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Obesity a multifactorial medical problem, presentation to treatment: A Systematic Review.

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ABSTRACT… OBJECTIVE: The aim of the current article is to critically review the current literature on the presentation and treatment of obesity as it is one of the major health concerns, that can affect the metabolism of an individual by causing some of the most serious and devastating medical complications. **Results:** It affects the quality of normal human body function. During the process of aging, it causes weakness in overweight and obese individuals. Environment, diet, genetics, maternal factors are some of the major causes involved in the progression of obesity. A number of genes involved in metabolism, adipogenesis, and lipolysis have a proven role in weight gain. Obesity is associated with various diseases such as type II diabetes, cardiovascular disorder, metabolic abnormalities, cancer, cataract, and Urinary Incontinence, etc. Treatment of obesity is important, but treatments under consideration are controversial as obesity causes health risks related to the increased body mass and weight loss in the older population. **Conclusion:** Moreover, the therapies involved in weight loss have to keep an eye on the side effects of instant weight loss for the human body.

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INTRODUCTION

Now a day individuals living in an industrialized world, have one of the most prevalent condition, increasing quickly is obesity. Biology of obesity is quite complex as it is under the influence of multiple factors i-e roles of genes, climate, environment, diet, living style and their combined effects.[1] The gain or increase in fat of the body is known as obesity. On the basis of different studies, obesity is defined primarily as an increase in the weight and circumference of waist. Such parameters provide knowledge about the degree and stage of obesity. A person is considered as obese if the BMI of a person is 30 kg/m^2 and overweight if Body Mass Index is equal or higher that 25 kg/m^2 according to World health organization. There are a lot of other means cited in literature to define obesity. Fat distribution with reference to "waist to hip ratio" is recorded as obesity.[2] One third of the US and 10-25 percent of the European population is affected by Obesity, this number is increasing continuously. It is estimated that, in the United States, every year there are more than 0.3 million deaths are reported due to obesity. Poor diet including low nutrient, but maximum caloric diet and less physical activity are some of the risk factors for obesity. It also results in several medical conditions such as heredity diseases, age, gender, endocrine imbalance and genetic alterations.[3] In both male and female, effect of obesity and overweight with increasing age is different in different regions such as Africans and American population; this rate is higher but relatively lowers in Asian population. It is highly frequent in women and peoples with low socioeconomic status. Another factor that causes increase in weight is the diet and exercise behaviors that result in obesity related diseases. Malnutrition, premature death, birth defects, malignancies, CVD, thrombosis, diabetes, depression, infertility, chronic venous insufficiency, renal disorder, gout, loss of immunity and respiratory efficiency, fatty liver, arthritis, loss of sleep and stroke are some of medical disorders that are linked to obesity.[4]

Prevalence of Obesity

Over the past few decades, the increased obesity incidence has been observed in different age groups. By comparing the results of obesity in the US, during the late 20th century and in the start of the 21st century, almost 10 years incidence of obesity has been increased in different age group. Statistics from different population surveys showed that the probability of being obese increases during the age of 20 to 60 years and then declines later. Older people like 80 years of age are less prone to it. The reason behind this low rate of obesity in these people is the benefit of being lean as the probability of obesity decreases after 60 years of age.[5] National statistics of obesity in male and female is shown in Table-I.

Pathogenesis

Energy intake and utilization are the parameters that are involved in the determination of FM (fat mass). There are two important parameters that are involved in the increase of total fat mass i-e an elevated intake of energy as well as decline in total energy expenditure. Most of the studies revealed that age has no particular effect on energy intake with aging, so it is an indirect change in the overall energy expenditure that declines with age and results in increased body fat mass.[6]

Fat accumulation, free fat mass reduction and energy imbalance are enhanced by the hormonal changes induced by aging. Decreased GH (growth hormone) secretion, reduced sensitivity for TH (thyroid hormone), leptin resistance and less serum testosterone are associated with aging. Leptin resistance results in increased appetite while TH causes oxidative bursts. With increasing age decrease in the production of GH and testosterone results in the accumulation of fat mass and reduction of free fat mass.[7]

Genes and Obesity

There are hundreds of genetic diverse regions and positive natural selection regions in the human genome. Alteration in diet, communicable diseases and adaptations are the reasons for certain positive mutations in human body. Sometimes obesity occurs due to the mutation in a single gene for example MC4R gene that encodes for Melanocortin 4 receptor present at 18q22. A mutation in MC4R results in loss of its function is present in prevalence of <5% in obese persons. Children affected by this mutation feel extreme hunger and become obese due to overeating habit.[8] Following are the major genes involved in regulation with obesity as in Table-II.

