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A REVIEW ON OBESITY

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Abstract:
The accumulation of excess body fat causes obesity, a complicated multifactorial disease with detrimental effects on health. The rate of obesity is still rising, leading to an unparalleled crisis that doesn't appear to be abating anytime soon. Elevated body mass index (BMI) is associated with a significant reduction in life expectancy and quality of life due to its role as a risk factor for noncommunicable diseases such diabetes, cardiovascular diseases, and musculoskeletal problems. Long-term energy imbalance between calories taken and calories burned is the primary cause of obesity. Here, we examine the molecular underpinnings of obesity in an effort to offer practical therapeutic approaches for achieving a healthy body weight through both nature and nurture.

KEYWORDS:

Obesity,genetics,modifiable,genetics,causes,pathophysiologyIntroduction

INTRODUCTION:

Now a days obesity is a major problem in all overall world. It is a multifactorial disease, accumulation of excess of adipose tissue in the body resulting to various causes. increased BMI >25.0-29.9 leads to other diseases like diabetes mellitus(T2DM),cardiovascular disease, hyperglycaemia ,musculoskeletal disorders ,CANCERS and also decreased quality of a life.(1)

CAUSES

Obesity or overweight is result of imbalance between how much calorie intake and how much calorie expenditure in an individual and is generally calculated by through BMI (kg/m2).(2)
It is described in two factors
Modifiable and non-modifiable factors Obesity factors

Non-modifiable	Modifiable
Genetic	Lack of exercise
Monogenic	Excess calorie intake
Polygenic	Hormones
Syndromic	Sleep disturbances
	Drugs
	Diseases
	Stress

Nonmodifiable factors:

Over the past 20 years, a number of studies on genetic obesity have revealed that variations in gene expression—the process by which information encoded in a gene is translated into a function—polymorphisms—normal variation in a DNA sequence that is common in the population—and genetic mutations—abnormal changes in DNA sequence—all contribute to an individual's susceptibility to obesity. At first, certain genes were found to be pathogenic for severe early-onset obesity or monogenic (rare) obesity by candidate gene studies, which examine the genetic variation linked to disease in particular genes .(2) Later, other genes were discovered by genome-wide association studies (GWAS), which aid in the discovery of new genes linked to specific disorders.

Genetic obesity comes in three flavors: syndromic, polygenic, and monogenic. Monogenic obesity is an uncommon but serious kind of obesity caused by a mutation or lack of a single gene. It happens when one of the genes connected to the leptin-melanocortin pathway is mutated . Early-onset obesity (beginning at age 3–5) and hyperphagia, or insatiable appetite, are typical characteristics of monogenic obesity. Multiple gene variations present at the same time can lead to polygenic obesity because of their cumulative effect. This kind of genetic obesity is linked to multiple genes. Syndromic obesity, on the other hand, is linked to additional indicators of a developmental abnormality and may or may not be accompanied by a congenital malformation syndrome. Typical symptoms include dysmorphic characteristics and organ abnormalities.(3)

Through the use of GWAS, researchers were able to determine that an individual's susceptibility to common or polygenic obesity is caused by the accumulation of gene variations. The genes that were shown to be more prevalent in obese people were then evaluated for their potential correlation with body mass index (BMI), body fat percentage, and other characteristics of body composition, including fat free mass (15, 16, and 30 percent), circulating leptin levels, and leptin receptor (LEPR) levels. These investigations proved that epigenetics has a part in obesity.(3)

1.Melanocortin-leptin pathway

The majority of studies on hereditary obesity have shown that genes expressed primarily in the leptin–melanocortin circuit in the hypothalamus play a critical role in obesity and that this circuit is essential for regulating appetite.(4) The hormone leptin, which controls appetite and is released by fat cells, is released into the bloodstream at amounts according to fat mass.(5) Similar to insulin resistance, obesity causes an excess of leptin to be secreted, which ultimately results in leptin resistance. The signal for satiety is not received when leptin-resistant hypothalamic cells develop, which keeps the person hungry. After eating, leptin levels rise. Leptin levels fall during periods of fasting.

