

## UNDERSTANDING OBESITY: HOW AND WHY?

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### ABSTRACT

**Obesity is currently recognised as a chronic disease that is often relapsing and progressive. This requires attention for long-term monitoring to treat or prevent obesity-related complications. This article discusses the biology of weight regulation as a basis for understanding obesity as a disease, and to appreciate the complex and multifactorial pathogenesis of obesity. With this understanding of the factors involved in perpetuating obesity in different individuals, the approach to patients with obesity should be as comprehensive and systematic as with other chronic diseases. Management strategies and treatment plans, which need to have long-term weight maintenance and weight regain prevention in mind, can be more individualised for patients with obesity.**

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### INTRODUCTION

Over the last 40 years, the prevalence of obesity has risen substantially in almost all world regions, such that there are now more than 600 million obese adults and 100 million obese children worldwide.<sup>1</sup> This increasing burden of obesity has been identified in Singapore and other Asia-Pacific countries.<sup>2</sup> From 1992 to 2010, the prevalence of obesity more than doubled from 5.1 percent to 10.8 percent. A parallel rise in the prevalence of diabetes mellitus has also been seen, reflecting the burden of obesity.<sup>3</sup> Based on body mass index (BMI) categories that indicate increased health risks in Asian populations, 52.5 percent of Singaporeans have a BMI in the moderate- to high-risk groups ( $\geq 23.0 \text{ kg/m}^2$ ), heralding the potential for a greater burden of adiposity-related comorbidities in Singapore.<sup>3</sup>

Obesity has often been viewed as a result of a simple lack of self-discipline and willpower to “eat less and move more” or plain laziness on the part of the person with obesity.<sup>4</sup> This oversimplified perception results from the lack of understanding that beyond the passive accumulation of excess energy as adiposity, obesity is a chronic, often relapsing and progressive disease resulting from a multitude of factors. It has also led to weight bias and obesity stigma against people living with obesity (PwO), including by healthcare professionals (HCPs).<sup>4</sup> Despite being at further risk of many obesity-related diseases, PwO often do not seek medical attention early, and the weight bias by HCPs also impedes them from providing quality care.<sup>4</sup>

As with many chronic diseases, the pathogenesis of obesity involves many roots (aetiologies and associated factors). We now understand that there is a complex interplay of physiologic, genetic, epigenetic, and developmental factors with variables of behavioural, psychological, socioeconomic, medications, and environmental ones, both intrinsic and extrinsic, leading to the pathogenesis and perpetuation of obesity.<sup>5</sup> Only by addressing these roots and understanding obesity as a chronic condition can we adequately manage and prevent obesity and its multitude of associated costly comorbidities.<sup>4,5</sup>

### BIOLOGY OF WEIGHT REGULATION

The body's adipose tissue represents energy stores to survive energy-scarce conditions. Hence, it would not be surprising that that body weight (or more accurately, adipose tissue in the body) is tightly regulated by an extremely complex neuroendocrine energy balance circuitry. This circuitry is composed of specific nuclei in various brain regions, most prominently the hypothalamic arcuate nucleus (ARC), the paraventricular nucleus, the lateral hypothalamic area, and the nucleus of the solitary tract of the hindbrain (refer to **Figure 1**).<sup>6,7</sup>

Under relatively constant environmental conditions, this regulatory system senses and processes various metabolic signals regarding the current energetic status and adjusts the metabolic responses to maintain a stable weight without conscious control.<sup>6</sup> This homeostatic regulation of body weight is similar to that of other physiologic parameters, such as body temperature, blood pressure or blood glucose, where a “set point” seems to exist and deviation from this “set point” elicits a compensatory response in the opposite direction to restore this “set point”. Therefore, weight regains after weight loss is actually physiological<sup>8,9</sup> and not necessarily due to a failure of conscious efforts (to lose weight). For example, energy expenditure is reduced in response to weight loss, in an effort to resist further weight loss so that the “set point” can eventually be restored.

