less obesogenic environment for prevention and treatment of ABCD on a population basis.

If ABCD will eventually be curable, this will depend on a clear understanding of the molecular mechanisms that determine the set point regulation of body weight, and an ability to permanently modulate the set point to oscillate around and a lean body mass. The conceptualization of ABCD as a chronic disease, however, does present us with opportunities for primary, secondary, and tertiary prevention to avert disease progression. For tertiary care, the advent of new, more effective, second-generation obesity medications will allow clinicians to treat-to-target via active management of body weight into a target range that will ameliorate specific complications.
I. Introduction

In 2012, the American Association of Clinical Endocrinology (AACE) designated obesity as a chronic disease and explained the rationale for that designation (1). First, like other chronic diseases, the pathophysiology of obesity is complex involving interactions among genes, biological factors, the environment, and behavior. Second it met the three criteria for what constitutes a disease established by the American Medical Association; a disease must have outward signs or symptoms, cause morbidity or mortality, and involve impaired function in one or more tissues (2). In obesity, an increase in adiposity commonly assessed by body mass index (BMI; kg/m$^2$) is the primary outward sign or symptom. Obesity is associated with multiple complications which confer morbidity and mortality and amply satisfy the second criterion for a disease. Finally, two examples of abnormal tissue function can readily be identified: (i) with expansion, adipose tissue becomes inflamed and secretion of adipocytokines is dysregulated resulting alterations in metabolism and the vasculature and the progression of cardiometabolic disease; (ii) the interactions involving satiety hormones and central nervous system (CNS) feeding centers is abnormal resulting in increased caloric intake and increased body mass. In 2013, the American Medical Association also designated obesity as a chronic disease (3).

The question before us is whether obesity is curable, or can at least be placed into a state of prolonged remission, or are these disease manifestations and the underlying pathophysiology unrelenting and lifelong. This will require discussion of two aspects that are integral to obesity: the development of increased adipose tissue mass and the ensuing complications. Both the basic disease process and related complications are essential and inseparable components of a chronic disease. As will become evident, the term obesity is used when referring to increased BMI, and the diagnostic term Adiposity-Based Chronic Disease (ABCD) used when referring to the full measure of the chronic disease including both excess adiposity and ensuing complications.

II. Is Obesity Curable: The Development of Increased Body Mass

A. Interactions between Genetic and Environmental Factors

The last two decades have featured substantial advances in our understanding of obesity pathogenesis, and these findings are important in considering whether obesity is a permanent condition. Obesity is a disease of energy balance that produces excess adiposity sufficient to impair health (1). Like other chronic diseases, the pathophysiology of obesity is complex involving interactions among genes, biological factors, the environment, and behavior (Figure 1). These factors give rise to abnormalities in the regulation of energy balance and produce a degree of caloric intake that generates and sustains a state of excess adiposity. There is a strong heritability component to BMI that varies between 0.4 to 0.7 (4,5), and over 100 susceptibility genes for elevated BMI have been identified in genome wide association studies (6). Monogenic forms of the disease are rare, such as in families with leptin or leptin receptor mutations or deletion of the $SNORD116$ gene cluster in patients with Prader-Willi syndrome. Susceptibility to obesity in the majority of individuals results from the inheritance of multiple genes, with each individual allele conferring a very small relative risk for the disease. Those
individuals who inherit larger subsets of susceptibility genes will tend to be more overweight in any given environment (7). Progressive weight gain is not a lifestyle choice and cannot be viewed in terms of a simple thermodynamic equation of greater energy in than energy out. Rather, gene-environment interactions generate a human biological and behavioral interface unique to each individual that not only determines body weight but also explains individual variation in the net effect on body weight for any given amount of food intake or physical activity. To this point, among monozygotic twin pairs, the intra-twin changes in body weight are highly correlated in response to overfeeding (8) and underfeeding (9) of the same number of calories, such that if one member of the twin pair lost a greater or lesser amount of weight, so too did the corresponding twin. Thus, the genetic background determines differences in the amount of weight gained or lost in response to an identical degree of caloric excess or deficit.

