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Review Article

Obesity And Gut Microbiota: A Comprehensive Review

Chandan Sood[1], Dr. Saurabh Sharma*[2], Saurav Anand[3], Neha Gupta[4]

[1,2,4]Department of Pharmacology, Shiva Institute of Pharmacy, Chandpur, Distt. Bilaspur, Himachal Pradesh-174004, India.

[3]Department of Pharmacology, University School of Pharmaceutical Sciences, Rayat Bahra University, Mohali, Punjab-140301, India.

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ABSTRACT

Obesity is the multifactorial metabolic disease with worldwide interest, which leads to high non-communicable disease burden like type 2 diabetes, cardiovascular disease, and metabolic syndrome. Over the recent years, gut microbiota has been revealed as a master regulator of obesity pathogenesis. The imbalance of the composition of microbes in the gut or dysbiosis has been linked to higher energy harvest, lower energy expenditure, a change in lipid metabolism, and failing to control the appetite. Remarkably, a higher Firmicutes to Bacteroidetes ratio among the obese is a common behavior, which improves fermentation of the indigestible polysaccharides and leads to the production of short-chain fatty acids (SCFA) to facilitate adipogenesis. In addition, metabolites produced in the gut, including SCFAs, have context-specific effects on the metabolism of the host, and current evidence demonstrates that SCFAs exert both positive and negative effects on the rate of lipogenesis and inflammation. Neuroendocrine signaling by microbial metabolites regulating the gut-brain axis mediates the role of appetite and energy homeostasis. Moreover, Gram-negative bacterial endotoxin, lipopolysaccharides (LPS), causes metabolic endotoxemia and low-grade systemic inflammation to enhance insulin resistance and accumulation of lipids. Taken together, these mechanisms emphasise the imperative role of gut microbiota in development of obesity. Knowledge of the intricate host microbiota interactions may have therapeutic potentials, such as microbiota-specific treatments, namely probiotics, prebiotics, dietary manipulations, and fecal microbiota transplantation to treat the treatment of obesity.

INTRODUCTION

Introduction of Obesity:

***Corresponding Author:** Dr. Saurabh Sharma
Address: *Department of Pharmacology, Shiva Institute of Pharmacy, Chandpur, Distt. Bilaspur, Himachal Pradesh-174004, India.*
Email ✉: ssm.research@gmail.com

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Obesity: The disease is obesity, which has become one of the major problems of global health in all aspects, as far as the present times are concerned. Obesity has come to be the 5th cause of deaths all over the world. World Health Organization defines obesity as excess or abnormal fat which may negatively affect the health, and the primary cause of obesity is, imbalance of energy i.e. excess body calories taken against the calories burnt by body.[1,2] Obesity is another international public health problem of high prevalence among all age strata. It produces significant social and economic effects, as it influences the health and quality of lives of people.[3] There is evidently a raging problem of obesity as far as worldwide health is concerned; and according to estimates, obesity and overweight rate will rise to 25 per cent and 32 per cent overall respectively in 2030.[4] Obesity is a 21 st century disease and a serious nutritional problem, which comes along with heart disease, diabetes, cancer in addition to inflammation and metabolic syndrome.[5] The health status obesity is a critical contributor of metabolic syndrome which are cluster of metabolic abnormalities such as elevated blood sugar, excess body fat, excessive serum triglycerides, blood pressure and diminished volume of high-density-lipoproteins. The metabolic syndrome is allied among an exorbitant hazard of acute disease like type 2 diabetes, cardiovascular disease and stroke.[6,7] Its causation is caused by the interaction between various factors with a support on genetic and environmental factors, specifically, over-consumption of food and lifestyle. According to research conducted in 2018, it was revealed that even among kids younger than five years old, 5.9 percent people (40 million people) were classified as overweight whereas in 2016 an estimated 2 billion adults fell into this category.[8] According to some estimates, 18% of males and 21% of women in the population will become obese by the year 2025.[9,10] Another report released by WHO in 2021 shows that at least 1 billion people were already obese, with 650 million adults, 340 million adolescents, and 39 million of them being children according to data collected in 2016. The global trend of overweight and obesity has risen by 27 percent in adults and by 47 percent in children between the period 1980 and 2013.[11] This figure is still rising and WHO puts the number at it is bound to rise to about 167 million people by 2025.[12]

