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A SHORT REVIEW ON OBESITY: INTRODUCTION, PATHOPHYSIOLOGY AND TREATMENT

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Abstract:

Obesity is a complex multifactorial disease that accumulated excess body fat leads to negative effects on health. Obesity continues to accelerate resulting in an unprecedented epidemic that shows no significant signs of slowing down any time soon. Raised body mass index (BMI) is a risk factor for noncommunicable diseases such as diabetes, cardiovascular diseases, and musculoskeletal disorders, resulting in dramatic decrease of life quality and expectancy. The main cause of obesity is long-term energy imbalance between consumed calories and expended calories. Here, we explore the biological mechanisms of obesity with the aim of providing actionable treatment strategies to achieve a healthy body weight from nature to nurture. This review summarizes the global trends in obesity with a special focus on the pathogenesis of obesity from genetic factors to epigenetic factors, from social environmental factors to microenvironment factors. Against this background, we discuss several possible intervention strategies to minimize BMI.

Keywords: *obesity,epidemiology, pathophysiology, genetics, epigenetics, microenvironment*

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INTRODUCTION:

Obesity has become an epidemic and worldwide problem. The prevalence of obesity in adults is estimated to be over 40% and is expected to increase further after the corona virus disease 2019 (COVID-19) pandemic. There are many risk factors, from low birth weight to aging, but lifestyle choices have always been the biggest contributor.[1]

Obesity has been associated with cardiovascular (CV) diseases, type-2 diabetes, immune dysfunction, arthritis, hypertension, stroke, hyperlipidemia, and cancer. The global burden of disease investigators showed that more than two-thirds deaths related to high BMI were due to CV disease. Once thought of as an illness of the industrialized countries, it is now known that due to the decreased nutritional value of low-cost food and lack of physical exercise obesity can affect both underdeveloped and developing countries. As obesity pandemic grows further it becomes more costly. It is projected that in 2030 medical costs associated with obesity - related diseases will increase to $ 48-66 billion/year in the United States.[2]

there are several therapeutic options to treat the diseases obesity is related to, agents that can solve the main problem are limited.

Treatment of obesity always starts with lifestyle changes. A healthier diet and a moderate exercise routine are a must in obesity treatment. However although randomized trials have shown > 8% decrease in weight in the first year, cumulative data shows that most patients cannot sustain this lifestyle and, more than half of the lost weight was regained within two years.

Anti obesity drugs are developed to help to patients who fail to lose weight with lifestyle measures, but these therapeutic options are limited.

Obesity is one of the medical disorder that is very easy to recognize and most difficult to treat. It is a chronic metabolic condition resulting from the imbalance between energy intake and energy expenditure where low physical activity, high fat diets and in adequate adjustment of energy intake are the culprits of the obesity.

Causes of obesity[3]

At individual level, the combination of excessive food energy intake and lack of physical activity is thought to explain most of obesity causes. In limited cases, obesity is due to genetic factors, medical reasons, or psychiatric illness. On the other hand, increasing rates of obesity at a societal level are felt to be due to easily accessible and palatable diet, increased reliance on cars, and mechanized manufacturing. A 2006 review identified ten other possible contributors to the recent increase of obesity including insufficient sleep, endocrine disruptors, decreased variability in ambient temperature, decreased rates of smoking, as smoking suppresses appetite, increased use of medications that can cause weight gain (e.g., atypical antipsychotics), proportional increases in ethnic and age groups that tend to be heavier, pregnancy at a later age (which may cause susceptibility to obesity in children), epigenetic risk factors passed on generationally, natural selection for higher BMI, and assortative mating leading to increased concentration of obesity risk factors.

Diet

Obesity rates in the US (1971–2000) increased from 14.5% to 30.9%.24 During the same period, there was an increase in the average amount of food consumed (average increase for women 335 and 168 cal./day). Most of this extra food energy was due to the increase in carbohydrates rather than fat consumption.[4]

Sedentary lifestyle

There is a large shift toward less physically demanding work worldwide. Currently, at least 60% of the world's population gets insufficient exercise, due to increased use of mechanized transportation and a greater prevalence of labor-saving technology at home. The WHO indicates people worldwide are taking up less active recreational pursuits. In both children and adults, there is an association between television viewing time and the risk of obesity.

Genetics

Like many other medical conditions, obesity is the result of interplay between genetic and environmental factors. Polymorphisms in various genes controlling appetite and metabolism predispose to obesity when sufficient food energy is present. People with two copies of the FTO gene (fat mass and obesity associated gene) have been found on average to weigh 3–4 kg more and have a 1.67 fold greater risk of obesity compared to those without the risk allele.