One mechanism by which environmental factors can influence biology is through alterations in DNA and histone structure that can be inherited from maternal or paternal germ cells or arise de novo in a tissue specific manner. These epigenetic changes can be induced by nutritional and environmental factors (10,11) and alter gene expression, providing a mechanism by which environmental exposures can produce persisting changes in metabolism over the lifespan. Accumulating evidence indicates that differential CpG methylation of DNA can occur as a function of the in utero environment and participate in the programming of body weight and metabolism in offspring with increased risk for obesity, T2DM, and CVD persisting into adulthood (12-14). For this reason, maternal health has become recognized as an important factor in decreasing rates of cardiometabolic disease.

To add to the complexity of the disease, susceptibility genes interact with each other and with the environment, behavioral and cultural factors, biological factors, and co-morbid diseases (Figure 1). In particular, lifestyle patterns based on personal or cultural preferences have a substantial impact in the pathogenesis of obesity, particularly as relates to nutrition and physical activity. Cultural identification and acculturation regarding diet and food preferences, body image, and emphasis on physical activity are important determinants and can affect obesity risk in individuals as well as populations. Biological factors unrelated to obesity also affect pathogenesis, including aging, menopause, concurrent diseases, birth weight, and effects of the in utero environment on offspring. It is well documented that social and environmental factors are associated with higher rates of obesity and help explain differences in prevalence and health disparities in populations (15). Low socioeconomic status and reduced economic viability are associated with greater obesity risk. This is often accompanied by a lower education level affecting capacity for income generation, health literacy, and access to care determined by lack of health insurance, ability to afford care, availability of health care professionals, and transportation. The built environment can contribute to higher obesity prevalence when there is lack of access to unprocessed food and resources enabling physical activity. Social stigmatization of obesity is widespread and contributes to high rates of anxiety, depression, poor self-esteem, self-blaming, and emotion-driven eating (16). Patients are also shamed in their contact with health care systems which is a deterrent obesity care, and the bias against obesity as a life-style choice as opposed to a chronic disease limits the provision and access to evidence-based care (17).
Overall, these social determinants prevent access to resources and the capacity to prevent and/or manage obesity.

**Abnormality in Satiety Hormone-CNS Interaction**

In obesity, a major consequence of gene-environment interactions is an alteration in caloric intake as regulated by homeostatic satiety factors acting on CNS feeding centers. Satiety hormones produced by peripheral organs register fuel availability and are released into the bloodstream to act on two cell types in the arcuate nucleus of the hypothalamus. Ghrelin from the stomach binds its receptor on neurons that release neuropeptide Y (NPY) as a neurotransmitter. This sends signals to higher cortical centers and activates the orexigenic pathway to increase hunger. Leptin from fat tissue and hormones from the gastrointestinal tract including GLP-1, peptide YY, and amylin activate proopiomelanocortin synthesizing cells to release alpha melanocyte stimulating hormone (αMSH) as a neurotransmitter. αMSH binds the melanocortin-4 receptor and signals to higher centers to activate the anorexigenic pathway that decreases appetite. This system in obesity is dysregulated and produces increased caloric intake to the extent that it generates and sustains an increase in adipose tissue mass (18-20). The abnormal interaction between satiety hormones and CNS feeding centers is an essential component of obesity pathophysiology.

The pathophysiology of obesity is further operational in response to a weight loss intervention. Weight loss activates multiple maladaptive responses that act to increase energy intake and decrease energy expenditure, thus driving weight regain back to the previous high level of body weight. The combination of decrements in levels of anorexigenic hormones below baseline levels and an increase in the orexigenic hormone ghrelin result in greater hunger (18). Psychological food preferences become oriented to food of greater caloric density with high fat and sugar content. In addition, there is decrease resting energy expenditure rates in response to weight loss as well as a decrease in the energy that muscles use for any given amount of work (i.e., increased muscle energy efficiency). These energetic changes also promote a positive energy balance (19). All of these factors promote weight regain and help to maintain a degree of excess adiposity that is harmful to health. In this sense, obesity perpetuates obesity. Body weight is not a cognitive decision but rather the result of these pathophysiological processes that produce and maintain an increase in body weight. This makes it difficult for patients with obesity to reduce adiposity and to sustain weight loss.