Classification of Obesity:

The degree of BMI rise has historically been used to define obesity. Body Mass Index (BMI) and ethnicity-specific cut-points have formed the foundation for the traditional classifications of overweight and obesity.[13] Overweight is defined as having a BMI of 25.0 to 29.9 kg/m^2, whereas class 1, class 2, class 3, class 4 (Super Obesity) and class 5 (Hyper Obesity) include BMIs of 30.0 to 34.9 kg/m^2, 35.0 to 39.9 kg/m^2, 40.0 to 49.9 kg/m^2, 50.0 to 59.9 kg/m^2, and over 60 kg/m^2 and those with a BMI of 18.5 to 24.9 are considered normal weight.[14,15] In the case of Asian populations, BMI between 23.0 and 24.9 kg/m^2 were weighted as overweight, 25.0 kg/m^2 and above were weighted as obese and 18.5 to 22.9 kg/m^2 were taken as normal.[13,16] The ease of measurement index of Body Mass Index (BMI) that is [(weight in kg)/(height in m^2) serves as a convenient guide in the classification of the adult body as underweight, overweight or obese. BMI was invented in the 1830s by the Belgian mathematician and sociologist, who still applies this value in the assessment of obesity rates.[17]

Table 1.1 WHO Classification of Weight Status WHO (2000) [17]

Body Mass Index (BMI) (Kg/m^2)	Classification	Weight Status
<16.0	Severe thinness	Underweight
16.0-16.9	Moderate thinness	Underweight
17.0-18.4	Mild thinness	Underweight
18.5-24.9	Normal range	Healthy weight
25.0-29.9	Overweight	Overweight
30.0-34.9	Obesity class I	Obese
35.0-39.9	Obesity class II	Obese
40.0-49.0	Obesity class III	Morbidly obese
50.0-59.9	Obesity class IV (Super obesity)	Extremely obese
≥60.0	Obesity class V (Hyper obesity)	Extremely obese

Causes of Obesity: Obesity causes are multilateral and interrelated. To ease the discussion we refer to them here as non-modifiable and modifiable factors. Non-Modifiable factors include Genetic,[18] leptin-melanocortin pathway,[19,20] Hypothalamic obesity[21] and the modifiable factors are Epigenetics,[22,23] Physical inactivity,[24] Excessive caloric intake,[25] The intrauterine environment,[26] Postnatal influences,[27] Insufficient sleep,[28] Drugs,[29] Medical conditions, Socioeconomic status,[30] Ethnicity, Psychosocial stress, Endocrine disrupting chemicals,[31] Gastrointestinal microbiome.[32,34]

Pathophysiology of Obesity:

Such long-term stability of body mass and body composition is possible with the energy intake being equal to his or her energy expenditure. Sufficient body energy supply has to go in effect. Our bodies have many short-term and long-regulations that come into action to maintain the utilization of the energy, storage of energy and the energy consumption. The hypothalamus has a number of nerve centers that have a great control on the quantity of food that we consume. The feeding centre is the lateral nucleus of the hypothalamus. The stimulation of this area or center causes hyperphagia. The hypothalamus paraventricular nucleus, dorsomedial nucleus, and the arcuate nucleus are also important in controlling the food intake levels. Lesions on paraventricular nuclei consistently cause over-consumption of food. In case of damage or any lesion to the dorsomedial nuclei, the same tends to decrease the stimuli to consume food. Usually, the food intake and the expenditure of energy are regulated by the arcuate nuclei of the hypothalamus. Many gastrointestinal humorous and the adipose product hormones are believed to act here. The gastrointestinal tract sends neural messages to the hypothalamus. These nerve impulses provide sensory data which indicates the stomach is full. Also, the glucose, amino acids, and fatty acids present in the blood send messages concerning satiation to the brain through their molecules. The feeding behavior is determined by the information within the hypothalamus of the cerebral cortex (sight, taste and smell). Hypothalamic feeding and satiety centers also possess a large number of receptors to many neurotransmitters and hormones which mostly manipulate the actions of feeding heavily. [35,36,37,38]

