Opinion: An urgent need of better criteria for the diagnosis and classification of obesity

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According to a recent World Health Organization (WHO) estimate, almost a quarter of the world's adult population is above the ideal body weight,[1] ie. they are either overweight or obese. This fraction has been steadily increasing over the last few decades, and is expected to continue to increase in the foreseeable future unless something is done about it.[2] The WHO defines a body mass index (BMI) of between 25 and 30 kg/m^2 as overweight, and a BMI greater than 30 kg/m^2 as obese.

The consequences of being overweight and obese on health are well recognised and documented. Although initially recognised as a risk factor for a number of non-communicable diseases, which include high blood pressure, ischaemic heart disease, atherosclerosis, diabetes mellitus, chronic respiratory diseases, some types of cancers, dyslipidaemia, fatty liver disease, the WHO, in its right wisdom, declared obesity as a disease in 1997. This was adopted by the American Medical Association (AMA), some 16 years later, where the AMA defined it as a chronic condition, with multiple pathophysiological aspects and complications.[3] In the more recent years, obesity has also been linked to mild cognitive impairment, altered hippocampal structure and function, Alzheimer's type dementia, autonomic and somatic nervous system dysfunction, and to some obstetric, reproductive, perinatal and pelvic disorders. Clearly, obesity is a disease that is responsible for countless other conditions, and desperately in need of a better diagnostic criteria than just the BMI.

Obesity is a state of low-grade inflammation. The exact point on the BMI scale or percentage body fat inflammation begins remains unknown. In other words, the precise relationship between BMI and inflammation needs to be clearly established. It is unknown if this particular point is the same for all populations, races, adults and children, and whether there are gender differences[4] and what factors influence this point. Whether regular physical activity impacts this cut-off point is unknown. Moreover, and equally importantly, the precise factor/s responsible for this low-grade inflammation in obesity remains to be clearly established.

There is considerable evidence in the literature that the distressed adipocytes in obese individuals may be the source of this factor/s that triggers inflammation. In this regard, the increased secretion of leptin and a number of other pro-inflammatory cytokines from the over-stretched, distressed adipocytes in the white adipose tissue may be directly responsible for the inflammation. Being a pro-inflammatory adipokine, leptin causes widespread endothelial activation. In addition to that, raised BMI has been found to disrupt the chromatin accessibility in human adipocytes, which could underlie obesity related inflammation.[5] In this regard, leptin has been found to alter the expression of numerous genes in cells. Studies in our lab have shown that leptin alters the expression of over 5000 genes, including apoptosis-inducing factor, histone acetyl transferase, respiratory chain reaction enzyme, cell necrosis and DNA repair genes. It also downregulates antioxidant enzyme and upregulates tumorigenic genes.[6-8]

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In addition to increased secretion of leptin and other pro-inflammatory adipokines, death of some of the distressed adipocytes increases the recruitment of macrophages into the adipose tissue, which then get polarised into pro-inflammatory M1-like macrophages.[9] These macrophages secrete many pro-inflammatory cytokines, including TNF. The raised circulating levels of leptin and other pro-inflammatory adipokines are the most likely factors responsible for the chronic low-state inflammation that is often noticed in the obese, together, of course, with the accompanying array of metabolic disorders.