States	Age Ranges	Overall Obesity Prevalence	
		Men	Women
Albania (1986)	≥25	22.8	35.6
Pakistan (2004)	18-65	25	70
Pakistan (2014)	20-60	34	60
Bahrain (1998-99)	19+	23	34
Brazil (1996)	≥20	8.4	12
Canada (2000-01)	20-64	16	14
Chile (1988)	≥15	13.3	22.9
Chile (2001)	24-64	15.7	23.1
China (1990-2000)	20+	2	4
China(1984)	18-49	15.3	17.1
Cook Islands (1998)	17+	41	50
Cuba (1996)	20-59	5.1	12.2
Denmark (1982)	30-60	10	9
Denmark (1994)	16+	9	-
Egypt (1998-99)	18-60	13	33
Fiji (1993)	18+	7	21
French Polynesia (1995)	16+	36	44
Germany (1998)	18-79	19	22
Ghana (1987-89)	20-65	1	6
India (1990-91)	≥15	4.8	7.8
India (1998)	18+	0.3	0.5
Iran (1999)	15+	6	14
Ireland (1997-99)	18–64	20	16
Japan (2001)	15+	3	3
Kuwait (1980-81)	18+	15	30
Kuwait (1998-2000)	18+	28	30
Latvia (1997)	19–64	10	17
Lesotho (1993)	20-65	-	23
Lithuania (1999)	20-64	16.2	16
Morocco (1998-99)	18+	4	16
Nauru (1994)	25-69	80	79
Norway (1994)	16–79	5	6
Peru (1987)	≥18	16	22.7
Philippines (1998)	20+	2	4
Russian Federation (1993)	19-55	10.3	21.7
Samoa (2000)	25-74	48.7	68
Saudi Arabia (1987-92)	18+	16	26
Saudi Arabia (1995)	18+	13	20
Singapore (1998)	18-69	5	7
South Africa (1998)	15+	9	30
Sweden (1996-97)	16–84	7	7
USA (1999-2002)	16+	26	32
Vanuatu (1998)	20+	12	20

Table-I. Global, national statistics of obesity, according to gender from recent surveys[5]

Gene Abb.	Locus	Gene Type	Function
ADIPOQ	3q27.3	Protein Coding	Involved in Hormonal and metabolic processes.
BMIQ-1	7q32.3	Unknown	_ _ _ _ _
BMIQ-2	13q14	Unknown	_ _ _ _ _
BMIQ-3	6q23-25	Unknown	_ _ _ _ _
BMIQ-4	11q24	Unknown	_ _ _ _ _
BMIQ-5	16p13	Unknown	_ _ _ _ _
BMIQ-6	20pter-p11.2	Unknown	_ _ _ _ _
TMEM-18	2p25.3	Protein Coding	Sequence specific dsDNA and ssDNA binding protein.
GNPDA-2	4p13	Protein Coding	Convert glucosamine-6-P into fructose-6-P and Ammonium. Variations result in altered BMI and Obesity.
NEGR-1	1p31.1	Protein Coding	Involved in cell adhesion pathway. Variations results in Obesity andPodoconiosis.
BDNF	11p13	Protein Coding	Involved in CREB pathway and p70S6K signaling.
KCTD-15	19q13.12	Protein Coding	Involved in Signaling of Sweet Taste and Hepatic ABC Transporters. Variations results in Obesity.
SH2B-1	16p11.2	Protein Coding	Activate various kinases, GFR and cytokine signaling.
MTCH-2	11p11.2	Protein Coding	Involved in differentiation of adipocytes.
PCSK-1	5q15-21	Protein Coding	Involves in the hormonal proteolytic activation.
NPC-1	18q11-q12	Protein Coding	Involves in intracellular cholesterol trafficking
FTO	16q12.2	Protein Coding	Involves in improved food intake.
LEP	7q32.1	Protein Coding	Synthesized by fat cells.
LEPR	1p31.3	Protein Coding	Inhibits appetite when leptin binds.
INSIG-2	2q14.1-q14.2	Protein Coding	Biosynthesis of Fatty acid and cholesterol regulation
MC4R	18q22	Protein Coding	Stimulation of Hormones and hunger.
PCSK-1	5q15	Protein Coding	Insulin regulation.
PPARg	3p25.2	Protein Coding	Lipid uptake and Fat tissue formation
Table-II. Location and Functional description of genes associated with obesity			

