# CHAPTER 2

# REVIEW OF LITERATURE

This chapter assembles the available literature pertaining to the study and is divided in to following sections.

2.1 History of Obesity

2.2 Global and National Prevalence of Non Communicable Diseases

2.3 Global and National Prevalence of Obesity

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## 2.1 History of Obesity

Obesity is not a recent phenomenon. Its origin can be traced back to our prehistoric ancestors. Statues dating from the Stone Age provide the earliest depiction of Obesity. The Venus of Willendorf is a figurine of an obese woman that dates back to 22000 BC. It is thought to represent a fertility Goddess. Through the centuries obesity has been depicted in the arts, literature and medical opinion both as a highly desirable state and as an unhealthy condition to be avoided. Egyptian temples prominently displayed statues of obese men and women while medical opinions written on papyrus at the time described obesity a disease state. Hippocrates, known as the father of medicine, noted that fat people were more prone to sudden death than were lean people. Stories and Chronicles from the Middle Ages portray obese individuals who are wealthy and powerful. Peter Paul Rubbens, a well-respected artist of the 17$^{th}$ century, painted ample, robust women who today would be labeled as obese but were considered idols of female beauty at that time. In 1737, Benjamin Franklin observed in his Poor Richard's *Almanack- "*To lengthen thy life, lessen thy meal". In the 1930's, it was rumored that the duchess of Windsor declared, "You can never be too rich or too thin", setting a benchmark for socialites then and now.

Although overweight was sometimes linked with disease and a shorten life span, in general, extra fat was related to wealth, health and attractiveness. Low weight and thinness were associated with poverty and malnutrition and wasting diseases such as tuberculosis. Scarcity of food throughout most of history meant that most people did not have the opportunity to become obese. The tendency to store in the form of fat results from thousands of years of evolution in an environment characterized by limited or uncertain food supplies. Those who could store energy in times of plenty were more likely to survive periods of famines and to pass this tendency to their off spring. Obesity as a disease with pathologic consequences for a large percentage of the general public is less than the century old. The current availability of inexpensive, high energy food and the reduced need to expend energy for daily living and work has allowed obesity to become "equal opportunity" state of health. (Stern and Kazaks 2009).

## 2.2 Global and National Prevalence of Non Communicable Diseases

**NCDs are estimated to kill around 38 million people per year, accounting for 68% of all deaths worldwide.**

**(WHO 2015)**

**WHO 2015 Factsheet**

- Non communicable diseases (NCDs) kill 38 million people each year.
- Almost three quarters of NCD deaths - 28 million - occur in low- and middle-income countries.
- Sixteen million NCD deaths occur before the age of 70; 82% of these "premature" deaths occurred in low- and middle-income countries.
- Cardiovascular diseases account for most NCD deaths, or 17.5 million people annually, followed by cancers (8.2 million), respiratory diseases (4 million), and diabetes (1.5 million).
- These 4 groups of diseases account for 82% of all NCD deaths.
- Tobacco use, physical inactivity, the harmful use of alcohol and unhealthy diets all increase the risk of dying from an NCD.

A non-communicable disease, or NCD, is a medical condition or disease which by definition is non-infectious and non-transmissible among people. NCDs may be chronic diseases of long duration and slow progression, or they may result in more rapid death such as some types of sudden stroke. They include autoimmune diseases, heart disease, stroke, and type of cancers, asthma, diabetes, chronic kidney disease, osteoporosis, Alzheimer's disease, cataracts, and many more. Non-communicable diseases continue to be important public health problems in the world, being responsible for sizeable mortality and morbidity.

Non-communicable disease continues to be an important public health problem in India, being responsible for a major proportion of mortality and morbidity. Demographic changes, changes in the lifestyle along with increased rates of urbanization are the major reasons responsible for the tilt towards the non-communicable diseases (Upadhyay PR 2012). Total deaths from NCDs are projected to increases by a further 17% over the next 10 years. In India, 53% of all deaths in 2005 were estimated to be due to non-communicable diseases (WHO 2007).

The projected cumulative loss of national income for India due to non-communicable disease mortality for 2006-2015 is expected to be USD237 billion. By 2030, this productivity loss is expected to double to 17.9 million (WHO 2005).

## 2.3 Global and National Threat of Obesity

As developing societies like India industrialize and urbanize, and as standards of living continue to rise, weight gain and obesity are beginning to pose a growing threat to the health of the citizens (Shetty 2002). In addition, 44% of the diabetes burden, 23% of the ischemic heart disease burden and between 7% and 41% of certain cancer burdens are attributable due to overweight and obesity. Approximate 1.5 billion adults, 20 years and older, are overweight. Of these 1.5 billion overweight adults, over 200 million men and nearly 300 million women are obese. Overall, more than one in ten of the world's adult population is obese (Visscher and Seildell 2010).

### 2.3.1 International Status:

**WHO 2015 Fact sheet for overweight and obesity**

Some recent WHO global estimates follow

- In 2014, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 600 million were obese.
- Overall, about 13% of the world's adult population (11% of men and 15% of women) were obese in 2014.

- In 2014, 39% of adults aged 18 years and over (38% of men and 40% of women) were overweight.
- The worldwide prevalence of obesity more than doubled between 1980 and 2014.

Once considered a high-income country problem, overweight and obesity are now on the rise in low- and middle-income countries, particularly in urban settings. In developing countries with emerging economies (classified by the World Bank as lower- and middle-income countries) the rate of increase of childhood overweight and obesity has been more than 30% higher than that of developed countries. Overweight and obesity are linked to more deaths worldwide than underweight. Most of the world's population live in countries where overweight and obesity kill more people than underweight (this includes all high-income and most middle-income countries).

**Projections**

Overall 23.2% of the world's adult population in 2005 was overweight. The estimated total numbers of overweight and obese adults in 2005 were 937 million and 396 million (388–405 million), respectively. By 2030, the respective number of overweight and obese adults was projected to be 1.35 billion (Kelly and He 2008).

**2.3.2 National status:**

Obesity has reached epidemic proportions in India in the 21st century; with morbid obesity affecting 5% of the country's population. India is following a trend of other developing countries that are steadily becoming more obese. According to the NFHS III, 10 percent of India's population was either overweight or obese in 2006. The prevalence of obesity in males and females is going to increase in the next five years, while another from urban Delhi, among a large representative sample of 13,414 adults (aged 25–64 years), showed an overall prevalence of 27.8% (Gothankar, 2011).

Lancet in 2014 reported that India with 41 million obese people, ranks third after the US and China in having the highest number of overweight people in the world, says a study. Together, India and China represent 15 percent of the world's obese population, with 46 million and 30 million obese people, respectively. One in five Indian men and women are either overweight or obese (NG. et al., 2014) (Figure 2.1).

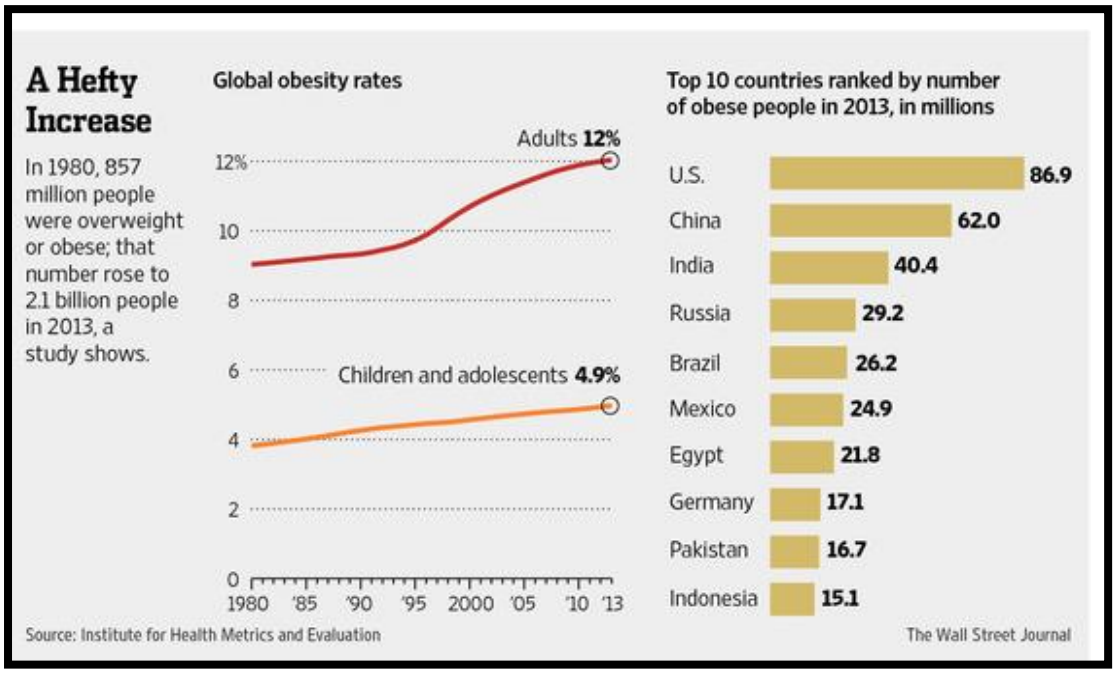


**Figure 2.1: Status of rise in obesity in top 10 countries of World from 1980-2013**

### 2.3.3 Gujarat status:

A research carried out in Maharashtra, Delhi and Gujarat from November 30, 2009 to January 6, 2010, revealed that obesity is highest among Gujaratis (Iyer, Dhruv and Patel, 2011). Nearly 25 percent adults in Gujarat were found to be overweight. According NFHS 3, (2006-06) 15.4% males and 20.3% females were found to be obese in Gujarat.

## 2.4 Defining and Measuring Over Weight and Obesity

Defining Over weight and obesity is somewhat subjective and imprecise. “Overweight” is defined as having more body weight (BMI ≥23 and <25 kg/$m^2$ for Asians and ≥25 <30 kg/$m^2$ Caucasians. The term “Obese” is used for very overweight people who have a high percentage of body fat (≥25 for male and ≥30 for females)

and BMI ≥ 25 kg/m2 for Asians and ≥30 kg/m2 for Caucasians (WHO 2015). Normal weights have been variously referred to as “Ideal”, “Desirable”, or “Healthy”. In addition to these subjective terms, there are several objective measured that are used to classify the individual weight.

### 2.4.1 Indirect Measuring Methods

#### a. Height – Weight Tables

In 1942, Louis Doublin of statistician metropolitan life insurance company, grouped some 4 million people who were insured with metropolitan life into categories based on their height, body frame (small, medium or large), and weight. He discovered that those who live the longest were the people who maintained their body weight at the level for average 25 year old. The results were published in the MetLife standards height – weight tables form men and women, which were transformed for a record of national averages of weight in relation to age, sex and height to the accepted guides for a healthy weight (MLIC 1942, 1943). In 1959, research indicated that the lowest mortality rates were associated with lower than average weights, and the phase “Desirable weights” replaces “ideal weights” in the height and weight table (MLIC 1959). The weights were derived from those weights for height proportion associated with lowest mortality among people in United States and Canada who purchased Life Insurance policy from 1935 to 1954. However, these weights were associated with the lowest death rates but not necessarily with the lowest morbidity (The rate of illness or disease). In 1983, the tables were revised once again and called simply “Height and Weight tables”. The weights given in 1983 tables are heavier than the 1942 tables because, in general, heavier people were living longer (MLIC 1983). It is interesting to note that neither medical nor academic experts were the authoritative voices in setting weight guidelines. It was the life insurance industry that established the system of weight classification that became part of medical practice throughout the United States (Stern and Kazak 2009).

A number of criticisms surrounded the use of a table to determine whether an individual is at the right weight or even what “ideal weight” means. Experts have criticized the validity of the MetLife tables for several reasons:

- Insured people tend to be healthier than uninsured people.
- Frame size was not consistently measured.
- The tables were based on predominantly whites, middle class population.
- Some individuals were actually weighed and some reported their estimated weight.
- Height and weight were measured in people wearing shoes and clothing of varied amounts and weights.
- Both smokers and non-smokers were included.
- Smoking is a significant factor that increases risk of disease and death.

Thus, height – weight table should be used only as a guide and other measurements should be included for health evaluation.

People in United States were able to find out how much they weighed when Penny scales were imported from Germany in the 1880's. Soon after, The National Scale Company manufactured the first coin operated scales in United States. These scales were amongst the first automatic vending machines. Being able to weigh oneself was a novelty at that time and during the 1920 and 1930, coin operated scales appeared in the drug stores in almost every city and town. In the 1940's, improvement in the mechanical scale technology made inexpensive personal scales available for in home use. Today we can choose from the scales that are "digital", "solar powered", "talk" and say the weight aloud. The accuracy in these scales may vary, but they serve the general purpose of measuring weather body weight is going up or down.

**b. Estimated Ideal Body Weight**

In 1964, Doctor GJ Hamwi developed a simple rule for estimating an Ideal Body Weight (IBW). The Hamwi formulas have become very popular since they first appeared in the publication of American Diabetes Association (*Geriatric Nutrition Handbook 1998*). They have remained well-accepted methods of calculating ideal weight in clinical situations. The formula for IBW are –

MEN - 106 Pounds for the first 5 Ft.; 6 pounds for each inch over 5 Ft.

WOMEN- 100 Pounds for the first 5 Ft; 5 Pounds for each inch over 5 Ft.

In addition, a range of 10% variation above or below the calculated weight was allowed for individual differences.

The IBW does not correlate weight to health or prevention of disease. Divine in 1974 reported that one criticism of IBW formula is that it does not allow form body composition or body type. Someone with large bones or with a high percentage of lean tissue (Muscle) would appear to be over-weight according to this method. Form some, the IBW may be unrealistic range and they may try unnecessary or sad dieting to reach the "ideal" number.

**c. Body Mass Index (BMI)**

As definition of overweight has varied widely, health experts have struggled to develop a useful definition of healthy weight. Their recommendations have evolved from weight for height standards to sex specific references. The most recent proposal is to use a single number, the Body Mass Index (BMI) that is applied to all adults. BMI is calculated number based on Height and Weight of an individual.