LEPR is expressed in various parts of the central nervous system and is activated by leptin.(6) A gouti-related protein (AGRP) and pro-opiomelanocortin (POMC) are the two types of neurons that express LEPRb, an isoform of the leptin receptor, in the arcuate nucleus of the hypothalamus. These neurons are important players in the melanocortin pathway(7)37. Melanocortin, which signals a reduction in food intake, is transferred from POMC neurons in the arcuate nucleus to melanocortin-4 receptor (MC4R) neurons in the paraventricular nucleus.(6) On the other hand, MC4R neurons are stimulated to increase food intake by AGRP neurons.(7, 8)38 Eating behavior is shown to be regulated by the interaction of these two types of neurons in balance.(8)

Obesity at the hypothalamus

Other uncommon causes of non-genetic obesity, best characterized as hypothalamic obesity, are associated with the leptin–melanocortin pathway. Lesional hypothalamic obesity can be caused by either anatomical alteration of the hypothalamus, as is the case with cancers involving the cranium, such as gliomas, craniopharyngiomas, or other malignancies involving the hypothalamus. Hypothalamic obesity can also occur from diseases affecting the hypothalamus, such as neurosarcoidosis, TB, and Langerhans cell histiocytosis, as well as from the treatment of such tumours with surgery and radiotherapy. Quick Initiation of Hypoventilation The hypothalamic autonomic disorder syndrome, or ROHHAD, is associated with positive anti-pituitary and anti-hypothalamic antibodies and is most likely autoimmune mediated. Quick Initiation of Hypoventilation One paraneoplastic illness that combines hypothalamic obesity with neuroendocrine tumors

(NETs) is called Hypothalamic Autonomic Disorder with Neuroendocrine Tumours (ROHHADNET) syndrome.(9)

MODIFIABLE FACTORS

Lack of exercise

Physical activity was found to reduce the risk of obesity in a study including 109,000 individuals from the UK Biobank. The association between physical activity and the genetic risk score for obesity was also examined. Despite only little exercise, those with higher genetic risk scores really benefited the most.(10) A World Health Organization assessment from 2016 found that 81% of teenagers and more than 28% of adults worldwide were physically inactive. There has been a decline in physical activity as passive forms of transportation have become more popular. Worldwide, lockdowns during the Covid19 outbreak have greatly lowered activity levels.(11)

Excess calorie intake:

Traditionally, the prevailing belief in the scientific study of obesity has been that it is only an imbalance in energy intake and expenditure—calories in, calories out. In other words, everyone should benefit from eating less and moving more if the energy-based model (EBM) of obesity is accurate. That isn't the case, though. A high-carb diet causes postprandial hyperinsulinemia, which causes the body to feel starved generally and cause a person to have a lower metabolic rate and feel more hungry. The high insulin level causes calories to be transferred into fat cells rather than lean tissues.(11)

It's interesting to note that Hall and colleagues contested this model in 2022,(12), arguing that EBM is a "more robust theory of obesity than CIM" and that the CIM is erroneous. According to their argument, the brain regulates body weight by a complex interplay of signals from the neurological system, endocrine system, and metabolism. These signals react to the body's inherent energy needs as well as external environmental factors. Hall et al. claim that fat tissue functions as an endocrine organ and that elevated food intake is directly linked to the release of leptin and other adipokines.(12)

In addition to the internal causes of obesity, we also need to acknowledge the external factors that contribute to the issue, such as the quick rise in fast-food chains, meal plans, larger drinks, and the accessibility of low-cost, highly processed food. It is also necessary to step back and consider why such a large portion of the global population now suffers from an energy balance disorder.

There are lots of possibilities to eat foods rich in calories these days. A few other factors are the decreased price of food and beverages, the increased promotion of food items, technological advancements (like better TV and computer screens, a wider selection of video games, and virtual reality simulators that promote sedentary behavior), a rise in the number of sedentary jobs, longer workdays, and easier access to food (convenience stores).

Hormones:

Now a day many are having hormonal imbalance due to their poor diet and changes in life style .our hunger and satiety signals are controlled by hormones, numerous factors from less common ones like genetic variations to more prevalent ones like stress and sleep deprivation, might interference with these regulatory systems. even when you don’t need any extra calories, harmones might make you crave food more and more. It may be difficult to know when to give up because of hormones so at last it causes weight gain and make yoy obese

sleep disturbances:

Neuroendocrine function and glucose metabolism are regulated by sleep. Sleep deprivation lowers leptin, insulin sensitivity, glucose intolerance, and cortisol levels while raising ghrelin and cortisol levels (and, consequently, hunger).(13)62 Both exercise and sleep are helpful to one another because, as recent studies have demonstrated, both improve sleep quality and physical activity levels are correlated with better sleep. Exercise has long been linked to better sleep quality.(14)63Additionally, one study discovered that by altering the effects of fat mass and obesity-associated gene (FTO) variations on BMI, a variation in the mean duration of sleep raised the risk of obesity.(15)64

Drugs :

Certain drugs causes weight gain which leads to obesity such as a anti depressants,steroids,anti-seizure,beta blockers etc

Diseases :