Causes of Obesity

Though the mystery behind chubbiness is not yet clearly understood, but it is obvious that the person becomes obese when it stores the more energy than the required one. There are many studies regarding the imbalance in energy utilization, but we cannot define the main cause of the prevalence of obesity by a single result. There are many genetic as well as the epigenetic factors that influence the prevalence of obesity.[9] Under secretion of thyroid hormones and GH leads to the obesity in children. Leptin deficiency may also cause obesity in children.[10] Person's environment, culture, lifestyle, eating habits has a greater influence on chubbiness.

a) Genetics

Parsons and colleagues systematically reviewed the child's early life predictors of adulthood obesity. They also summarized the findings that how the phenotype is inherited. The authors concluded, that 'obesity is inherited, means the offspring's of those parents who were obese in their early adulthood, have more chances to get obese in their adulthood'. Recently it has been confirmed that a significant heritability component are associated with obesity these are the parent's height, BMI, total body fat and weight (kg or pounds).[11] Mothers' birth-weight is also an important consideration in relation to the offspring birth weight. Maes and collaborators, in their studies, suggested that variations in BMI up to 20-90% are due to inherited issues. Farooqi in his most recent studies investigated the heritability of BMI at around 40% to 70%.[12]

b) Maternal Factors

Huang and colleagues systematically reviewed; in their studies, they found a co-relation between pre gestational or gestational diabetes with the prevalence of obesity. A study by Highest also provides significant associated results. Many studies reported that the exposure of mother to smoking and childhood obesity are in direct association with obesity. It has been observed through many studies, along with the factors mentioned above; lack of nutrition during earlier pregnancy stages may cause the variations of the endocrine system in terms of structure and function.[13]

ADVERSE EFFECTS OF OBESITY

1) Mortality

The survival rate of an individual decreases due to obesity. Result from Framingham Heart Study reveals adults having Body Mass Index ≥ 30 lived 6-7 years less which are suffering from obesity compared with their normal aged person.[14] Similarly, there is another study, which concludes the different data sets; these are the NHANES (National Health & Nutritional Examination Survey) I, II and III. In younger adults due to overweight/obesity, there is decrease in life expectancy. For example, in white male and female population of 20 to 30 years, having BMI ≥45 life expectancy lost by 13 to 8 years respectively.

Male and female with a BMI ≥ 30 mostly have a high mortality risk and are considered obese than do those have a BMI: 25.0–29.9. Due to the increasing BMI in adulthood, death rate is relatively less, as compared to older age, concluding that increased BMI is more lethal during old age. There is a misrepresentation of the data as it indicates obesity is less dangerous in older than in younger.[15]

2) Risk Factors Associated with Obesity

Severe physiological issues as a result of obesity lead to serious problems, especially premature death of an organism. But most of the studies conducted on a middle aged group, reveals that diabetes, hypertension, cardiovascular disease, and osteoarthritis are some of medical complications that increase with time. Hence, different medical complications result from an increase in body weight during middle aged group.