It is calculated as: **BMI= Weight (Kg) / Height$^2$ (m)**

This number is used to analyze the health effects of body weight. Because it is independent of age and reference population, BMI can be used for comparisons across studies both in The United States and Internationally. The BMI is most generous than the IBW. BMI calculations are to be only to adults over age 20. At age 2, children can be given a BMI number; however, they are rated differently from the adults.

The BMI was first developed in the mid 1800's by a Belgian mathematician named Adolph Quetelet. He worked with life insurance companies to determine factors relating to birth and death. These types of correlations using body weight are common now, but in 1833, the idea was revolutionary. More recently, governmental agencies and scientific health organizations have defined a BMI that correlates with the health risk of overweight using a statistically derived definition from a series of professional surveys called the National Health and Nutrition Examinations Surveys (NHANES). These surveys are designed to gather information on health and

nutritional status of the population of The United States. From 1985 to 1988, the definition of overweight in government publication was a BMI of at least 23.7 for Women and 27.8 for Men. In 1995, the World Health Organization recommended a new classification system that included 3 “Grades” of overweight using BMI cut off points of 25, 30 and 40. The international obesity task force suggested and additional cut off point of 35. Eventually, in June 1988, an expert panel convened by the National Institutes of Health (NIH) released a report that identified being overweight as having a BMI between 25 and 29.9 and being Obese as having a BMI of 30 and above. These definitions widely used by the federal government and increasingly used by the broader medical and scientific communities are based on evidence that health risk increase more steeply in individuals with a BMI greater than 25. The term “morbid obesity” is still used for medical coding purposes for individuals with a BMI of 40 or above; however, the NIH recommends the use of other descriptive terms, such as “Class 3 Obesity”, “extreme Obesity” or “Clinically severe Obesity”. Use of BMI cutoffs have been varied, yielding contrasting results. A shift in BMI criteria can have a large effect on the population at risk ( Beydoun and Wang 2009).

**Limitations and Short Comings**

Measuring body weight and body dimension- or anthropometry- is a quick and inexpensive way to estimate body fatness. However, using calculated numbers such as BMI does have limitations. A problem with using BMI as a measurement is that very muscular people may be identified as overweight. Similarly people who have lost muscle mass, such as elderly, may have a weight that is in the healthy BMI category when they actually have a high percentage of Body Fat. The health risks associated with overweight and obesity are based on a continuum and do not necessarily correspond to strict cut off points. For example, an overweight individual, with a BMI of 29 does not substantially add to his or her consequences simply by moving up one notch to a BMI of 30, the threshold of obese category (CDC 2009a). Because health risks generally do increase with increasing BMI, it is a useful screening tool for individuals and a general guide line to monitor trends in the population. By itself, BMI is not diagnostic form individual health status. Further assessment should be performed to evaluate associated health risks.

BMI does not account how people of different races and ethnicities vary in muscle mass vs. fat mass. People of African and Polynesian ancestry may have less body fat and more lean mass for a given weight and thus higher base line BMI for overweight and obesity may be appropriate for these populations. At the other end of the scale, one study found that current BMI thresholds significantly underestimate health risks in many non-Europeans (Gallagher 2004). The Body Fat percentage of an Asian would be higher than that of Caucasian of the same height and weight (Deurenberg 2002; Seidell and Kahn 2001; Norgan 1994). Even within normal BMI ranges, Asian groups have a higher risk of weight related health problems and they begin to have abnormalities in their blood glucose levels above a BMI of 21. It has been suggested that BMI level be dropped to 23 and 25 for overweight and obesity, respectively among Asian populations (Jane et al. 2014; Stevens and Juhaeri 2002; James 2002).

**d. Waist circumference**

The presence of excess fat in the abdomen, out of proportion to total body fat, is an independent predictor of risk factors and morbidity (Ley and Hamdy 2014). Fat located in the abdominal region is associated with greater health risks than that in peripheral regions, e.g., the gluteal-femoral area (Donahue and Abbott 1987; Ducimetiere and Richard 1989). Presence of increased total abdominal fat appears to be an independent risk predictor when the BMI is not markedly increased (Lemieux and Prud'homme 1996). Therefore, waist or abdominal circumference, as well as BMI, should be measured not only for the initial assessment of obesity, but also as a guide to the efficacy of weight loss treatment.

**e. Waist to Hip Ratio**

The waist-to-hip ratio (WHR) also has been used in a number of epidemiologic studies to show increased risk for diabetes, coronary artery disease, and hypertension (Albu and Murphy 1997). However, waist circumference has been found to be a better marker of abdominal fat content than is WHR (Rosito, et al., 2008). Whether WHR imparts any independent information about disease risk beyond waist circumference is uncertain, but between the two, the waist circumference appears to carry greater prognostic significance. Therefore, in clinical

practice, abdominal fat content should be assessed and followed by measuring waist circumference.

**f. Assessing percentage of body fat**

BMI is not the specific index of fatness because its numerator-measured body weight- may reflect muscle, bone or body water in addition to fat. The percentage of body fat is difficult to measure directly. Fat or adipose is stored underneath the skin as subcutaneous fat; as intramuscular fat, interspersed in skeletal muscle; and as visceral adipose tissue, found deep in the body around vital organs.

**i. Bioelectric impedance:** *Bioelectric impedance analysis* (BIA) measures impedance of the body to a small electric current. The generic theoretical model treats the body as a single cylinder, with measurements made between electrodes placed manually on the wrist and ankle. Adjustment of bioelectrical data for height allows estimation of total body water (TBW). In practice, this requires the empirical derivation of regression equations relating height$^2$/impedance to TBW. These equations are then applied subsequently to predict TBW, which is converted to FFM as described below (Wells and Fewtrells 2006).

**ii. Dual energy x ray absorptiometry:** Dual energy x ray absorptiometry (DXA) was developed to measure bone mineral mass, which is calculated from the differential absorption of x rays of two different energies. Because this calculation requires allowance for (and hence quantification of) overlying soft tissue, values of fat and FFM are also calculated for whole body scans, using instrument specific algorithms (Wells and Fewtrells 2006).

**iii. Magnetic resonance imaging:** MRI is an imaging technique that estimates the volume rather than the mass of adipose tissue. By analyzing the absorption and emission of energy in the radio frequency range of the electromagnetic spectrum, the technique produces images based on spatial variations in the phase and frequency of the energy absorbed and emitted. It primarily addresses hydrogen nuclei, located either in water or fat, and uses these data to discern tissue types in "imaging slices" which can then be summed to calculate regional tissue volumes (Wells and Fewtrells 2006).

## 2.5 ETIOLOGY OF OBESITY

### a. Socio demographic

A number of factors have been linked to obesity, including age, gender and socio-economic status (Figure. 2.2) the prevalence of overweight and obesity have emerged across in different socio-economic groups. In developed countries, levels of obesity are comparatively higher in the lower socio-economic groups (Braunschweig et al., 2005). A person's education is closely linked to his income and wellbeing (Battle and lewis 2002). Researches have shown that obesity rose with a nation's economic development. In lower-income countries, people with higher SES were more likely to be obese. Conversely, in high-income countries, those with higher SES were less likely to be obese (Pampel and Denney 2012; Caballero 2007; Astrup 2008). Why the reversal? It may be that in lower-income countries, higher SES leads to consuming high-calorie food and avoiding physically tough tasks. But in higher-income countries, individuals with higher SES may have responded with healthy eating and regular exercise. The implication is that while economic development improves health, "problems of malnutrition are replaced by problems of overconsumption that differentially affect SES groups," noted the authors (Mayén et al., 2014; Pampel and Denney 2012). But some developing countries, such as India, are facing continued high levels of malnutrition along with a rise in obesity (Ravishankar 2012).

Globalization of agrifood has brought about remarkable shifts in diet patterns especially in developing countries which has shown to be a major underlying factor for increasing prevalence of obesity and associated NCDs. With long standing history of infectious diseases, developing countries are now facing a rising tide of non-communicable diseases which is popularly known as the double burden of malnutrition (Coexistence of over- and undernutrition) (Bishwajit 2015).

Age is also a major key factor in determining the role of childhood obesity. Studies have demonstrated that there are specific periods in the growth and development of a child which may lead to obesity. The childhood obesity has been identified as a risk

factor for obesity in adulthood and is associated to an increased adult morbidity and mortality (Oner et al., 2004).

It has been established through long term follow up studies that obese children and adolescents tend to become obese adults (Warden and Warden 1997). A child or adolescent with a high BMI percentile had a high risk of being overweight or obese at 35 year of age (Guo and Roche 2002).


**Figure 2.2: Etiology of Obesity**

**b. Dietary factors**

Food habits are the way in which individuals responds to social and cultural pressures, choose, consume, and make use of available foods. As populations become more westernized, dietary composition changes to include more saturated fat and less fiber (Taylor and King 1992). According to Popkin, an urban population has a distinctly different diet from a rural population. The urban diets include superior grains, more milled and polished grains, higher fat content, more animal products, more sugar, and more prepared and processed food (Mayén, et al 2014; Popkin 1996). When nutrition transition occurs, the impact is usually seen first among the affluent, than among the lower income classes (Bishwajit 2015; Delpeuch and Marie 1997). Within income groups, these changes are often seen first among

adults then among adolescents and subsequently in children. The growing popularity of fast food is just one of many cultural changes that have been brought about by globalization and is a part of nutrition transition (Jeffery 2006; Popkin and Barry 2004; Drewnowski and Popkin 1997, Popkin 1994).

The fat intake plays a major role in the energy imbalance and thus results in body weight changes (Poti and Duffey 2014; Morton 2006; Drewnowski, and Specter 2004). The dietary fat has a higher energy density and is responsible for overeating and passive over consumption of high fat diets. The results revealed that infrequent intake of breakfast, frequent consumption of fast foods, low serving of fruits, vegetables and milk and milk products per day along with frequent consumption of sweets/candy and carbonated beverages all were proctors of the obesity and overweight (Poti and Duffey 2014; Amin et al.,2008).

Consumption of high sugar beverages is becoming more and more popular amongst children and adolescents. Various studies have shown an association of consumption of these beverages and increased prevalence of adolescent obesity (Pereira, 2006; Sharma 2006). The increasing portion sizes especially of processed food items in developed countries are contributing to obesity (Canella et al., 2014; Morland 2006). Several investigators have shown that food portion size positively related to energy intake. The increase in portion sizes of food items like processed food, bakery, beverages, fast food *etc*. have led to increased caloric intake and obesity (Muñoz-Pareja,et al.2013; Nestle 2003, Wright 3003).The dietary intake patterns have a role to play in causing obesity (Nozue et al., 2007). The dietary pattern varies widely across population and cultures. Regular snacking has been associated with the increased overall dietary intake in the affluent societies (Muñoz-Pareja, et al., 2013; Bertéus et al., 2005; Drummond 1996).

**c. Physical Activity level**

Although, the etiology of obesity is likely to be multi factorial, the energy balance equation suggests that the obesity results from an imbalance between energy intake and expenditure (Hall et al., 2011; Zhang and Zhang 2008; Blackburn 2002, Gortmaker and Cheung 1990). The components of energy expenditure are the basal

metabolic rate (BMR, about 60%), thermogenesis (about, 10%) and physical activity (about 30%) (Rising and Harper 1994). The BMR varies by a small amount amongst individual. Similarly, adaptations in thermogenesis are also small. However, large variations occur in physical activity (PA) as it forms a major and modifiable component of energy expenditure. The low and decreasing levels of PA are primarily responsible for obesity (Du and Bennett, 2013; Andreasen 2008; Larsen, and Nelson 2006; Esparza et al., 2000).

Increased physical activity and reducing sedentary behaviors have been suggested as the key elements of the strategy to reverse this epidemic of obesity (Blanchard et al., 2005; Treuth, 2007). Several studies have suggested an inverse relationship between the BMI and the physical activity both among adults and children (Duvivier et al., 2013; Ross and Janssen 2001, Larsen and Popkin 2000). A beneficial effect of PA on obesity has been demonstrated in many studies. A study showed that the prevalence of obesity was lower among individuals who were in the habit of performing exercise (Johansson et al., 2014; Collings et al 2013; Hiraoka 1998). Similar findings were observed in other studies also (Ekelund et al., 2015; Miller et al., 2013; Moayeri 2004).

The process of modernization has led to changes in lifestyle of people leading to improvement in their standard of living. This has been associated with unwanted life styles changes like decreased physical activity and increased sedentary work. Improvement in motorized transport and availability of house hold gadgets like washing machines, vacuum cleaners, dish washers *etc*. all have caused reduction in the PA level. Obese and overweight individuals are less physically active than their lean counterparts.

**d. Genetic factor**

The genetic determinants of obesity have been intensely studied in the past decades. Family studies have shown that heritability rates of total body fat mass are 50% ((Henkin et al., 2003; Katzmarzyk and Malina 2000). A Human Obesity Gene Map has been generated and updated in the recent years. In the last updates of this authoritative review, as many as 135 candidate genes had been identified as being

linked and/or associated with obesity-related phenotypes, in addition to 253 quantitative trait (Perusse et al., 2005). A recent study on obesity-related genetic variants was performed in close to 250,000 individuals in whom 2.8 million single-nucleotide polymorphisms were genotyped. However, the combined effect of these genetic variants on obesity was modest, accounting for 6–11% of the genetic variation in BMI. Hence, factors other than DNA sequence variants alone are likely to explain the high heritability rates of obesity. These possibly include gene-gene interactions, gene-environment interactions, as well as epigenetics (Speliotes and Willer 2010).

With regard to body fat distribution, rather high heritability rates have been reported. Indeed, familial transmission reaches 50% of the age, sex and total body fat-adjusted variance (Hong et al., 1998). Segregation analyses even pointed toward a major gene effect accounting for 51% of the variance in visceral adipose tissue accumulation (Bouchard et al., 1996). This notion is further supported by seminal twin studies in which weight gain was induced by overfeeding. These studies showed that the variance in visceral adipose tissue gain between pairs of twins was approximately six times higher than within twin pairs, again supporting a major genetic effect on visceral fat distribution.