Overview of Human Gut Microbiota:

The gastrointestinal tract (GI) is one of the major surfaces in the human body (250–400 m^2) where antigens, the host, and the environment come into touch. About 60 tons of food pass through the human GI tract at any given time throughout an average lifespan, along with the numerous microbes that the body meets.[39] The gut microbiota is the collection of all the bacteria, archaea, and eukarya that live in the GI tract. Over thousands of years, they have co-evolved with the host to form a complex mutually beneficial relationship.[40,41] The GI tract's germs are thought to number over 1014, which is more than 100 times the human genome's genomic content (microbiome) and 1014 times more bacterial cells than human cells.[40, 42] However, a revised perspective has shown that the human:bacterial cell ratio is 1:1.[43] The microorganisms and body that harbors them are sometimes referred to as superorganisms because of the large numbers of bacterial cells in the body.[44] The microbiota has considerable benefits to the host, in various physiological functions, like integrity as well as strength of the gut, shaping of intestinal epithelium,[45] energy harvesting,[46] protection of the pathogens as well as controlling host immunity.[47,48] Yet, these processes can be interfered with due to the altered microbial composition, which is called dysbiosis. As more and more advanced ways of profiling and characterising complex ecosystems emerge, a contribution of the microbiota to most intestinal and extra-intestinal diseases emerged increasingly strongly.[49,50]

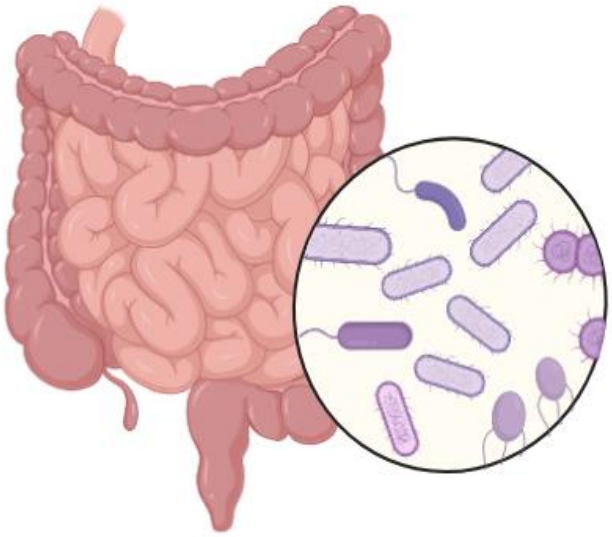

Figure 1.1 Human Gut Microbiota

Organization and makeup of the human gastrointestinal microbiota

The great bulk of data on the mature microbiota of humans was being collected by time-consuming culture-based fixations around 10 years ago.[51] The development of culture-independent techniques, such as high throughput and inexpensive sequencing methods, has greatly improved our ability to survey the extent of gut microbiota in recent years. Since the (16S) ribosomal RNA (rRNA) genome is present in all living organisms and can be easily distinguished between species thanks to its nine highly variable sections (V1 to V9), it is one of the most often targeted genes.[52,53] Earlier, the focus was on sequencing the whole 16S rRNA gene. 76 percent of the rRNA sequences obtained in an adult male fecal sample were in unique and uncharacterized

species, highlighting the severe insensitivity as well as bias of culturing procedures in an early experiment using this methodology.[54] Though shorter read lengths introduce mistakes, the sequencing of 16S rRNA has advanced in recent years to concentrate on specific gene subregions in greater detail.[52,53] Because whole-genome shotgun metagenomics approaches have better resolution and sensitivity, they may also provide more accurate estimates of the diversity and composition of microbiotas. Joint data on the MetaHit and that of the Human Microbiome Project have yielded the largest picture ever of the human-associated microbial repertoire so far.[55,56] Summarized data of these studies had one hundred and twenty phyla of two thousand and seventeen species isolated in human beings out of which ninety three and half percent belonged to Proteobacteria, Firmicutes, Actinobacteria and Bacteroidetes. The identified phyla were reduced to three single species species isolated of the 12 phyla only one of which, the intestinal species, was identified as Akkermansia muciniphila and was the sole representative of the Verrucomicrobia phylum that was known. Within man 386 of the species so far identified completely anaerobic and therefore will tend to be located in areas of mucosa like the mouth and the GI tract.[55] The gut microbiota exhibits high degrees of functional redundancy and is not as diverse in makeup as the community of microbes at certain other body sites.[57,58,59]Recently, a thorough inventory concerning the human gut microbiome's functional potential was obtained, and utilizing 248 newly sequenced and 1018 reported samples, 9879896 genes were found.[56] As a result of the study's identification of nation-specific microbial signatures, the gut microbiota's composition is influenced by environmental factors, such as nutrition and maybe host genetics. It is however important to also note that although different microbiotas are different in the sense that they vary in composition, there could be functional redundancy of some sort in different microbiotas resulting in similarity in protein or metabolic profile.[60] Such information is vital in establishing therapeutic measures to alter and manipulate the microbial community in disease.

