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Influence of gut microbiome over obesity: A relationship study

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Abstract
The human gastrointestinal tract is colonized by large numbers of microorganisms, including bacteria, archaea, viruses, fungi and protozoa, collectively known as the gut microbiota. The human gut microbiota consists of up to 100 trillion microbes and possesses at least 100 times more genes (the microbiome) than are present in the entire human genome.[1] These microbes serve a number of important functions including: producing additional energy otherwise inaccessible to the host by breaking down soluble fiber; producing vitamins such as biotin, folate and vitamin K; metabolizing xenobiotics such as the inactivation of heterocyclic amines formed in meat during cooking; preventing colonization by pathogens; and assisting in the development of a mature immune system. Currently, the bulk of microbiome research is focused on the gut microbiota since this is where the majority of bacteria are found. However, most data are obtained from analysis of stool samples because these are easily accessible. Comparisons of microbiota from colonic mucosal biopsies and stool samples have shown that there are compositional differences between the mucosa-associated and the luminal (fecal) microbiota and thus stool analysis might not accurately reflect the gastrointestinal tract. [2] Regardless, microbiome analysis has revealed a relationship between nutrition, the gut microbiota and a number of human diseases including obesity.

Keywords: Gut micriobiome, obesity, metabolic disorder

Introduction
Obesity is derived from the Latin word "obesus" which means having eaten or having eaten until fat.

- "Ob" means " by reason of"
- "edo " means " I eat "

According to W.H.O "Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health [1]."
Another definition says that "Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems" [2].
A person is considered to be overweight if he/she has a BMI of 25.0 or more and obese if the BMI is 30.0 or more [3].
Obesity is divided into three classes:

- Class 1 BMI 30 to 34.9 (also a waist circumference 102.0cm plus for males & 88.0 cm plus for females).
- Class 2 BMI 35 to 39.9.
- Class 3 BMI 40 and over. Such individuals are also called morbidly obese.

The Body mass index (BMI) used here is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m^2).
Many countries in the Asian region have witnessed sustained economical growth and have an increased political stability, thereby bringing rapid advances in Socio-economic status since the last three decades. Changes in diet coupled with increasingly inactive lifestyles have sparked off epidemics of obesity in several countries [4].
Recent surveys show that there are more than 1 billion obese adults worldwide. Among all countries, India ranks among the top 10 obese nations of the world and about one million urban Indians are extremely obese. More to add, 1 out of every 10 Indian child is overweight.
The risk of obesity in India is highest in the 20% of the population that consumes 80% of visible dietary fat.

School surveys in Indian cities show that 30% of adolescents from India's higher economic groups are overweight and a study has also shown that 14% of urban school children are overweight, two thirds of who are from families with high income. There is also data on the increasing prevalence of over-weight among rural areas in the last 10 years.

Assessment of obesity

Assessment of obesity is done with the following parameters [5].

1. Body weight

It is not an accurate measure to calculate excess fat, but is widely used index. In epidemiological studies it is conventional to accept +2 S.D (standard deviation) from the median weight for height as a cut-off point for obesity.

2. Body mass index (BMI)

It is a measure for human body shape based on an individual's weight and height. It was devised between 1830 and 1850 by the Belgian polymath, Adolphe Quetelet. Body mass index is defined as the individual's body mass in kg divided by the square of their height in meter square. This formulae universally used in medicine, has a unit of measure of kg/m^2. BMI can also be determined using a BMI chart. A person is considered to be overweight if they have a BMI of 25.0 or more and obese if the BMI is 30.0 or more.

3. Skin Fold Thickness (SFT)

A large proportion of total body fat is located just under the skin. Since it is most accessible, by measuring skin fold thickness obesity can be measured. It is a rapid and "non-invasive" method for assessing body fat. Several varieties of callipers like Harpenden skin callipers are available.

4. Waist – hip ratio (WHR)

This is the waist circumference in centimetres divided by the hip circumference in centimetres. The waist circumference is usually measured halfway between the superior iliac crest and the rib cage in the mid-axillary line. Whereas the hip circumference is measured one-third of the distance between the superior iliac spine and the patella. WHR in central distribution of body fats i.e. a waist hip circumference ratio of more than 1 in men and more than 0.9 in women is associated with a higher risk of morbidity and mortality i.e. WHR less than 0.85 in men and less than 0.75 in women.

5. Body fat percentage

This is the total weight of fat divided by total weight; body fat includes essential body fat and storage body fat. Essential body fat is necessary to maintain life and reproductive functions. The percentage of essential body fat for women is greater than that for men, due to the demands of childbearing and other hormonal functions. The percentage of essential fat is 3-5% in men, and 10-16% in women. Storage body fat consists of, fat accumulation in adipose tissue, part of which protects internal organs in the chest and abdomen. A number of methods are available for determining body fat percentage, such as measurement with callipers or through the use of bioelectrical impedance analysis.