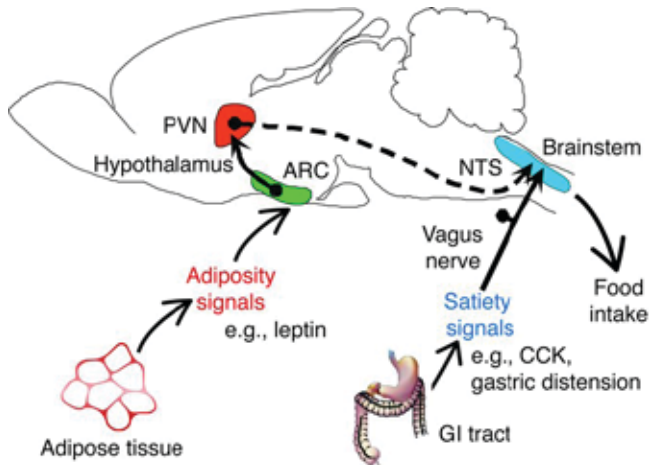
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However, in PwO, it has been observed that such responses can go beyond what is expected of the weight loss, and based on experimental data, these responses can even persist for years despite weight regain, further predisposing the individual to further weight (re)gain.<sup>5,8,9</sup>

**Figure 1. Model for regulation of the hindbrain response<sup>7</sup>**



Additionally, a different set of neuroendocrine signals guide food intake based upon the reward value of the food, also known as the reward or “hedonic” system.<sup>6,10</sup> The brain regions responsible for this reward system are dispersed in the corticolimbic structures. A primary characteristic of this system is its ability to override the signals from the homeostatic circuits as described.<sup>6</sup> Hence, the reward system is non-homeostatic regarding energy balance. This system integrates basic midbrain and hindbrain functions with more complex cortical functions involving arousal at the sight of palatable food items and the procurement of food, mediating the “liking” (level of pleasure or reward) and “wanting” (the motivation or drive to consume food), which are subconscious processes.<sup>6</sup> In human studies, functional MRI (fMRI) studies have shown overactivation of reward-encoding brain regions and/or deficiency in cortical inhibitory networks in PwO.<sup>6,10</sup>

## OBESITY AS A DISEASE: ABNORMAL PHYSIOLOGY AND ROOTS OF OBESITY

With the understanding of the biology of weight regulation, obesity is now understood to signify abnormal physiology whereby there has been a surplus intake of energy and an elevated body weight set point is now defended.<sup>5,8,9</sup> A mismatch of as little as 3 percent can lead to a weight gain of 1-2 kg per year and, if persistent over the years, can ultimately result in severe obesity.<sup>5</sup> The factors are known to cause this are complex and multiple. They range from genetic to socioeconomic to environmental and emotional factors that are well-known to be potent modulators of appetite and energy expenditure.<sup>7</sup> Twin, family, and adoption studies show that the rate of heritability of BMI is high, ranging from 40 to 70 percent,<sup>11</sup> demonstrating a major genetic component. In addition to syndromic and monogenic

forms of obesity (e.g., MC4R mutations, leptin deficiency), which account for less than 5 percent of general obesity in adults, genome-wide association studies (GWAS) have identified more than 700 independent loci associated with BMI and/or obesity without.<sup>12-14</sup> These, however, attribute to less than 5 percent of the inter-individual variation in BMI and traits linked to obesity. It is more likely that the presence of a combination of various gene alleles (giving rise to a high polygenic risk score) and epigenetic factors make one susceptible to weight gain in a conducive obesogenic environment (gene-environment interaction).<sup>11,14</sup>

Maternal obesity, malnutrition, gestational weight gain, or weight loss, especially in early pregnancy, have been found to result in childhood adiposity, adverse cardiometabolic profiles, and insulin resistance, which may persist into adulthood.<sup>15</sup> The adverse effect of maternal obesity and metabolic ill-health on offspring have been postulated to be mediated through epigenetic modifications, which alter gene function without any DNA defects.<sup>11</sup> In the Growing Up in Singapore Towards healthy Outcomes (GUSTO) study involving a cohort of nearly 1,000 mother-offspring sets, greater maternal adiposity and higher polygenic risk scores linked to maternal obesity were associated with higher birth weights and early childhood adiposity. This suggests that prenatal genetic influences and epigenetic factors can influence childhood adiposity, which can be lasting.<sup>16</sup> Intra-uterine exposure to endocrine-disrupting chemicals has also been postulated to be associated with childhood obesity.<sup>5</sup>