Family studies have shown a clear clustering of visceral adiposity (Rice and Pérusse 1996). Genome-wide scans for measures of body fat distribution including waist circumference, or CT-measured visceral adipose tissue area, have led to the identification of several loci and candidate genes that could be of potential interest (Fox and Costa 2007; Norris et al., 2009; Perusse et al., 2001; Rice et al., 2002). Similarly, several recent studies have identified genetic variants that may be related to preferential accumulation of visceral adipose tissue accumulation in various populations (Katsuda et al., 2007, Berthier et al., 2004; Bouchard et al., 2004; Mussig 2009; Pausova 2010; Peeters and Beckers 2007). Several studies have also identified genetic variants that are associated with an increased susceptibility to the metabolic complications of visceral obesity (Couillard et al., 2003; Pierre et al., 2003). Most of these genetic variants need to be further validated and functionally characterized. Moreover, the relative impact of isolated variants, much like with overall adiposity

measures, is quite low (Perusse et al., 2001). Yet, clear genetic influences have been noted at the level of overall obesity, regional fat distribution, as well as the presence of altered metabolic parameters. This underscores the complex nature of the genetic contribution to visceral obesity.

The expression of obesity varies with social, environment, cultural, economic and physiological influences. The general consensus among scientists is that the genetic factors do modulate environmental risks of obesity. A study on twin adoption and family strongly suggests that the biological family members exhibit similarities in the maintenance of body weight (Wu and Suzuki 2006; Maffeis and Schutz 1997; Alison et al., 1998).

**e. Environmental factor**

Changing societal structures due to economic transition have given rise to various problems like unemployment, overcrowding and family breakdown. These negative consequences play direct or indirect role which determine the nutritional and physical activity patterns which contribute to the development of obesity. Culture affects both food intake and physical activity pattern (Cruwys and Bevelander 2015; Agne and Daubert 2012; Richer 2002). Cultural behaviours and beliefs are learned in childhood, are often deeply held. The cultural factors are among the strongest determinants of food choice (Verstraeten et al., 2014; WHO 1997). There is increasing evidence that children and adolescents of affluent families are overweight possibly because of decreased physical activities, sedentary lifestyles, altered eating patterns and increased fat content of the diet (Du and Bennett, 2013; PAN 2000, Kapil and Bhasin 2002).

**f. Ethnicity**

The pronounced differences in regional adipose tissue distribution among various populations worldwide are well known. For a given amount of weight gain, some populations may be prone to accumulate adipose tissue in the subcutaneous adipose depots, whereas other populations may be more likely to accumulate adipose tissue in the visceral cavity. Ethnicity, therefore, critically needs to be considered in the identification of high-risk cases of obesity, especially in the definition of cut-off

values of anthropometric measurements (Lear and James 2010; Lear and Humphries 2007; Katzmarzyk and Bray 2011).

A national United States study of 9,179 individuals with over sampling of minority ethnic groups showed significant ethnic differences in body weight, with African-American and Hispanic populations at highest risk of obesity compared with Caucasian populations (McTigue and Garrett 2002). In Asian populations, a higher body fat content was reported at lower BMI values compared with Caucasians (Deurenberg 2002). The significant ethnic differences in mean BMI may possibly be explained by intrinsic differences in body composition (Lear 2009). Asians and Indian Asians seem to be especially prone to visceral fat accumulation despite lower total adiposity values compared with individuals from other ethnic backgrounds (Lear et al., 2007; Misra and Hurana 2009). Several hypotheses have been put forward regarding the physiological explanation of ethnicity-related differences in body fat distribution, the most plausible being related to genetic and epigenetic programming of the propensity of each fat compartment to store lipids (Misra and Khurana 2009; Sniderman 2007). Overall, the greater propensity of some populations to accumulate visceral adipose tissue could contribute to their higher rates of type 2 diabetes and CVD.

**g. Birth Weight factor**

Studies have documented that adult obesity has an association with birth weight (McDonald and Han 2010). It has been reported that in intrauterine growth retardation (IUGR) newborns, a fetal programming is caused due to a limited nutrient supply during pregnancy, which makes these children to alter their physiology of handling nutrients later in life. These affected children have persistent elevated insulin secretion that results in developing cardiac disease (Barker 1999). Recent studies suggest that the metabolic syndrome originates at fetal stage (Ozanne and Hales 2002, Levitt NS, Lambert 2002). A birth cohort study undertaken in Finland on 5,210 subjects revealed that the incidence of obesity increased with increase in birth weight and ponderal index (Cnattingius et al., 2012; Eriksson 2001).

Another study done on 1,750 men and women has shown a positive association between birth weight and adult BMI (Tene 2003).

Birth weight and attained physical size during childhood were positively correlated with increased prevalence of obesity and overweight in adulthood (Monteiro and Monteiro 2003). Evidence from the animal and human studies suggests that malnutrition in utero or in early life, endocrine development may be affected, which results in hormonal alteration and a predisposition to metabolic disorders and obesity (Barker 1999).

**h. Hypothalamo-Pituitary-Adrenal Axis, Stress, and Glucocorticoids**

Excessive circulating glucocorticoid concentrations, as observed in Cushing's syndrome, create a pathological phenotype of abdominal obesity, dyslipidemia, insulin resistance, and hypertension (Peeke and Chrousos 1995). In most cases, cortisol hypersecretion origins from the pituitary gland (Cushing's disease) and results from excessive adrenocorticotropic hormone secretion. While individuals with idiopathic abdominal obesity share several of the morphological and metabolic alterations observed in Cushing's syndrome, alterations in the sensitivity and drive of the hypothalamo-pituitary-adrenal (HPA) axis have been shown to be much more subtle (Pasquali and Vicennati 2000; Duclos et al., 2001). Early studies by the group of Björntorp and collaborators (Björntorp 1993) had demonstrated that the cortisol response to stress induced by cognitive tests or cold exposure was positively related to abdominal sagittal diameter in premenopausal women. More recently, primate studies have suggested that social stress in primate colonies may be related to increased visceral obesity and coronary artery disease (Shively and Register 2009). A number of studies and review articles seem to point toward such an effect in humans (Dallman et al., 2004; De Vriendt and Moreno 2009; Donoho 2011; Kyrou and Tsigos 2008; Kyrou and Tsigos 2007; Weigensberg and Corral 2008; Vines et al., 2007). These studies suggest that chronic stress or poor coping in stressful situations is associated with mild hypercortisolemia and prolonged sympathetic nervous system activation, which in turn could favor accumulation of visceral fat (Kyrou and Tsigos 2009).

**i. Hypothyroidism**

In this condition there is not enough thyroid hormone (thyroxine) to control normal rate of metabolism (Knudsen et al., 2005). Hence, the metabolism slows down. It can lead to fatigue and weakness of muscles, reducing the activity of the person. Thus underactivity of the thyroid gland can lead to increase in body weight (Moon et al., 2013).

**j. Central mechanism in body weight regulation**

In the CNS, the hypothalamus is the key region involved in the regulation of appetite (Murphy and Bloom 2004). It had previously been hypothesized that satiety was controlled by the ventromedial hypothalamic nucleus, and that feeding was controlled by the lateral region (Vettor and Fabris 2002).

**i. Leptin:** Early propositions surrounding the regulation of body weight implicated body fat content as a key player in a so-called adipostat mechanism (Kennedy 1953), which hypothesized the presence of an unknown circulating factor capable of relaying information to the hypothalamus. Several factors were subsequently proposed, but inconclusively proven, until the revolutionary discovery of leptin in 1994 (Zang 1994).

Expressed and secreted exclusively by white adipose tissue adipocytes, the circulating levels of leptin are proportional to fat mass (Ferrannini and Rosenbaum 2014; Murphy and Bloom 2004). Either peripheral or central administration of leptin has been demonstrated to reduce food intake and body weight and increase energy expenditure in rodents (Rosenbaum and Leibel, 2014; Friedman and Halaas 1998), and activation of hypothalamic neurons expressing the leptin receptor has suggested the mediation of its effects via this central region (Murphy and Bloom 2004). Leptin represents one of the core components of the physiological system that controls body weight in mammals. Humans with leptin deficiency are obese (Katarina 2014; Montague et al., 1997) and decreased leptin production from white adipose tissue has been demonstrated to contribute to a plethora of metabolic abnormalities associated with visceral obesity (Paz-Filho 2009).

A study in obese men demonstrated that circulating leptin levels adjusted for body fat were inversely correlated with body weight, suggestive of a leptin deficient state associated with obesity (Paz-Filho 2009). Obesity, however, is also often associated with increased circulating leptin levels (Maffei et al., 1995)This, combined with the lack of expected corresponding leptin-mediated effects, has given rise to the concept of leptin resistance (Enriori et al., 2007). In many of these cases, despite high circulating levels and the presence of functional receptors, the expected anorexigenic effects of leptin are significantly diminished (Rabe and Lehrke 2008) Receptor overstimulation, and thus activation of negative feedback loops that serve to block leptin signaling, has been proposed as a possible contributing factor to the development of leptin resistance (Knight and Hannan 2010).

**ii.** **Insulin**: As an adiposity signal, insulin is believed to have a similar lipostatic role to that of leptin, although its central effects on food intake and energy homeostasis are less efficient (Katarina 2014; Frutos et al., 2007). Similar to leptin, circulating insulin levels are proportional to the degree of adiposity (Rocha et al., 2011)Central administration of insulin in rodents has been shown to reduce food intake and body weight (Air and Benoit 2002), as with leptin, increased adiposity can lead to a decrease in insulin sensitivity and a state of insulin resistance (Adam et al., 2009). Adiposity might in fact be a consequence of insulin resistance itself (Morrison and Glueck 2008).

**iii.** **Gut Hormones**: Feeding is ultimately controlled by the central nervous system but is strongly influence by numerous physiological signal arising from the periphery that either promote or limit energy intake (Hameed and Dhillo 2009). Broadly speaking these gut hormone act via neuroendocrine mechanism to communicate information on changing energy status from the periphery of brain Ritter 2004; Grill and Hayes 2012; Moran 2006). Some of these peptides are produced by gastro intestinal tract itself. Most of these gastro intestinal derived signal, including cholecystokinin, glucagon-like peptide-1, and peptide YY, promote meal termination; in contrast the hunger hormone ghrelin promotes the ingestion of food when readily available energy is low (Mietlicki-Baase and Hayes 2015; Cho 2011; le Roux et al., 2007) (Table 2.1).

## 1. Cholecystokinin

CCK, the first gut hormone reported to affect appetite (Gibbs and Young 1973), has been shown to dose-dependently reduce food intake in both rats (Gibbs and Young 1973) and humans (Geliebter, 2013; Lieverse and Jansen 1995) and in response to meal initiation, plasma levels have been reported to rise within 15 min (Liddle 1985). Within the GI tract, CCK is predominantly synthesized and released from the duodenum and jejunum (Buffa and Solcia 1976), where its local regulatory effects include stimulation of gallbladder contraction and inhibition of gastric emptying (Hon et al., 2013; Dufresne and Seva 2006). Centrally-administered CCK has been shown to reduce food intake in rodents (Matson CA, Reid 2000), whereas peripheral administration has been shown to reduce food intake in both rodents and humans, through a reduction in meal size and duration (Ronveaux and Tome 2015; Kissileff 1981). As a result, CCK has been investigated as a potential therapeutic target for the management of obesity (Hameed and Dhillo 2009).

**Table 2.1: Peripheral effects of selected food intake-regulating gut hormones**

| Gut hormone | Site of synthesis | Food intake-regulating receptor | Peripheral effect on food intake |
|---|---|---|---|
| CCK | Intestinal L-cells | $CCK_A$ | Decrease |
| Ghrelin | Stomach | GHS | Increase |
| PP | Pancreas/colon | Y4R | Decrease |
| PYY | Intestinal L-cells | Y2R | Decrease |
| GLP-1 | Intestinal L-cells | GLP1R | Decrease |
| OXM | Intestinal L-cells | GLP1R? | Decrease |

**Abbreviations:** CCK, cholecystokinin; $CCK_A$, cholecystokinin receptor subtype A; GHS, growth hormone secretagogue receptor; GLP-1, glucagon-like peptide-1; GLP1R, GLP-1 receptor; OXM, oxyntomodulin; PP, pancreatic polypeptide; PYY, peptide YY; Y2R, PYY Y2 receptor; Y4R, PP Y4 receptor

## 2. Ghrelin

The 28–amino acid peptide hormone ghrelin, produced predominantly in the stomach (Kojima et al., 1999) represents the only known orexigenic gut hormone identified to date (Schubert and Sabapathy 2014; Hameed and Dhillo 2009). Ghrelin binds to the growth hormone secretagogue receptor which is highly expressed in the hypothalamus and brain stem (Kojima 2000). Since its discovery in 1999 (Kojima et al., 1999) ghrelin has been proposed to function as a meal initiator, in part due to its potent), appetite-stimulating effects in free-feeding rats (Tschop and Smiley 2000).

Ghrelin has also been shown to stimulate appetite in both lean and obese humans (Gamma et al., 2014; Wren et al., 2001; Druce 2005), and infusion (intravenous) in healthy volunteers, at a concentration similar to that observed after a 24 h fast, has been shown to increase appetite and food intake at a buffet-style meal by almost 30% (Murphy and Bloom 2004; Gamma et al., 2014). Subcutaneous injection has also been shown to significantly induce appetite and increase food intake (Druce et al., 2006) however, numerous other studies have reported no changes and increases (Garcia-Fuentes et al., 2008; Ybarra et al., 2009) in circulating fasting and post-prandial ghrelin levels following GI surgery, thus highlighting the incomplete understanding of the effect of the surgery on circulating levels of this orexigenic gut hormone.

## 3. Pancreatic polypeptide

The 36-amino acid anorexigenic peptide PP, is primarily synthesized and released from the endocrine pancreas, and to a lesser extent, from the colon and rectum (Hameed and Dhillo 2009). Levels are low during the fasting state and rise in proportion to caloric intake (Schubert and Sabapathy 2014; Track and McLeod 1980). Peripherally-administered PP reportedly leads to a reduction in food intake, in both rodents and humans (Malaisse-Lagae 1977; Batterham et al., 2003). Peripheral PP administration has also been demonstrated to lead to an increase in energy expenditure and a reduction in body weight in rodents, and a demonstrated reduction in appetite and food intake in both lean and obese humans has shed further light on its potential anti-obesity utility (Batterham et al., 2003).

