

Revisiting the Name, Definition and Classification of Obesity

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The world is facing an escalating epidemic of overweight and obesity, causing a major public health threat in both the developed and developing countries [1]. The World Health Organization (WHO) defines a body mass index (BMI) of between 25 and 30 kg/m² as overweight, and a BMI greater than 30 kg/m² as obese [2]. Much debate, however, continues on this classification and its applicability to all populations.

A recent WHO estimate suggests that almost 1.9 billion adults aged 18 years and above are overweight and 690 million adults are obese [3]. By 2030, it is estimated that over one billion adults globally will be obese [4]. Obesity is currently considered a major risk factor in many non-communicable diseases. An analysis of the Global Burden of Disease Study in 2019 involving 204 countries and territories showed that obesity contributed to approximately 5 million deaths from cardiovascular diseases, diabetes, neurological disorders, chronic respiratory diseases, cancers and digestive disorders [5]. In addition, obesity is also recognised as a risk factor in psychiatric, obstetric, reproductive, perinatal and pelvic disorders. Whether obesity is a risk factor in all of these comorbidities or these comorbidities are complications of obesity would be an interesting topic to debate.

In 1997, the WHO declared obesity as a disease; followed by the American Medical Association (AMA) in 2013 and the European Commission in 2021 [6, 7]. The AMA highlighted that obesity is a disease because it is a chronic condition, with multiple pathophysiological aspects, leading to various complications, and requiring a range of interventions [7].

They made an interesting comparison that if obesity is not a disease because it is merely the consequence of lifestyle choices, then lung cancer is also not a disease as it is the result of people choosing to smoke cigarettes [7].

Despite obesity being declared a disease, and the existence of evidence showing a strong link between obesity and several non-communicable diseases, the precise criteria for the diagnosis of obesity remains to be clearly established. The current criteria used for the diagnosis of obesity are incomplete, and may even be misleading in some instances. It has become apparent that the measurements presently used for the diagnosis of obesity have their inherent limitations and weaknesses. BMI, waist-hip ratio and percentage body fat are currently used in defining overweight and obesity. They are also commonly used in the calculation of the risk of cardiovascular or metabolic diseases in individuals. Although BMI significantly correlates with the amount of fat mass in the general population, it, however, loses its predictability when applied on an individual level. Besides that, BMI does not directly assess body fat, and, in fact, it may not reflect the actual body fat percentage in individuals who have a large muscle mass but minimal body fat. Additionally, BMI cannot differentiate between lean and fat mass in the body and, therefore, does not give an accurate representation of an individual's muscle/bone mass or even their body fat mass and distribution. According to the AMA's Council on Science and Public Health, the current BMI classification system is also misleading about the effects of body fat mass on mortality rates [7].



Bioelectrical impedance analysis (BIA) has been proposed as an alternative technique for the measurement of body composition and fat percentage. Although its precision has improved significantly in recent years, it is still not suitable enough to estimate the precise body fat percentage [8, 9]. Numerous factors influence BIA, which could limit its usage in the diagnosis of obesity. For example, BIA in dehydration or when done soon after food consumption underestimates body fat [10, 11]. On the other hand, BIA following moderate physical activity overestimates body fat [12]. Alternatively, measurement of skinfold thickness using a skinfold caliper only measures subcutaneous fat, and, therefore, does not reflect the total percentage of body fat. Moreover, it is also beset with operator variability. The most accurate methodologies for the measurement of percentage body fat are dual X-ray absorptiometry and underwater weighing or hydrodensitometry. However, these are too expensive to be performed in a clinical setting. There is, therefore, a need for more reliable tests or methods that can be performed clinically for accurate determination of percentage body fat and for the diagnosis of obesity. This is necessary if we want to accurately link the level of fat mass with disease and mortality. However, the question remains whether there is a precise critical body fat percentage above which disease results. If there is, is this 'cut-off value' the same for all? It may not be so, as factors like race/ethnicity, gender, age, and body fat distribution influence the impact of fat on obesity-related comorbidities. As a matter of fact, there may not be one 'cut-off' that fits all. Besides that, there is also one other question which remains unanswered. Will the determination of the exact percentage of body fat in itself indicate disease? Again, this may be unlikely because there are those, albeit a few, who are classified as obese but live to be 80 years or more without any major health complaints.