Medical and psychiatric illness

Certain physical and mental illnesses and medications used to treat them can increase the risk of obesity. Medical illnesses that increase obesity risk include several rare genetic syndrome (Cohen syndrome), as well as some congenital or acquired conditions: hypothyroidism, growth hormone deficiency, and

eating disorders (binge eating disorder and night eating syndrome). The risk of overweight and obesity is higher in patients with psychiatric disorders than in persons without psychiatric disorders.[5]

Social determinants

Genetic influences are important to understand obesity. They cannot explain the current dramatic increase in obesity. Though, excess energy consumption than energy expenditure leads to obesity on individual basis. In developing countries women of a high social class were less likely to be obese. Those who quit smoking will gain an average of 4.4 kg (men) and 5.0 kg (women) over ten years. However, changing rates of smoking have little effect on the overall rates of obesity.

Infectious agents

The study of infectious agent's effect on metabolism is still in its early stages. The gut flora in obese and lean individuals can affect the metabolic potential. This apparent alteration is believed to confer a greater capacity to gain energy contributing to obesity. An association between viruses and obesity has been found in humans and several different animal species.[6]

SYMPTOMS OF OBESITY IN ADULTS

The American Medical Association considers obesity itself a disease that needs to be diagnosed and treated. That's due to symptoms and complications that are common among people with obesity.

Common symptoms of obesity in adults include:

- Excess body fat, particularly around the waist
- Shortness of breath
- Sweating more than usual
- Snoring
- Trouble sleeping
- Skin problems from moisture accumulating in the folds
- Inability to perform simple physical tasks you could easily perform before weight gain
- Fatigue, which can range from mild to extreme
- Pain, especially in the back and joints
- Psychological issues such as negative self-esteem, depression, shame, and social isolation.

SYMPTOMS OF OBESITY IN CHILDREN

The CDC says the rate of childhood obesity in the U.S. has tripled in the last 50 years.[6] In 2020, nearly 20% of American children and adolescents (ages 2 to 19) were considered to have obesity.[7]

Common childhood obesity symptoms may include:[8]

- Fatty tissue deposits (may be noticeable in the breast area)
- Stretch marks on the hips and back
- Acanthosis nigricans (dark velvety skin around the neck and other areas)
- Shortness of breath with physical activity
- Sleep apnea
- Constipation
- Gastroesophageal reflux disease (GERD)
- Low self-esteem
- Early puberty in biological females/delayed puberty in biological males
- Orthopedic problems, such as flat feet or dislocated hips[10]

RISK FACTORS FOR OVER WEIGHT AND OBESITY:

- Type 2 diabetes[11]
- High blood pressure
- Heart disease
- Stroke
- Metabolic syndrome
- Fatty liver disease
- Some cancers
- Breathing problem
- Osteoarthritis
- Gout
- Disease of the gallbladder and pancreas
- Kidney diseases
- Pregnancy problems
- Fertility problems
- Sexual function problems
- Mental health problems

Type 2 diabetes

Type 2diabetes is a disease that occurs when your blood glucose, also called blood sugar, is too high. Nearly 9 in 10 people with type 2 diabetes have overweight or obesity.[12] Overtime, high blood glucose can lead to heart disease, stroke, kidney disease eye problem, nerve damage and other health problems.

High blood pressure

Overweight and obesity may raise your risk for high blood pressure. High blood pressure also called hypertension, is a condition in which blood flows through your blood vessels with a force greater than normal. High blood pressure can strain your heart, damage blood vessels, and raise your risk of Heart attack, stroke, Kidney disease, and death.

Heart Disease

Heart disease is a term used to describe several health problems that affect your heart, such as a heart attack, angina or an abnormal heart rhythm. Having overweight or obesity increases your risk of developing conditions that can lead to heart disease, such as high blood pressure, high blood cholesterol and high blood glucose.

Metabolic syndrome

Metabolic syndrome is a group of conditions that increase your risk for heart disease, diabetes, and stroke. To be diagnosed with metabolic syndrome, you must have at least three of the following conditions

- Large waist size
- high level of triglycerides in your blood
- high blood pressure
- high level of blood glucose when fasting
- low level of HDL cholesterol —the "good" cholesterol—in your blood.[13]

Fatty liver diseases

Fatty liver diseases develop when fat builds up in your liver, which can lead to severe liver damage, cirrhosis, or even liver failure. These diseases include nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). NAFLD and NASH most often affect people who have overweight or obesity.

