

**OBESITY UPDATES: UNDERSTANDING OBESITY AS A DISEASE AND INTERMITTENT FASTING**

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**ABSTRACT**

**Obesity is now recognised as a chronic disease which needs chronic treatment to treat or prevent obesity related complications. This article discusses the biology of weight regulation as a basis to understanding obesity as a disease, and to appreciate the complex and multi factorial nature of the obesity problem. Finally, the article highlights the dietary approaches as part of the multi-pronged approach to treating obesity and gives a brief update on intermittent fasting.**

**Keywords:** Obesity; Chronic Disease; Body Weight Regulation; Intermittent Fasting.

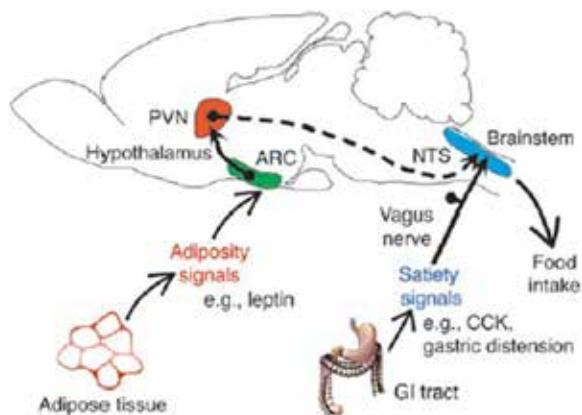
**Introduction**

Over the last 40 years, the prevalence of obesity has risen substantially in almost all regions of the world, such that there are now more than 500 million obese people worldwide.<sup>1</sup> This increasing burden of obesity is identified in Singapore and other Asia-Pacific countries.<sup>1</sup> The National Health Survey reports that 10.8 percent of adult Singaporeans are now obese, more than double the rate in 1992<sup>2</sup>; and this prevalence of obesity has been reported to reach 15 percent by 2024.<sup>3</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 body weight (or more accurately, adipose tissue in the body) is tightly regulated by an extremely complex neuroendocrine energy balance circuitry, which 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 solitary tract of the hindbrain (Figure 1).<sup>4,5</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>4</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 an opposite direction to restore this body weight 'set point'. Therefore, weight regain after weight loss is actually physiological<sup>6,7</sup> and not necessarily due to a failure of conscious efforts (to lose weight).

**Figure 1: Model for regulation of the hindbrain response to satiety signals by hormonal input from the ARC<sup>5</sup>**



Additionally, there exist a different set of neuroendocrine signals which guides food intake based upon the reward value of the food, also known as the reward or 'hedonic' system.<sup>4,8</sup> The brain regions responsible for this reward system are dispersed in the corticolimbic structures, and a primary characteristic of this system is its ability to override the signals from the homeostatic circuits as described.<sup>4</sup> Hence, the reward system is non-homeostatic with regard to 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>4</sup> In human studies, functional MRI (fMRI) studies have shown over activation of reward-encoding brain regions and/or deficiency in cortical inhibitory networks in obese people.<sup>4</sup>

**Obesity as a Disease: Abnormal Physiology and Health Consequences**

With the understanding of the biology of weight regulation, obesity (defined as a disproportionate body weight for height with an excessive accumulation of adipose tissue<sup>9</sup>) is now understood to signify an abnormal physiology whereby there has been a surplus intake of energy and an elevated body weight set point is now defended.<sup>4,10</sup> The factors known to cause this are complex and multiple, and they range from genetic to environmental to emotional factors which are well-known to be potent modulators of appetite.<sup>8</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, genome-wide association studies (GWAS) have identified more than 200 common genetic variants influencing BMI and adiposity traits.<sup>12,13</sup> Environmental and lifestyle factors favouring