a) Metabolic Abnormalities

Metabolic disorder components are more prevalent in older individuals like increase in abdominal fat, resistant to insulin, the metabolism of glucose, increase of high blood pressure. The incidence of metabolic syndrome is directly related to the age factor and rise periodically after 30 years of age with a peak during 50-70 years in male and during 60-80 years of age in female. According to the CDCP (Centers for Disease Control and Prevention) report in 1998, approximately type 2 diabetes is diagnosed in 12.7 % of the older population after the age of 70 years and there is an 11.6% increase in number since 1990.[16] In the older population, hypertension is more common after the age of 65 years, affecting approximately 30-50 % of all people. According to HHP (Honolulu Heart Program) and a survey of JDB (Japanese Data Bank) in older age, obesity is comparatively correlated with hyper blood pressure. In some studies even waist circumference was better than BMI in predicting hypertension.[17,18]

b) Arthritis

In the older population main cause of physical disability is Arthritis. Moreover, in older population increased risk of knee osteoarthritis (OA) is resulting from high BMI, as an increase in body weight occur more across knee as a result of increase in weight also, as a result of obesity OA increases by decades, supporting that obesity is the main cause of OA. OA after 65 years commonly occurs in female 68%, men 58% and its symptoms appear usually after age of 40 years. As a result of increase prevalence of OA it causes different changes in the body as its result in overweight of an affected person, which also causes lots of complications particularly on joints.[19]

c) Pulmonary Abnormalities

PFA (Pulmonary functional abnormality), OSA (obstructive sleep apnea), and OHS (obesity hypo-ventilation syndrome) all are associated with obesity as a result of increase weight on

chest wall causes respiratory problem difficulty in breathing. In obese men it results in sleep apnea related to weight gain. According to 5 year study data shows that in older, obese person there is rise in RDI (respiratory disturbance index).[20] An increase of 5% of BMI in 20 years of women leads to increase in 2% RDI and in there is increasing by 27% of RDI in older obese men of 60 years

d) Urinary Incontinence
After the age of 65 years >15–30% people are affected by urinary incontinence and obesity is the major cause of its increase mainly in older populations, and it is directly linked with high BMI.

e) Cataract
Cataracts affect 20% of persons aged. One group study of 40 – 84 years and second for 5-14 years shows that increased prevalence of cataract result due to overweight and obesity but the main cause is unknown that obesity is involved in early cataract as different abnormalities that basically result from obesity are involved in the cataracts formation. These abnormalities are elevated circulating inflammatory mediators, resistance to insulin and hyper uric acid.[21-22]

h) Cancer
Another cause of the complications resulting from obesity is cancer as obesity is linked to certain forms of malignancies/cancer are more prevalent in older populations, for example including bladder cancer, prostate cancers, colon, pancreatic malignancies, renal, breast, bladder, uterine and cervical cancer. According to recent data in old obese female ≥ 60 years with BMI ≥30 the frequency of breast cancer is higher than normal women.

i) Cardiovascular Complications
In the progression of cardiovascular disorder, obesity is one of the major risk factors reported worldwide. Individuals diagnosed as obese or overweight are more prone towards number of medical complications; those are directly in contrast with morbidity and mortality. Along with cardiovascular disorders, it is responsible for the development of coronary heart disease, dyslipdemia and hypertension. Obesity leads to the increase of overall energy and metabolic demands, which directly affects the blood volume and cardiac output.[23]

j) Type 2 Diabetes Mellitus
The relationship of type 2 diabetes and obesity is in contrast to each other as studies shown that obesity is particularly involved in the pathogenesis of diabetes, that is why the relationship between both disorders is termed as "Diabesity". Studies have revealed that about 3.6 billion individuals are diagnosed with type 2 diabetes and the ratio indicates that almost about 10% of adult individuals will be affected by 2030 globally. Approximately, 0.35 billion individual deaths are reported due to diabetes due to type 2 diabetes.[24] Both diabetes type 2 and obesity often coexist, and literature shows that about 60-90% of individuals are diagnosed with diabetes type 2 are obese.

