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OBESITY – An Overview

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Abstract: **Obesity is a global heath issue presenting increased mortality and morbidity. It is characterised by multifactorial diseases (Diabetes, fatty liver, hypertension, hyperlipidemia and cardiovascular disease and cancer). Obesity is due to chronic imbalance between energy intake and energy expenditure leading to excess accumulation of fat in adipose tissue. This review endeavours on key factors, metabolites, neuroendocrine regulation, microbiota and role of adipokines on obesity which can be applied in development of new strategies in combating obesity.**

Keywords: **Obesity, Adipose tissue, gut microbiota and adipokines.**

1. INTRODUCTION

In the current scenario obesity is one of the major global health consequence prevailing in the 21st century comprising an increased risk of morbidity and mortality across the world. Obesity is one of the confronting chronic metabolic syndromes. Obesity is likely to be multifactorial in origin, with genetic, environmental, and pathophysiological factors contributing to various degrees in different individuals. It is defined as imbalance in chronic positive energy with excess body weight leading to excess accumulation of body fat at an extent that causes adverse effect on health leading to reduced life expectancy and increase health problems. (1)Thermodynamically, it is an imbalance between energy intake (dietary fuel supply) and energy expenditure (physical activity or breakdown in regulatory process) (2).

The rise in global obesity rates over the last three decades has been widespread, creating major public health epidemic in both the developed and the developing world. Nearly 30% of the world's population that is 2.1 billion people are either obese or overweight, according to institute of health metrics and evaluation data from 188 countries. Rate of overweight and obesity among adults have increased for both men (from 29% to 37%) and women (from 30% to 38%). In developed countries, men had higher rates of overweight and obesity, while women in developing countries exhibited higher rates. Also in developed countries, the peak of obesity rates is moving to younger ages. Looking in individual countries, the highest proportion of the world's obese people (13%) live in the United States. China and India together represent 15% of the world's obese population. India has the ranked in 3rd highest obese population (3).

MEASURING OBESITY

When calorie intake exceeds energy expenditure leads to excess accumulation of body fat. There are different methods to measure body fat: (a) Basal adiposity index (BAI), (b) Waist to hip ratio, or (c) Body mass index (D) Skin fold thickness

Body Mass Index (BMI) is commonly used. BMI is defined as the weight in kilograms divided by the square height in meters (kg/m^2), and the resulting index is classified as underweight, overweight, obese, or over-obese.(4)

Table 1: BMI values according to the WHO data.

Classification	BMI*
Under weight	<18.5
Normal weight	18.5–24.9
Over weight	25–29.9
Class I obesity	30–34.9
Class II obesity	35–39.9
Class III obesity	≥40
*** BMI of ≥40–44.9 or 49.9 is morbid obesity. BMI of ≥45 or 50 is super obese**	

BAI measures percentage of body fat it is used in measurement of central obesity.

BAI = (HC / (HM) $^{1.5}$) - 18

Where
BAI = Body Adiposity Index

HM = Height in Meters

HC = Hip Circumference in Centimetres

Waist to hip ratio used as measurement in obesity and indicator of metabolic syndrome and used in measurement of abdominal obesity.WHR is predictor for cardiovascular diseases.WHR ratio for men 0.9 and women 0.85 above this considered as health risk.(4)

WHR = waist circumference/ hip circumference.

Skin fold Thickness

In this method, researchers use a special calliper to measure the thickness of a "pinch" of skin and the fat beneath it in specific areas of the body (the trunk, the thighs, front and back of the upper arm, and under the shoulder blade). Also called subcutaneous adipose tissue to predict body fat percentage based on these measurements (5).

ADIPOSE TISSUE (AT)

It is a major energy reservoir, thermal regulator and provides protective padding for vital organs. It is also a major metabolically active endocrine organ which secretes hormones known as adipokines and cytokine which help in regulating whole body metabolism maintain homeostasis.