## 4. Peptide YY

PYY, a member of the PP-fold family of proteins to which PP also belongs, is so named because of the tyrosine residues at both its N- and C-termini (Tatemoto and Mutt 1980). The full-length 36-amino acid peptide is synthesized and released from the L-cells of the GI tract. Circulating levels of $PYY_{3–36}$ are influenced by meal composition and calorie content, and become elevated within 1 h post-feeding (Adrian et al., 1985) Similar to PP, peripherally-administered $PYY_{3–36}$exerts its food intake-inhibiting effects (Schubert and Sabapathy 2014; Lumb et al., 2007) As circulating $PYY_{3–36}$ levels are often lower in the obese state (Cahill et al., 2014), it has been suggested that this characteristic may in fact have a causative role in the development of obesity (Cahill et al., 2014; le Roux et al., 2006).

## 5. Glucagon-like peptide (GLP-1)

In the gut, GLP-1 is released from small intestinal and colonic L-cells in proportion to ingested calories (Herrmann and Goke 1995) In both lean and obese humans, peripherally-administered GLP-1 has been shown to exert anorexigenic effects (Schubert and Sabapathy 2014; Gutzwiller et al., 1999), with other possible influences on food intake being linked to a reduction in gastric emptying and a suppression of gastric acid secretion (Verdich et al., 2001). Both centrally- and peripherally-administered GLP-1 or GLP-1 receptor agonists have been shown to enhance satiety, reduce food intake, and promote weight loss in rodents and humans (Baggio and Drucker 2014; Vilsboll et al., 2007). GLP-1 are now in trial, and determination of their efficacy as anti-obesity agents is ongoing (Baggio and Drucker 2014; Steinert et al., 2014; Neary and Batterham 2009). Further to the currently investigated approaches, future research aimed at better understanding the mechanisms involved in endogenous GLP-1 production would be beneficial. With the known additive satiating effects of GLP-1 and PYY, exploiting endogenous GLP-1 production may also yield a novel combinatorial anti-obesity approach.

### 6. Oxyntomodulin

Early work in rats on a peptide with inhibitory action on stomach oxyntic glands lead to the advent of the name OXM for the now well established gut hormone (Dubrasquet and Bataille 2006) OXM shares the same precursor molecule as GLP-1, is co-secreted with GLP-1 following feeding, and its release is also proportional to meal calorie content (Schubert and Sabapathy 2014; Druce and Bloom 2006). Centrally- and peripherally-administered OXM reduces food intake and increases energy expenditure in rodents, and reductions in body weight have been reported in response to chronic injections (Gamma et al., 2014) Peripheral administration in humans increases satiation and reduces food intake, with repeated injections leading to decreases in body weight (Wynne et al., 2005). There has also been data in support of OXM promoting increased energy expenditure in humans (Murphy and Dhillo 2006).

### k. Gut microflora, Low Grade Inflammation and Obesity a vicious cycle

Obesity and related metabolic disorders are associated with low-grade inflammation, which contributes to the onset of these diseases (Greevenbroek and Schalkwijk 2013; Olefsky and Glass 2010; Cani et al., 2007a, 2009). The gut microflora has been linked with chronic diseases such as obesity in humans (Cani et al., 2007; Cani et al., 2008; Tremaroli and Backhed 2012; Everard and Cani 2013). It has been shown that obese and lean subjects present different gut microflora composition profile. Obese subjects present lower proportion of Bacteroidetes in comparison to lean subjects (Angelakis et al., 2012). These differences in microbiota composition may contribute to weight imbalance and impaired metabolism. The evidences from animal models suggest that it is possible that the microbiota of obese subjects has higher capacity to harvest energy from the diet providing substrates that can activate lipogenic pathways. In addition, microorganisms can also influence the activity of lipoprotein lipase interfering in the accumulation of triglycerides in the adipose tissue. The interaction of gut microflora with the endocannabinoid system provides a route through which intestinal permeability can be altered. Increased intestinal

permeability allows the entrance of endotoxins to the circulation, which are related to the induction of inflammation and insulin resistance in mice (Zao 2013).

Lipopolysaccharides (LPS) are unique glycolipids in the cell wall of gram-negative/pathogenic bacteria. LPS molecules, also known as bacterial endotoxins, may trigger acute and chronic inflammation, leading to immune cell activation and cytokine release (Laetitia et al., 2013). HDL cholesterol is one of the most important factors involved in the elimination of LPS molecules from circulation. In healthy subjects, LPS is mainly bound to HDL, whereas in patients with sepsis, LPS is redistributed toward LDL and VLDL lipoproteins (Tran-Dinh et al., 2013; Wendel and Paul 2007). High LPS activity combined with low HDL levels increases the risk for type II diabetes mellitus and cardiovascular disease (Jayashree et al., 2014; Pussinen et al., 2007). LPS infusion in mammals leads to the appearance of factors known to be associated with the (Metabolic Syndrome) MetS: elevated levels of proinflammatory markers, dyslipidemia, fasting hyperglycemia, insulin resistance, and obesity (Jayashree et al., 2014; Parekh et al., 2014).

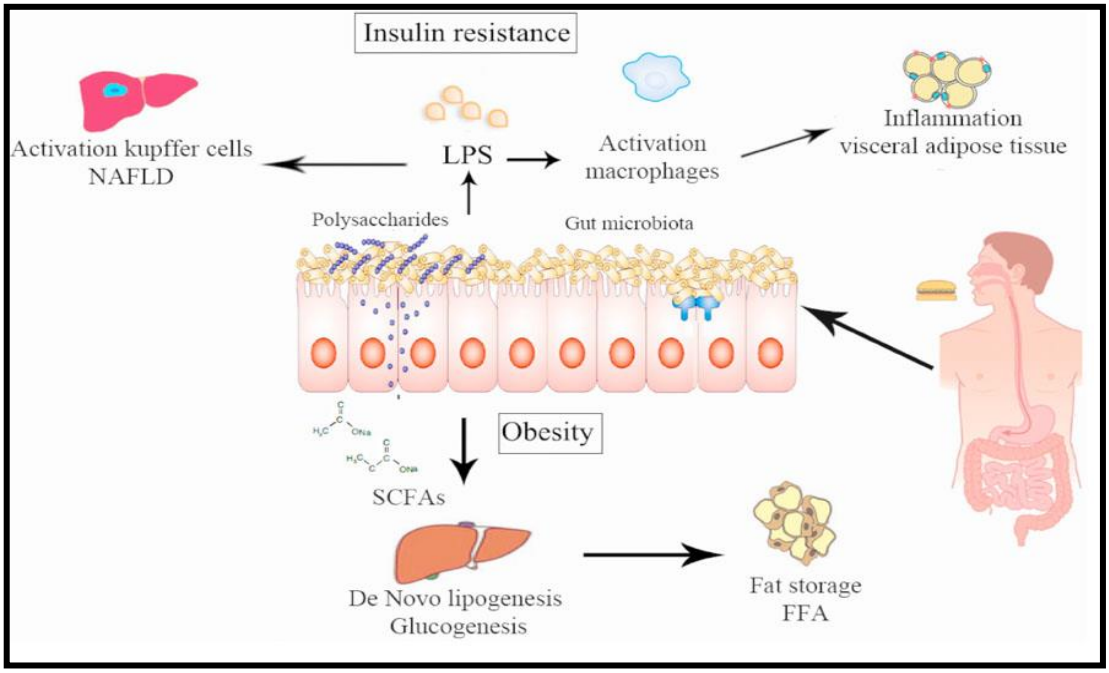


**Figure 2.3: Pathway via which intestinal microbiota can alter human metabolism producing obesity and insulin resistance.** (1) chronic bacterial translocation due to increased intestinal permeability that drive a systematic inflammation leading to macrophage influx into visceral adipose tissue, activation of hepatic Kupffer cells and insulin resistance. (2) Short chain fatty acids normalize intestinal permeability and alter de novo lipogenesis and gluconeogenesis via reduction of free fatty acid production by visceral adipose tissue. ***(source:*** *Moreno-Indias 2014****)***

### l. Miscellaneous Factors

Miscellaneous factors linked to development of obesity include excessive alcohol consumption (Bhatt and Mehan 2014; Croezen, et al., 2009; Lourenço 2009; Grochow 1985), The experimental metabolic evidence suggests that the consumption of moderate amounts of alcohol has to be accounted for in the energy-balance equation and may represent a risk factor for the development of a positive energy balance and thus weight gain. There seems to be a large individual variability according to the absolute amount of alcohol consumed, the drinking frequency as well as genetic factors. Presently it can be said that alcohol calories count more in moderate nondaily consumers than in daily (heavy) consumers. Further, they count more in combination with a high-fat diet and in overweight and obese subjects (Suter and Tremblay 2005).

## 2.6 Pathophysiology of obesity

Obesity is a multifactorial disease in which genetic and environmental factors are involved (Cruwys and Bevelander 2015; Geni and Giselia 2004; Speliotes and Willer 2010). A family trait is noted, which means that children whose parents are obese are at a greater risk of becoming obese. Moreover, there is some evidence that genetic factors can modulate the body's response to changes in environmental factors, such as diet and physical activity (Speliotes and Willer 2010). An individual's first nutritional experiences are believed to influence his/her susceptibility to certain chronic diseases in adulthood, including obesity. (Figure 2.4).

Increased energy intake and reduced energy expenditure have been described as the major causes of obesity. In addition to the total caloric content, the composition of the diet is also important, as a diet rich in simple carbohydrates and lipids is a risk factor for obesity (Mayén et al., 2014; Poti and Duffey 2014). With regard to energy expenditure, several studies have revealed that it tends to be lower in obese individuals, in whom any of its three components may be altered - resting metabolic rate, thermogenesis, or physical activity (Duvivier et al., 2013; Hall et al., 2011).

However, recent advancements in the understanding of the neuroendocrine regulation of energy balance, of the genetics of obesity and of the interactions between genetics and environment make us believe this classification should be revised in the future and that this rate shall change considerably. As new hormones, neurotransmitters, receptors, and genes are discovered, the etiology of obesity assumes another dimension (Mietlicki-Baase and Hayes 2015; Cho 2011; Murphy and Bloom 2004).

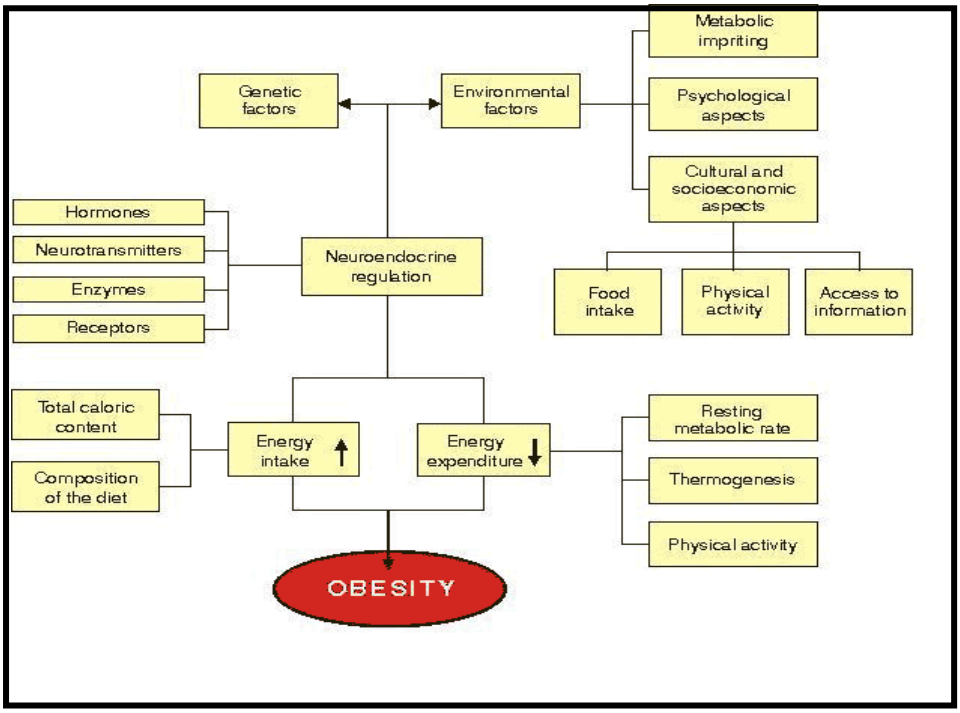


**Figure 2.4: Pathophysiology of obesity *(source:*** *Balaban, and Silva 2004)*

## 2.7 Co morbidities associated with obesity

Obesity is associated with an increased incidence of hypertension, diabetes, coronary artery disease, osteoarthritis and overall increase in morbidity during adult life (Winter and MacInnis, 2014; PAN 2000; Wormser et al., 2011) (Figure 2.5).

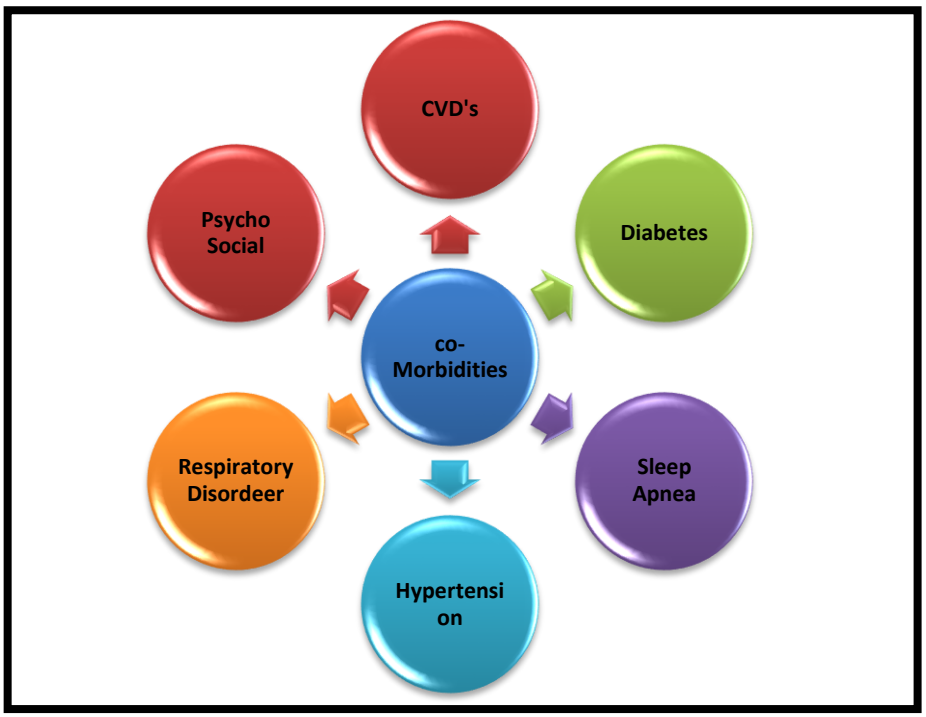


**Figure 2.5: Co-morbidities with obesity**

**a. Obesity, metabolic syndrome and other co morbidities.**

The transition from the traditional diet to calorie dense food and a sedentary lifestyle has led to a rapid increase in the prevalence of obesity both in children and adults. The constellation of abnormalities associated with obesity or abdominal obesity has been termed "metabolic syndrome," Although visceral adiposity and features of the metabolic syndrome are associated with an increased relative risk of CVD (Mottillo et al., 2010 Galassi A, Reynolds 2006; Gami et al., 2007). This has been followed by the appearance of other 'diseases of affluence' such as diabetes mellitus and cardiovascular diseases (Belenchia and Tosh 2013; Fall 2001; Calle 2003). Obesity is a risk factor for a number of diseases including type 2 diabetes, cardiovascular disease. Other diseases related to obesity are hypertension, gallstones, sleep apnea, dyslipidemia, insulin resistance, psychological disorders and certain type cancers (Gallagher 2009; Kotronen 2008; Wormser et al., 2011; WHO 1998 a).