The body fat percentage is a measure of fitness level, since it is the only body measurement which directly calculates a person's relative body composition without regard to height or weight. The widely used body mass index provides a measure that allows the comparison of the adiposity of individuals of different heights and weights. While BMI largely increases as adiposity increases, due to differences in body composition it is not necessarily an accurate indicator of body fat; for example, individuals with greater muscle mass will have higher BMIs. The thresholds between "normal" and "overweight" and between "overweight" and "obese" are sometimes disputed for this reason. The table below from the American Council on Exercise shows how average percentages differs according to the specified groups.

Table 1: Distribution of Body fat percentage [6]

Description	Women	Men
Essential fat	10–13%	2–5%
Athletes	14–24%	6–18%
Average	25–31%	18–24%
Obese	32%+	25%+

At one level, the pathophysiology of obesity seems simple: a chronic excess of nutrient intake relative to the level of energy expenditure. However, due to the complexity of the neuro-endocrine and metabolic systems that regulate energy intake, storage, and expenditure, it is difficult to list out all the relevant parameters [7].

Physiologic regulation of energy balance [8]

Substantial evidence suggests that body weight is regulated by both endocrine and neural components; this ultimately influences the energy intake and expenditure. This complex regulatory system is necessary because even small imbalances between energy intake and expenditure will ultimately have large effects on body weight.

Body weight regulation or dysregulation depends on a complex interplay of hormonal and neural signals. Alterations in stable weight by forced overfeeding or food deprivation induce physiologic changes that resist these perturbations: with weight loss, appetite increases and energy expenditure falls; with overfeeding, appetite falls and energy expenditure increases.

"Appetite" is influenced by many factors that are integrated by the brain, most importantly within the hypothalamus. Signals that impinge on the hypothalamic centre include neural afferents, hormones and metabolites. Vagal inputs are particularly important, bringing information from viscera, such as gut distention. Hormonal signals include leptin, insulin, cortisol, and gut peptides. Among the latter is ghrelin, which is made in the stomach and stimulates feeding, and cholecystokinin, which is made in the small intestine and sends signal to the brain through direct action on hypothalamic control centres. Metabolites, including glucose, can influence appetite, as seen by the effect of hypoglycemia to induce hunger; however, glucose is not normally a major regulator of appetite.

Here is a list of causes for obesity [9]

1. Neuro-endocrine disorders

a. Hypothalamic disorder: Injury to the ventromedial region of the hypothalamus
b. Hypothyroidism: Thyroid deficiency presents with clinical features of myxoedema.
c. Cushing's syndrome: The pattern of weight gain in Cushing's syndrome is characteristic, with accumulation of fat in the trunk, supraclavicular fossa and dorsal cervical region.

d. Polycystic ovary syndrome consists of irregular or absent menses, hirsutism, obesity and infertility.
e. Hyperinsulinism: Hypersecretion of insulin occurs in insulinoma; this can increase body weight.

2. Genetic syndromes
Certain rare syndromes like Lawrence-Moon-Biedl syndrome, Prader-Willi syndrome, Alstrom syndrome, Cohen syndrome etc are associated with obesity with dysmorphic features.

3. Drug-induced obesity
Drugs such as corticosteroids, tricyclic antidepressants, cyproheptadine, phenothiazines and lithium can lead to weight gain.

4. Genetic/ Inherited obesity
Obesity is commonly seen in families, and the heritability of body weight is similar to that for height. Inheritance is usually not mendelian.

5. Excess calorie intake and physical inactivity
Obesity can result from increased energy intake, decreased energy expenditure, or a combination of the two. Thus, identifying the etiology of obesity should involve measurements of both parameters.
Identifying the causes of obesity not only helps in preventing the disease, it also helps in the treatment and prevention of reoccurrence of the disease.

Treatment of obesity
The primary goal of treatment is to improve obesity-related co-morbid conditions and reduce the risk of developing future co morbidities. Information obtained from the history, physical examination, and diagnostic tests is used to determine the risk and to develop a treatment plan.

Lifestyle Management [10]
Obesity care involves attention to three essential elements of lifestyle: dietary habits, physical activity, and behaviour modification. Because obesity is fundamentally a disease of energy imbalance, all patients must learn how and when energy is consumed, how and when energy is expended, and how to incorporate this information into their daily life.