Human gastrointestinal microbiota's development

It is suggested that the microbiota's development starts at the time of birth, but this dogma is questioned by a small body of experiments where the microbes were found in the tissues of the womb, including the placenta. [61,62] The GI tract is quickly colonized following birth and life experience like illness, antibiotic therapy or dietary alteration leads to the random experimenting.[63] The microbiota composition and the manner of delivery appear to be related as well; children born vaginally had a high lactobacilli abundance in their microbiota during the first few days, which is indicative of the high lactic acid bacteria in the vaginal environment.[64,65] On the other hand, facultative anaerobes such as Clostridium species inhabit the microbiota of newborns delivered via caesarean section, which is shortened and delayed in the colonization of Bacteroides genus.[66,67] While the fecal microbiota of 72% of newborns delivered vaginally is comparable with the one of their mothers, this percentage drops to 41% in babies born via caesarean section.[68] During early development, microbiota are typically low-diversity and only contain 2 primary phyla, namely Actinobacteria and Proteobacteria.[62,69] The microbial diversity rises and microbiota composition tends to mature with a specific adult-like microbial profile during the first year of life with unique and different temporal patterns between the different babies.[70] By about 2.5 years old, the microbiome make-up, variety and functionality of the infant microbiota can match

adult microbiome functionality.[62,63] Undoubtedly, the makeup of the gastrointestinal tract's microbiota remains relatively constant in adulthood, nonetheless, it is prone to disruption by life events.[71] In the subjects older than 65 years, microbial community is changed, and there are more Bacteroidetes phylum and Clostridium cluster IV, unlike younger participants who have a more predominant cluster XIVa.[72] On the other hand, another study found that while the gut bacteria among a young population and a group of seniors (70 years) were very similar, the microbioma diversity of a cohort of seniors was much lower.[73] The enhanced prevalence of facultative anaerobes (like Escherichia coli) and changes in the pattern of butyrate makers (like a decrease in Faecalibacterium prausnitzii) were two more group-specific modifications in the centenarian microbiome.[72,73] Diversity and living arrangements, whether in the community or in long-term residential care, have been found to be egregiously correlated among elderly citizens.[74] In general, metabolic activities of the microbiota such as the production of short-chain fatty acids (SCFAs), amylolysis are impaired in old age, whereas proteolytic activity is enhanced.[75] Since it became more evidenced that SCFAs are crucial metabolic and immune mediators, the hypothesis was generated that the fall of SCFAs provides the environment that fosters the intestinal inflammation-aging process of elderly individuals.[76]

Gut Microbiota's Pivotal Role in The Onset and Progression of Obesity:

Complex microorganism community or microbiota in the gastrointestinal tract, gut microbiota, is crucial in causing and exacerbation of obesity. Change in its makeup usually called as dysbiosis can result into new influence on various physiological systems, such as energy homeostasis, lipid metabolism, appetite control, as well as continual inflammation. All of these mechanisms lead to additional energy taking, fat deposition, deranged appetite signals, and low-grade inflammation, which are features manifestations of obesity.