There are various ways in which medical disorders might lead to weight increase. For instance, an uncommon neuroendocrine tumor of the pancreas called an insulinoma, which is primarily benign, causes weight gain and hypoglycemia symptoms due to the tumor cells' excessive release of insulin. It may manifest independently or in conjunction with multiple endocrine neoplasia (MEN-1) syndrome. Insulinomas develop just 1-3 times per million annually, making them extremely uncommon.(16) Hormonal imbalances have been linked to obesity as well. For instance, weight gain results from the general metabolism slowing down due to hypothyroidism's lower thyroxine levels. Elevated serum cortisol levels lead to elevated serum insulin levels, which accelerate the synthesis of fat and glucose metabolism in Cushing's syndrome.
Additionally, a high cortisol level stimulates appetite and salt and sweet food desires. Patients with polycystic ovarian syndrome gain weight due to a similar process linked to increased insulin levels. The co-occurrence of hypertension, insulin resistance, impaired glucose tolerance, abdominal obesity, increased triglycerides, and low high-density lipoproteins is known as metabolic syndrome. In this syndrome, elevated insulin levels are the primary cause of weight gain. Gaining weight can cause airway restriction, sleep apnea, and disrupted sleep, often referred to as obstructive sleep apnea, especially around the neck. If untreated, this disease makes it more difficult to lose weight since a disrupted sleep cycle raises cortisol levels. Last but not least, oedema-producing illnesses such congestive heart failure and hypoproteinemia brought on by malabsorption or abnormal liver and renal function can result in general weight gain.

Psychological stress:

A study conducted on 2,983 persons from a Chicago, USA community revealed that a number of stressors raises the likelihood of obesity.(16) Additional research has shown that hereditary propensity and long-term psychological stress can interact to determine an individual's level of obesity. Stress leads to emotional/comfort eating and raises long-term glucocorticoid exposure, which promotes belly fat.

***Obesity Types (BMI Range*):**

Physicians use the Body Mass Index (BMI) to categorize different forms of obesity.
BMI is calculated by dividing weight (kg) by squared height (m).
Ideal weight ranges from 18.5 to 24.9 kg/m2. Weight gain = BMI 25–29.9 kg/m2 Over 30 kg/m2 is considered obese.

Types of Fatality:

obese types according to BMI
Based on BMI, obesity is classified into three categories. These are the following;
Weight for Class 1 Obesity: 30 to 35 kg/m2
Class 2 Obesity: 35–40 kg/m2 BMI
Class 3 Obesity is 40 kg/m2 or more.
Morbid or severe obesity are other names for class 3 obesity. Depending on where the fat is distributed, there are three types of obesity.

TYPES OF OBESITY ACCORDING TO THE LOCATION OF FAT IN THE BODY

PERIPHERAL OBESITY

Excessive fat deposition in the buttocks, thighs, and hips is known as peripheral obesity.

Central obesity

Excessive fat deposition in the abdomen is known as central obesity. It raises the risk of obesity-related conditions such diabetes, hypertension, heart disease, renal disease, and several types of cancer. Obesity by combination: The buildup of extra fat in both the central and peripheral areas.

OBESITY DETERMINED BY THE QUANTITY AND SIZE OF FAT CELLS

Based on the properties of fat cells, the following forms of obesity exist:
Hypertrophic obesity: The enlargement of adipose (fat) cells is the cause of this form of obesity. Adults are typically affected.
Obesity that is hyperplastic: This kind of obesity is brought on by an increase in fat cells. This kind is more common among young people.(17)

PATHOPHYSIOLOGY:

It is believed that prolonged positive energy balance—energy intake above energy expenditure—and the resetting of the body weight "set point" at an elevated amount are two separate but connected processes that contribute to the development of obesity. The difficulty in discovering efficacious treatments for obesity can be attributed to the second step. Research is starting to provide light on the mechanisms involved in this process, even if the underlying biology is still unknown.(18)

Numerous pathophysiological pathways may play a role in the development and maintenance of obesity on a biological level.(19) Until J. M. Friedman's lab found the leptin gene in 1994, this field of study had been virtually unexplored.(20) Despite being produced peripherally, leptin and ghrelin regulate appetite by acting on the central nervous system. They specifically affect the hypothalamus, a portion of the brain that is essential for controlling food intake and energy expenditure, along with other hormones linked to appetite. Although the melanocortin route is the most well-studied, the hypothalamus contains other circuits that are involved in regulating appetite.(19)The lateral hypothalamus (LH) and ventromedial hypothalamus (VMH), the brain's food and satiety regions, respectively, receive outputs from the hypothalamus' arcuate nucleus, which forms the first part of the circuit.(21)