Based on the location of AT in the body, is divided into two forms apple or pear shapes. In apple-shape adiposity (visceral or central obesity), adipose tissue is accumulated mostly in the upper part of the body in abdominal cavity and around intra-abdominal organs. Central obesity increases the risk for metabolic syndromes. In pear-shape adiposity (peripheral obesity or gynoid obesity), fat is stored in lower part of the body subcutaneously and around hips, thighs and buttocks. This form of fat has protective effects against metabolic syndrome and provides thermal regulation (6) the expansion of adipose tissue in obesity occurs via adipocyte hypertrophy (increased size of adipocytes) hypertrophy constitutes an endocrine function and adipocyte hyperplasia (increased adipocyte number). Adipocyte hyperplasia is involved in adipocyte differentiation. (7)

Adipose tissue is classified into two major types according to its morphology, function, location and colour. It is divided into 1.White adipose tissue (WAT) 2. Brown adipose tissue (BAT)

1. White adipose tissue

WAT Adipocytes are unilocular and contain unique lipid droplets which store triglycerides (7).

White adipose tissue differentiate into pre adipocyte, fibroblast and macrophage together form stromal vascular fraction which releases mediators that act in both paracrine and endocrine. Role of mitochondria in white adipose tissue (WAT) is significant. WAT require large amounts of ATP to maintain their diverse functions during adipogenesis, that is lipolysis and lipogenesis. In lipogenesis, adipose tissue generates glycerol 3-phosphate and acetyl-CoA for esterification into triglyceride in mitochondrial matrix. Lipolysis is the breakdown of triglyceride to free fatty acid and glycerol.

2. Brown adipose tissue

BAT contains a higher number of mitochondria and lower number of lipid droplet. It is metabolically active and is mainly present in new borns. During cold temperatures activation of the sympathetic nervous system and β - adrenergic receptor leads to brown adipocyte lipolysis. The resulting FFAs are oxidized in the BAT mitochondria and generate heat. This process involves transport of FFA complex to fatty acid binding proteins (FABPs) in the mitochondria by the carnitine shuttle system, where they are oxidized and used to generate heat by uncoupling protein 1 (UCP1), by a process called thermogenesis. Increase UCP1 expression and energy expenditure can be used in treatment of obesity (8). The largest region of brown adipose tissue is found in the upper back region of rodents (interscapular BAT). In humans, small areas are found in the thorax region (supra clavicular) expression of transcription factors PRDM16 and C/EBP- β is sufficient to

generate brown fat cells from myoblastic precursors. The activation of PPARγ by different agonists has been shown to induce the expression of brown adipose genes in white adipocytes. AMPK could be involved in this metabolic switch that increases adipocyte fatty acid metabolism decreases lipolysis, and up-regulates mitochondrial biogenesis (9)

2. OBESITY AND INFLAMMATION

WAT consist of two types of macrophages M1 and M2. M1(specific surface marker (CD11c+) releases iNOS and IL- 1 IL-6, MCP-1and TNF α are classical pro inflammatory cytokines. M2 enzyme involved in the inhibition of nitric oxide synthase, iNOS and IL-10, IL-1Ra anti-inflammatory cytokines. Normal WAT is characterised by an anti-inflammatory tissue able to protect from the development of obesity related inflammation by activity of peroxisome proliferator-activated receptor-(PPAR)s (PPAR-α and -γ) and liver X receptor-(LXR) families, involved in nutrient transport and metabolism and able to antagonize inflammatory activity with increases release of adiponectin and also antagonizes TNF-α effects on inflammatory and metabolic (10).