Environmental and lifestyle factors favouring a positive energy balance and weight gain include increasing per capita food supplies and consumption, particularly of highly processed, energy-dense, and palatable foods that are often served in large portions. These factors are influenced by one’s socioeconomic situation, such as decreasing time spent in occupational physical activities, displacement of leisure-time physical activities with sedentary activities such as television watching, use of electronic devices, growing use of medicines that have weight gain as a side effect, stress, and inadequate sleep.<sup>11</sup> More recent studies have identified a potential role for the gut’s microbial content in determining a broad range of metabolic abnormalities, including obesity.<sup>17,18</sup> The evidence supporting causation includes animal studies that show that obesity, as a phenotype, is transmittable via the transfer of gut microbiota from the obese (mice/humans) to germ-free mice,<sup>19,20</sup> and mechanistic studies that demonstrate the possible mechanisms linking the gut microbiota with obesity.<sup>17,21</sup>

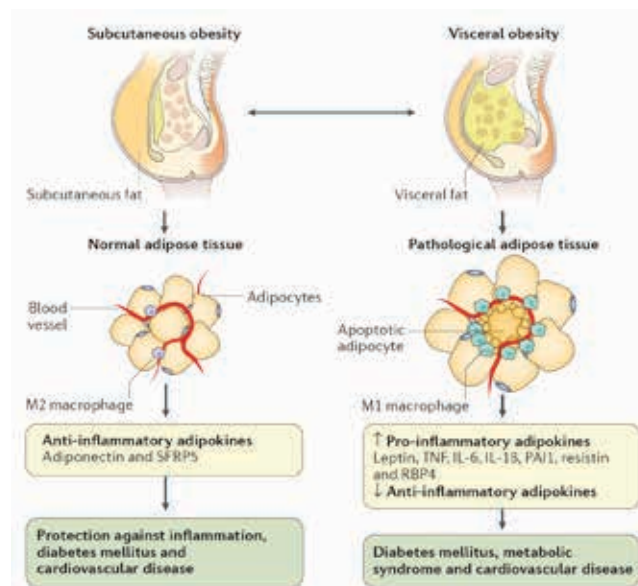
Apart from the mentioned factors mentioned that are linked to the pathogenesis of obesity, numerous other factors contribute to or exacerbate obesity and may lead to the attenuation of obesity treatment (refer to **Figure 2**). These should also be considered and adequately addressed when assessing and managing patients with obesity.<sup>22</sup>

**Figure 2. ROOTS of Obesity Fact Sheet. World Obesity Federation 2021<sup>22</sup>**

## OBESITY AS A DISEASE: HEALTH CONSEQUENCES

Obesity is not benign. The failure of adipose tissues to continually expand lead to pathological changes in the adipose tissue, which is characterised by macrophage invasion and/or increased release of pro-inflammatory adipokines and decreased release of anti-inflammatory adipokines such as adiponectin (refer to **Figure 3**).<sup>23</sup> In addition, this failure to further expand and act as a “metabolic sink” results in harmful ectopic fat deposition in lean tissues such as the heart, liver, pancreas, and kidneys.<sup>23</sup> These two phenomena contribute to a pro-inflammatory and insulin-resistant milieu, giving rise to metabolic complications such as type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), and cardiovascular disease (CVD).<sup>23,24</sup> Additionally, the mechanical forces resulting from excessive adipose tissue can give rise to biomechanical consequences (such as Obstructive Sleep Apnoea (OSA) and low back pain), and obesity as a condition has been associated with various psychosocial issues, impacting on mental health.<sup>25</sup>

