Obesity: Overview of a Universal Health Conundrum

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ABSTRACT

Obesity is a worldwide health issue which is displaying increasing prevalence trend. World Health Organisation (WHO) has already given it as epidemic status. Many physiological parameters such as Body Mass Index (BMI), Waist Circumference (WC), Waist to Hip Ratio (WHR) are used for measurement of obesity. This review was written with the aim to give an inclusive picture of current prevalence of obesity along with discussing the physiology and function of different adipocytes and the numerous chemical messengers released by them. The manifold impact of obesity on various body systems can be elucidated by exploring the adipocytes, adipokines, its functions and signalling mechanism. The adipokines enlist as key players in numerous systemic diseases. Obesity has a significant pathophysiological role in morbidity and mortality causing conditions globally. Obesity can potentially be the leading reason of economic burden on global healthcare, adversely impacting the comprehensive quality of life. This review is an effort to provide a better understanding of the current obesity status and emphasise further researches on its diverse aspects.

Keywords: Adipocyte, Adipokines, Body mass index, Morbidity, Mortality

INTRODUCTION

The idea of excessive body fat has been in human evolution since centuries, but paradoxically it was considered to be a criterion for a healthy body, which can survive numerous diseases compared to slimmer counterparts [1]. It was only in the last century, that excessive body fat raised a serious health concern among medical fraternity. The etymology of the word obese was from Latin word 'obedere' means 'over eat' and 'obesitas' means 'being very fat' [2].

Obesity is defined as an accumulation of excessive body fat and is closely related to ill health and several major diseases. Obesity remains a highly enigmatic, multifaceted, complex conditions which is accepted as an extreme of health rather than a disease.

PREVALENCE

Obesity is an ignored health condition, non communicable and multifactorial. The increasing number of obese individuals in all age groups as well as in different strata of society is alarming. The prevalence of obesity is tripled from 1975 to 2016 [3]. The World Health Organization (WHO) published latest reports in which the most obese country in the world is "The island of Nauru", where 61.0% of its adult population is obese [3]. By 2030, USA can reach disturbing number of over 85% of population being overweight or obese [4]. In 1997 WHO consultation officially recognised the global nature of obesity as an epidemic [5]. The overweight or obese individuals outnumbered the percentage of underweight individuals by 2000 [6]. The recent fact about obesity from WHO as published in 2021 states that 39% of adults aged 18 years and above were overweight in 2016, and 13% were obese. In 2019 under the age of 5 years an approximately 38.2 million children were overweight or obese. Over 340 million children and adolescents aged 5-19 were overweight or obese in 2016 [7].

However, the obesity prevalence variation is based on modifiable and non modifiable factors. The non modifiable and modifiable factors affecting the obesity prevalence, data are discussed later in the article. Ashraf Hassan Humaidan Al Zaabi from Zayed Military Hospital in Abu Dhabi conducted one of the largest population studies on young Emirati population in the age of 18-20 years. The research pointed towards a high incidence of cardio-metabolic disorders such as high triglycerides, obesity, impaired fasting glucose, hypertension and high cholesterol in the subjects. It showed that over 70% population under 30 years of age were obese [8].

PARAMETERS FOR OBESITY

Body Mass Index (BMI)

BMI is the most common tool to measure weight element of body. It is measured by body weight in kilogram divided by square of the height in meters hence expressed as kg/m^2. Eknoyan G, a Belgian astronomer and statistician was working extensively on concept of "Social averages" to define normal average for a person [9]. In an attempt to reach the Gaussian or normal distribution expressed as Bell curve, Quetelet concluded that ratio of weight to the height square followed the Bell curve better when compared with weight to height or weight to third power of height [10]. Hence, BMI is also called Quetelet Index, the squaring of the height for the weight lead to a more uniform weight distribution over the height of the person. However, the limitation to measure BMI is that, it expresses weight distribution uniformly over the height, which is not the actual finding as the truncal adiposity is more than the extremities [10]. BMI has been classified by numerous authors under different categories and ranges. A report, BMI: Considerations for Practitioners, published by the Department of health and human service of the Centers for Disease Control and Prevention (CDC), mentioned details of BMI into four categories, as presented in [Table/Fig-1] [11].

In 1981 Garrow, had presented a similar classification with different terminology [Table/Fig-2] [12,13].

Categories	Body mass index (kg/m²)
Underweight	Below 18.5
Normal	18.5-24.9
Overweight	25-29.9
Obese	30 and above

[Table/Fig-1]: Categories of Body Mass Index (BMI) by Centers for Disease Control and Prevention (CDC) [11].