The shift from anti-inflammatory (M2) to pro-inflammatory (M1) increases the differentiation of monocytes recruitment in WAT. An increased infiltration of macrophages, aggregate in "crown like structures" constituted by necrotic-like adipocytes, which leads to hyperplasia, hypertrophy and production of pro inflammatory cytokine such as toll like receptor (TLR – 2,4) which are cell surface receptors which activate NFκB potent transcription factor for pro inflammatory cytokines increase phosphorylation of mitogen activated protein kinase and reduce the key regulatory enzyme AMP kinase which leads to anabolism. Thus obesity leads to chronic low grade inflammation because of shift between M2 to M1 macrophages. (11)

Table 2: List of adipokines and inflammatory cytokines their role in obesity (12 -13)

Adipokines	Biological role
Leptin	Satiety signal with direct effects on the hypothalamus; stimulates lipolysis; inhibits lipogenesis; improves insulin sensitivity; increases glucose metabolism; and stimulates fatty acid oxidation. Released with low calorie intake and low body fat levels.
Adiponectin	Increases fatty acid oxidation with reduction in plasma fatty acid levels; decreases plasma glucose levels, increases insulin sensitivity, anti-inflammatory, antioxidant, anti atherogenic and anticancer properties through the inhibition TNF-α-mediated of NF-κB pathway
Resistin	Induces insulin resistance-increased rate of glucose production and regulation of inflammation
visfatin	Hypoglycaemic effect by stimulating glucose uptake promotes insulin sensitivity and induces pro inflammatory cytokines.
Adispin	Enhance fat storage by inhibiting lipolysis
Omentin	Enhances insulin stimulated glucose transport
Apelin	Insulin sensitizing effect by AKT signalling
Ghrelin	Regulation of food intake, stimulates release of growth of hormone enhance eating and act to regulate energy balance for long term.
Chemerin	Regulation of adipogenesis
Cholecystokinin	Released when fat enters small intestine and triggers satiety signals in brain
Amylin	Released after food intake slows down, slows down emptying of stomach.
RPB- 4	Promotes insulin resistance by IRS-1 phosphorylation and GLUT 4 expression
VEGF	Stimulate vasculogenesis T cell cytokine production
Transforming growth factor	Regulation of cell growth
Plasminogen activator inhibitor	Inhibits plasminogen activator
C-reactive protien	Endothelial dysfunction production of ROS and amplifies pro inflammatory effects.
β3-adrenergic	fatty acid hydrolysis and uncouple energy production from storage
PPAR- γ	Improve insulin resistance Inhibit NFκB activation and down regulate pro inflammatory cytokine
SREBP	Involved in lipid metabolism
AMPK	It affects food intake and energy balance involved in whole body energy metabolism. Leptin activates AMPK increase fatty acid oxidation and adiponectictin activates increasing glucose utilization and fatty acid oxidation

C/EBP-β ,δ and α	Induces adipocyte differentiation
FTO	Involved in energy intake regulation
Inflammatory Chemokine and Cytokine	
TNF -α	Pro inflammatory inflammation and insulin resistance by IRS-1 phosphorylation and GLUT 4 expression decreases adiponectin
Interleukin 1	Pro inflammatory early mediator of inflammation inhibitor of PPAR
Interleukin 4	Anti inflamatory inhibition of pro inflammatory cytokines
Interleukin 6	Pro inflammatory, decrease insulin and leptin signalling induces release of c-reactive protein and lipolysis
Interleukin 1Ra	Anti-inflammatory and associated with insulin resistance
MCP1	Increases lipolysis and leptin secretion decrease insulin stimulated glucose uptake

Neuroendocrine Regulation of Energy Balance

The food intake is regulated by arcuate nucleus of hypothalamus in neuroendocrine control of energy balance. There is a complex interaction between central nervous system, stomach, small and large intestine. There are two competing neuronal systems. The main afferent signals several gut-derived hormones ghrelin- secreted of stomach cell crosses blood brain barrier and stimulate food intake by transducing ororexigenic signals (eg, neuropeptide Y and agouti-related protein) this induces hunger stomach stretches choleocytokinin is released which inhibit neuropeptide Y and agouti-related protein. Leptin is secreted by adipocytes in response to energy storage, under the control of insulin and glucocorticoids. Circulating leptin levels correlate with percent body fat and thus transmit information to the hypothalamus inhibiting neuropeptide Y and agouti-related protein. Peptide YY3-36 secreted by the large intestine after meals effect inhibits neuropeptide Y and agouti-related protein. Involved in anorexigenic signals efferent pathway (eg._melanocyte stimulating hormone, POMC and cocaine-amphetamine-regulated transcript) which inhibit food intake (14)