1. Energy homeostasis disturbance:

1.1 Increased Digestible Energy Absorbing Mass:

The gut microbiota of obese people has an increased ability of metabolism of the food in terms of retrieving energy. This is mainly because of increased abundance of Firmicutes and raised Firmicutes/Bacteroides ratio, which is positively correlated with digestion of otherwise un-digestable polysaccharides into absorbable monosaccharides and SCFAs like acetate and butyrate.[77,78] Of particular importance is increasing energy uptake though increasing glucose transporter (Glut2) components (Firmicutes phylum) through the over-expression of fatty acid translocase (CD36).[77] Moreover, on gut bacteria enriched with obesity, the expression of enzyme, such as, a-amylase and amylomaltase, which enables fermentation of carbohydrates into energy-yielding SCFAs, is high by rate.[78] These SCFAs are taken up in the colon and may be able to furnish 5-15 percent of the daily dietary energy intake as well as 70 percent of the energy demand of colonic epithelial cells.[79] Besides, the microbial interspecies hydrogen (H_2) has been used to boost the fermentation efficiency. Methanogenic Archaea that use H_2, partner with H_2-producing bacteria to alleviate thermodynamic constraints of fermentation thereby enhancing outputs of SCFA and energy recovery.[80] Such synergy between microbes occurs more often in microbiomes of obese people and further adds to the calorie uptake.

1.2 Impaired Energy Expenditure:

Other than rising dietary consumption, another reason why obese individuals have low energy expenditure is due to gut microbiota dysbiosis. Gut microbes control the activation of bile acid that activate TGR5 and FXR receptors that control thermogenesis. Adipose tissue that is brown, TGR5 agonist enhanced the expression of PPARy coactivator-1alpha and iodothyronine- deiodinase type 2, which facilitates mitochondria production and increases the rate of energy burning through heat.[81] In the intestine, FXR stimulates FGF15/19 that alters bile acid composition and enhances white adipose tissue browning as well as BAT stimulation.[82,41] Nonetheless, in obesity, the amount of bacteria that manufacture bile acid including the structure of the bacteroides and Lactobacillus are lowered,[83] and these pathways are damaged thus lowering thermogenic capability. Short-chain fatty acids (SCFAs), are involved in energy expenditure in a complex role as well. On the one hand they inhibit release of fasting-induced adipose factor (FIAF), lowering the stimulation of AMP-activated kinase (AMPK) and thus minimizing of.[84,85,86] Conversely, SCFAs such as butyrate have the potential to induce AMPK and the increase of the mitochondrial uncoupling protein 1 (UCP1) and peroxisome proliferator-activated receptor (PGC-1alpha) in BAT to stimulate thermogenesis and fatty acid oxidation.[87] These two reasons represent a complicated context-specific control of energy expenditure that should be further studied.

2. Modulation of Lipid Synthesis and Storage:

2.1 Gut Microbiota and Hepatic Lipogenesis:

Deregulated gut microbiota alters liver lipid metabolism mainly acting via bile acids signaling. Depleted bile acids cause lower FXR body positioning in the liver, which leads to a decrease inhibition of liver receptor homolog 1 and enhance SREBP1c which is a transcription factor that is involved in de novo lipogenesis.[88] Activating intestinal FXR also triggers FGF19 that suppressed hepatic lipogenesis through FGFR4 activation and inhibition of co-activators such as PGC-1B or activation of SHP.[89] Therefore, liver stores fat in obesity via modifications in the activities of these bile acid routes. Enhanced level of serum glucose as a result of escalated expression of Glut2 also augments hepatic lipogenesis as a result of escalated SREBP1 and carbohydrate response element binding protein (ChREBP).[90] Also, acetate, another SCFA that is elevated in obesity is a precursor of fatty acid and cholesterol production, and butyrate boosts the production of lipids via the β-hydroxy-β-methylglutaryl CoA pathway.[91,92] In offspring, butyrate supplementation increased expressions of lipogenic genes and decreased lipolysis in offspring.[93] Butyrate has, however, also been shown by other studies to inhibit lipogenesis through decreasing PPAR.[90] This contradicts the twofold utility depending upon biological circumstance proposed in the study.[94]