All these adverse consequences affect the quality of life, increase healthcare costs, and increase mortality.<sup>26</sup> Therefore, based on the current knowledge that the development of obesity results from abnormal physiology, with attending health consequences (complications, morbidities, and mortality), obesity fulfils the criteria for a disease state and is now determined to be a disease<sup>27</sup> rather than just a lifestyle risk factor. Several associations and organisations, including the World Health Organisation (WHO), have now declared obesity as a disease (refer to **Figure 4**). This is an important first step to tackling the problem of obesity, which has emerged as an epidemic that poses an unprecedented public health challenge.<sup>27</sup>

**Figure 3. Pathological changes in adipose tissue<sup>23</sup>**



**Figure 4. Organisations that have declared obesity as a disease<sup>27</sup>**

Box 1 Associations or organizations that have declared obesity is a disease
<ul style="list-style-type: none"> <li>• National Institutes of Health</li> <li>• US Food and Drug Administration</li> <li>• Federal Trade Commission</li> <li>• American Medical Association</li> <li>• World Health Organization</li> <li>• American College of Physicians</li> <li>• American Association of Clinical Endocrinologists</li> <li>• American College of Cardiology</li> <li>• The Endocrine Society</li> <li>• American Academy of Family Physicians</li> <li>• Institute of Medicine</li> <li>• The Obesity Society</li> <li>• World Obesity Federation</li> <li>• American Heart Association</li> <li>• American Diabetes Association</li> <li>• American Academy of Family Physicians</li> <li>• American Society for Reproductive Medicine</li> <li>• American Urologic Association</li> <li>• American College of Surgeons</li> </ul>
<p>Data from Kahan S, Zvenyach T. Obesity as a disease: current policies and implications for the future. <i>Curr Obes Rep</i> 2016;5(2):291-7; and Bray GA, Kim KK, Wilding JPH. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. <i>Obes Rev</i> 2017;18(7):715-23.</p>

## APPROACH TO MANAGEMENT OF OBESITY AS A DISEASE AND ITS COMPLICATIONS

Recognising obesity as a disease is a pertinent first step in the management of PwO. This will aid assessment using a systematic approach similar to how we approach any chronic disease and devise management plans from an aetiologic perspective.<sup>22,27</sup> As with any disease state, its management requires an understanding of how severe the disease is.<sup>28</sup> For obesity, management guidelines have slowly moved from a BMI-centric approach, where the goal of therapy is to lose a given amount of weight (e.g., 5-10 percent) to a complications-centric approach, where weight is no longer the major determinant of appropriate treatment, but now based on the risk, presence, and severity of obesity-related complications.<sup>28,29</sup> For example, at least 10 percent weight loss is needed to improve NAFLD and OSA significantly.<sup>28,29</sup> Hence, for a person with multiple complications, including NAFLD and OSA, modest weight loss (defined as 5-10 percent weight loss) may be inadequate, and more aggressive treatment options effecting more than modest weight loss need to be considered. Although more aggressive treatment may involve higher risk, the benefit of treating the various obesity-related complications should outweigh this risk. Therefore, the main goal of therapy now is to treat or prevent obesity-related complications, rather than to purely lose weight per se.<sup>28</sup>

## IMPORTANCE OF A MULTI-LEVEL AND INDIVIDUALISED MULTI-PRONGED APPROACH TO TREAT OBESITY

It is now known that the simple calculations underlying the traditional adage of “eat less, exercise more” are fatally flawed.<sup>30</sup> Aiming for a 500 kcal deficit (energy expenditure

more than energy intake) per day, cumulating to 3,500 kcal per week (equivalent to ~0.5 kg of fat) will not result in a 0.5 kg/week weight loss indefinitely, because this calculation does not consider the homeostatic mechanisms that will resist further weight loss, and in fact, will conspire to regain weight to restore the original “set point”.<sup>8,9,30</sup> It is also important to note that the same diet and exercise plan (often prescribed once in the beginning) will not suffice to maintain that 500 kcal deficit per day as a declining weight will mean declining energy expenditure.<sup>5,30</sup> Nonetheless, the point here is that asking all obese people to just “eat less and exercise more” overly simplifies the obesity problem.<sup>4,27</sup>