It is becoming apparent that determining the exact amount of fat mass on its own may not be sufficient to diagnose obesity as a disease or determine at what point obesity becomes a risk factor or a disease. There is, therefore, a need to have evidence of altered or disturbed physiological measurements showing the existence of disease alongside BMI and percentage

body fat measurements for a better diagnosis of obesity. The most relevant parameters that need to be measured for the accurate diagnosis of obesity would be those representing adipocyte function, together, of course, with the usual anthropometric measurements, such as BMI and waist-hip circumference ratio, etc. In addition, parameters showing the presence of inflammation and endothelial activation must also be included. There is sufficient evidence in the literature indicating that a disturbed adipose tissue function, promoting a chronic low inflammatory state, underlies the pathogenesis of obesity-related cardiovascular and metabolic diseases [13]. In fact, obesity has long been recognised as a low-grade chronic inflammatory state, although the precise reason or the mechanism responsible for this remains unclear [14].

For a long time, it has been held that the function of adipocytes is primarily to store energy or excess fat and produce heat. However, evidence in recent years has shown that the adipocytes produce a huge number of adipokines and cytokines, which, under normal circumstances, serve numerous physiological functions, including regulation of energy balance and body weight, immune function, and in reproduction [15,16]. Some of these adipokines are pro-inflammatory and some are anti-inflammatory, and the secretion of these is drastically altered in obesity. There is an up-regulation of pro-inflammatory adipokines and a down-regulation of anti-inflammatory adipokines in obesity [17, 18]. The exact mechanism responsible for the altered adipokine release from the adipocytes is uncertain but it may be due to the distress incurred by the expanding and over-stretched adipocytes, particularly, those in the visceral adipose tissue. The hypertrophy of the adipocytes exacerbates hypoxia leading to metabolic dysfunction in the adipocytes and dysregulated differentiation and maturation of preadipocytes [17]. This impacts the secretion of adipokines, favouring the secretion of more pro-inflammatory adipokines. The secretion of anti-inflammatory adipokines like adiponectin and SFRP5 is decreased in obesity. The secretion of pro-inflammatory adipokines like leptin, TNF-alpha, IL-6, resistin, chemerin, visfatin, PAI-1, RBP4, lipocalin 2, IL-18, ANGPTL2, CCL2, CXCL5 and NAMPT is increased in obesity [18], particularly that of leptin

whose circulating level in the blood is directly proportional to the adipose tissue mass. It is released constitutively, and its secretion increases further when the adipocytes are hypoxic. Pro-inflammatory and cell proliferative activities of leptin are well documented [19, 20, 21]. Leptin is also believed to mediate the relationship between blood pressure and fat mass [22], and leptin injections result in increased blood pressure and serum levels of markers of endothelial activation [23, 24, 25].

In general, apart from mature adipocytes, the adipose tissue also consists of preadipocytes, mesenchymal cells, and stromal vascular fraction (SVF) cells. The latter also include fibroblasts, vascular endothelium, smooth muscle cells, and subsets of leukocytes. In addition, the adipose tissue also contains resident macrophages, mast cells, monocytes, dendritic cells, natural killer cells, B-cells, T-cells, neutrophils, and eosinophils. Their activation state, differentiation, and proliferation in the adipose tissue are impacted by the pro- and anti-inflammatory adipokines produced within the adipose tissue. The preponderance of pro-inflammatory adipokines will stimulate some of these cells to release more inflammatory cytokines that causes the chronic low-grade inflammation often evident in obese individuals.

Given the information that we have, it is clearly evident that we need better criteria for the diagnosis of obesity as a disease. We, in fact, need a set of tests that will specifically identify the inflammatory state associated with increased adipose tissue mass. This will certainly help in identifying the disease a lot earlier; long before the manifestations of its cardiovascular and metabolic consequences. Alongside the usual anthropometric measurements, there is a need to include the measurement of some of the pro-inflammatory adipokines like leptin and cytokines like IL-6, and TNF-alpha, and serum levels of markers of inflammation like C-reactive protein (CRP) and markers of endothelial activation (e.g., endothelial adhesion molecules such as ICAM, VCAM, e-selectin etc.). It is very likely that changes in these parameters may be evident even at BMIs of between 25 and 29 kg/m². We know that cardiovascular and metabolic diseases also affect individuals in the overweight population and not just those who are classified as obese.

Evidence is accumulating in the literature, underlining the role of leptin in reproductive dysfunction in obese males [26, 27, 28] and the role of leptin, adiponectin and inflammation in obesity-related chronic kidney disease [29] and a number of other diseases.