2.2 Gut Microbiota and Lipid Storage:

Obese people's gut flora contributes to increased fat accumulation through hormone changes and inflammation. Increased LPS concentrations of Gram-negative bacteria such as of a type of bacteria known as Veillonella, trigger the metabolic endotoxemia and the inflammatory process through the activation of the TLR4 signaling pathway.[95,96,97] LPS produces activation of macrophages and adipocytes which stimulates the release of cytokines that promote inflammation (TNF-a, IL-6, and MCP-1), which inhibit insulin signaling through phosphorylation of the insulin receptor consequently facilitating the buildup of lipids in the adipose tissue and liver.[98,99] Adipocyte precursor proliferation caused by LPS is also mediated by the CD14 and Activin A pathways.[100] Additionally, the gut

microbiota can facilitate storage of fat by decreasing the expression of such anorexigenic peptides encoding genes as Gcg and Bdnf and causing leptin resistance by inducing SOCS3.[101] Decrease in the level of the "Lactobacillus paracasei" in obesity dissolves its repression to the lipoprotein lipase and permits triglycerides to be stored in adipocytes.[102]

3. Regulation of Central Appetite and Feeding Behavior:

3.1 The Microbiota-Gut-Brain Axis:

A two-way communication system: Gut-brain axis is a communication system that includes neural, hormonal and immune channels. Central nervous system can be subjected to microbial metabolites and signals, and its effect influences the appetite and feeding behavior.[103,104,105] Food intake and energy balance can be related to obesity dysbiosis through this axis.[106,107]

3.2 Microbial Control of Satiety and Mood:

Low-intensity metabolomics, such as lactate (of Lactobacillus and Bifidobacterium), maintains the energy needs of the neurons and enhances satiety.[108] Acetate has an effect on the expression of hypothalamic neuropeptides though its entry into the citric acid cycle[109] whereas butyrate is known to stimulate vagal afferents and the hypothalamus immediately upon crossing the blood-brain barrier.[110] Further, SCFAs and bile acids regulate anorectic bowel hormones (GLP-1 and PYY), which in turn directed the brain through their receptors and results in the reduction of appetite.[111,112] The gut microbiome as well affects production of neurotransmitters e.g. serotonin and GABA. GABA enhances appetite and serotonin blocks the impulse to eat and support the balance of energy[113,114] by effect on melanocortin neurons. Microbial signals also mediate emotional and hedonic mechanisms of regulating eating behavior, as SCFA propionate inhibits brain reward reactions to high-calorie food using striatal pathways.[107]

4. Chronic Low-Grade Inflammation:

4.1 LPS-Mediated Inflammation:

One of the characteristics of obesity is low grade inflammation which is predominantly microbial LPS induced. The gram negative bacteria like the yaquo Veillonella multiply in a body that is obese, there is excessive LPS95. This endotoxin destroys the resistance of the intestinal barrier through the TLR4 / MyD88 / IRAK4 signaling pathway in epithelial cells, and LPS translocation into the organism occurs.[115] Depleted abundance of a mucosal-integrity bacterium, the "Akkermansia muciniphila " enhances this leaks[116] and high-fat diets increase the absorption of LPS through chylomicron transportation.[117] LPS becomes systemic and then binds to LBP and CD14 to create a complex which activates TLR4 on macrophages and adipocytes, thereby resulting in the inflammatory cytokines releasing through the process of NF-kB (TNF- six, IL-6, MCP-1).[96,97] This inflammation attracts macrophage into the adipose tissue in an ongoing inflammatory cycle.[118]

4.2 Anti-inflammatory Role of SCFAs:

SCFAs, and particularly butyrate have been shown to be anti-inflammatory, through stimulation of IL-18, differentiation of regulatory T cells, and activation of GPR109a.[119,120] Butyrate prevents LPS-induced NF-kB activity as well as inducing PPAR-y, decreasing inflammation.[121]

CONCLUSION:

Gut microbiota contributes significantly to the pathogenesis of obesity involving numerous interrelated mechanisms. Dysbiosis increases

digestible energy and the absorption of live energy, lowers energy consumption, favors the deposition of lipids and changes in the regulation of appetite and tabulates with chronic inflammation. As much as SCFAs have been shown to be beneficial as well as harmful in certain situations, they continue to be the main connection between the metabolism of host and the microbes in the gut. This knowledge of these complex microbial-host interactions has paved a way to a new treatment of obesity with microbiota-based therapies.

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