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Review Article

Obesity: a global health problem

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ABSTRACT

Since time immemorial, obesity has engulfed the mankind. It's a pandemic. The prevalence is increasing by leaps and bound. Evidences date back to 30,000 BC. Earlier it was linked to wealth and status and it took a long time for it to be considered as a disease. This change in mind-set of the people occurred in mid-19th century. Different formulas for calculating the BMI (Body Mass Index) were invented which was different for the world and the South-East Asians. Slowly it became a topic for research among the scientific society and first priority was given to finding out the cause of obesity. It could not be pointed down to one as many factors were found to contribute to the menace of obesity. Age, gender, genetics, environment, food habits, various co-morbid conditions and the list of contributing factors is endless. Studies done at the molecular level have shown that various cytokines like TNF, Interleukins, Monocyte Chemoattractant Protein, adipokines, etc., have been implicated in the pathogenesis of obesity. The first line in the management of obesity is to take preventive measure. Those who have started to develop the disease should undergo a few non-pharmacological treatment options like lifestyle modification, change in food habits and behavioural therapy. Initially drugs like fenfluramine and sibrutramine were developed. With newer researches coming up more safer and consistent molecules like Tesofensin have been found and undergoing trial. If not benefited by medical treatment the last option what remains for the patient is bariatric surgery but they are too costly for general population to afford. Finally, it is best seen that it is wise enough to follow the saying "Prevention is better than cure" for a disease with such a vast etiology.

Keywords: BMI, Lifestyle, Anorectic drugs, Bariatric surgery

INTRODUCTION

Obesity is defined as a medical condition in which excess body fat has accumulated to the extent that it may have a negative effect on health.[1] It is not just a cosmetic concern but a root cause of many diseases affecting from head to toe important ones being the diseases of cardiovascular system, type 2 diabetes mellitus, obstructive sleep apnoea, certain cancers, osteoarthritis and depression.[2,3] It's prevalence has nearly tripled since 1975. Currently 13% of the world's adult population i.e. 650 million are obese.[4] To this figure India alone contributes about 192 million which is almost 30%. Scientists have identified a Single Nucleotide Polymorphism (SNP) named rs12970134 having high prevalence in people of Indian origin.[5] This SNP is associated with waist circumference.[4] Thus, due to this genetic susceptibility obese for Indians has been set at Body Mass Index (BMI) >25 kg/m^2. The World Watch Institute quoted in the year 2000 that "For the first time in human history, the number of overweight people rivals the number of underweight people. While the world's underfed population has decreased slightly since 1980 to 1.1 billion, the number of overweight people has surged to 1.1 billion".

HISTORY OF OBESITY

Obesity arises from the Latin word "*obesitas*" which means "stout, fat or plump". "*Ēsus*" is the past particle of edere (to eat) with "*ob*" (over) being added to it.[6] It's first usage was by Randle Cotgrave in 1611. Some 30,000 years ago prehistoric statuettes including the famous "Venus of Willendorf" depicted an abdominally obese female. It took a very long time for obesity to come up as a disease. In some cultures, obesity was linked to wealth and status. During Renaissance the upper class of society flaunted their large size which can be seen in the portrait of Henry VII of England and The Tuscan General Alessandro del Borro.[7] Since the beginning of 19th century perception regarding ideal bodyweight has changed. This is evident from the fact that average height of Miss America pageant winner increased by 2% from 1992-1999 while their weight has decreased by 12%.[8] But, the public moved in other direction. This was evident from the change in the mindset of people of Britain regarding the weight at which they considered themselves overweight which was significantly higher in 2007 than in 1999.[9] Point to be emphasized is that in today's era obesity is not only a problem statement for developed countries but also for low and middle income countries. The latter group faces a "double burden". Infectious diseases and under-nutrition are already crippling the health sector and over it now there is a upsurge of overweight and obesity which leads to increase in chronic diseases like coronary artery disease, diabetes, etc. It is interesting to find that under-nutrition and obesity exist side by side in the same country.