Understanding the biology of weight regulation and the appreciation of the complex and multifactorial nature of how this regulation can go wrong resulting in obesity would indicate that there is no one-size-fits-all intervention or solution.<sup>31</sup> Considering the different (roots) factors that lead to weight gain in different individuals (e.g., sleep disruption in one patient, stress-eating or medications causing weight gain in another) would necessitate a multi-level and individualised multi-pronged approach to treating obesity. Multi-level, apart from the individual, would include the social and community, physical (environment), and economic levels of interventions<sup>31</sup>, while a multi-pronged approach at the individual level would encompass not just the lifestyle and behavioural modifications but also the possible combination with pharmacologic and even bariatric surgical procedures based on individualised risk-benefit assessment.<sup>28,32,33</sup>

Since obesity is a chronic, often relapsing and progressive disease, weight regain (“relapse”) after weight loss is common, in part consequent to the physiologic counter-response to negative energy balance. Long-term follow-up for monitoring of weight regains and obesity-related comorbidities is necessary and prudent.<sup>28,32</sup> Management strategies for weight maintenance/weight regain prevention of at least 6-12 months should be considered during weight loss treatment, understanding that there is also reduced adherence to lifestyle changes with time.<sup>30,33</sup> Some of these measures may involve staying in frequent contact with the patient even after weight loss is attained (e.g., once a month), long-term use of anti-obesity medications, initiation of anti-obesity medications after weight plateau with lifestyle changes, and/or intermittent use of very low- or low-calorie diets.<sup>30,32,33</sup>

Obesity stigma and discrimination that PwO face can be pervasive and poses an often unrecognised detrimental effect on their mental and physical health. This extends to the workplace, schools, healthcare settings, and social circles. As HCPs, understanding obesity as a disease and its causes (roots) and refraining from using language and narratives that unfairly stereotype our patients with obesity as unmotivated and lazy is a form of addressing the obesity stigma and helping our patients overcome this discrimination. Educating patients and their families on the nature of obesity as a disease will also help to fight weight

bias and stigma. Compositely, such measures can help PwO obtain the quality healthcare they need.<sup>4,27</sup>

Lastly, obesity prevention remains key to reducing the burden of disease associated with obesity as a population moving forward.<sup>31</sup> Primary care practitioners are often the first point of patient contact. Initiating the conversation in obesity with patients and addressing childhood obesity are important roles primary care practitioners play in tackling the obesity epidemic. With obesity being prevalent in women in their reproductive years, the potential impact of maternal obesity on the adiposity and metabolic health of future generations may be colossal and under-addressed. While major public health measures to drastically reduce maternal obesity for a downstream impact seem unlikely at the present moment, HCPs can play an important role in educating women in their reproductive years to maintain a healthy weight to improve pregnancy outcomes and potentially the health of future generations.<sup>15</sup>

## CONCLUSION

Obesity is now recognised as a disease and has been described as a complex, chronic medical condition with a major negative impact on human health.<sup>27</sup> Many associations and organisations, including the World Health Organisation (WHO), have now declared obesity as a disease, and this is an important first step to tackling the problem of obesity. Understanding the biology of weight regulation and the appreciation of the complex and multifactorial nature of how this regulation can go wrong resulting in obesity would indicate that there is no one-size-fits-all intervention or solution<sup>31</sup> and would necessitate a multi-level and individualised multi-pronged approach to treating obesity and its related conditions. Strategies for long-term weight maintenance, chronic follow-up with monitoring of weight regain and obesity-related diseases, and addressing the stigma and bias that PwO face are pertinent for successful obesity management. Primary care practitioners play a pivotal role in initiating the conversation in obesity and addressing obesity prevention.

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## LEARNING POINTS

- **Obesity is now recognised as a chronic disease that is complex and of a multifactorial nature.**
  - **Understanding the various roots in the individual will allow interventions to be tailored to address these aetiologies and aggravating factors. There is no one-size-fits-all solution, and management necessitates a multi-level and individualised multi-pronged approach to treating obesity and its related conditions.**
  - **Long-term follow-up is required for assessment of treatment, monitoring of weight regain and obesity-related diseases. Alongside addressing the obesity stigma and bias, these practices are pertinent in managing and preventing obesity and its related complications.**
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