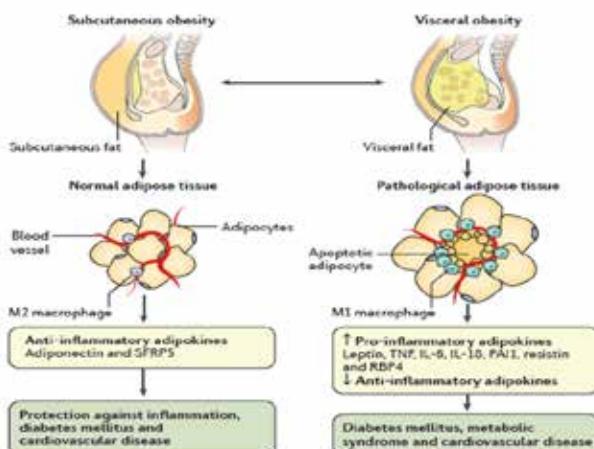
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a positive energy balance and weight gain include increasing per capita food supplies and consumption, particularly of highly processed, energy-dense and palatable food that are often served in large portions; decreasing time spent in occupational physical activities and displacement of leisure-time physical activities with sedentary activities such as television watching and use of electronic devices; growing use of medicines that have weight gain as side effect; stress and inadequate sleep.<sup>11</sup> More recent studies have identified a potential role for the microbial content of the gut in determining a broad range of metabolic abnormalities, including obesity.<sup>14,15</sup> The evidence supporting causation includes animal studies which show that obesity, as a phenotype, is transmittable via the transfer of gut microbiota from the obese (mice/humans) to germ-free mice<sup>16,17</sup>, and mechanistic studies which demonstrate the possible mechanisms linking the gut microbiota with obesity.<sup>14,18</sup>

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 (Figure 2).<sup>9</sup> Also, 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 the kidneys.<sup>9</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>9,19</sup> Additionally, the physical forces as a result of excessive adipose tissue can give rise to biomechanical consequences (such as Obstructive Sleep Apnea (OSA) and lower back pain), and obesity as a condition has been associated with various psychosocial issues, impacting on mental health.<sup>20</sup> All these adverse consequences affect the quality of life, increase health-care costs, and finally, increase mortality.<sup>21</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>10</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(Figure 3), and this is an important step to tackling the problem of obesity which has emerged as an epidemic that poses an unprecedented public health challenge.<sup>10</sup>

**Figure 2: Pathological changes in adipose tissue<sup>9</sup>**



**Figure 3 : Associations or organisations that have declared obesity is a disease<sup>10</sup>**

**Box 1  
Associations or organizations that have declared obesity is a disease**

- National Institutes of Health
- US Food and Drug Administration
- Federal Trade Commission
- American Medical Association
- World Health Organization
- American College of Physicians
- American Association of Clinical Endocrinologists
- American College of Cardiology
- The Endocrine Society
- American Academy of Family Physicians
- Institute of Medicine
- The Obesity Society
- World Obesity Federation
- American Heart Association
- American Diabetes Association
- American Academy of Family Physicians
- American Society for Reproductive Medicine
- American Urologic Association
- American College of Surgeons

*Data from Kahan S, Zvenyach T. Obesity as a disease: current policies and implications for the future. Curr Obes Rep 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. Obes Rev 2017;18(7):715-23.*

## Severity of Obesity and Treatment Approach to Obesity and its Complications

As with any disease state, the management of it requires an understanding of how severe the disease is. 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 it is based on the risk, presence, and severity of obesity-related complications.<sup>22</sup> For example, at least 10 percent weight loss is needed to significantly improve NAFLD and OSA.<sup>22</sup> Hence, for a person with multiple complications which include NAFLD and OSA, modest weight loss (defined as 5-10 percent weight loss) may be inadequate, and more aggressive treatment options, achieving 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 lose weight per se. In line with this shift in paradigm, the Working Group on Obesity, Diabetes and the High-risk Patient from the European Society for Hypertension, and the European Association for the Study of Obesity recently published a consensus document that discusses the mechanisms of obesity induced hypertension, diabetes and dyslipidemia, and highlights practice guidelines for treatment of these conditions.<sup>23</sup> Essentially, this document calls for treatment of the underlying obesity in people with obesity induced hypertension, diabetes and dyslipidemia. Hence, for some of these people, the first medication may not be an anti-hypertensive medication (for example) but an anti-obesity medication. The other important point is that medications to treat these conditions should not worsen the underlying obesity, hence awareness of the potential weight effects when selecting pharmacologic agents for the treatment for these conditions is important. For example, sulphonylureas promote weight gain and should be avoided in obese patients as far as possible.