There are two different neuronal groupings in the arcuate nucleus(19). The first group has stimulatory inputs to the LH and inhibitory inputs to the VMH. They also coexpress agouti-related peptide (AgRP) and neuropeptide Y (NPY). Pro-opiomelanocortin (POMC) and cocaine- and amphetam
ine-regulated transcript (CART) are coexpressed in the second group, which also has inhibitory inputs to the LH and stimulatory inputs to the VMH. Thus, while POMC/CART neurons increase satiety and inhibit feeding, NPY/AgRP neurons stimulate feeding and inhibit fullness. Leptin regulates both subsets of arcuate nucleus neurons. While elevating the POMC/CART group, leptin suppresses the NPY/AgRP group. Therefore, overeating is caused by a lack of leptin signaling, which can occur through leptin resistance or deficiency. This may also be the cause of some hereditary and acquired types of obesity.(19)

THERAPEUTICS OF OBESITY;

Modifications in behavior In the absence of targeted pharmaceutical therapies, "lifestyle modification" continues to be the mainstay of managing obesity (22). It is recommended that obese individuals lose at least 10% of their body weight through diet, exercise, and behavior therapy (or lifestyle change) (23). Consuming portion-controlled diets can result in significant short-term weight loss (24). High levels of physical exercise and ongoing patient-provider communication can lead to long-term weight control. A change in lifestyle frequently causes a considerable drop in body weight, which significantly lowers the risk of cardiovascular disease (25).

medications for weight loss If a person has a BMI of 30 or above (or a BMI of 27 with concomitant diseases), and they are not able to lose weight with lifestyle adjustment alone, pharmacotherapy is advised (26). Since Lorcaserin was withdrawn, only four drugs—Naltrexone-Bupropion (Contrave), Orlistat (Xenical, Alli), Liraglutide (Saxenda), and Phentermine-Topiramate (Qsymia)—as well as Gelesis, which is now the fifth—have been approved for the long term (27,28,29). By the end of 2020, the FDA also authorized the use of the MC4R agonist, setmelanotide, in patients with extreme obesity brought on by POMC, PCSK1 (proprotein convertase subtilisin/kexin type 1), or LEPR (leptin receptor) deficiency (30).

Bariatric surgery Bariatric surgery, often known as weight reduction surgery, is an additional option for those with a BMI of 40 or higher or BMI of 35 with comorbidities who are not able to reduce their weight by medication or lifestyle changes (26). Individuals' metabolic profiles benefit to varied degrees from standard bariatric surgeries, such as SG (sleeve gastrectomy), RYGB (roux-en-Y gastric bypass), AGB (adjustable gastric banding), and BPD (bilio-pancreatic diversion) (31). According to studies, bariatric surgery has advantages beyond weight loss. Bariatric surgery modifies the gut microbiome, biomarkers, and long-term remission for type 2 diabetes by reducing the chronic inflammation linked to obesity (32–33). Consider RYGB as an example. Following RYGB surgery, the overall microbial richness of the human stomach rose (34). Additional investigation showed that RYGB enhanced the expression of a few particular white adipose tissue genes. Subsequent investigation demonstrated that RYGB influenced the upregulation of genes essential to the transforming growth factor-β signaling pathway, the downregulation of genes implicated in metabolic pathways and inflammatory responses, and the upregulation of some specific genes expressed in white adipose tissue (35). After bariatric surgery, serum leptin levels, which are linked to a lowered BMI, usually decrease. It's interesting to note that post-procedure weight loss was simpler for women with greater presurgical baseline leptin levels, whereas weight regain was easier for those with lower presurgical baseline levels. Although a patient's serum leptin level cannot predict the degree of surgical success, there is a

correlation between baseline levels and changes in body mass, BMI, and overall weight loss.(36)

Transplanting F ecal Microbiota

FMT has gained great study interest recently in the treatment of obesity (37). There are encouraging signs that the FMT of microorganisms from obese patients' healthy donors may have an impact on weight loss and maintenance. Ridaura et al. transplanted fecal slurries from human twins discordant for obesity into germ-free mice in a ground-breaking major study (38). While the mice with the microbiota of healthy individuals stayed thin, the mice with the microbiome of obese individuals effectively developed obesity. The human microbiomes were successfully injected, according to the sequencing results of mice's post-procedure stool samples, indicating the transfer of activities associated with the lean or obese microbial communities, respectively (38). Promising human investigations are also being attempted: Vrieze et al. found that transplanting taxa from slim donors improved insulin sensitivity and microbial diversity in adult males with diabetes who were obese (39). Butyrate-producing bacteria and Bacteroidetes were found to be more prevalent, which suggests a shift in the microbial community toward one that is associated with a slimmer phenotype. FMT is a potential replacement for obesogenic microbial communities, but it is still in its early phases (40).

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