CLASSIFICATION OF OBESITY

Classifying obesity has always been a debatable topic. The most commonly used is the BMI. Developed in 19th century by Adolphe Quetlet today merely stands as an imprecise mathematical estimate[10]. BMI classifies general population into 5 categories: i) underweight (BMI <18.5 kg/m^2), ii) normal weight (18.5-24.5 kg/m^2), iii) class I obesity or overweight (25.0-29.9 kg/m^2), iv) class II obesity or obese (30.0-39.9 kg/m^2), v) class III obesity or extremely obese (>40 kg/m^2). These cut-offs are related to Caucasian population. For Indians, due to increased genetic susceptibility this classification has been altered to normal BMI as: 18.0-22.9 kg/m^2, overweight: 23.0-24.9 kg/m^2 and obesity: >25 kg/m^2. Current classification ignores several important factors like age, gender, etc., which affects the adiposity of a person. This formula basically gives an approximate idea of the relative quantity of adiposity thus helping to predict and evaluate disease risk in epidemiological studies, qualifying for a population level indicator of obesity.[10] Talking about adipocytes, they have got both endocrinal and inflammatory properties. So, it has become necessary to classify obesity on the basis of body fat composition and distribution. For body fat distribution or Peripheral Body Fat (PBF), waist circumference (WC) or the waist-hip ratio has been used. WC singly or in conjunction with BMI is a better predictor of obesity related health risk than BMI alone.[11] Classifying different phenotypes of obese individuals we have: i) normal weight obese (NWO), ii) metabolically obese normal weight, iii) metabolically healthy obese and iv) metabolically unhealthy obese or "at risk obese". This classification is best achieved by measurement of the PBF by MRI, computed tomography, DEXA-scan, bioimpedence analysis, total body water or hydrometry and skin fold thickness.[10]

CAUSES OF OBESITY

Coming to as what causes obesity. In simple words it is the imbalance between total calories consumed and expended. It's not about how much we eat, it's about what we eat. This is explained by the fact that obesity affects both poor as well as rich. Poor people are malnourished as they don't have enough to feed themselves yet a few become obese because they eat poorly which leads to calorie imbalance. Rich people are obese because they consume more than required. There are various risk factors for obesity: i) genetic factors as in case of Prader-Willi syndrome, ii) family history dictated by the food regularly consumed in the family, iii) age as with advancing age people become less active, iv) gender because female sex has more body fat as compared to male in their natural built, v) calorie consumption, which depends on our food habit, vi) environment, vii) Medications, viii) eating disorders, ix) lack of exercise, x) diseases like hypothyroidism, xi) high glycemic diet, xii) stress, xiii) insufficient sleep.

Interestingly, not everyone taking a high calorie diet becomes obese. This suggests a genetic mechanism which is responsible for this difference. There are reports suggesting 40-70% heritability of high BMI.[12] Though rare forms of monogenic obesity have been found including leptin and melanocortin4-receptor deficiency, studies are going on for the search of SNP associated with BMI.[13] When there is surplus amount of food available for long time there is fat storage and this results in obesity. Fatty acids are stored in adipocytes as triglycerides (TG) but when the storage capacity exceeds, these fatty acids are poured into the vasculature thus inciting an oxidative stress. They also inhibit lipogenesis which leads to inadequate use of TG thus leading to hypertriglyceridemia. Thus, the pathophysiology of obesity revolves around the adipocytes and also the various adipokines they secrete.

PATHOPHYSIOLOGY

"Adipocytes" the fat cells of the body are the energy reserve tanks which are required at the time of starvation or prolonged fasting. A total of 1 billion adipocytes are present in the body. With such a huge number it also becomes the largest endocrine gland of the body. It releases lectin, adiponectin, visfastin, inflammatory cytokines like TNF-α, IL-1, IL-6, anti-inflammatory