The physiological risk factors like adipose tissue saturation, dyslipidemia, lipotoxicity, insulin resistance, chronic inflammation, oxidative stress are inter-related and associated with pathogenesis and progression of metabolic abnormalities like

obesity, type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), hypertension, etc. These conditions often lead to pathophysiology of metabolic syndrome, which increases the risk of cardiovascular diseases as shown in the following Figure 2.6.

**b. Obesity and Cardiovascular Disease**

Cardiovascular disease encompasses Cardiovascular Heart Disease (CHD), stroke and peripheral vascular disease. Obesity predisposes an individual to a number of cardiovascular risk factors including hypertension, raised cholesterol and impaired glucose tolerance. Evidence suggests that the obesity is associated with increased risk for cardiac diseases (Wu, et al., 2014; Lavie and Milani 2009; Golley et al., 2006). On the basis of the robust evidences abdominal obesity and excess visceral adiposity is linked to an atherogenic dyslipidemic state (Dagenais and Mann 2005; Yusuf et al., 2005; Wormser et al., 2011; Després2011) (Figure 2.7).

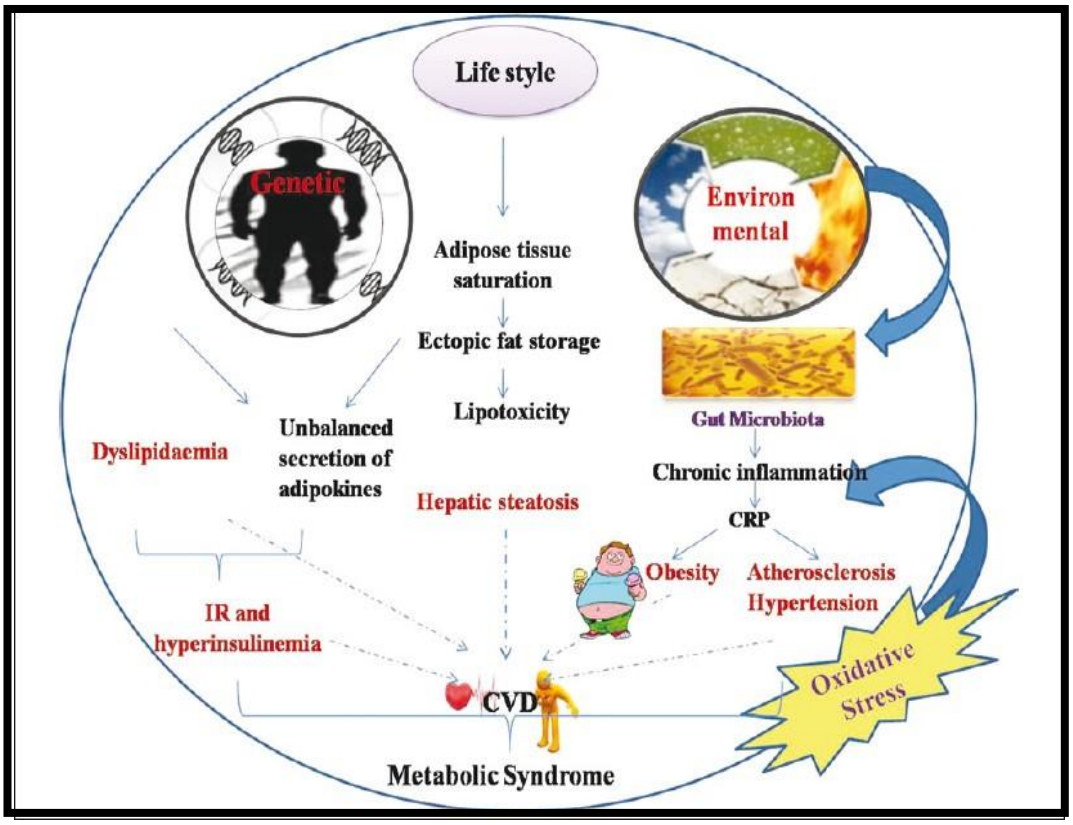


**Figure 2.6: The pathophysiology of obesity leading to metabolic syndrome**
***(source:** Mallappa et al., 2012)*

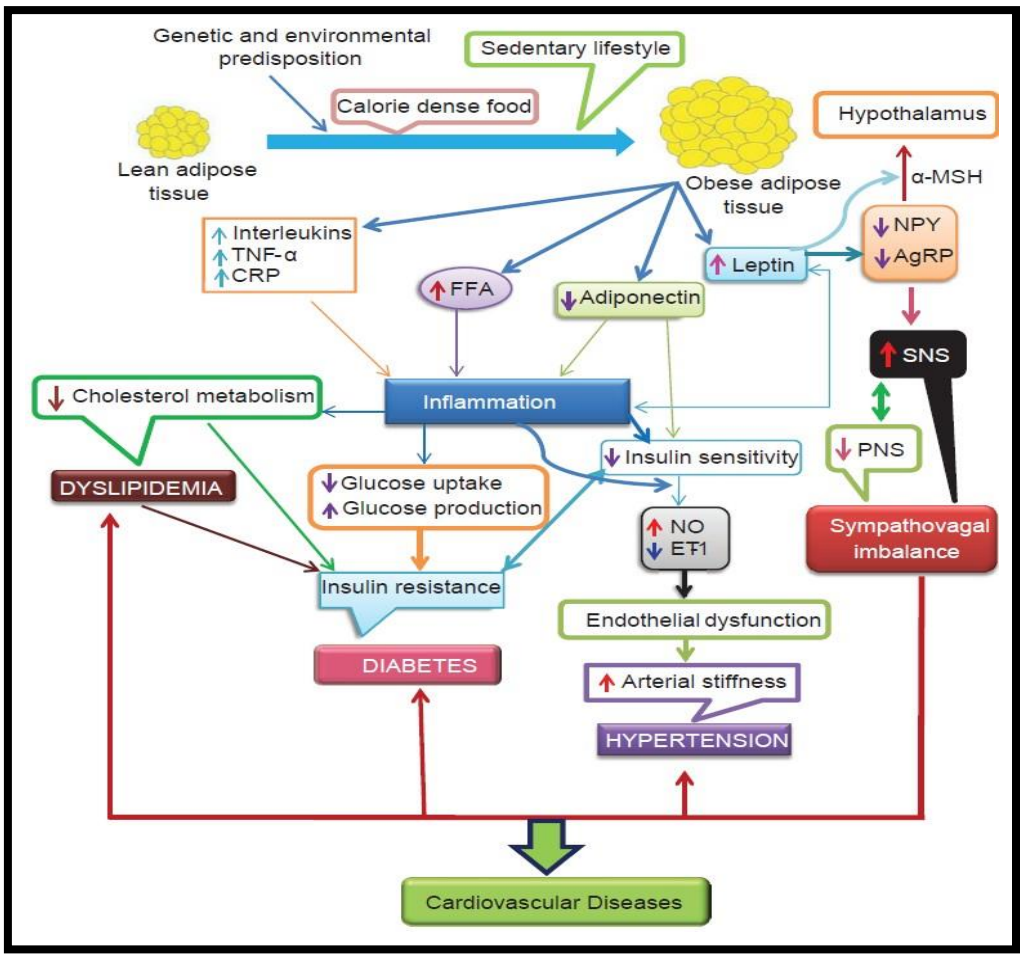


**Figure 2.7: Link of sympathovagal imbalance and altered biomarkers in the genesis of cardiovascular dysfunctions in obesity.** hs-CRP: High specific-C-reactive protein, TNF-α: Tumor necrosis factor-alpha, FFA: Free fatty acids, NPY: Neuropeptide Y, AgRP: Agouti-related peptide, SNS: sympathetic nervous system, PNS: Parasympathetic nervous system, α-MSH: Alpha-melanocyte stimulating hormone, NO: Nitric oxide, ET-1: Endothelin-1. ***(Source:*** *Indumathy et al., 2014)*

### c. Obesity and Diabetes Mellitus

For more than two decades, abdominal obesity has been repeatedly associated with insulin resistance, and several seminal review papers have been published on this topic (Lovegrove 2007; Misra et al., 2008; Mahendra 2013). A study conducted on Asian Indians documented that the fasting insulin correlated significantly with the body mass index and waist circumference (Ley and Hamdy 2014). The odds ratio for hyperinsulinemia was 4.7 in overweight subjects and 6.4 with high waist circumference (Mishra et al., 2004), a finding fully concordant with the published evidence that patients with type 2 diabetes have more abdominal visceral fat and more ectopic fat than nondiabetic individuals matched for BMI (Ley and Hamdy

2014; Karter et al., 2005; Wang and Hu 2005; Balkau et al., 2007; Gallagher 2009; Kotronen 2008) (Figure 2.8).

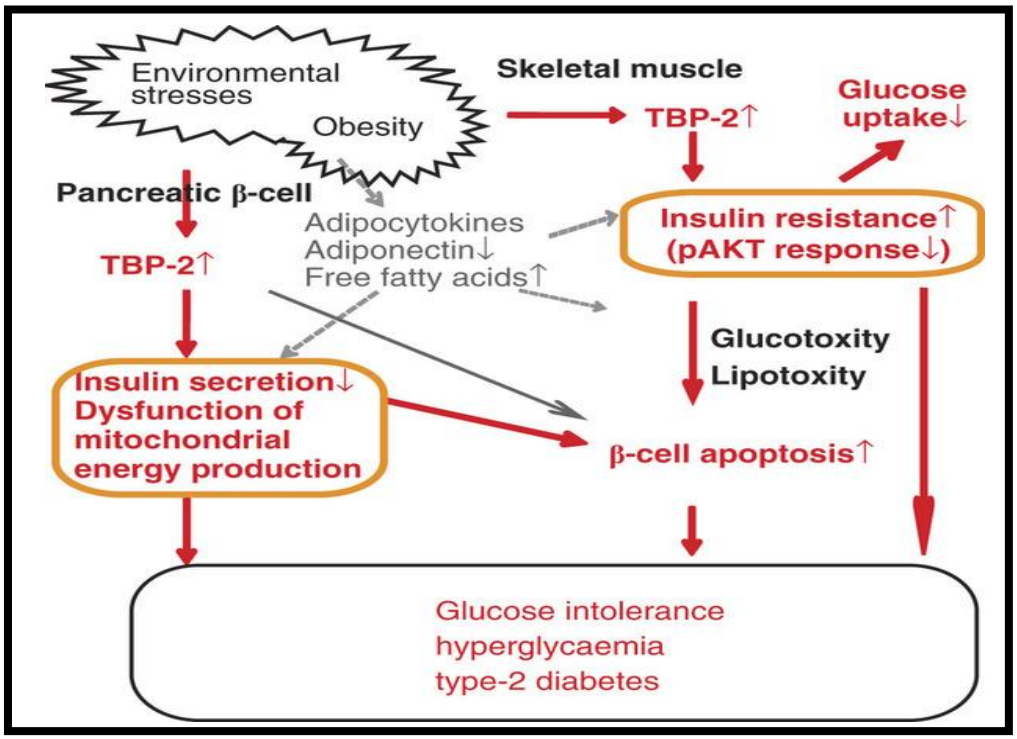


**Figure 2.8: Role of TBP-2 in promoting obesity-induced type 2 diabetes.** Environmental stresses including obesity cause upregulation of TBP-2. Sustained expression of TBP-2 may impair mitochondrial function and insulin secretion in β-cells and aggravate insulin resistance in skeletal muscle. Augmented expression of TBP-2 may also result in β-cell apoptosis. These changes lead to glucose intolerance and hyperglycaemia and obese-induced type 2 diabetes. ***(Source:*** *Yoshihara et al., 2010****)***

### d. Hypertension

The link between obesity and hypertension has long been recognized, with obese patients having higher rates of hypertension than normal-weight individuals (Chiang and Perlman 1969; Stamler and Riedlinger 1978). Waist circumference has been reported as the strongest independent predictor of systolic blood pressure and diastolic blood pressure (Hall et al., 2014; Lavie and Milani 2009; Hayashi et al., 2003). Furthermore, excess visceral fat has been found to be associated with hypertension (Hall et al., 2014) (Figure 2.9).