## 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>24</sup> Aiming for a 500 kcal deficit (energy expenditure more than energy intake) per day, cumulating to 3,500 kcal per week (equivalent to ~0.5kg of fat) will not result in a 0.5kg/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>6,7,24</sup>. Also, it is important to note that the same diet and exercise plan (often prescribed once in the beginning) will not be suffice to maintain that 500kcal deficit per day as a declining weight will mean declining energy expenditure.<sup>24</sup> Nonetheless, the point here is that asking all obese people to just 'eat less and exercise more' overly simplifies the obesity problem. An understanding of 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>25</sup> and 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>25</sup>, while a multi-pronged approach at the individual level would encompass not just the lifestyle and behavioral modifications but also the possible combination with pharmacologic, and even bariatric surgical procedures based on individualised risk-benefit assessment.<sup>9,22</sup>

## Dietary Approaches to Obesity Treatment

Lifestyle management remains a cornerstone in a multi-pronged approach to the treatment of obesity and dietary modifications is foundational in this management. General dietary advices which have Randomised Controlled Trials (RCT) level of evidence include decreasing sugar-sweetened beverages consumption and portion control (e.g. plate concept)<sup>26</sup>, both of which can be routinely advocated. More specific dietary approaches can be broadly categorised into energy-focused (e.g. use of meal replacements, low/very low energy diets), macronutrient-focused (e.g. low carbohydrate diet, low fat diet), dietary pattern-focused (e.g. DASH diet, Mediterranean diet) and dietary timing-focused (e.g. intermittent fasting, time restricted feeding).<sup>26</sup> These diets usually involve some form of controlled intake and will on average induce weight loss if followed strictly.<sup>9,26</sup> Hence, adherence to diet seems to be key as long-term diet trials have not shown clear superiority of one diet over another with respect to average weight loss.<sup>9,24</sup> However, while patient preference plays a part in adherence, the preceding discussion on the biology of weight regulation informs us that homeostatic mechanisms such as increased hunger and cravings will be triggered upon weight loss, posing a challenge to diet adherence in the long-term. Therefore, the satiating effect of a diet may become particularly important for long term dietary adherence and weight maintenance. For example, diets with

higher protein (protein has a greater satiating effect compared with carbohydrates and fats), especially when the overall diet has a low glycemic index, has been shown to be more beneficial for maintaining weight loss<sup>24</sup>; and there is suggestion that meals containing carbohydrates may have a weaker satiating effect on individuals with impaired glucose metabolism and hence, obese individuals with impaired glucose metabolism may benefit more from a diet with higher fat and protein.<sup>27,28</sup>

## Finally: A Brief Update on Intermittent Fasting

Recent years have seen a surge in popularity of timing-focused dietary approaches whereby such eating patterns involve restricting energy intake by varying degrees for a pre-defined period of time and eating ad libitum (i.e. to satisfy appetite) at all other times.<sup>29</sup> These can range from complete (no energy containing foods or beverages consumed) alternate day fasting, to modified fasting regimens which allows the consumption of 20-25 percent of energy needs on scheduled fasting days (e.g. alternate days, 2 days per week (the '5:2 diet')), to time restricted feeding (which allows ad libitum energy intake within specific time frames inducing regular, extended fasting periods), and finally, to a variety of fasting regimens undertaken for religious or spiritual purposes.<sup>30</sup> Based on the current available evidence in humans, it appears that almost any intermittent fasting regimen can result in some weight loss and improvements in multiple health indicators including insulin resistance and reductions in risk factors for cardiovascular disease, with no significant harm demonstrated.<sup>30-31</sup> However, human studies have largely been limited to observational studies of religious fasting, cross-sectional studies of eating patterns associated with health outcomes, and experimental studies with modest sample sizes.<sup>30</sup> Hence, large-scale randomised trials of longer duration (>1 year) are needed for more conclusive evidence on efficacy and potential harm so that sound recommendations can be made.<sup>30</sup> In any case, consistent with points made in the preceding sections, intermittent fasting could potentially be a treatment option but unlikely to be that 'silver bullet', and the treatment of obesity would still require a multi-level and individualised multi-pronged approach.