cytokines like TNF-β, IL-10, growth factors, complement proteins, rennin, angiotensin, C-reactive proteins.[14,15] Along with insulin it regulates the body fat mass. It is basically the white adipose tissue which releases these protohormones. Point to be noted is that the visceral fat is the one which is endocrinologically most active.[16] The buttocks fat is very inert and largely serves the function of long term energy reserve.[17] These visceral fat release pro-inflammatory cytokines which are responsible for all the co-morbid conditions associated with obesity. Adipocytes stimulate fat associated macrophage which secrete monocyte chemoattractant protein 1 (MCP-1), macrophage migration inhibiting factor (MMIF), and resistin, all of which decrease insulin sensitivity (i.e, enhance insulin resistance).[18-20] Also, the inflammatory cytokines destroy the pancreatic β-cells leading to decrease in insulin synthesis. This leads to development of diabetes in obese people much faster than the general population. Similarly, development of non alcoholic steatohepatitis is attributable to release of inflammatory cytokines into the portal circulation which initiates the inflammatory cascade in the hepatocytes. The rennin, angiotensin when secreted from their physiological sources increase the vasomotor tone but when secreted by adipocytes (specially peri-vascular) it leads to hypertension as it is not physiological.[18] Also the inflammatory cytokines along with the growth factors contribute to the increased atherogenicity of the vessels. Inflammation occurs leading to endothelial injury. This attracts the macrophages (due to increased MCP-1) followed by formation of foam cells. Normally our body ensures that lipolysis occurs but both endothelial and adipose cell lipoprotein lipase activity are also decreased by inflammatory cytokines such as IL-6.[21-23] Thus by inhibiting lipolysis they increase serum triacylglycerol levels which accentuates hyper-triglyceridemia. Plasminogen activator inhibitor-1, IL-6, tumor growth factor-β, and TNF-α are other adipokine procoagulants secreted which cause thrombosis, particularly from ruptured atherosclerotic plaques. As the atherosclerosis progresses plaque formation and remodelling of collagen results from the action of matrix metalloproteinases also secreted by adipocytes causing atheroma cap thinning and plaque rupture.[24] This precipitates release of the tissue factor further promoting intravascular thrombosis.

Just opposite to these hormones adipocytes secretes anti-inflammatory hormones like adiponectin, visfastin, complement proteins which have both anti-inflammatory and anti-atherogenetic property. They concomitantly enhance insulin sensitivity and improve vascular endothelium dysfunction. This effect is evident when these anti-inflammatory adipokines become deficient due to decreasing level of adiponectin with increasing obesity.[14]

MANAGEMENT OF OBESITY

The old saying "Prevention is better than cure" hold perfect for obesity. The only way to achieve this is by balancing the energy expenditure and following a healthy lifestyle. The three main types of preventions were described by the Institute Of Medicine for mental disorder can be applied for obesity also.[25] They are- "Universal prevention" which is applicable to everyone in the eligible population, "Selective prevention" applicable to subgroup of population who have higher chance than the general population to develop obesity and the last is "Indicated prevention" directed towards those who have minimal but detectable amount of obesity. Universal prevention is achieved by preventive education and ideas targeted towards individuals like nutritional values and importance of exercise so that the unaffected population can avoid the negative consequences. These when applied selectively to high risk group becomes a selective prevention. Indicative prevention acts as an early intervention. This includes lifestyle modification, change in food habits and behavioural therapy to those in the category of overweight.

TREATMENT

Treatment of obesity stands on five pillars of dieting, exercise, weight loss programme, medications and surgery. Meta-analysis of various types of diet which included- low fat diet, low carbohydrate diet and low calories diet showed same amount of weight loss of approximately 2-4 kgs.[26] As such there is no best weight loss diet. We need to make healthier choices by eating more plant based food like fruits, vegetables and whole grain carbohydrates. Energy dense food such as desserts, candies and fat processed food should be avoided. Very low calories diet (200-800 kcal/day), crash diet, fad diets may look tempting by causing 1.5-2.5 kgwt loss per week but one should wary of these quick fixes as they have very short term outcome and the chances of gout and electrolyte imbalance increases.