Categories	Body mass index (kg/m²)
Desirable	<25
Grade I obesity	25 and 29.9
Grade II obesity	30 and 40
Grade III obesity	>40

[Table/Fig-2]: BMI categories as per Garrow JS et al., [12,13].

The International Obesity Task Force (IOTF) in 1997 added to the number of BMI categories to include different degrees of obesity and changed the terms [Table/Fig-3] [14].

Determinant	Body Mass Index (BMI) (kg/m^2)
Underweight	15-19.9
Normal weight	20-24.9
Overweight	25-29.9
Class I obesity	30-34.9
Class II obesity	35-39.9
Class III obesity	$\geq$40

[Table/Fig-3]: Body Mass Index (BMI) categories by the International Obesity Task Force (IOTF) in 1997 [14].

Nevertheless, the BMI assessment has its innate limitations like the interpretation varies based on region and ethnicity. The BMI measures excess body weight with the square of height ratio, considering that the excess weight is all due to fat, which is interpreted as obesity [15]. Nevertheless, the additional weight can be due to muscle mass as in BMI of a sports person, which is frequently miscalculated as increased fat mass and thereby giving increased BMI [16].

Waist Circumference (WC)

The body fat is not uniformly distributed all over the height. The visceral or abdominal fat is prominent area for fat deposition. Hence, measurements like WC and Waist Hip Ratio (WHR) become significant indicators of body fat or obesity. WC is a routine and simple method to measure visceral adiposity. Abdominal obesity however, fluctuates based on gender, body type and race.

Waist to Hip Ratio (WHR)

WHR is another parameter to assess obesity. It is computed by taking the measurement around the waist at its slimmest point and by dividing the width around the hips and buttocks at their broadest positions [17].

Measurement protocol: The measurement of WC can be done in many ways given by different authors such as exact measurement at the umbilicus [18] or 2.5 cm above the umbilicus [19].

Diverse factors influence the measurement of WC. The subject related factors are the posture, the phase of respiration, the stomach content and the abdominal tension. As per WHO, the posture of the subject should be standing with arms at the sides, feet positioned close together, and weight evenly distributed across the feet. The measurement should be done with overnight fasting by the subject at the end of normal expiration with no tension on the stomach wall [20]. The measurement tape should be non stretchable and snug fit to the measurement site and parallel to the floor [21]. The International Diabetes Federation (IDF) 2006 suggested WC as a measurement for central obesity and cut off marks calibrated at >94 and >80 cm for European men and women, respectively, and >90 and >80 cm for the South Asian, and South and Central American ethnic groups. The obesity cut-off for WHR as given by WHO is 0.90 for males and 0.85 for females with BMI over 30 kg/m^2 [22].

PHYSIOLOGY OF ADIPOCYTES

Adipocytes are the primary cells for storage of excess fat in the form of triglycerols. It reflects the positive energy balance of the body, which is utilised during negative energy state of the body as during starvation [23].

There are three known types of adipocytes: White Adipose Tissue (WAT), Brown Adipose Tissue (BAT) and Biege Adipose Tissue. White adipocytes are also called 'unilocular' and portrayed by the presence of a single large lipid droplet. It typically serves as an "Energy Bank" [24]. WAT regulates energy homeostasis it senses the demand for the energy based on the complex coordination of internal and external messengers and release or uptake energy, accordingly. Nevertheless, in obesity when it becomes functionally impaired and cannot store excess energy, it gets deposited in ectopic sites and interferes with glucose metabolism, leading to a phenomenon called lipotoxicity. An increase in insulin resistance occurs as a result of lipotoxicity [25].

Besides the WAT another type of adipocytes is BAT, its primary function is to protect the body from cold by acting like padding, hence called Hibernating organ [24]. It develops during embryonic development and is mostly concentrated in the interscapular region of small mammals and infants. The main structural difference between the two adipocytes is related to cellular contents and vascularity.

In WAT, 90% of the cell is filled with lipid or triglycerol, with few scattered mitochondria and meagre blood supply. In BAT there is multilocular arrangement of triglycerides with abundance of mitochondria. It has higher neural and vascular supply. The brown colour is due to mitochondria and vascularisation [26].

Recent developments show the presence of adipocytes with features of both white and brown hence called Beige Adipocytes, which are present in significant number contrary to previous conclusions [27]. The genetic information for the beige (brite) adipocytes is different than both white and brown types. Interestingly, it has a reversible thermogenic profile wherein, in warm conditions it undergoes a morphological transformation into white adipocytes [27-29]. The presence of a distinct type of adipocytes called bone marrow adipose tissue has been recorded [30].