## 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>10</sup> Several 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. An understanding of 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 and would necessitate a multi-level and individualised multi-pronged approach to treating obesity and its related conditions.

## REFERENCES

1. NCD Risk Factor Collaboration. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19• 2 million participants. *The Lancet.* 2016 Apr 2;387(10026):1377-96.
2. Singapore: Epidemiology & Disease Control Division, Ministry of Health, Republic of Singapore; 2011. [Accessed 12 February 2019]. National Health Survey 2010. Available from:[https://www.moh.gov.sg/content/moh\\_web/home/Publications/Reports/2011/national\\_health\\_survey2010.html](https://www.moh.gov.sg/content/moh_web/home/Publications/Reports/2011/national_health_survey2010.html).
3. Linette Lai. Singapore risks hitting obesity rates of 15% in seven years. *The Straits Times* [Internet]. 2017 June 20 [assessed 12 February 2019]; Available from: <https://www.straitstimes.com/singapore/singapore-risks-hitting-obesity-rates-of-15-in-seven-years>
4. Yu YH, Vasselli JR, Zhang Y, Mechanick JI, Korner J, Peterli R. Metabolic vs. hedonic obesity: a conceptual distinction and its clinical implications. *obesity reviews.* 2015 Mar;16(3):234-47.
5. Morton GJ, Blevins JE, Williams DL, Niswender KD, Gelling RW, Rhodes CJ, Baskin DG, Schwartz MW. Leptin action in the forebrain regulates the hindbrain response to satiety signals. *The Journal of clinical investigation.* 2005 Mar 1;115(3):703-10.
6. Sumithran P, Proietto J. The defence of body weight: a physiological basis for weight regain after weight loss. *Clinical Science.* 2013 Feb 1;124(4):231-41.
7. MacLean PS, Bergouignan A, Cornier MA, Jackman MR. Biology's response to dieting: the impetus for weight regain. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology.* 2011 Jun 15;301(3):R581-600.
8. Farr OM, Chiang-shan RL, Mantzoros CS. Central nervous system regulation of eating: Insights from human brain imaging. *Metabolism.* 2016 May 1;65(5):699-713.
9. González-Muniesa P, Martínez-González MA, Hu FB, Després JP, Matsuzawa Y, Loos RJ, Martinez JA. Obesity. *Natural Reviews Disease Primers.* 3, 17034.
10. Upadhyay J, Farr O, Perakakis N, Ghaly W, Mantzoros C. Obesity as a disease. *Medical Clinics.* 2018 Jan 1;102(1):13-33.
11. Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. *New England Journal of Medicine.* 2017 Jan 19;376(3):254-66.
12. Xia Q, Grant SF. The genetics of human obesity. *Annals of the New York Academy of Sciences.* 2013 Apr 1;1281(1):178-90.
13. Singh RK, Kumar P, Mahalingam K. Molecular genetics of human obesity: a comprehensive review. *Comptes rendus biologies.* 2017 Feb 1;340(2):87-108.
14. Boulangé CL, Neves AL, Chilloux J, Nicholson JK, Dumas ME. Impact of the gut microbiota on inflammation, obesity, and metabolic disease. *Genome medicine.* 2016 Dec;8(1):42.
15. Rial SA, Karelis AD, Bergeron KF, Mounier C. Gut microbiota and metabolic health: the potential beneficial effects of a medium chain triglyceride diet in obese individuals. *Nutrients.* 2016 May 12;8(5):281.
16. Stephens RW, Arhire L, Covasa M. Gut Microbiota: From Microorganisms to Metabolic Organ Influencing Obesity. *Obesity.* 2018 May;26(5):801-9.
17. Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, Griffin NW, Lombard V, Henrissat B, Bain JR, Muehlbauer MJ. Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science.* 2013 Sep 6;341(6150):1241214.
18. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, Waget A. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes.* 2007 Jul 1;56(7):1761-72.