**B. The Body Weight Set Point**

Obesity protects obesity in response to changes in energy intake and expenditure. This has given rise to the idea of a set point around which the body maintains an equilibrium body weight (21). This is illustrated in Figure 2. If body weight is reduced by diet and exercise, the maladaptive changes in satiety hormones and in energy expenditure signal an increase in appetite and slowing of metabolism, resulting in positive energy balance until weight is regained. This cycle is repeated whenever weight deviates from the equilibrium weight as determined by the set point. The same thing
is happening in a second individual in Figure 2 who is lean and has a normal set point, in which case oscillation occurs around a lean degree of adiposity. While interactions between environment and susceptibility genes produce dysregulation of satiety factors and energy metabolism, the molecular mechanisms that explain this dysregulation are unknown. Therefore, the set point regulation of body weight remains a theory. The Set Point Theory is based on inductive reasoning and reliably explains biological observations regarding the natural history of obesity. Whether the set point can be changed or manipulated is of overriding importance in developing definitive therapies for obesity. While set point mechanisms appear to be fixed around an equilibrium body weight in adults, there are events that can alter the set point as will be discussed. For this reason, the term ‘settling point’ is sometimes preferred to accommodate observations that the set point can be mutable (21). Even so, alterations in the set point continue to maintain excess adiposity and are an unrelenting feature of obesity. Thus, the set point(s) is an essential and persistent aspect of the pathophysiology of obesity and is not currently curable.

1. Effects of Lifestyle Interventions and Obesity Medications on the Set Point

The set point is not permanently altered by lifestyle interventions or obesity medications. Lifestyle interventions can produce clinically meaningful weight loss; however, weight is regained in the clear majority of patients over time as a consequence of the ongoing pathophysiological mechanisms driving weight regain (22). In other words, set point mechanisms remain operative. Similarly, the set point is not changed by any obesity medication currently available. Obesity medications are effective in achieving and sustaining a reduced body weight but once the medications are discontinued, body weight rises back to baseline or back to the level determined by the prevailing lifestyle intervention (23). The efficacy of medication is not retained and, once discontinued, the ensuing weight regain indicates that the set point mechanism for equilibrium body weight is still operative.

It is also important to consider that body weight and body composition can be altered over the lifespan and are not necessarily stable entities. For example, body weight can change as a function of aging, which can be associated with alterations in body composition and muscle mass affecting energy expenditure. New equilibria for body weight can be established following childbirth or menopause in females. These life events appear to be associated with changes in the body weight set point, Again, for this reason, investigators have suggested the term “settling point” as opposed set point to account for the fact that the body weight equilibria can be altered and that one set point does not remain operative over a lifetime (21).

2. Effects of Bariatric Surgery on the Set Point
Of all treatment modalities for obesity/ABCD, bariatric surgery on average produces the greatest amount of weight loss that is sustained for the longest duration of time. Importantly, the resulting weight loss is sufficient to ameliorate a broad range of ABCD complications. Moreover, the best case for an intervention that can alter the set point exists for bariatric surgery. Following procedures such as Roux-en-Y gastric bypass and sleeve gastrectomy, patients become less hungry and maintain lower body weights for extended periods of time. These procedures alter the experiential relationship that patients have with food and the impact that food consumption has on daily life (24). Eating becomes more conscious, slow, and less automatic resulting in more prolonged chewing, and patients more accurately recall dietary intake. The fact that patients are less hungry after bariatric surgery stands in contrast to weight loss following a lifestyle intervention when neuro-hormonal maladaptive mechanisms are activated that increase hunger and drive weight regain. This does not routinely occur after bariatric surgery, and it appears that the set point around which satiety hormones regulate caloric intake has been changed.