Some cancers

Cancer is a collection of related diseases. In all types of cancer, some of the body's cells begin to grow abnormally or out of control. The cancerous cells sometimes spread to other parts of the body.

Osteoarthritis

Osteoarthritis*NIH* is a common, long-lasting health problem that causes pain, swelling, stiffness, and reduced motion in your joints .Obesity is a leading risk factor for osteoarthritis in the knees, hips, and ankles.

Having overweight or obesity may raise your risk of getting osteoarthritis by putting extra pressure on your joints and cartilage. If you have excess body fat, your blood may have higher levels of substances that cause inflammation. Inflamed joints may raise your risk for osteoarthritis.

PATHOPHYSIOLOGY

The pathogenesis of obesity involves regulation of calorie utilization , appetite ,and physical activity, but have complex interactions with availability of health-care systems , the role of socioeconomic status, and underlying hereditary and environmental factors.[14]

Food Intake and Energy Balance

The essential causes of obesity remain somewhat controversial, Current health recommendations to manage obesity are based on the underlying physiological property that fat accumulation is driven by an energy imbalance between consumed and expended calories. Diet and various social, economic, and environmental factors related to food supply have a significant effect on patient's ability to achieve the balance.

Microenvironment and Gut Microbiome

Our knowledge of the intestinal microbiome has grown substantially over recent years, as has our understanding of its intricate relationship to disease. For example, obesity is involved in an altered gut microenvironment that supports more diverse viral species than found in leaner hosts. Increasing evidence shows that variations of gut microbiome cause alterations in host weight and metabolism. For example, compared with those with normal gut microbiota, germ-free male mice (without gut microflora) had 42% less total body fat, even while consuming 29% more food a day. However, after cecal microbe colonization, the total body fat of these mice increased 57%in, lean body mass decreased 7%, and daily food intake decreased 27% . A follow-up study suggested that these alterations resulted from decreased metabolic rates, with concomitant increased adipose tissue deposition, as capillary density in distal small intestinal villi increased 25% after microflora colonization. Similar results were also observed from female mice.[15]

Genetic Factors and Causes

The studies from family and twin studies showed that around 40-70% of the obesity variation in human are resulted from genetic factors. While during the last 20 years, environmental alterations have increased obesity rates, the genetic factors play key roles in development of obesity. GWAS (Genome-wide association scans) approaches have identified over 400 genes associated with T2DM , however, these genes only predict 5% of obesity risk .The low predictive power may be due to the situation that gene-gene, gene-environment, and epigenetic interactions have not been thoroughly identified using the current methods based on population genetics.

Epigenetic Modification

We have been able to identify some of the genes that contribute to monogenic forms of obesity, but the human genome alterations on timescales that are too long for the genome to be a major player in the current obesity pandemic. Epigenetics, however, may offer a logical explanation for increasing obesity

prevalence over the past few decades without necessitating a radical change in the genome. In multicellular organisms, the genetic code is homogenous throughout the body, but the expression of code can vary across cell types. Epigenetics studies showed that the heritable regulatory alterations in the genetic expression do not require alterations in the nucleotide sequence. Epigenetic modifications can be thought of as the differential packaging of the DNA that either allows or silences the expression of certain genes across tissues.[16]

Family History and Lifestyle

Family history, lifestyle, and psychological factors all function in propensity for obesity. The likelihood of becoming obese can be affected by nature and nurture, enhanced by family genetics (propensity to accumulate fat) or life style (poor dietary or exercise habits). A child with one obese parent has a three time risk to become obese as an adult, while when a child's parents are both obese, this child has a 10-fold risk of future obesity. A cross-sectional observational study of 260 children (139 female, 121 male, aged 2.4 and 17.2 years) demonstrated that the family history of cardio metabolic diseases and obesity are critical risk factors for severity of obesity in childhood.

TREATMENT OF OBESITY

The goal of obesity treatment is to reach and stay at a healthy weight. This improves overall health and lowers the risk of developing complications related to obesity.[17]

The treatment methods that are right for you depend on your weight, your overall health and your willingness to participate in a weight-loss plan.

1. Dietary changes
2. Behaviour changes
3. Exercise and activity
4. Weight loss medicines

Dietary changes

Reducing calories and practicing healthier eating habits are key to overcoming obesity. Although you may lose weight quickly at first, steady weight loss over the long term is considered the safest way to lose weight. It's also the best way to keep weight off permanently.