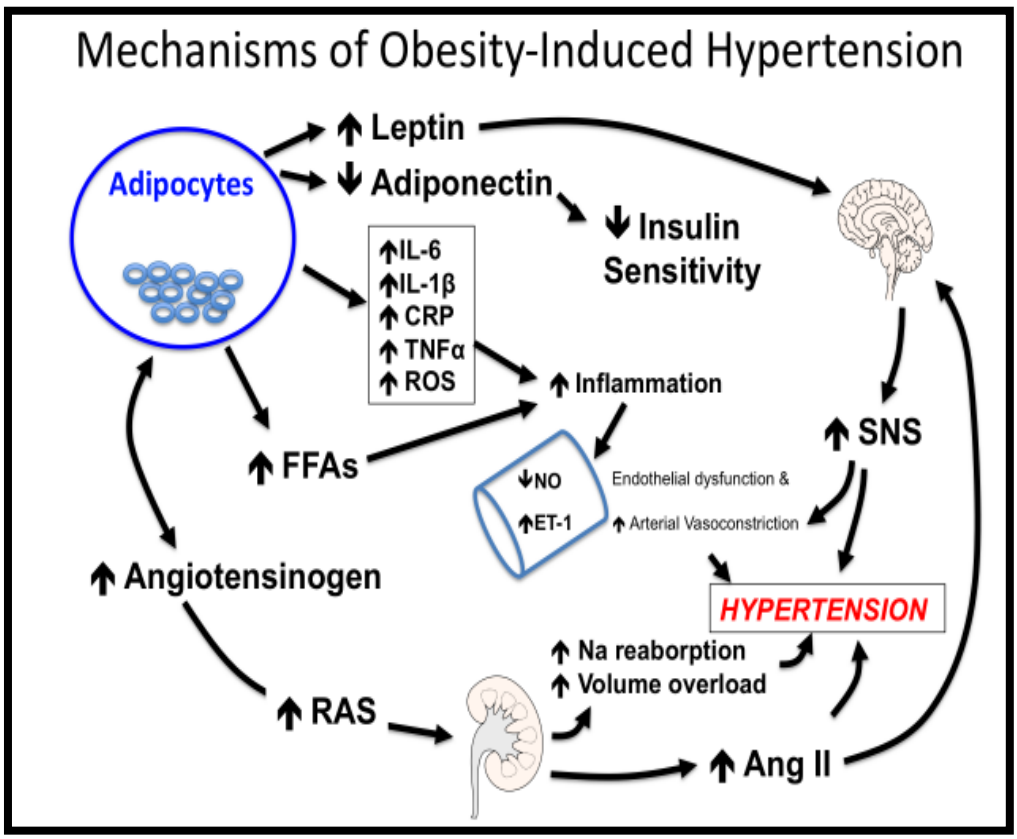


**Figure 2.9: Proposed mechanisms involved in the pathogenesis of obesity-induced hypertension.** IL-6: interleukin-6; IL-1β: interleukin-1β; CRP: C-reactive protein; ROS: reactive oxygen species; FFAs: free fatty acids; NO: nitric oxide; ET-1: endothelin-1; RAS: renin-angiotensin system; SNS: sympathetic nervous system (increased tone). ***(source:** Kotsis et al., 201**0).***

### e. Respiratory Diseases

Obesity carry a risk of (i) restrictive airway disease caused by the difficulty in respiration from the mass of adipose tissue (ii) obstructive airway disease caused by fatty deposition along the airway, added to the tonsillar and adenoidal hypertrophy. Obstructive sleep apnea with carbon dioxide retention, hypoxia and right ventricular hypertrophy is a potential cause of severe morbidity and mortality in obese subjects (Rutten et al., 2010; Mottin and Canani 2007; Malhotra and White 2002; Spiegel and Tasali 2004).

Sleep disorder breathing is highly prevalent in childhood obesity. Several cross-sectional studies have demonstrated an association between breathing disorders related to sleep and metabolic syndrome (Verhulst 2009). A cross-sectional analysis

of 48 cohort was conducted on obese children with BMI ≥ 40 Kg/$m^2$ in age group of 8-17 years found that 77.1 percent had asthma, small airways disease or both.

**f. Insulin Resistance**

The term insulin resistance implies an impaired cellular responsiveness to insulin. It is well established that insulin resistance is precursor for two major diseases: type 2 diabetes mellitus and coronary heart disease. Sensitivity to insulin varies widely among group of people, but one major factor of insulin resistance is obesity (Abate et al., 1996). Obesity in childhood and adolescence has been shown to increase the risk of insulin resistance (Srinivasan and Berenson 2002).

A strong association between insulin resistance and cardio-metabolic risk factors amongst obese subjects has been documented (Weiss et al., 2004). Several studies have shown that insulin resistance, dyslipdemia and hypertension, are highly correlated and significantly more common in obese children than in overweight and obese individuals (Invitti 2003, Freedman 2001).

**g. Psycho-Social Consequences of Obesity**

Overweight and obese people are stigmatized and discriminated in various field of daily life, including education, employment and health care. In addition to the health risk factors, obesity has a considerable impact on quality of life. The obesity has been described as a major social prejudice, and there is a significant social tendency toward stigmatizing overweight individuals as lazy and slothful. It is often treated as personality problem. The obesity is neither a psychological nor psychiatric disorder. On the contrary, it may predispose to the psychological or psychiatric disorder. The obesity in childhood leads to low self-esteem, leading to depression and suicidal tendency and to engage in substance abuse (Strauss 2000).

Few studies have examined the psychological consequences of obesity. The obese subjects with history of weight cycling have significantly more psychological problems and lower levels of satisfaction with life than those who have stable weight Obesity Resource Information Centre (ORIC).

A marked self-awareness of body shape and physical appearance develops during adolescence that is why the pervasive, negative social messages associated with obesity have a major impact at this stage. Overweight in adolescent is also associated with later social and economic problems (Gortmaker 1993). The problems of the severity overweight have been described in terms of laziness, dishonest, lack of self-confidence, emotional complication *i.e.* sense of isolation Petroni et al., 2007, Mundell 2000).

**Psychological Disorders**

**i. Binge Eating Disorder:** It is a recognized psychological disorder prevalent especially in adolescence and young adults. The frequency of occurrence of this disorder is 30% among obese individuals. The disorder is characterized mainly by uncontrolled binge-eating episodes, usually in the early evening or at night. It is associated with severe obesity, high frequency of weight cycling and pronounced psychiatric co-morbidity. The obese binge-eaters have worse moods, more severe psychological problems and are more likely to drop out of weight control programmes based on behavior modifications (Wing and Greeno 1994).

**ii. Night-Eating Syndrome:** This psychological disorder is characterized by the consumption of at least 25% and upto 50% of total energy intake after the evening meals. This syndrome is more common in morbidly obese patients and is related to sleep disturbance. The possible reason behind is that due to alteration in the circadian rhythm, affecting both food intake and mood of an individual (Nelson and Gidycz 1993). Evidence suggests that night eating disorder is the primarily caused due to weight gain. It has been suggested that the increasing incidence of night eating disorder is associated with psychological pressure to reduce weight Tiggemann and Pickering 1996).

**h. Other Related Disorders**

**i) Cancer:** Increasing body weight is associated with increased risk for specific cancers (Balentine et al., 2010; Bansen and Chang 2011; Pischon and Nothlings2008; Renehan and Tyson 2008). A number of studies have found a positive association between overweight and the prevalence of cancer, particularly hormone dependent

and gastrointestinal cancers (Kim and Lee 2009). Greater risks of endometrium, ovarian, cervical and postmenopausal breast cancer have been documented for obese women, while there is small evidence for an increased risk of prostate cancer among obese men. The increased incidence of cancers in the obese subjects is greater in those with excess abdominal fat (Tiggemann and Pickering 1996). The incidence of gastrointestinal cancers, such as colorectal (Kang et al., 2010; Guiu et al., 2010; Nitori et al., 2009; Yamamoto et al., 2010) and gallbladder cancer has also been reported to be positively associated with body weight. The renal cell cancer has consistently shown to be associated with overweight and obesity (Schapira 1994, Merchand 1992).

**ii) Sub-clinical Inflammation:** Obesity contributes to the development of vascular inflammation which raises markers of inflammation. High levels of C-reactive protein (CRP) levels denote future risk for development of type 2 diabetes mellitus and cardio vascular heart disease. In a recent study in Indian adolescents, high CRP levels were seen in 22 per cent in overweight subjects and in about 25 per cent in obese (Al-Hamodi 2014; Turer and Scherer 2012; Vikram et al., 2006). CRP levels show an association with per cent body fat, waist-hip ratio, waist circumference and triceps skin fold thickness in Indian children (Vikram et al., 2003). Excess dietary intake of saturated fat has been found to be strongly correlated to high CRP levels in Indian adolescents (Nettleton et al., 2006; Arya et al., 2006).

**iii) Osteoarthritis:** The extra weight an obese person carries, especially with fat distribution in the abdomen, puts increased stress on the weight-bearing joints. The common joints affected are knee join, hip joint and joints of the back bone. The individuals with BMI 30 Kg/$m^2$ or more had markedly higher risk for osteoarthritis as compared to the normal weight individuals. Obese children can suffer from orthopedic complications, including abnormal bone growth, degenerative disease and pain (Thijssen and Caam 2014; Gupta and Meuller 2002). Elevated risk of back pain has been observed in relation to obesity, particularly amongst adults who had childhood obesity (Han and Schoutel 1997). Recent studies have shown that adipocytokine leptin is a possible link between obesity and OA: Leptin levels in synovial fluid are increased in obese patients, leptin receptor (Ob-R) is expressed in

cartilage, and leptin induces the production of matrix metalloproteinases (MMPs), pro-inflammatory mediators and nitric oxide (NO) in chondrocytes, not only leptin levels in the joint but also leptin sensitivity in the cartilage are enhanced in obese OA patients (Vuolteenaho and Koskinen 2014).

## 2.8 TREATMENT

### Obesity treatment modalities

Treatment modalities currently available for weight loss work by inducing a state of negative energy balance. Negative energy balance may be achieved by consuming fewer calories than needed, by increasing the level of physical activity or a combination of both. Dietary intervention, physical activity, pharmacotherapy and surgery are the treatment modalities currently available to accomplish the goal of negative energy balance. Combinations of these approaches may also be used to achieve clinically significant weight loss, as many studies have examined the effectiveness of using different combinations of these treatment methods (Bray and Bouchard 2014; Wadden et al., 2005, Wadden and Wilson 2007). Decreasing body fat to improve appearance, physical function, quality of life and medical health are the goals of obesity treatment (Klein et al., 2004) (Figure 2.10).

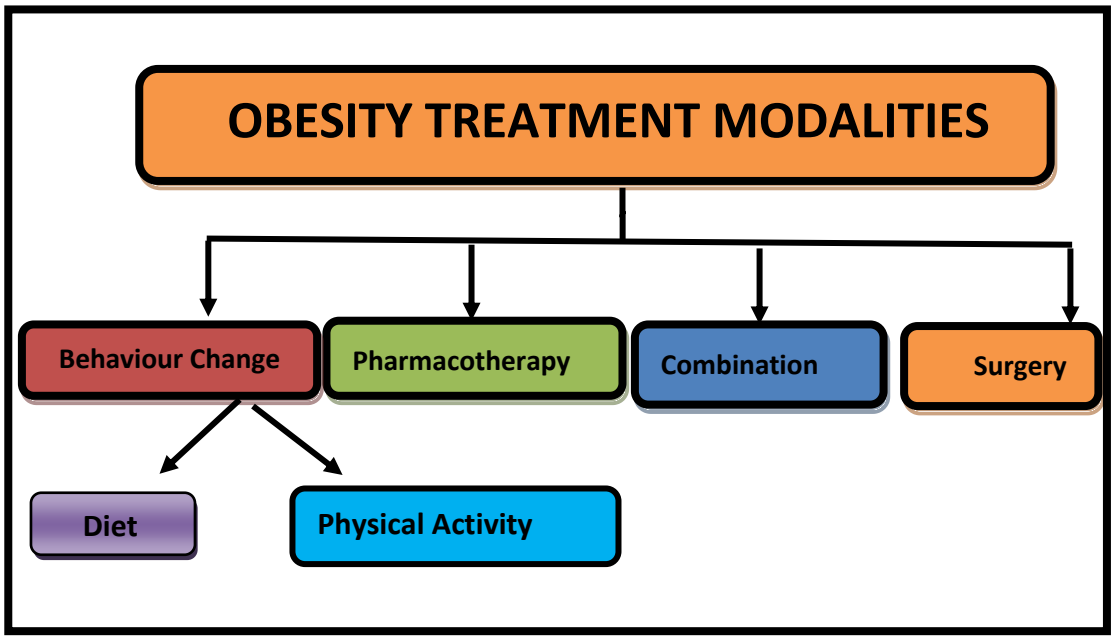


**Figure 2.10: Obesity treatment modalities**

### 2.3.1 Behavior Change (Diet and Physical Activity)

Behavioral weight loss approaches may include dietary modifications, physical activity components or a combination of the two (Bhatt and Mehan 2014). There are many well-known dietary modification techniques available to induce weight loss. Most methods suggest either a reduction in caloric intake or changes in the macronutrient (protein, fat and carbohydrate) composition of the diet (Sarafino and Smith, 2014; Hankey and C.R. 2010). Another study compared various modifications in diet macronutrient composition, and found that by year on in the intervention period, macronutrient composition only made a small difference in the amount of weight lost; compliance to the diet was the most important factor in this study (Sacks et al., 2009).

An alternative method of inducing weight loss is increasing one's level of physical activity to increase the amount of calories metabolized. Physical activity can be challenging for overweight individuals, as the amount of exercise recommended (AASM 2007) to achieve a clinically significant weight loss is 60-90 minutes, 5 days per week. Physical activity has been shown to be more important for weight maintenance (prevention of weight regain) (Du and Bennett, 2013; Hall et al., 2011; Jakicic et al., 2001). The difficulty in maintaining weight loss through behaviour changes has led to a search for other treatment modalities that are more effective for long term weight maintenance.

**Educational efforts should pay particular attention to the following topics (Bhatt and Mehan 2014):**

- Energy value of different foods.
- Food composition—fats, carbohydrates (including dietary fibre), and proteins.
- Evaluation of nutrition labels to determine caloric content and food composition.
- New habits of purchasing—give preference to low-calorie foods.