Alterations in satiety hormone levels do occur following bariatric surgery and have been implicated in the reduction in caloric intake and maintenance of lower body weights (24-31). GLP-1 and peptide YY concentrations are increased, ghrelin levels are decreased over values observed prior to surgery, and leptin levels are generally found to be decreased after gastric bypass and sleeve gastrectomy. Both foregut and hindgut hypotheses have been proposed to explain the rise in GLP-1 levels: the foregut hypothesis supposes that it is the exclusion of the duodenum and proximal jejunum from exposure to nutrients; while the hindgut hypothesis suggests that it is the more rapid delivery of nutrients to the distal small bowel or distal ileum, the location of the GLP-1 secreting L cells. In fact, they are not mutually exclusive, and both mechanisms may act to increase GLP-1 levels. However, the foregut hypothesis has been challenged by data suggesting that the sleeve gastrectomy, which does not exclude the foregut, also increases incretin levels and leads to comparable degrees of weight loss as with gastric bypass. Alterations in satiety hormones vary as a function of the bariatric procedure performed as delineated in Table 1.

In addition to alterations in satiety hormones, other mechanisms implicated in sustained weight loss following bariatric surgery include alterations in bile acids (32-36) and bile acid signaling through farnesoid X receptor, a ligand-activated nuclear receptor, and the membrane-bound G protein-coupled receptor TGR5. Both pathways are likely to act in multiple ways to modulate glucose and energy metabolism (35,36). Another hypothesis pertains to alterations in the gut microbiome (37-40) which could mediate changes in energy and glucose homeostasis by: (i) impacting the efficiency of nutrient extraction from food, (ii) producing metabolites that act in signaling pathways involved in energy metabolism, and (iii) modulating an overall inflammatory state by affecting intestinal permeability and plasma lipopolysaccharide levels in the bloodstream.

Before concluding that changes in satiety hormones, bile acids, or the gut microbiome are responsible for a change in the body weight set point, there are other potential explanations for maintenance of lower body weights following bariatric surgery. For example, there is a variable level of malabsorption and intestinal maldigestion depending upon the procedure (41). Also, gastric
restriction limits gastric volume and distention producing earlier satiety and ingestion of smaller meals and portion sizes. Finally, there may be fears or anticipation of dumping syndrome with vomiting that limit intake and force the patient to consume smaller portion sizes.

Moreover, any change in the setpoint following bariatric surgery may be transient or incomplete. Most patients reach an equilibrium of weight loss that remains in the overweight or obese range of BMI. Further, substantial numbers of patients regain weight. Weight regain is largely due to the appearance of maladaptive eating behaviors, including subjective and objective binge eating as well as grazing eating behavior (42). Clearly, mechanisms are operative that alter eating behavior and caloric intake and driving weight regain indicating that set point mechanisms are still operative. Patients require life-long medical follow-up after bariatric surgery to monitor for weight regain and development of obesity complications; therefore, bariatric surgery can hardly be considered as curative for the disease of obesity.

3. Effects of the Environment on the Set Point

We also know that the body weight around which the set point regulates an equilibrium can change as a function of the environment. In the early 1900s, we were a leaner society and we lived in a relatively non-obesogenic environment. There was still a variation in body weight and some patients with high set points did develop obesity. Over the decades the environment became more obesogenic and more people developed obesity and more severe degrees of obesity (43), despite the fact that our genetics have not changed substantially. The environment has been made more obesogenic by changes in portion sizes, ready availability of palatable calorie dense foods, food processing including use of high fructose corn syrup, sedentary lifestyle, built environments that rely on motorized travel, air conditioning, and environmental obesogens among other factors. While some individuals remain lean, the overall prevalence of obesity increased dramatically. Individuals with a high set point in the current environment with obesogenic qualities have higher degrees of adiposity and the set point operates around a higher equilibrium body weight. Other individuals with a low set point maintain their leanness, and people with an intermediate set point maintain higher body weights than would be the case in a less obesogenic environment. To summarize, equilibrium body weight determined by the Set Point can vary as a function of environment. The implication is that, if we could convert to a less obesogenic environment, we could decrease BMI on a population basis.