ADIPOKINES

Unlike the previous theories where adipocytes were believed to be only a source of energy storage along with insulation and lining tissue, these are now proved to be active cells. These are now considered as endocrine organs which release plentiful of chemical mediators or "adipocytokines" [31]. The adipokines mediate role in insulin resistance, glucose metabolism besides playing role in inflammatory conditions along with other pro and anti-inflammatory cytokines. Adipokines are categorised as hormones, growth factors, angiogenic factors, and cytokines. The prominent adipokines discussed here are adiponectin, resistin, leptin and visfatin.

Adiponectin

A plasmatic protein expressed mostly in subcutaneous tissues and one of the few, which is inversely related to obesity [32,33]. The plasma level of adiponectin in a healthy individual is in a range of 1.9 to 17.0 mg/mL [34]. Adiponectin exerts its effect through the receptors AdipoR1, AdipoR2 and T cadherins due to its structural homology to complement factor C1q. Through various signalling pathways it shows effect on adipose tissues, endothelial, macrophages and skeletal cells. The key signalling mechanism of adiponectin is primarily based on receptor-ligand interaction wherein adiponectin binds to its receptors and brings about the signalling cascades through different pathways. Binding of adiponectin to its receptors AdipoR1, AdipoR2 and T cadherins, activates adaptor protein containing a pleckstrin homology domain, adaptor protein, phosphotyrosine interacting with pH domain and leucine zipper 1 (APPL1). APPL1 is the first directly interacting protein which then mediates several signalling cascades pathways. The main pathways are Adenosine Monophosphate-activated Protein Kinase (AMPK), mammalian Target of Rapamycin (mTOR), Nuclear Factor-kappa B (NF-κB) and c-Jun N-Terminal Kinase (JNK) [35].

Activated APPL1 initiates complex signal transduction by activating Peroxisome Proliferator-Activated Receptor-α (PPAR-α) and phosphorylating AMPK and p38 Mitogen-Activated Protein Kinase (p38-MAPK) and therefore APPL1-AMPK signalling that translocate

transcription factors into the nucleus [36]. Phosphorylation of the above key signalling proteins showed enhanced adipocyte differentiation, glucose uptake, and lipid metabolism [37].

Due to its wide scope of action, it becomes a target messenger for management of metabolic syndrome. The adiponectin has positive effect on insulin sensitivity, fatty acid oxidation and glucose uptake. It increases adipogenesis, enhances glucose metabolism and free fatty acid metabolism in muscles [38].

The anti-inflammatory functions of adiponectin on monocytes are by subduing its migration and suppressing the differentiation of foam cells. Through inhibition of Tumour Necrosis Factor-alpha (TNF-α) induced NF-κB activation it suppresses the inflammatory response of endothelial cells [39]. The skeletal muscle, liver, and adipose tissue exhibit the adiponectin receptor AdipoR1 and AdipoR2, via these receptors adiponectin expresses its anti-inflammatory and metabolic activities leading to anti-atherogenic and antidiabetic action [39].

Resistin

Resistin an adipokine, is a member of cysteine rich secretory family, known as Resistin Like Molecule (RELM) [40]. It is secreted by adipocytes and triggers Insulin resistance {in (insulin) + resisit (resistance)}, hence the name. This is studied as a pivotal hormone causing obesity mediated insulin resistance. Nevertheless, the hormone possesses variable structural expression in different species, its role and behaviour in animals cannot be interpolated directly in human beings. Primarily secretion of resistin in humans is from monocytes in contrast to mice where it is secreted from white adipocyte cells [41]. Some studies reported significant increase in the levels of resistin in obesity related Type 2 Diabetes Mellitus (Type 2 DM) [42,43], whereas some of them showed no strong correlation between the two hence, its role remains controversial [44]. The resistin functions in autocrine, paracrine and endocrine pathways through vast range of cell receptors and signalling molecules [45,46].

The atherogenic action of resistin is exerted by an increase in the expression of endothelin 1, the Intercellular Adhesion Molecule (ICAM) and the Vascular Cell Adhesion Molecule (VCAM) by activating endothelial cell. The other studies showed the systemic effect of resistin is in gastric cancer [47], breast cancer [48], colorectal cancer [49], and endometrium cancer [50], and oesophageal squamous cell cancer [51]. Numerous autoimmune conditions have also been linked to levels of resistin such as rheumatoid arthritis, and systemic lupus erythematosus [52].

The pleiotropic role and different fate of secretory resistin implicates its role in various diseases besides obesity and diabetes; with respect to Cardiovascular Diseases (CVD) and atherosclerosis, resistin has been found to have possible roles in the development of endothelial dysfunction, thrombosis, angiogenesis, inflammation and smooth muscle cell dysfunction [53].