List of neurotransmitters affects food intake [15]

Factors increasing food intake	**Factors inhibiting food intake**
Endocannabinoids, serotonin, prolactin, dopamine, galanin and GABA	**Amylin, bombesin, glucagon like receptor urocortin, oxyntomodulin, neurotensin and neuromedin U.**

Table 3: Some of the neurotransmitter and their role (14 -15)

Neurotransmitter	**Role**
Endocannabinoids	They participate in glucose and insulin metabolism in muscle and fat tissue endocannabionoids receptor are blocked leads to less food intake and fat mass.
Norepinephrine	Impairs digestive function
Acetylcholine	Stimulates digestive activity
Neurotension	Released by small intestine when fat reaches intestinal walls blocking stomach acids.
Neuropepetide Y	It is released when body fat is low or food scare in gut generally slows gastric emptying
Serotonin	Released in small intestine reduce stomach acid production
PYY3-36	Suppress pancreatic enzyme secretion and inhibits stomach motility.
POMC	Synthesize α-MSH, a key neuropeptide that inhibits appetite in the hypothalamus.

Impact gut of microbiota in obesity

The intestinal gut microbiota has co- evolved with human host physiology and metabolism. The gut microbiota is an integral part of complex network coordinating intestinal barrier with immune, sensory and neuromotor endocrine system. It determines food and weight by affecting host metabolism through regulation of intestinal glucose metabolism, lipogenesis and fat deposition. In recent studies there is a sustainable change in composition of gut microbiota which is linked to obesity with relative decrease in the proportion of bacteroides to fermicutes. Microbiota promote absorption of monosaccaride and short chain fatty acids from the gut lumen and induce hepatic lipogenesis. When blood glucose level is above normal GLP-1 release by gut in accordance to the amount of energy ingested, expressed by enteroendocrine of the gut epithelium that reduces the expression of PYY, an enteroendocrine cell – derived hormone that inhibits gut motility, thereby increasing intestinal transit rate and, possibly, reducing nutrient contact time.(16 -17)

Metabolomics of obesity

Metoblomics is a study to understand the change or alteration in metabolic pathway leading to obesity. Bio- analytical technique used in determination of metabolite profile involve high end techniques for analysing metabolites such as NMR spectroscopy and MS. It provides link between phenotype and genetics in disease progression (18)

Table 3: Metabolites involved in obesity

Sl. no.	Metabolite	Mechanism
1.	Lactate	Under anaerobic condition during glycolysis pyruvate is conserved to lactate. Increase in lactate concentration causes perturbation of hepatic glucose production and hepatic lipid synthesis leading to obesity. (19)
2.	Carnitine	Fatty acids can only produce energy via β-oxidation after esterification and transport into the mitochondrion with the help of carnitine. The decreased carnitine levels in obesity could be insufficient for β-oxidation to compensate the elevation of Free fatty acids, results in fat accumulation in adipose tissue (20-21)
3.	Taurine	It is an important metabolite in bile acid metabolism and has many important biological roles such as conjugation of cholesterol and bile acids. Increase taurine levels overcome obesity. (22 -23)
4.	Choline	Choline play role in cellular structure and lipid/cholesterol transport and metabolism. In the mitochondria of liver and kidney, choline can be oxidized to betaine, betaine plays a key role in fatty acid metabolism related to carnitine production. Depletion of betaine results in a decreased hepatic carnitine level, and eventually lead to decreased β-oxidation and increased fatty acid storage. (24)

3. CONCLUSION

As the epidemic of obesity is continuing to increase, this review provides new avenues for future therapeutic targets to fight obesity for prevention and treatment.

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