The influence of environment on the body weight set point is underscored by the change in obesity prevalence when ethnic groups migrate from a rural to an urban environment or from an agrarian society to a more sedentary, developed, or ‘Westernized’ society. This is exemplified by Gullah-speaking African Americans living in the South Carolina low-country compared with the genetically-related ancestral population in Sierra Leone, West Africa (44-46). Gullah-speaking African Americans have high obesity prevalence and consume a diet rich in animal fats (45,46) compared to relatively low rates of obesity and dietary patterns high in carbohydrates in Sierra Leone (47). Another example is the group of Pima Indians who moved from northern Mexico to southern Arizona ~2,000 years ago while the group remaining in Arizona since the early 1900s have adopted a more sedentary
and ‘Westernized’ lifestyle (48-50). The Pima Indians who continue to live in northern Mexico and have retained an agrarian lifestyle have low rates of obesity and diabetes compared to corresponding rates in the Arizona Pimas which are among the highest of world populations. Obesity and diabetes susceptibility genes have been identified in both the Gullahs (44) and Pimas (51). In the Gullahs, we identified a polymorphism in the uncoupling protein-3 (UCP3) gene that has a 10% allele frequency in both the Gullahs and current ancestral Sierra Leonese tribal populations (52). This polymorphism shifts the preferred fuel for energy expenditure from fat to carbohydrate, leading to greater fat storage, and is associated with severe obesity in the Gullah who tend to consume a high fat diet. These environmental changes in the Gullahs and Pimas interact with genetic susceptibility genes to predispose to the development of obesity and diabetes, while genetically similar ancestral subpopulations living in a different environments experience lower rates of these diseases. Thus, while set point mechanisms are operative and determine which individuals will have greater or lesser degrees of adiposity in any environment, the overall prevalence of obesity is highly affected by the environment in these genetically similar subgroups on a population basis.

III. Is Adiposity-Based Chronic Disease Curable: The Development of Complications

Thus far the discussion has centered on the permanence of set point mechanisms that act to sustain an elevation in body mass. However, obesity as a disease entails more than an increase in body mass. The conventional diagnosis of obesity is based on BMI (weight in kg/height in m²), an indirect measure of adiposity that provides no information regarding the impact of excess weight on health (53). As with other chronic diseases, it is the complications of obesity that impair health and confer morbidity and mortality (54,55). Obesity gives rise to biomechanical complications such as obstructive sleep apnea and osteoarthritis, while abnormalities in the mass, distribution, and function of adipose tissue contribute to cardiometabolic disease complications. Cardiometabolic disease begins with insulin resistance which is initially subclinical but eventually produces clinical manifestations that include Metabolic Syndrome, prediabetes, elevated blood pressures, dyslipidemia, and hepatic steatosis. These manifestations indicate risk for progression to the end-stage manifestations of cardiometabolic disease, namely Type 2 Diabetes (T2D), non-alcoholic steatohepatitis (NASH), and cardiovascular disease (CVD). The development of obesity exacerbates insulin resistance and impels progression of cardiometabolic disease towards these ultimate outcomes (56).

The AACE obesity guidelines call for a complications-centric approach to the management of obesity, and employ two components for diagnosis (55). The first is the anthropometric component to confirm excess adiposity. BMI can be used for screening and for diagnosis once an elevated BMI is confirmed to represent increased adiposity on inspection of the patient. Ideally, adipose tissue mass would constitute a more precise anthropometric measure for diagnosis and management. The second component of the diagnosis, the clinical component, involves a screen for the presence and severity of complications. In this context, Adiposity-Based Chronic Disease (ABCD) has been suggested as a more precise clinical and diagnostic term for obesity by AACE (57) and the European Association for the Study of Obesity (58). ABCD indicates what we are treating, namely, abnormalities in the mass, distribution,
and function of adipose tissue, and why we are treating it, a chronic disease that gives rise to complications that require prevention and treatment. Accordingly, the complications-centric AACE clinical guidelines for obesity emphasize the prevention and treatment of complications as the end point of therapy rather than the amount of weight lost per se (55).