- Food preparations—avoid adding high-calorie ingredients during cooking (e.g., fats and oils). Avoiding overconsumption of high-calorie foods (both high-fat and high-carbohydrate foods).
- Adequate water intake.
- Reduction of portion sizes
- Limiting alcohol consumption

### 2.3.2 Pharmacotherapy

The development of obesity pharmacotherapy has been a very difficult quest as the safety record of some of the agents that were developed and introduced in clinical practice has led to their withdrawal due to undesirable side effects (Taylor 2009; Williams 2010; Ioannides-Demos 2006; Li and Cheung 2011). For example, three drugs that had been previously approved by regulatory authorities for weight loss (dexfenfluramine, sibutramine, and rimonabant) and with different mechanisms of action were found to induce variable losses of visceral adipose tissue but were removed from clinical use because of various side effects (Taylor 2009; Williams 2010; Ioannides-Demos 2006; Li and Cheung 2011). Currently, the only remaining drug still indicated in clinical practice for the long-term management of obesity is orlistat. It inhibits the activity of gastric and pancreatic lipases and decreases dietary lipid digestion and absorption by 30% (Hauptman and Jeunet 1992). Although many clinical trials have reported that it can induce a slightly greater weight loss than the use of a placebo combined with a lifestyle modification program, there is no evidence that this pharmacological approach can selectively mobilize visceral adipose tissue/ectopic fat depots beyond what is to be expected by overall weight loss.

Two new weight loss drugs have been approved by the Food and Drug Administration for chronic management of obesity. The first, lorscaserin, is a selective serotonin 2C receptor agonist that has been shown to reduce body weight in obese patients as well as in obese patients with type 2 diabetes (Martin et al., 2011; O'Neil et al., 2012). The other drug approved is actually a combination of phentermine, a central norepinephrine-releasing agent, with topiramate which has

been used for the treatment of epilepsy and migraine (Gadde et al., 2011; Garvey et al., 2012). Although both lorscaserin and phentermine/topiramate have been considered by the Food and Drug Administration to have a favorable benefit-to-risk ratio and to induce greater weight loss than a placebo combined with a lifestyle modification program, both drugs have been largely tested in lower risk obese women rather than in higher risk men. Therefore, these drugs have not been selectively tested in high-risk viscerally obese patients, and we do not know whether these compounds could have a selective effect on visceral adiposity/ectopic fat beyond the mobilization of "harmful" fat depots to be expected from weight loss per se. Rather, as a general rule, patients receiving weight management medication should be properly selected, and health improvements rather than weight loss per se should be the main goal of therapy.

### 2.3.3. Combination Approaches

Diet modification, physical activity, and pharmacotherapy may all be used in combination to achieve weight loss. Wadden et al., 2005 studied the effectiveness of weight loss medication (sibutramine) in combination with lifestyle modification (group therapy providing instruction and support for diet modification, physical activity and other important components of weight loss) to medication or lifestyle modification alone in 224 subjects in a randomized study. This study revealed that patients receiving sibutramine in combination with lifestyle modification lost nearly double the weight of those receiving the treatments in isolation. Also, nearly twice the number of the participants lost 10 percent or more of their initial body weight. This study indicates the potential value in combining medication therapy with lifestyle modification for the most optimal outcome.

### 2.3.4 Surgery

Treatment of obesity continues to be a topic of significant discussion as the obesity epidemic all over the world. Surgical weight loss has become an important component of the treatment arsenal for those with Class III obesity, as other weight loss modalities often fail to result in successful outcomes in these individuals. In the past 20 years, bariatric surgery has become increasingly more accepted as a

treatment option internationally, prompting physicians and other health professionals who care for individuals who have had bariatric surgery to seek the most effective methods of treatment that yield optimal weight loss and resolution of co-morbid conditions (Colquitt et al., 2014).

**Bariatric surgery**

Weight loss surgery includes a variety of procedures performed on people who are obese. Weight loss is achieved by reducing the size of the stomach with a gastric band or through removal of a portion of the stomach (sleeve gastrectomy or biliopancreatic diversion with duodenal switch) or by resecting and re-routing the small intestines to a small stomach pouch (gastric bypass surgery) (Chang et al., 2014; Sjöström et al., 2007; Inge et al., 2004).

## 2.9 Preventive strategies in Obesity

**Strategies and Aims to reduce obesity:** As a Public Health Approach, essentially all children, adolescents and families should benefit from counselling to prevent excess weight gain and obesity.

**1. Life style approach (Bray and Bouchard 2014):**

- Healthy eating patterns: Emphasis should be on nutrition rather than 'dieting'. It is important to maintain healthy components of traditional diets and guard against heavily marketed energy dense fatty and salty foods.
- Increase physical activity levels: (A period of atleast one hour a day) (Duvivier et al., 2013).
- Decrease sedentary behavior (Du and Bennett, 2013).
- Television restricted to no more than 2 hours a day (Falbe et al., 2014).
- 'Target' Populations: Urban from higher and mid socio economic status.
- Address 'Behaviour' Change (Bhatt and Mehan 2014).
- Focus on involvement of entire family.
- Build supportive infrastructure.

- Impart health education skills to make healthy food choices El Modify environments to promote physical activity. Educate about the consequences of alcohol/tobacco to adolescents (Bhatt and Mehan 2014).

**Governmental Authorities:**

- Devising national strategies
- Providing safe exercise opportunities.
- Consider taxation on 'fatty food

## 2.10 Functional Foods and their Health Claims

A wide variety of foods are characterized as functional food with a variety of components affecting a various of body functions relevant to either a state of well-being and health and/or to the reduction of risk of a disease (Noomhorm and Ahmad 2014). According to the European concept (FUFOSE), the following features characterize a functional food: conventional/everyday food or food ingredient; naturally occurring in foods; proven beneficial effect on target functions beyond nutritive value/basic nutrition; and convincing human nutrition intervention studies demonstrating enhanced well-being and health and/or reduced risk of a disease and/or improved quality of life including physical, psychological, and behavioral performances (Mellentin and Heasman 2014; Roberfroid 2000, Diplock 1999; Noomhorm and Ahmad 2014).

If a functional food demonstrates a positive modulation of target functions after (long-term) consumption of the potential functional food components, such a modulation can be translated into claims based on its effect. If the effects concern a target function or a biological activity without direct reference to a particular disease or pathological process, claim will be made for an "enhanced function." But, if the benefit is clearly a reduction of the risk of a disease or pathological process, claim will be made for a "disease risk reduction". Among the functional foods one area that is rapidly expanding is the Probiotic and prebiotic category (ILSI India 2009). Probiotics and prebiotics are known to have a role in prevention or treatment of some diseases

like CVD's, hypertension, obesity and diabetes (Guarner and Malagelada 2003; Noomhorm and Ahmad 2014; Tripathi and Giri 2015).

## 2.11 Overview of Human Gut Microflora

Formation of the gut is one of the first outcomes of multicellularity. It appears on the first impression to be quite a simple organ as it is an epithelial tube comprising different cells surrounded by a layer of muscle. However, the human gastrointestinal tract is a highly dynamic ecosystem (Figure 2.11). The total area of the mucosal surface of the human gastrointestinal tract is 300 $m^2$ which makes it the largest surface area in the body that interacts with the external environment (Bjorksten B 2006). It comprises a series of complex and dynamic organs ranging from the stomach to the distal colon, which harbor immense microbial assemblages that are known to be vital for human health. Many species of bacteria have evolved and adapted to live and grow in the human gut. The number of bacteria in the human gut has been estimated to exceed the number of somatic cells in the body by an order of magnitude and that the biomass of the gut microflora may reach up to 1.5 kg (Karlsson 2013).

Due to the cost of weight reducing drugs and its side effects and inability to maintain healthy weight by means of life style modifications, recent studies have enlighten the importance of human gut microflora in various essential metabolic pathways. The various activities performed in the gut can play an outstanding role in treatment and prevention of metabolic disorders using prebiotics which have little side effects.

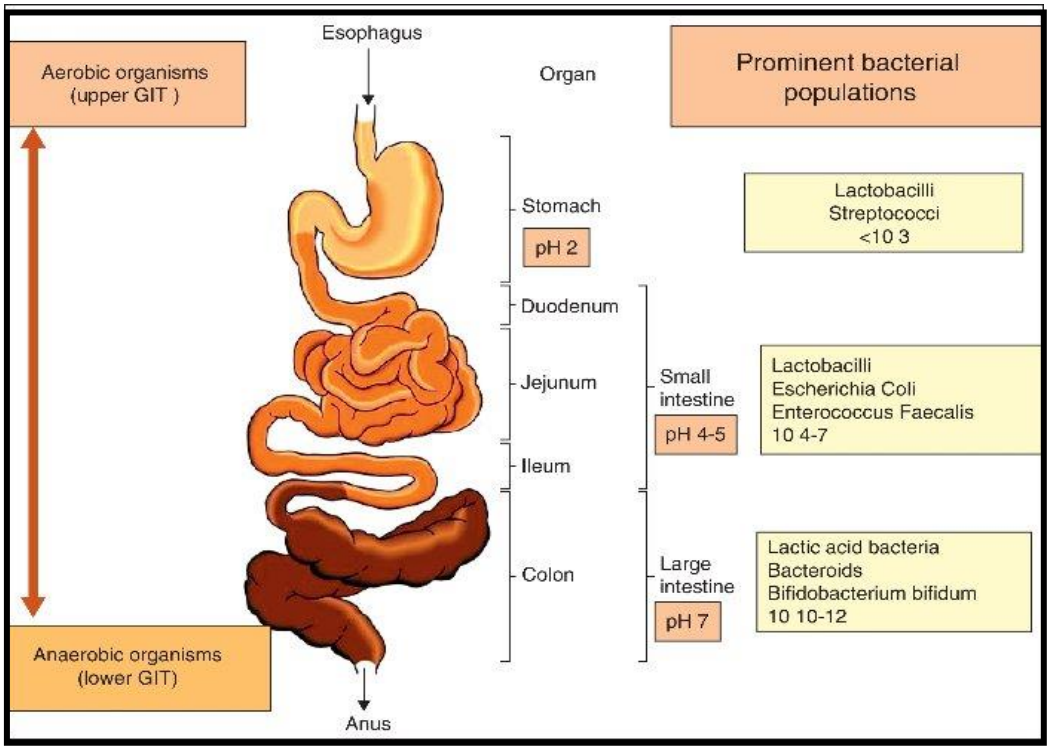


**Figure 2.11: Diagram showing Gradient of intestinal microbiota along the gastrointestinal tract** ***(Source:*** *Tsabouri 2014****)***

**Composition of gut microflora during life cycles**

Colonization of the gastrointestinal tract of newborn infants starts immediately after birth and occurs within a few days. Initially, the type of delivery (the birth canal versus caesarean section) and the type of diet (breast versus formula feeding) might affect the colonization pattern (Harmsen HJ et al., 2000; Hooper LV 2001). The initial colonization is therefore very relevant to the final composition of the permanent flora in adults (Guarner F and Malagelada JR 2003). The choice of diet for the newborn is also of great importance as the microbiota of breast-fed infants is predominated by *Bifidobacteria,* whereas formula fed infants have a more complex flora which resembles the adult gut in that *bacteroids, clostridia, Bifidobacteria, lactobacilli, gram positive cocci, coliforms* and other groups are all represented in fairly equal proportions (Benno Y et al., 1984) (Figure 2.12).

During the weaning stage, the microbiota becomes more developed and the ecosystem is thought to be fairly stable around 2 years of age. During the first few years of life and upon weaning, the infant microbiota normalizes. This composition

will remain stable throughout most of adult life. Recent studies have shown that the gut microflora changes in old age, with an increased number of bacterial groups represented in the predominant elderly gut microflora (Kimura K 1997; Mitsuoka 1982).

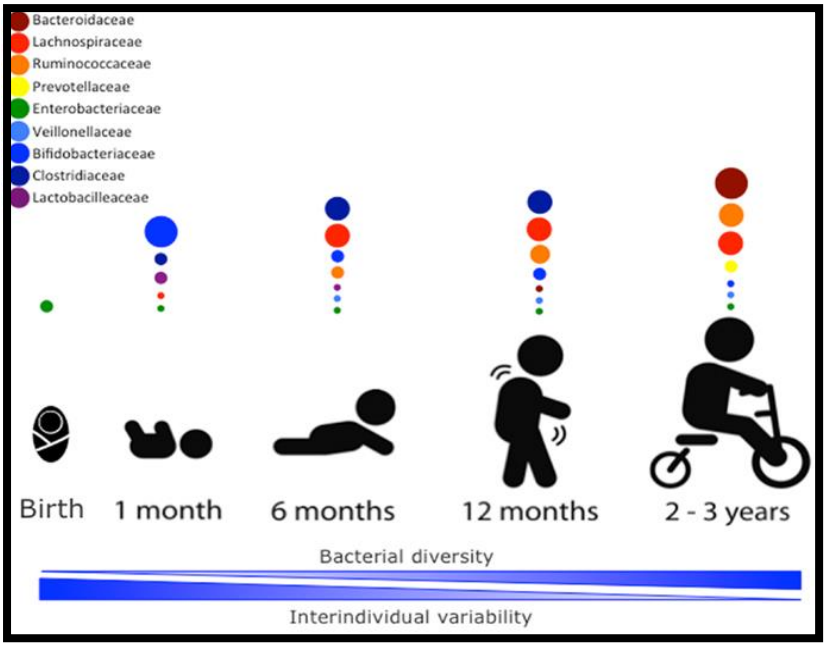


**Figure 2.12: Stages of microbial colonization of the infant and child intestine** ***(source:*** *Arrieta 2014****)***

Most abundant bacterial families are depicted in circles, where the size of the circle is proportional to the relative abundance of the bacterial taxa at each growth stage. The intestinal microbiota of the newborn is initially colonized by *Enterobacteria*. In the days after, strict anaerobic bacteria dominate the microbial community. During the first month, Bifidobacterial species predominate in the gut, but the introduction of solid foods at around 4–6 months is accompanied by an expansion of clostridial species (Lachnospiracea, Clostridiaceae, and Ruminococcaceae). Members of the Ruminococcaceae family continue to increase in abundance in the following months. By 2–3 years of age, the microbiota composition consists of mainly Bacteroidaceae, Lachnospiraceae, and Ruminococcaceae, which then remains stable into adulthood (Arrieta et al., 2014).

**Microbial diversity in the human gut**

Metagenomic analyses show that in adults, the major constituents of the colonic microbiota are represented by the phyla *Bacteroidetes, Firmicutes, Actinobacteria* and *Proteobacteria* (Lewis and Ruemmele 2014; Ventura et al., 2009). A number of factors influence the composition and the metabolic activity of the colonic microbiota (Schnabl and Brenner 2014; Gibson et al., 1995). Nutrient availability is believed to be the most important regulator of bacterial metabolism (David et al., 2014) (Figure 2.13).