Parameters on adipocyte morphology could also be included in the diagnosis of obesity as the morphology of adipocytes is altered when in distress. An alteration in any of these would further indicate the presence of disease.

Whether we want to continue to call the disease 'obesity' or give it another name that reflects the increased fat mass and its link to the disease is worth a discussion. Some feel that the word obesity, which was adopted from the Latin word *obesitas* in the early 17th century is stigmatized with misperception and misunderstanding and, therefore, has to be replaced. There are others who feel that it does not reflect the true nature of the disease. If the name 'obesity' is found inappropriate or lacking, then perhaps a more accurate name that may be considered is "adipocyte dysfunction syndrome" (ADS). After all, obesity-related diseases are all due to disturbed adipocyte function. The usage of ADS will also exclude those classed as overweight or obese but without any evidence of obesity-related diseases or adipocyte dysfunction. Clearly, the call to develop proper criteria for the diagnosis of obesity is appropriate and long overdue. The present widely used BMI classification of overweight and obesity certainly needs to be revisited and refined, and perhaps reclassified based on the level of adipocyte dysfunction and inflammation rather than based just on the body weight and height or the percentage of body fat.

REFERENCES

1. World Health Organization. WHO acceleration plan to stop obesity. 2022. <https://www.who.int/publications/i/item/9789240075634>. Accessed 10 December 2023.
2. World Health Organization. Global Database on Body Mass Index: BMI Classification. 2006. <http://www.assessmentpsychology.com/icbmi.htm>. Accessed 23 Nov 2023.

3. World Health Organization. Fact Sheets: Obesity and overweight. 2021. <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>. Accessed 23 Nov 2023.
4. World Obesity Atlas. World Obesity Federation. London: 2022 (https://s3-eu-west-1.amazonaws.com/wof-files/World_Obesity_Atlas_2022.pdf). Accessed 10 December 2023.
5. Chong B, Jayabaskaran J, Kong G, Chan YH, Chin YH, Goh R, Kannan S, Ng CH, Loong S, Kueh MTW, Lin C, Anand VV, Lee ECZ, Chew HSJ, Tan DJH, Chan KE, Wang JW, Muthiah M, Dimitriadis GK, Hausenloy DJ, Mehta AJ, Foo R, Lip G, Chan MY, Mamas MA, le Roux CW, Chew NWS. Trends and predictions of malnutrition and obesity in 204 countries and territories: an analysis of the Global Burden of Disease Study 2019. *EClinical Medicine*. 2023; 57: 101850. doi: 10.1016/j.eclinm.2023.101850.
6. Kyle TK, Dhurandhar EJ, Allison DB. Regarding Obesity as a Disease: Evolving Policies and Their Implications. *Endocrinol Metab Clin North Am*. 2016; 45(3): 511-20. doi: 10.1016/j.ecl.2016.04.004.
7. American Medical Association (AMA). Recognizes Obesity as a Disease. 2013. <https://www.nytimes.com/2013/06/19/business/ama-recognizes-obesity-as-a-disease.html>. Accessed 30 November 2023.
8. Buchholz AC, Bartok C, Schoeller DA. The validity of bioelectrical impedance models in clinical populations. *Nutrition in Clinical Practice*. 2004; 19(5): 433-46. doi:10.1177/0115426504019005433
9. Fosbøl MØ, Zerahn B. Contemporary methods of body composition measurement. *Clinical physiology and functional imaging*. 2015; 35(2): 81-97. doi:10.1111/cpf.12152
10. Coppini LZ, Waitzberg DL, Campos AC. Limitations and validation of bioelectrical impedance analysis in morbidly obese patients. *Current Opinion in Clinical Nutrition & Metabolic Care*. 2005; 8(3): 329-32. doi: 10.1097/01.mco.0000165013.54696.64.
11. Slinde F, Rossander-Hulthén L. Bioelectrical impedance: effect of 3 identical meals on diurnal impedance variation and calculation of body composition. *The American journal of clinical nutrition*. 2001; 74(4): 474-8. doi:10.1093/ajcn/74.4.474.
12. Kushner RF, Gudivaka R, Schoeller DA. Clinical characteristics influencing bioelectrical impedance analysis measurements. *The American journal of clinical nutrition*. 1996; 64(3): 423S-7S. doi:10.1093/ajcn/64.3.423S
13. Khanna D, Khanna S, Khanna P, Kahar P, Patel BM. Obesity: a chronic low-grade inflammation and its markers. *Cureus*. 2022; 14(2). doi:10.7759/cureus.22711
14. Kolb H. Obese visceral fat tissue inflammation: from protective to detrimental?. *BMC medicine*. 2022; 20(1): 1-4. doi:10.1186/s12916-022-02672-y
15. Clemente-Suárez VJ, Redondo-Flórez L, Beltrán-Velasco AI, Martín-Rodríguez A, Martínez-Guardado I, Navarro-Jiménez E, Laborde-Cárdenas CC, Tornero-Aguilera JF. The Role of Adipokines in Health and Disease. *Biomedicine*. 2023; 11(5): 1290. doi: 10.3390/biomedicine11051290.
16. Almabhouh FA, Muhammad FI, Ibrahim H, Singh H. Leptin: A pleiotropic factor in physiology. *Journal of Clinical and Health Sciences*. 2019; 4(2): 31-57. doi:10.24191/jchs.v4i2.7551
17. Liu F, He J, Wang H, Zhu D, Bi Y. Adipose morphology: a critical factor in regulation of human metabolic diseases and adipose tissue dysfunction. *Obesity surgery*. 2020; 30: 5086-100. doi:10.1007/s11695-020-04983-6
18. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nature reviews immunology*. 2011; 11(2): 85-97. doi:10.1038/nri2921