The evolution of ABCD is consistent with a chronic disease model, similar to other chronic diseases such as diabetes or hypertension, with opportunities for prevention and treatment over the natural history of the disease (55,59) (Figure 3). Primordial prevention involves the entire population and is needed because we live in an obesogenic environment. Some individuals will be at increased risk of ABCD due to the inheritance of susceptibility genes and interactions involving lifestyle preferences and environmental determinants. These individuals require primary prevention that targets these specific risk factors to prevent the emergence of the disease. Many individuals develop excess adiposity and under the influence of these risk factors and ultimately meet diagnostic criteria for ABCD/obesity. In the absence of complications, clinicians are in a secondary treatment mode and the goal is to prevent the emergence of complications and further weight gain. Once complications occur, however, this indicates that the prevailing degree of adiposity is sufficient to impair health regardless of the BMI level. Clinicians are then in a tertiary treatment mode and must prevent further disease deterioration and achieve weight loss sufficient to ameliorate the complications (59).

The development of complications, whether cardiometabolic or biomechanical, can arise at different levels of adiposity in different individuals. In addition, the severity of any one complication will vary among individuals at any given BMI and not all patients are susceptible to the same complications. This is analogous to the variable development of vascular complications in diabetes at different levels of HbA1c and occurrence of congestive heart failure and stroke in patients with hypertension who differ in their degree of blood pressure control. As shown in Figure 3, complications in ABCD variably arise in individuals as a function of distinct subsets of susceptibility genes that interact with at-risk environmental and behavioral determinants under the influence of excess adiposity (5-9,44,51). These predispositions to complications are integral to the pathophysiology and natural history of ABCD as a chronic disease. These risks do not go away and are not curable similar to the risks of excess adiposity driven by set point regulation. The risks for complications can be lessened by changes in behavior, the environment, and social determinants of health, as well as by weight loss and quality of medical care, but the risks and predispositions to complications in individual patients are always present. Thus, both the “adiposity-based” component (i.e., excess adipose mass) and the “chronic disease” component (i.e., complications) of ABCD are imminently treatable but not curable. Indeed, clinicians and patients must commit themselves to long-term treatment and follow-up in the management of this disease.

IV. Clinical Implications

**Key Point**
Complications arise due to genetic-environment interactions under the influence of excess adiposity. These risks are modifiable but do not disappear and are integral to ABCD as a chronic disease.
If ABCD will eventually be curable, this will depend on a clear understanding of the molecular mechanisms that determine the set point regulation of body weight, and an ability to permanently modulate the set point to oscillate around and a lean body mass. Hopefully, this will be possible in the future. However, the conceptualization of ABCD as a chronic disease process does present us with opportunities for primary, secondary, and tertiary prevention to avert disease progression (56) as illustrated in Figure 4. The full force of our medical chronic care model should be brought to bear on the prevention and treatment of ABCD, a disease nexus that presents such a huge burden of social costs and patient suffering.

Primordial and primary prevention for ABCD as a common disease relevant to the general population includes public health messaging, built environment, healthy lifestyles, access to preventive care, and maternal-fetal health. Primary prevention for those at increased risk due to genetic predisposition and exposure to environmental determinants require more targeted preventive measures regarding personalized prescriptions for healthy lifestyles and maintenance of healthy weight. With the development of obesity, secondary prevention efforts must prevent further weight gain and prevent the emergence of complications. If weight gain occurs on an insulin sensitive background, patients are at risk for biomechanical complications, and, if this occurs on an insulin resistant background, obesity will exacerbate insulin resistance and impel the progression of cardiometabolic disease. The presence of prediabetes, Metabolic Syndrome, dyslipidemia, prehypertension, and/or hepatic steatosis signals the presence of insulin resistance and cardiometabolic disease. These individuals are then at increased risk for one or all the end-stage manifestations of cardiometabolic disease, namely CVD events, congestive heart failure including heart failure with preserved ejection fraction, stroke, hypertension, T2D, NASH, and chronic kidney disease. Weight loss of $\geq$7-10% is sufficient for secondary prevention of many biomechanical and cardiometabolic complications (55,60).