19. Cuthbertson DJ, Steele T, Wilding JP, Halford JC, Harrold JA, Hamer M, Karpe F. What have human experimental overfeeding studies taught us about adipose tissue expansion and susceptibility to obesity and metabolic complications? *International journal of obesity.* 2017 Jun;41(6):853.
20. Akram DS, Astrup AV, Atinmo T, Boissin JL, Bray GA, Carroll K, Chitson P, Chunming C, Dietz WH, Hill JO, Jéquier E. Obesity: Preventing and managing the global epidemic. *World Health Organization Technical Report Series.* 2000(894).
21. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF, Abraham JP. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The lancet.* 2014 Aug 30;384(9945):766-81.
22. Cefalu WT, Bray GA, Home PD, Garvey WT, Klein S, Pi-Sunyer FX, Hu FB, Raz I, Van Gaal L, Wolfe BM, Ryan DH. Advances in the Science, Treatment, and Prevention of the Disease of Obesity: Reflections From a Diabetes Care Editors' Expert Forum. *Diabetes Care.* 2015 Aug;38(8):1567.
23. Kotsis V, Jordan J, Micic D, Finer N, Leitner DR, Toplak H, Tokgozoglu L, Athyros V, Elisaf M, Filippatos TD, Redon J. Obesity and cardiovascular risk: a call for action from the European Society of Hypertension Working Group of Obesity, Diabetes and the High-risk Patient and European Association for the Study of Obesity: part A: mechanisms of obesity induced hypertension, diabetes and dyslipidemia and practice guidelines for treatment. *Journal of hypertension.* 2018 Jul;36(7):1427-40.
24. Hall KD, Kahan S. Maintenance of lost weight and long-term management of obesity. *Medical Clinics.* 2018 Jan 1;102(1):183-97.
25. Amarasinghe A, D'Souza G. Individual, social, economic, and environmental model: A paradigm shift for obesity prevention. *ISRN Public Health.* 2012 Nov 26;2012.
26. Raynor HA, Champagne CM. Position of the Academy of Nutrition and Dietetics: interventions for the treatment of overweight and obesity in adults. *Journal of the Academy of Nutrition and Dietetics.* 2016 Jan 1;116(1):129-47.
27. Hjorth MF, Ritz C, Blaak EE, Saris WH, Langin D, Poulsen SK, Larsen TM, Sørensen TI, Zohar Y, Astrup A. Pretreatment fasting plasma glucose and insulin modify dietary weight loss success: results from 3 randomized clinical trials. *The American journal of clinical nutrition.* 2017 Jul 5;106(2):499-505.
28. Hwang JJ, Jiang L, Hamza M, Rangel ES, Dai F, Belfort-DeAguiar R, Parikh L, Koo BA, Rothman DL, Mason G, Sherwin RS. Blunted rise in brain glucose levels during hyperglycaemia in adults with obesity and T2DM. *JCI insight.* 2017 Oct 19;2(20).
29. Seimon RV, Roekens JA, Zibellini J, Zhu B, Gibson AA, Hills AP, Wood RE, King NA, Byrne NM, Sainsbury A. Do intermittent diets provide physiological benefits over continuous diets for weight loss? A systematic review of clinical trials. *Molecular and cellular endocrinology.* 2015 Dec 15;418:153-72.
30. Patterson RE, Sears DD. Metabolic effects of intermittent fasting. *Annual review of nutrition.* 2017 Aug 21;37.
31. Mattson MP, Longo VD, Harvie M. Impact of intermittent fasting on health and disease processes. *Ageing research reviews.* 2017 Oct 1;39:46-58.

## LEARNING POINTS

- **Obesity is now recognised as a chronic disease which needs chronic treatment to treat or prevent obesity related complications.**
- **The complex and multifactorial nature of obesity means that there is no one-size-fits-all intervention or solution and would necessitate a multi-level and individualised multi-pronged approach to treating obesity and its related conditions.**
- **Dietary approaches such as intermittent fasting could potentially be a treatment option but unlikely to be that 'silver bullet'.**