19. Taylor EB. The complex role of adipokines in obesity, inflammation, and autoimmunity. *Clinical Science*. 2021; 135(6): 731-52. doi:10.1042/CS20200895
20. Pérez-Pérez A, Sánchez-Jiménez F, Vilariño-García T, Sánchez-Margalet V. Role of leptin in inflammation and vice versa. *International journal of molecular sciences*. 2020; 21(16): 5887. doi:10.3390/ijms21165887
21. Sharma D, Saxena NK, Vertino PM, Anania FA. Leptin promotes the proliferative response and invasiveness in human endometrial cancer cells by activating multiple signal-transduction pathways. *Endocrine-related cancer*. 2006; 13(2): 629-40. doi:10.1677/erc.1.01169
22. Fujita Y, Kouda K, Ohara K, Nakamura H, Iki M. Leptin mediates the relationship between fat mass and blood pressure: The Hamamatsu School-based health study. *Medicine*. 2019; 98(12). doi:10.1097/MD.00000000000014934
23. Ibrahim HS, Omar E, Froemming GR, Singh HJ. Leptin increases blood pressure and markers of endothelial activation during pregnancy in rats. *Biomed Res Int*. 2013. doi:10.1155/2013/298401
24. Farhana K, Effendi I, Caszo B, Satar NA, Singh HJ. Exercise prevents leptin-induced increase in blood pressure in Sprague–Dawley rats. *Journal of physiology and biochemistry*. 2014; 70: 417-23. doi:10.1007/s13105-014-0319-2
25. Hassan MJ, Bakar NS, Aziz MA, Basah NK, Singh HJ. Leptin-induced increase in blood pressure and markers of endothelial activation during pregnancy in Sprague Dawley rats is prevented by resibufogenin, a marinobufagenin antagonist. *Reproductive biology*. 2020; 20(2): 184-90. *Reprod Biol*. doi: 10.1016/j.repbio.2020.03.004.
26. Almabhouh F, Aziz NA, Durairajanayagam D, Singh HJ. Could leptin be responsible for the reproductive dysfunction in obese men? *Reproductive biology*. 2020; 20(1): 106-10. <https://doi.org/10.1016/j.repbio.2020.01.003>.
27. Almabhouh FA, Singh HJ. Systematic Review of Literature Documenting the Link Between BMI, Sperm Parameters, and Leptin. *Fertility & Reproduction*. 2022; 4(01): 1-10. <https://doi.org/10.1142/S2661318222500013>.
28. Almabhouh FA, Md Mokhtar AH, Malik IA, Aziz NA, Durairajanayagam D, Singh HJ. Leptin and reproductive dysfunction in obese men. *Andrologia*. 2020; 52(1): e13433. <https://doi.org/10.1111/and.13433>.
29. Statman D. Inflammatory mediators could provide link between obesity, CKD. *Nephrology News and Issues*. 2023. <https://www.healio.com/news/nephrology/2023/11/30/inflammatory-mediators-could-provide-link-between-obesity-ckd>. Accessed 9 February 2024.