However, once end-stage complications occur, more aggressive weight loss is required for tertiary management of the complications and $\geq$10-20% is required for predictable improvements. In patients with T2D, the more weight loss the better where weight loss of >5% to 15% or more provides progressive improvements in HbA1c, blood pressure, and lipids (61); for obstructive sleep apnea, $\geq$ 10% weight loss is needed for predictable improvements in the apnea/hypopnea index (62,63); and in non-alcoholic fatty liver disease, 5-10% weight loss will reduce steatosis but $>10$% weight loss is required in NASH to improve inflammation and fibrosis (55,64,65). Prevention of CVD events and mortality may require $>10$% weight loss based on case-control studies and meta-analyses of bariatric surgery literature (65-67) and a sub-analysis of Look AHEAD study data in which outcomes were assessed as a function of degree of weight loss in patients with T2D (68). Overall, in considering the amount of weight loss required to ameliorate these common complications in ABCD, interventions are needed that reliably reduce body weight by 10-20%.
The approval of semaglutide 2.4 mg/week for chronic weight management provides clinicians with a medication that for the first time achieved >10% mean placebo-subtracted weight loss and more that half of patients >15% weight loss as an adjunct to lifestyle in phase 3 clinical trials (69-71). This level of efficacy is sufficient for the first time to ameliorate a broad range of ABCD complications and is approximately twice that achieved by other obesity medications in clinical trials. This unprecedented level of efficacy and clinical utility warrants its designation as a second-generation obesity medication. Even so, semaglutide 2.4 mg dose not result in permanent alteration in the set point since weight is regained once the medication is discontinued (71). While semaglutide 2.4 mg is the first drug to meet this definition of a second-generation medication, other medications under development appear to have these qualities in early phase trials. These include multi-agonist GLP-1/glucagon/GIP peptides (72,73), long-acting amylin analogs (74,75), activin II receptor agonists that reduce body fat while increasing muscle mass (76), and the combinations of GLP-1 receptor agonists with other satiety hormones such as amylin (75), PYY, and oxyntomodulin. Therefore, we appear to be on the threshold of a new paradigm for obesity management. With the ability to achieve 10-20% weight loss in the clear majority of patients, second-generation obesity medications permit active management of body weight into a range that effectively ameliorates a broad array of ABCD complications. Clinicians will be able to treat-to-target using body weight as a biomarker to assure effective tertiary prevention and treatment of complications and improve the health of patients with ABCD. This is analogous to diabetes and hypertension where therapy is directed at treating biomarkers to target, HbA1c and blood pressure, respectively, not because the biomarkers are of primary importance but because evidence indicates that the control of these biomarkers into a target range will prevent the complications of these diseases. Perhaps with more effective medications and an understanding of ABCD as a chronic disease, effective primary, secondary, and tertiary prevention strategies will become commonplace in medical practice, and a less obesogenic environment will be achieved through public policy. A chronic care model for ABCD must become operational as an integral component of the health care system and embraced by the larger society for the benefit or our patients in particular and public health in general.

V. Summary

ABCD is a chronic disease that is not currently curable and requires life-long treatment and follow-up. Obesity protects obesity through altered regulation of caloric intake and a set point that maintains a high equilibrium body weight. Lifestyle interventions and obesity medications do not permanently alter the set point which often makes weight loss achieved by lifestyle modifications short-lived and operates to drive weight regain once medications are discontinued. Bariatric surgery...
procedures (gastric sleeve and gastric bypass) can alter appetite and lower the “set point” for equilibrium body weight via unknown mechanisms. However, few patients attain ideal body weight, many regain weight, and all require long-term follow-up for the disease. The equilibrium body weight around which set point mechanisms operate can be modified by environment, which underscores the importance of a less obesogenic environment for prevention and treatment of ABCD on a population basis. The excess adiposity of ABCD gives rise to complications that impair health and confer morbidity and mortality; however, the genetic risks and potential interactions between genes and environment that give rise to complications cannot be eliminated. Therefore, clinicians and patients should be committed to long-term treatment of ABCD with the goal of achieving sufficient weight loss to optimize health by preventing and treating its complications.

References


Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial. *J Am Med Assoc.* 2021;325(14):1403-1413.


Figure Captions

Figure 1. The Complex Pathophysiology of Obesity. Obesity is a complex disease with interactions involving genetic, environmental, biological, and behavioral factors that favor a positive energy balance. These factors interact in a manner that is unique to each individual and create a human interface for regulation of energy balance by establishing a set point for equilibrium body weight.