The American Heart Association recommends a minimum of 30 minutes of moderate exercise or brisk walk at least 5 days a week. This helps in weight loss as exercise and brisk walking shifts to greater use of fat as a fuel. A five months of basic military training with no dietary restrictions resulted in weight loss of 12.5 kgs in recruits.[27] A pedometer has been shown to have a positive effect which keeps a person motivated. Exercises like walking, cycling, running are very effective as big muscles of leg are involved which consume energy derived from glycogen and fat. The most perfect example of a weight loss programme is seen to be implemented by Chinese government in the form of "fat farms" and enforced a law that every student is required to go for sports activity at school for minimum one hour daily. Coming to pharmacotherapy, it is indicated in people who have BMI >30 kg/m^2 or 27-29 kg/m^2 if there are other risk factors.[28] The drugs basically act by decreasing appetite, increasing satiety or decreasing calorie absorption. The first drug to be approved by FDA was methamphetamine in 1947 which was an appetite suppressant but was withdrawn due to epidemic of

amphetamine misuse. This was followed by introduction and removal of Fenfluramine in 1997 (a serotonergic drug) which decreased appetite but damaged heart valves. The drug sibutramine a potent inhibitor of serotonin and norepinephrine reuptake was also removed because of concerns about an increased risk of heart attacks and strokes. Rimonabant, which was a selective cannabinoid receptor CB-1 antagonist blocking hunger promoting action of cannabis was also withdrawn from the market due to psychiatric side effects. Currently the approved drugs include Orlistat, which acts by inhibiting gastric and pancreatic lipase and interfering with absorption of dietary triglycerides. Another drug is lorcaserin which acts by activating selective $5HT_{2C}$ receptor in pro-opiomelanocortin neurons located in the hypothalamus. This promotes satiety. Next drug is Phentemine which stimulates the release of norepinephrine, and to a lesser extent serotonin (5-HT, 5-hydroxytryptamine) and dopamine from nerve terminals which stimulates the hypothalamus and decreases the appetite. It is marketed in combination with topiramate. Lately, in September 2014 a sustained release combination of Bupropion and Naltrexone was approved for weight loss in USA and subsequently UK. Anti-diabetic medications like Metformin and GLP-1 analogues like Liraglutide have also shown to contribute to weight loss in diabetics and so is being tried in obese people. New drugs which are still undergoing clinical trials are: Tesofensine (NS2330) is a serotonin–noradrenaline–dopamine reuptake inhibitor from the phenyltropane family of drugs which has currently finished it's phase 1 and 2 of trial and phase 3 to be completed in 2018.[29] Despite having these many options physicians currently prescribe very less of these medications due to the fear of rebound obesity after leaving the drug or having to continue for lifetime. Last option people go for is bariatric surgery. They include: i) gastric bypass surgery**:** in this, surgeon creates a small pouch at the top of your stomach following which small intestine is cut a short distance below the main stomach and connected to the new pouch. Now the diet flows directly from the pouch into this part of the intestine, bypassing most of the stomach. ii) laparoscopic adjustable gastric banding (lagb)**:** in this procedure, stomach is separated into two pouches using an inflatable band. By pulling the band tight surgeon creates a small passage between the two pouches. It prevents the opening from expanding and stays in that place permanently. iii) biliopancreatic diversion with duodenal switch: here surgeon removes a large part of the stomach leaving the valve that releases food into the duodenum. Now, the middle section of the intestine is closed and the last part of intestine is directly to the duodenum. The separate section of intestine is re-anastomosed with the last part so that digestive juices flow into this part of the intestine. iv) gastric sleeve: it is a simple procedure in which a part of the stomach is removed, creating a smaller reservoir for food. It's a less complicated surgery than gastric bypass or biliopancreatic diversion with duodenal switch.[30]

The sad part of these five ways to treat obesity is that only a few people for whom these are indicated actually receive them. This happens due to many reasons like inadequate training of physicians regarding recognition of obesity in it's early phases and initiating the treatment, lack of effectiveness and sustained effort in the lifestyle modification programmes. Also, there is very less referral or self consultation of patients with severe obesity to experienced surgeons due to the fear of surgery, even though bariatric surgery is a level A health-improving treatment option (i.e., with improvement based on data from multiple randomized trials or meta-analyses).[31]

CONCLUSION

Obesity is one of the greatest challenges for today's population. As a practitioner we cannot manage all the pathophysiology leading to obesity instead an equal effort has to be taken from the affected population to achieve the desired goal. Also, the unaffected population should recognize the epidemic and avoid being a part of it by taking the preventive measures as discussed here.

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