Leptin

It is a non glycosylated peptide hormone of 167 amino acids discovered in1994 serendipitously [54]. It is secreted by WAT and shows diurnal variation with higher levels in the evening and early morning hours. Leptin exerts its effect through various receptors, which are extensively present in hypothalamus. Hypothalamus gauges the nutritional state of the body through signalling from leptin. It then modulates the levels of anorexigenic (appetite-diminishing) neuropeptides such as α-Melanocyte Stimulating Hormone (MSH) and orexigenic (i.e., appetite stimulating) neuropeptides such as neuropeptide Y to control food intake [55].

Genetic defects in these signalling mechanisms at different levels can lead to obesity. As opposed to Leptin ghrelin hormone secreted by gastric lining works to increase the appetite. A higher ghrelin to leptin ratio reflects increased hunger sensation [56].

Numerous studies showed that increase in the fat diet can lead to Leptin resistance hence, in obese people the high levels of leptin may be recorded [57,58]. This is the result of reduced central leptin sensitivity [59]. The raised levels of leptin have been linked to atherosclerosis; serum leptin levels are positively related to intima media thickness, thus having role in atherosclerosis [60]. Leptin deficiency and resistance are also associated with Type 2 DM, therefore Leptin can be therapeutically used in its treatment specifically for Lipoatrophic diabetes [61,62]. Research on female athletes inferred that leptin is a probable metabolic messenger that establishes connection between fat tissues, present energy and the reproductive axis [63]. Leptin is known to mediate inflammatory response through expression of proinfammatory cytokines in macrophages and T-cells via numerous signalling pathways [38].

Visfatin

The adipokine is a relatively new addition to the list of hormones secreted primarily by white fat cells. It was secreted by human peripheral blood lymphocyte as Pre B-cell colony Enhancing Factor (PBEF) [64]. Fukuhara A et al., identified it as a protein mediator secreted by fat cells, the amino acid sequence of which was similar to PBEF and Nampt (Nicotinamide phosphoribosyl transferase). Nampt is an enzyme involved in NAD+ salvage pathway [65]. An interesting fact about visfatin is that it mostly remained unchanged over the evolutionary chart the canine visfatin protein sequence is 96% and 94% identical to human and rodent visfatin, respectively [66]. It is secreted in wide range of tissues like bone marrow, liver, muscles, brain, kidney, spleen, testis, lungs, foetal membranes but predominantly expressed in tissue. It has antiapoptotic and proinflammatory roles in numerous pathophysiological visceral adipose conditions [67]. As for its wide array of functions and tissues which express it, necessitates further researches on it.

FACTORS AFFECTING OBESITY

The excessive consumption of calorie than utilisation leads to overweight and obesity. Several factors influence this equilibrium of total consumption and the utilisation of the calories. The non modifiable factors are gender, ethnicity or race, cultural background and genetics. The few modifiable factors affecting the obesity prevalence data are lifestyle, dietary habits and socio-economic status.

Gender

Kroll DS et al., gave an interesting insight about the gender difference of obesity based on neuroimaging. The authors discussed how taste perception, taste response, the choice of food, preference for comfort food varies with gender due to micro difference in brain structure [68]. The neurotransmitters like dopamine, opioid and serotonin signalling has gender based variation, which affects the BMI [68].

Genetics

Genes have direct influence on body characteristics and body metabolism hence, the body weight and circumference exhibit genetic predilection. Therefore, a person with familial trait of obesity is at a higher risk of being obese, the condition gets aggravated if other systemic factors like hormonal imbalance exist simultaneously. The genetic predisposition to obesity can be polygenic, monogenic or syndromic [69]. More than 100 syndromes have been related to obesity, other co-existing clinical presentations are mental challenge, dysmorphic facies, or organ-system specific abnormalities. The most common syndromic obesity is Bardet Biedl and Prader Willi syndrome [70]. O'Rahilly S and Farooqi IS in 2006 stated that a child with both obese parents have 80% chances of being obese and a child with normal weight parents has only 15 % risk of being obese [71].

Racial/Ethnicity

Racial and ethnic variations influence the onset, pattern and rapidity of weight gain and response to obesity management. Women in Africa, America and Hispanic women tend to experience weight gain earlier in life than Caucasians and Asians, and age-adjusted obesity rates are higher in these groups. Non Hispanic black men and Hispanic men have a higher obesity rate then non Hispanic white men, but the difference in prevalence is significantly less than in women [72].