Figure 2. The Set Point for Maintenance of Equilibrium Body Weight in a Lean Person and in a Patient with Obesity. The interaction between genes and environment determines a set point around which the regulation of caloric intake and energy expenditure determine the degree of adiposity in different individuals. Deviations from the equilibrium body weight induce set point mechanisms that drive a change in weight back to baseline. In obesity, a high set point is integral to the pathophysiology of obesity as a disease.

Figure 3. Chronic Disease Model for Adiposity-Based Chronic Disease/Obesity. The entire population is at primordial risk due to an obesogenic environment, but those with obesity susceptibility genes and at-risk behaviors are at increased risk of obesity and require primary prevention. Once obesity develops, secondary prevention is required to prevent further weight gain and the emergence of complications. Different subsets of genes and environmental cues predispose to complications under the influence of excess adiposity, and tertiary prevention is needed to prevent further disease deterioration and to treat complications.

Figure 4. Chronic Care Model for the Prevention and Treatment of Adiposity-Based Chronic Disease.
Table 1. Effects of bariatric surgery on intestinal neuroendocrine hormones

<table>
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<tr>
<th>Procedure</th>
<th>GLP-1</th>
<th>GIP</th>
<th>PYY</th>
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<td>Roux-en-Y gastric bypass</td>
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<td>Biliopancreatic diversion with duodenal switch</td>
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<td>Laparoscopic adjustable gastric banding</td>
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<td>Sleeve gastrostomy</td>
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Body Weight Set Point in a Lean Person

- Weight Gain
- Increased Appetite/Slowing of Metabolism
- Hormone Levels/Signally Change to Keep Weight On
- Diet & Exercise to Reduce Weight

Body Weight Set Point in a Person with Obesity

- Weight Gain
- Increased Appetite/Slowing of Metabolism
- Hormone Levels/Signally Change to Keep Weight On
- Diet & Exercise to Reduce Weight
**Primordial/Primary Prevention**
- Public health messaging
- Physical activity/healthy meal plan
- Built environment
- Social determinants of health
- Stress reduction, sleep hygiene
- Economic viability
- Healthy gestation (in utero)

**Secondary Prevention**
- ≥ 10% weight loss
- Physical activity & healthy meal plan prescription (e.g., Mediterranean diet)
- Manage LDL-c to target
- Tx of dysglycemia, elevated blood pressure, sleep apnea, etc., as appropriate after weight loss

**Tertiary Prevention**
- ≥ 10-20% weight loss
- Active management or prevention of all end-stage complications to target
- Cardioprotective and renal protective medications
- Continue lifestyle therapy

**Biomechanical and Psychological Complications**
- CVD Events
- CHF
- Stroke
- HTN
- T2DM
- NASH
• Abnormalities in satiety hormone-CNS interactions alter caloric intake and generate and maintain a state of excess adiposity in obesity.
• In response to weight loss, maladaptive processes alter regulation of caloric intake and energy expenditure and drive weight regain to the baseline high level of body weight. In this way, obesity protects obesity.
• The observations are consistent with a set point around which the body maintains an equilibrium body weight.
• Complications arise due to genetic-environment interactions under the influence of excess adiposity. These risks are modifiable but do not disappear and are integral to ABCD as a chronic disease.

Proposed Definition of a Second-Generation Obesity Medication:
• Ability to safely produce on average a >10% placebo-subtracted weight loss in randomized clinical trials (i.e., over that attributable to lifestyle interventions) in the majority of patients.
• Ability to safely produce on average a ≥15% weight loss in over half the patients as an adjunct to lifestyle.
Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr Garvey has served as a volunteer on advisory boards without receipt of financial compensation for Boehringer Ingelheim, JAZZ Pharmaceuticals, Novo Nordisk, and Pfizer; served on advisory boards for the non-profit organizations the Milken Institute and the National Diabetes and Obesity Research Institute; served as site PI for multi-centered clinical trials sponsored through his university and funded by Eli Lilly, Epitomee, Novo Nordisk, and Pfizer.