Despite the declaration of obesity as a disease, and the overwhelming evidence in the literature implicating it as a risk factor in a number of other diseases, the diagnosis and classification of obesity still continues to rely on the old WHO definition that is primarily based on BMI. There is a clear and urgent need for a better criterion for the diagnosis of obesity if we wish to better manage obesity and obesity-related diseases. The current criteria used for the diagnosis of obesity are incomplete, and have inherent limitations and weaknesses. They do not reflect or detect the silent or insidious pathological changes happening inside the body of the overweight and obese individuals. Unfortunately, there is no information or data in the literature showing the precise BMI or percentage body fat cut-off at which the ill effects of being overweight or obese become apparent. From all probability, these perhaps start to occur at BMIs between 25-30, or even below 25, in some populations. It is not the BMI but the extra adipose tissue mass that is the disease. BMI does not directly assess body fat, and cannot differentiate between lean and fat mass in the body. Skinfold thickness using a skinfold calliper only measures subcutaneous fat, and does not accurately reflect the total percentage of body fat. Bioelectrical impedance analysis (BIA) for the measurement of body composition and body fat percentage is influenced by factors like hydration status, food consumption and physical activity. The accurate methodologies for the measurement of fat mass like dual X-ray absorptiometry and hydrodensitometry are too expensive to be performed in a clinical setting. Whilst it is important to know the exact fraction of body fat, but accurate measurement of percentage body fat in itself does not automatically confirm the presence of disease. There are those, albeit a few, with BMIs of above 30, and live to be 80 years or more with no major health complaints. What we, therefore, need, in addition to the BMI or body fat percentage, are parameters for the detection of altered or disturbed physiological function, particularly those related to adipocyte dysfunction. The most relevant parameters that need to be measured for the accurate diagnosis of obesity as a disease would be those representing adipocyte function or dysfunction, and those showing the presence of endothelial activation and generalised inflammation, together, of course, with the usual anthropometric measurements, such as BMI and waist-hip circumference ratio, etc.

Adipocytes produce a large number of adipokines and cytokines, which, under normal circumstances, serve numerous physiological functions that include regulation of energy balance and body weight, immune function, and reproduction.[10,11] Some of these adipokines are pro-inflammatory and some are anti-inflammatory, and the secretion of these is drastically

altered in obesity. Secretion of pro-inflammatory adipokines is upregulated whereas the secretion of anti-inflammatory adipokines is down-regulated in obesity.[12,13] The hypertrophy of adipocytes, particularly those in and around the viscera, exacerbates hypoxia within the adipose tissue leading to metabolic dysfunction in the adipocytes and dysregulated differentiation and maturation of preadipocytes and even death of some of the adipocytes.[12] This internal milieu within the adipose tissue favours the increased 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 and decreased secretion of anti-inflammatory adipokines like adiponectin and SFRP5 in obesity. Serum leptin concentration is directly proportional to the adipose tissue mass. This has long been well established. Released constitutively, the secretion of leptin increases further when the adipocytes are hypoxic or distressed. Pro-inflammatory and cell proliferative activities of leptin have also been well documented.[14-16] Incidentally, leptin is also believed to mediate the relationship between blood pressure and fat mass,[17] and leptin injections into rats and mice result in increased blood pressure, proteinuria and serum levels of markers of endothelial activation.[18-20]

Given the information that we have, it is clearly evident that we need a set of tests that will specifically identify the inflammatory state associated with increased adipose tissue mass, not just BMI or the fraction of body fat. The measurements of these inflammatory parameters will certainly help in identifying the disease a lot earlier; perhaps long before its cardiovascular and metabolic manifestations become apparent. Measurement of 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 (eg., endothelial adhesion molecules such as ICAM, VCAM, e-selectin, etc.) are necessary for the diagnosis of obesity. As stated earlier, it is very likely that changes in these parameters may be evident even at BMIs below 25 or between 25 and 29 kg/m^2. As we know that cardiovascular and metabolic diseases also affect individuals in the borderline and overweight population and not just those who are obese.

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.

Clearly, the currently used BMI classification of overweight and obesity needs to be re-classified or revised based on the level of adipocyte dysfunction and inflammation rather than based just on BMI or percentage body fat, if we wish to manage obesity as a disease. Like with many other diseases, early diagnosis of obesity is important if we want to combat the scourge of obesity-related diseases, that are fast becoming a burden to the health care systems of most countries. Measures have to be put in place to reduce the prevalence of obesity in the community. These include education in schools and colleges on the importance of a balanced nutrition and regular physical exercise in the maintenance of normal body weight. Obesity in most instances primarily stems

from poor nutrition and low physical activity. Food has become a very important component of our social behaviour and we consume food even when we do not need to. We really need to learn to eat to live rather than living to eat, which is what we are doing at the present time.

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