There is no best weight-loss diet. Choose one that includes healthy foods that you feel will work for you. Dietary changes to treat obesity include:

Cutting calories. The key to weight loss is reducing how many calories you take in. The first step is to review your typical eating and drinking habits. . A typical amount is 1,200 to 1,500 calories for women and 1,500 to 1,800 for men.[18]

Feeling full on less . Some foods — such as desserts, candies, fats and processed foods — contain a lot of calories for a small portion. In contrast, fruits and vegetables provide a larger portion size with fewer calories. By eating larger portions of foods that have fewer calories, you can reduce hunger pangs and take in fewer calories. You also may feel better about your meal, which contributes to how satisfied you feel overall.

Making healthier choices. To make your overall diet healthier, eat more plant-based foods. These include fruits, vegetables and whole grains. Also emphasize lean sources of protein — such as beans, lentils and soy — and lean meats. If you like fish, try to include fish twice a week. Limit salt and added sugar. Eat small amounts of fats, and make sure they come from heart-healthy sources, such as olive, canola and nut oils.

Exercise and activity

Getting more physical activity or exercise is an essential part of obesity treatment:

- **Exercise.** People with obesity need to get at least 150 minutes a week of moderate-intensity physical activity. This can help prevent further weight gain or maintain the loss of a modest amount of weight. You'll probably need to gradually increase the amount you exercise as your endurance and fitness improve.
- **Keep moving.** Even though regular aerobic exercise is the most efficient way to burn calories and shed excess weight, any extra movement helps burn calories. For example, park farther from store entrances and take the stairs instead of the elevator. A pedometer can track how many steps you take over the course of a day. Many people try to reach 10,000 steps every day. Gradually increase the number of steps you take daily to reach your goal.

Behavior changes[19]

A behavior modification program can help you make lifestyle changes to lose weight and keep it off. Steps to take include looking at your current habits to find out what factors, stresses or situations may have contributed to your obesity.

- **Counseling.** Talking with a mental health professional can help address emotional and behavioral issues related to eating. Therapy can help you understand why you overeat and learn healthy ways to cope with anxiety. You also can learn how to monitor your diet and activity,

understand eating triggers, and cope with food cravings. Counseling can be one-on-one or in a group.

MEDICATIONS FOR OBESITY

Weight-loss medicines are meant to be used along with diet, exercise and behavior changes, not instead of them. Before selecting a medication for you, your health care professional will consider your health history, as well as possible side effects.[20]

The most commonly used medications approved by the U.S. Food and Drug Administration (FDA) for the treatment of obesity include:

DRUGS	MECHANISM OF ACTION
Orlistat	Gastric acid and pancreatic lipase inhibitor
Phentermine/ Topiramate	NE agonist / GABA agonist, glutamate antagonist
Naltrexonal/ bupropion	Opioid receptor antagonist and NE reuptake inhibitor
Liraglutide	GLP-1 analogue
Semaglutide	GLP-1 analogue
SEtmelanotide	Melanocortine (MC4R) agonist
Tirzepatide	GLP / GLP-1 dual agonist

Weight-loss medicines may not work for everyone, and the effects may wane over time. When you stop taking a weight-loss medicine, you may regain much or all of the weight you lost.

BMI CALCULATOR

CLASSIFICATION	BMI Cut-off Points (kg/m^2)
Healthy Weight	18.5 - 24.99
Overweight (including obesity)	≥25.00
Obesity	≥30.00
Sever Obesity	≥40.00

SEMAGLUTIDE[21]

Mechanism of action

Semaglutide is a glucagon-like peptide-1 receptor agonist. The drug decreases blood sugar levels. The decrease is theorized to be caused by the mimicking of the incretin glucagon-like peptide (GLP-1). It also appears to enhance growth of pancreatic beta cells, which are responsible for insulin production and release. Additionally, it inhibits the production of glucagon, the hormone that increases glycogenolysis (release of stored carbohydrate from the liver) and gluconeogenesis (synthesis of new glucose). It reduces food intake by lowering appetite and slowing down digestion in the stomach, helping reduce body weight.

Side effects

Nausea, Diarrhea, Vomitting, Constipaton, Abdominal pain, Headache, Fatigue, Heart burn, Dizziness, Hypoglycemia, Flatulence, Gastro Esophageal Reflux Disease (GERD).

It can also cause pancreatitis and bowel obstruction.

Contraindications

Data from rodent studies of GLP-1-mediated thyroid C-cel hyperplasia indicates that use is contraindicated in people with a personal or family history of medullary thyroid carcinoma or with multiple endocrine nepplasia type2.[22]

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