Treatment
Weight loss during any age in obese persons can prevent the medical complications, life quality and physical health, but the major reason of therapy can vary across different age groups. In case of young ones and adults the major achievement in weight loss therapy is to prevent and treat the medical issue while improved life quality and physical health are the major achievements in old persons. Muscle and bone mass prevention is the major decider for the approach of therapy used to lose weight in adults and older ones. For weight loss and management current therapies are.

1) Lifestyle Intervention
Moderate weight loss can be achieved by combining effect of low calorie diet, more physical activity as well as by behavior therapy, which includes self-monitoring (paying closer attention to social system), goal setting (the process of deciding what you want to achieve or what you want someone else to achieve), social support (social relationships) and stimulus control. At the same time with all these things a person can also stay away from the associated risk of weight-loss treatments. Among all energy-deficient diet shrinks energy consumption from 500 to 100kcal/d, which leads to ≈400 – 900 gm/

wk weight-loss and in 6 months 8 −10% weight loss.

2) Pharmacotheraputic Techniques

Pharmacotherapy use under random treatments in most randomized controlled trial assessment is conducted for obesity omitted old peoples, other reports comprised few samples of old persons. According to the recent clinical studies, it has been observed that the normal age of persons (subjects) lies in between 34 to 54 years. So, the available data is not enough in older persons to define the efficiency and security of pharmacotherapy in case of obesity.[25] In obesity Pharmacological agent uses among older patients as a treatment can cause an extra burden among older persons. Sometime it happens many older individuals are also suffering from many other problems and taking medicines. So by using obesity pharmacological treatment there is a chance for non-adherence or errors with other medicines as well.[26]

3) Surgery

Most efficient treatments in case of weight loss therapy are Bariatric surgery. NIH Conference held in 1991 recommendations for Bariatric surgery was established. The team (panel) decided that people who have morbid obesity (means people of BMI 35.0 to 39.9 along with severe medical complication due to obesity, for example BMI≥40, CVD, diabetes (Type II), sleep apnea, or depression, there is a chance of success is considered potential for surgical treatment.

4) Drug Treatment

Treatment with the help of drug can alter the metabolism of the body; it can reduce the intake of food and increase energy consumption. This methodology is the use in accessible and effective drugs uses for the treatment.

4a) Food Intake Control

(i) Nor-Adrenergic Receptors

Neuropeptides and Monoamines are recognized as food up taking modulators. Serotonergic and Noradrenergic receptors together provide site for those drugs that are clinically suitable to decrease food intake. The α_1- and β_2-adrenoceptors activation is also responsible for decreasing food intake in body. On the other hand, in experiments conducted on animals there is the opposite action of α_2-adrenoceptor, it elevates body's food intake. When a substance and drug has direct agonist effect to release or block of reuptake norepinephrine (NE), results in activation of receptors where norepinephrine is present.[25]

(ii) Serotonin Receptor System

There are seven different families of serotonin receptor system; Feeding is directly affected by the stimulation of 5 HT_1 and $5HT_2$. Food intake is increased by the activation of the $5\text{-}HT_{1a}$ receptor, but it is certainly down regulated so it is not considered in body weight regulation. Classes HT1B and HT2C are involved in down regulation of signal that is involved in increased food intake.[26]

4b) Changes in Metabolism

Extra fat is used as an indication of obesity. In order to modify and absorbed fat mechanism there a few metabolic schemes that are related to absorption and post absorption processes. A pre absorptive process has a direct effect on digestion and macronutrients absorption used to develop orlistat, it prevents fat digestion and decreases weight.

4c) Elevated Energy Expenditure

More energy consumption by the help of exercise is an excellent way for dealing with obesity. As well as those medicines having the same effect like exercise are also good approach of treating obesity in pharmaceutical ways.

CONCLUSION

In the list of public health concerns obesity is one of the major health issue associated with multiple chronic diseases and disorders. Genetic variants that are involved in the person's susceptibility towards obesity are critical to identify as number of persons suffering from obesity are increasing noticeably. Therefore, it is the need of time to use weight loss therapies primarily to improve physical condition and function and secondly preventing and lifting the medical complications in obese persons. Also the consideration of

adverse effects related to weight loss therapies must be considered to prevent muscle and bone mass.

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