Few of the modifiable factors are dietary habit, socio-economic status and lifestyle. People having higher consumption of carbohydrates, processed food and sugary drinks are at a higher risk of becoming obese with time. People belonging to more affluent class have easy accessibility to more processed and higher calorie food with less physically exerting daily routine, therefore causing increased tendency of weight gain. Other environmental and lifestyle factors such as sleep deprivation, psychological stress, depression, anxiety and certain medications such as antipsychotics, antidepressants, antidiabetic, antihypertensives and steroids all these can lead to increased BMI [73]. Physical inactivity and sedentary lifestyle and with most tasks being limited to onscreen involvement have presented some association with increased BMI, especially in adolescence life.

OBESITY AS A HEALTH CHALLENGE

The excessive body fat accumulation possesses serious threat to individual's physical and psychological health and growth. For decades, the role of obesity as a major health concern had been understated. However, recent developments have consolidated the role of obesity as the prime health concerns and linked it to various health maladies. The various co-morbidities related to obesity are type 2 diabetes, hypertension, stroke, coronary artery disease, congestive heart failure, asthma, chronic back pain, osteoarthritis, pulmonary embolism, gallbladder disease, and also an increased risk of disability. All this leads to more than three million deaths worldwide annually [74]. Obesity has been widely related to unfavourable lipid levels and cholesterol values. The BMI values have been used as a predictor for overall mortality. At the range of 30-35 kg/m^2, mostly median survival is reduced by 2-4 years; whereas at 40-45 kg/m^2, it is reduced by 8-10 years [75]. Obesity related sleep apnoea and shortness of breath have also impacted the quality of life, as the hypoventilation during sleep leads to interrupted sleep in the night thereby causing fatigue and exhaustion throughout the day [76]. The puzzling correlation of breast, colon, and gastric malignancy to obesity has been highlighted in the discussion of the adipokines. Both high and low BMI has been linked to cancer incidences.

Obesity has been for long considered as a social stigma leading to discrimination, mockery and rejection. All these have made a considerable bearing on mental health of overweight or obese people. The health complications as a consequence of these co-morbidities further add on to the inferior life quality and life expectancy. These health issues put sizable economic burden on the health system of the global community.

PREVENTION AND MANAGEMENT OF OBESITY

In near future, the obesity epidemic will be a worse health crisis than many other chronic diseases. Prevention of the condition still is a superior choice than its management. Preventive approaches include healthy lifestyle, reduced intake of high calorie and processed food. Incorporating better sleep hours, reduced anxiety and depression, following a structured life under a trained staff can play critical role in weight management [77]. Psychological intervention like Cognitive Behavioural Therapy (CBT) emphasises on altering unhealthy cognitions, emotions, and/or behaviours and promoting physical activities with better food choices and shown

appreciable outcomes in children and adolescence [78]. Besides this the surgical and pharmacological intervention has also given noticeable results in management of obesity. Nevertheless, these management modalities have some potential side-effects [79]. The management of obesity has better and more sustainable results with a holistic approach, where physical, mental and psychological health is in harmony with each other.

WHO has laid Global action plan on physical activity 2018-2030 with a motto of "More active people for a healthier world". This global action plan sets out four strategic objectives achievable through 20 policy actions that are universally applicable to all countries, recognising that each country is at a different starting point in their efforts to reduce levels of physical inactivity and sedentary behaviour. This system based approach guides each country to implement over the short term (2-3 years), medium term (3-6 years), and longer-term (7-12 years) based on its subpopulation. This includes monitoring and data reporting of inadequate physical activity among persons aged 18 years and over, and among adolescents (aged 11-17 years) [80].

Sedentary behaviour is defined as any waking behaviour characterised by an energy expenditure ≤1.5 metabolic equivalents, such as sitting, reclining or lying down [81]. Globally, 23% of adults and 81% of adolescents (aged 11-17 years) do not meet the WHO global recommendations on physical activity for health [82]. The sustainable development goals 2030 include increasing physical activity, which directly contributes to good health, ending all forms of malnutrition, quality education, gender equality, decent work and economic growth, industry, innovation and infrastructure, reduced inequalities, sustainable cities and communities, responsible production and consumption [80].

CONCLUSION(S)

It can be concluded that obesity adversely impacts the quality of life. The white fat cells were considered only as a passive store house of energy and not much was known about the cytokinetic activity of these cells. It's only of late that a medical science have explored the overwhelming functions, complex pathways, and profound effects of adiposity and related adipokines and its role in numerous pathophysiological functions. Nevertheless, much has to be investigated because of the magnanimous domain of obesity. In a world, where food scarcity is possessing a challenge to humankind at social, economic, and humanitarian levels having rising figures of obesity prevalence presents an equivalent thwarting situation.

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