1. Diet Therapy
The primary focus of diet therapy is to reduce the overall calorie consumption. The NHLBI guidelines recommend initiating treatment with a calorie deficit of 500–1000 kcal/d compared to the patient's habitual diet. This reduction is consistent with a goal of loosing approximately 1–2 lb per week. This calorie deficit can be accomplished by suggesting substitutions or alternatives to the diet. Examples include choosing smaller portion sizes, eating more fruits and vegetables, consuming more whole-grain cereals, selecting smaller cuts of meat and skimmed dairy products, reducing fried foods and other added fats and oils, and drinking water instead of caloric beverages. It is important that the dietary counselling remains patient centred and that the goals are practical, realistic, and achievable.
The dietary recommendations include, maintaining a diet rich in whole grains, fruits, vegetables, and dietary fibre; consuming two servings of fish high in omega 3 fatty acids per week; decreasing sodium to <2300 mg/d; consuming 3 cups of milk per day; limiting cholesterol to <300 mg/d; and keeping total fat between 20 and 35% of daily calories and saturated fats to <10% of daily calories.
A current area of controversy is the use of low-carbohydrate, high-protein diets for weight loss. These diets are based on the concept that carbohydrates are the primary cause of obesity and lead to insulin resistance. Most low-carbohydrate diets recommend a carbohydrate level of approximately 40–46% of energy. The Atkins diet contains 5–15% carbohydrate, depending on the phase of the diet.
Another dietary approach to consider is the concept of energy density, which refers to the number of calories (energy) a food contains per unit of weight. People tend to ingest a constant volume of food, regardless of caloric or macronutrient content. Adding water or fibre to a food decreases its energy density by increasing weight without affecting caloric content.

2. Physical Activity Therapy
Although exercise alone is only moderately effective for weight loss, the combination of dietary modification and exercise is the most effective approach for the treatment of obesity. The most important role of exercise appears to be in the maintenance of the weight loss. Currently, the minimum public health recommendation for physical activity is 30 min of moderate intensity physical activity on most, and preferably all, days of the week. Focusing on simple ways to add physical activity into the normal daily routine through leisure activities, travel, and domestic work should be suggested. Examples include walking, using the stairs, doing home and yard work, and engaging in sport activities. Asking the patient to wear a pedometer to monitor total accumulation of steps as part of the activities of daily living is a useful strategy. Step counts are highly correlated with activity level. Studies have demonstrated that lifestyle activities are as effective as structured exercise programs for improving cardio-respiratory fitness and weight loss.

3. Behavioural Therapy
Cognitive behavioural therapy is used to help change and reinforce new dietary and physical activity behaviours. Strategies include self-monitoring techniques (e.g., journaling, weighing, and measuring food and activity); stress management; stimulus control (e.g., using smaller plates, not eating in front of the television or in the car); social support; problem solving; and cognitive restructuring to help patients develop more positive and realistic thoughts about themselves.

Pharmacotherapy [11]
Adjuvant pharmacologic treatments should be considered for patients with a BMI >30 kg/m2 or with a BMI >27 kg/m^2, who also have concomitant obesity-related diseases and for whom dietary and physical activity therapy has not been successful. There are several potential targets of pharmacologic therapy for obesity. The most thoroughly explored treatment is suppression of appetite via centrally active medications that alter monoamine neurotransmitters. A second strategy is to reduce the absorption of selective macronutrients from the gastrointestinal tract. These two mechanisms form the basis for all currently prescribed anti-obesity agents.

Surgery [12]
Bariatric surgery can be considered for patients with severe

obesity (BMI ≥40 kg/m2) or those with moderate obesity (BMI ≥35 kg/m2) associated with a serious medical condition. Surgical weight loss functions by reducing caloric intake and, depending on the procedure, macronutrient absorption.

Gut micribiome cause for obesity

Initial Evidence of the Role of Gut Microbiota in Obesity. The worldwide increase in obesity has prompted researchers to investigate its aetiology which is multifactorial, involving environmental, dietary, lifestyle, genetic, and pathological factors. Although the gut microbiota were already established as a metabolic organ that could ferment non-digestible dietary components (particularly non-digested carbohydrates) to generate short chain fatty acids (SCFA), their role as a significant environmental factor affecting host adiposity through an integrated host signalling pathway was explored in 2004 by B¨ackhed and colleagues. This breakthrough evidence suggested that the gutmicrobiota induced adiposity by stimulating hepatic de novo lipogenesis and triglyceride storage through carbohydrate response element binding protein (Ch REBP) and sterol response element binding protein (SREBP1) and by suppressing fasting induced adipocyte factor (fiaf) which is an inhibitor of adipocyte lipoprotein lipase. The same group proposed that this intestinal "high efficiency bioreactor" [13-16] in certain individuals might promote energy storage (obesity), whereas a low-efficiency reactor would promote leanness due to lesser energy harvest from carbohydrate fermentation. Differences in the gut microbiota between obese and lean people were therefore worthy of further exploration [17-24].

Conclusion

Obese individuals and models all show a propensity for a dysbiosis that includes an increased ratio of Firmicutes: Bacteroidetes. This alteration in the proportion of bacteria in the lumen of the GI track affects not only the ability of the microbiome to generate energy sources from indigestible carbohydrates, but also the deposition of triglycerides in adipocytes. This altered bacteria also appears to have an increased exposure to the host immune system due to a leaky intestinal barrier and induces a constant state of chronic inflammation. This impact of the microbiota on obesity has led to multiple preliminary studies on the use of "good" probiotic bacteria to alter the obese phenotype.

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