Humans can be considered as "*super organisms*" with an internal ecosystem of diverse microorganisms. Their homeostatic balance is dependent upon the interactions between the host and its microbial components (Festi et al., 2014; Rezzi 2007). A balanced intestinal flora is a precondition for a fairly stable ecosystem in which both host-related factors and antagonistic interactions among intestinal bacteria play a role.

The numbers of *Bifidobacteria* are regarded as a marker of the stability of the human intestinal microflora (Tojo et al., 2014; Mutai M Tanaka R 1987; Turroni et al., 2008; Van Der Waaij et al., 1999; Harmsen et al., 2002). These beneficial bacteria may act as wards regulating the activity of the other bacteria in the colon. The other bacteria, such as *Salmonella, Shigella, Clostridia, Staphylococcus aureaus, Candida albicans, Campylobacter jejuni, Escherichia coli, Veillonella,* and *Klebsiella,* have varying potential to cause disease and are much less numerous (Tojo et al., 2014; Ventura et al., 2009).

However, these pathogenic bacteria can produce harmful local and systemic effects if they overgrow as a consequence of a gut microflora imbalance. Research has shown beneficial bacteria, particularly *Bifidobacteria* and *Lactobacilli* keep these potential disease-causing organisms under control, preventing several disease-related dysfunctions related to an imbalances GI situation (Tojo et al., 2014; Elmer GW 1996).

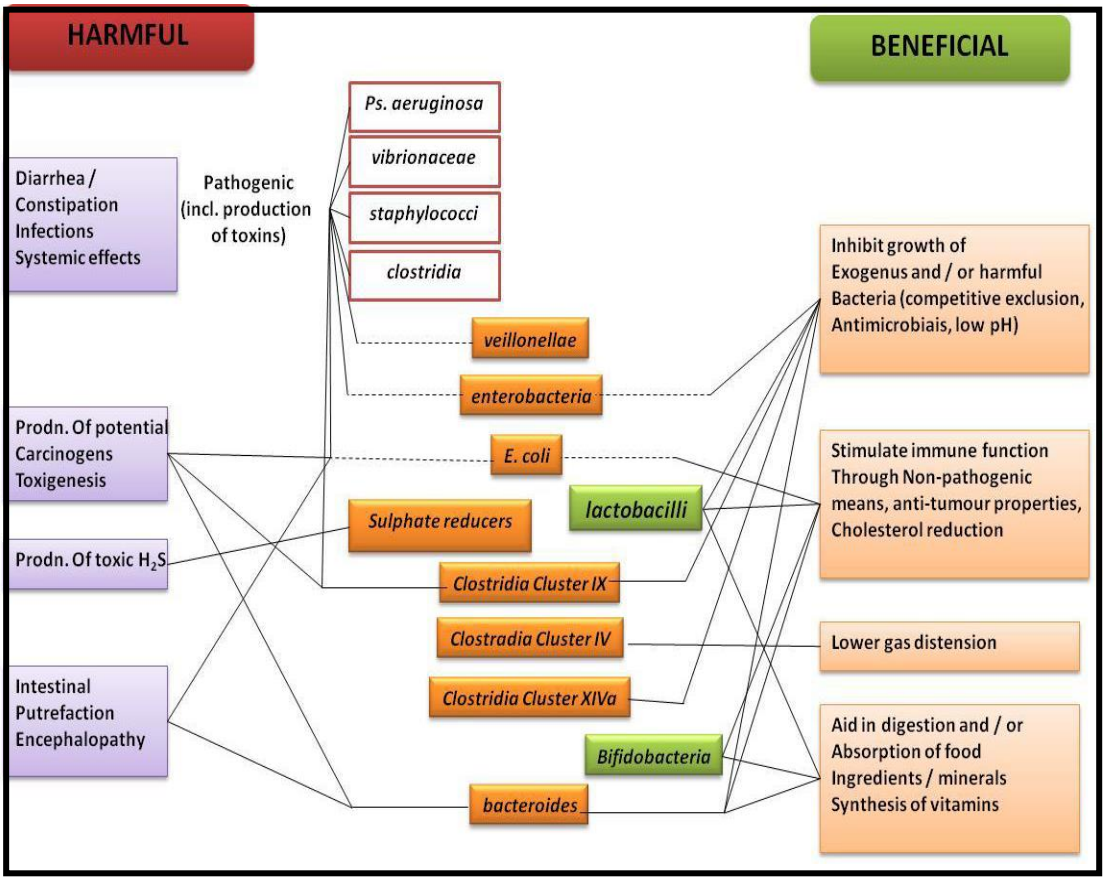


**Figure 2.13: Microbial diversity in human gut**

Pathogenic effects associated with harmful intestinal microflora such as *E. coli* not only include colonic disorders but also have implication with possible vaginal infections and systemic disorders (Geerlings 2014; Gibson GR and Roberfroid MB 1995). Major factors in the biology of these disorders are the overgrowth of pathogenic bacteria such as *clostridia, E. coli*. As well as parasites, viral infections, extensive burn injury, post-operative stress, and antibiotic therapy. These disorders are often associated with bacterial translocation due to intestinal barrier failure (Putignani 2013; Mondal 2012; Gibson GR and MacFarlane GT 1994). *Lactobacillus, Bifidobacteria* produce strong acids, i.e. butyric acid, acetic and lactic acid the production of these acids reduces intestinal pH which results in inhibit growth of pathogens and also alter the ecological balance of enteric commensals and also affects the turnover of enterocytes and neutralizes the activity of dietary carcinogens, such as nitrosamines, that are generated by the metabolic activity of commensal bacteria in subjects consuming a high-protein diet (Slavin 2013; Kailasapathy and Chin 2000).

Today, a great challenge is to expand and discover newer arenas of complex relationships and mechanisms related to responsiveness, diversity and resilience of the gut ecology, and its interactions with diet and related aspects of human host which affects each and every aspect of life.

## 2.12 Probiotics and Prebiotics

### a) Probiotics and its types and benefits

Probiotics—a word derived from Latin and Greek meaning literally ‘‘for life’’—has been defined in many ways since it was first coined 50 years ago. FAO/WHO joint report (2001) defines Probiotics are “living micro-organisms which when administered in adequate amount confer health benefits of the host”. This definition fits well in with that of functional foods. Probiotics are usually bacterial components of the normal human intestinal flora, for example *lactobacilli* and *Bifidobacteria*, that produce as end products of metabolism lactate and short chain fatty acids such as acetate and butyrate (Hill et al., 2014).

'Probiotic' is a useful and accepted term. The FAO/WHO definition has been widely adopted and has proven valuable to researchers, regulators and consumers. Organizations and agencies such as Codex (which comes under the FAO/WHO umbrella), Health Canada, the World Gastroenterology Organization, the European Food Safety Authority (EFSA) and the Institute of Food Technologists use the FAO/WHO definition when referring to probiotics. The panel noted, however, that a more grammatically correct definition would be worded as, “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” and supports use of this wording going forward. This definition is inclusive of a broad range of microbes and applications, whilst capturing the essence of probiotics (microbial, viable and beneficial to health). The definition differentiates live microbes used as processing aids or sources of useful compounds from those that are administered primarily for their health benefits. The distinction between commensal microorganisms and probiotics is also inferred from this definition. Although commensals in the gut are often the source of probiotic strains, until these strains are isolated, characterized and a credible case presented for their health effects,

they cannot be called 'probiotics'. So to claim any microflora as probiotic it should be member of a safe species which is supported by a sufficient evidence of general beneficial effect in humans or a safe microbe with a property (e.g. structure , activity or end product) for which there is sufficient evidence for beneficial effects in humans (Hill et al., 2014) (Table 2.2).

**Table 2.2: Microorganisms Used as Probiotics in Humans and Animals**

| ***Lactobacillus Species*** | ***Bifidobacteria Species*** | ***Other Lactic Acid Bacteria*** | ***Non Lactic Acid Bacteria*** |
|---|---|---|---|
| *L. acidophilus*<br>*L. brevis*<br>*L. casei*<br>*L. fermentum*<br>*L. gallinarum*<br>*L. gasseri*<br>*L. johnsonii*<br>*L. plantarum*<br>*L. reuteri*<br>*L. rhamnosus* | *B. adolecentis*<br>*B. animalis*<br>*B. bifidum*<br>B. breve<br>*B. infantis*<br>*B. longum* | *Enterococcus faecalis*<br>*Enterococcus faecium*<br>*Lactococcus lactis*<br>*Leuconostoc mesenteroides*<br>*Pediococcus acidilactici*<br>*Sporolactobacillus inulinus*<br>*Streptococcus salivarus* | *Saccharomyces cerevisiae*<br>*Saccharomyces boulardii* |

***Source:*** *Balcazar JL 2007*

**Positive health effects of probiotics**

**Mechanism of action***:* The mode of action of a probiotic may include host microflora modulation by a) improvement of the microbial balance via interaction of orally applied viable microbes with the microflora in the digestive tract lumen, b) the modulation of host metabolic activities, e.g., by stabilizing digestive enzyme pattern,

and immunomodulation, c) by activation and regulation of mucosa-associated and systemic immune system responses (Tripathi and Giri 2015; Fedork and Madsen 2004). The modes of action are also strain dependent. The intestinal microflora provides protection against a broad range of pathogens, including certain forms of *Clostridia, Escherichia coli, Shigella,* and *Pseudomonas,* as well as yeasts such as *Candida albicans. Lactobacillus casei* subsp *rhamnosus* (*Lactobacillus* GG) produces compounds that inhibit the growth of several gram-positive and gram-negative bacteria. Examples include hydrogen peroxide and pyroglutamate .A few other *lactobacilli* are capable of producing similar substances. Short chain fatty acids are commonly produced. These lower the colonic pH, which favors the growth of organisms with less pathogenicity. Colonization resistance occurs through this binding, competitively inhibiting adhesion of pathogenic bacteria (Tripathi and Giri 2015; Kleeman EG and Klaenhammer 1982). Probiotics may also compete for nutrients otherwise consumed by pathogenic organisms. For example, consumption of monosaccharides by a probiotic may reduce the growth of *Clostridium difficile*, which is dependent on monosaccharides for growth.

A major factor in determining the effectiveness of a probiotic is its ability to survive the digestive process and thrive in the gastrointestinal tract. Difficulties in establishing colonization are the focus of most investigations in search of effective probiotics (Argyri, et al., 2013; Kimoto et al., 2003; Perdigon and Alvarez 1995).

Probiotics are gaining importance because of the innumerable benefits, e.g. treating lactose intolerance, hypercholesterol problem, cardiac diseases and managing body weight. With the current focus on disease prevention and the quest for optimal health at all ages, the probiotics market potential is enormous. (Tripathi and Giri 2015; Arihara 2014) (Figure 2.14).

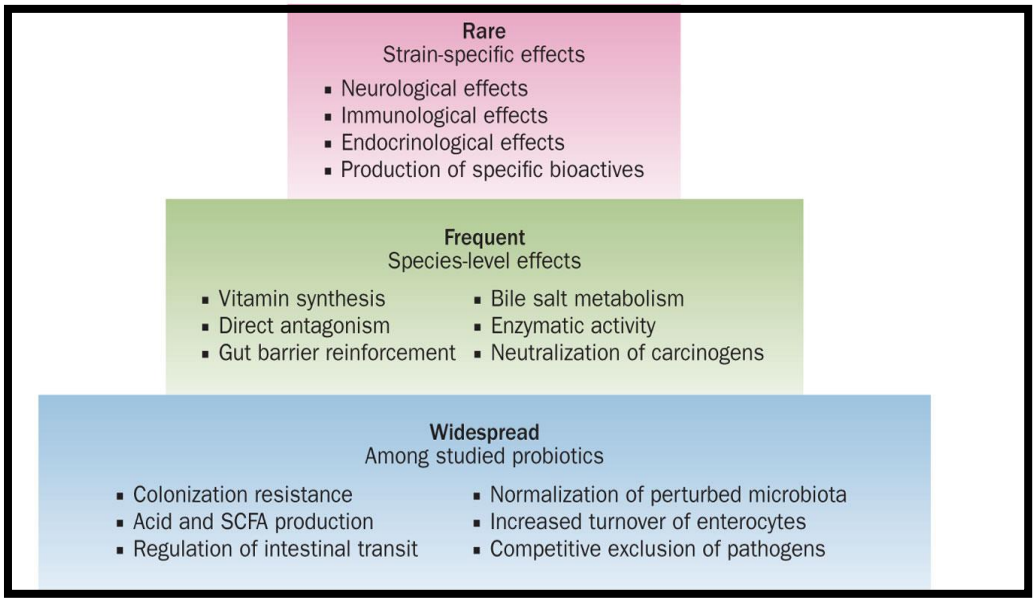


**Figure 2.14: Possible distribution of mechanisms among probiotics**
*(**Source**: Hill et al., 2014)*

### b) Prebiotics and its types and benefits

Prebiotic is a nondigestible substance of food origin when administered in adequate amounts, is beneficial to the consumer due to the selective promotion of growth and/or activity of one or more bacteria already present in the gastrointestinal tract or taken together with the prebiotic (Hill et al., 2014).

Any food that contains oligosaccharides is potentially a prebiotic but in order to be classified as a prebiotic it must fulfill the following criteria: it should neither be hydrolyzed nor absorbed in the upper part of the gastrointestinal tract and it should be selectively fermented by one or limited number of potentially beneficial bacteria commensal to the colon for example *Bifidobacteria* and *lactobacilli* which are stimulated to grow and become metabolically activated. These requirements have been classified as three prebiotic criteria (Table 2.3) (Hill et al., 2014; Bai 2014). Prebiotics are found naturally in some plants or are produced enzymatically from sucrose, and often are used in dietary supplements.

**Table 2.3: Criteria for Classification of a Food Ingredient as a Prebiotic**

- The must not be hydrolyzed nor absorbed in the upper digestive tract.
- The must represent selective substrate for one or more beneficial bacteria species in the colon stimulating their growth or activity.
- The must be able to modify the intestinal microflora of the colon promoting a healthy composition.

These includes non-digestible carbohydrates, which are often described as soluble fibers, include non-starch polysaccharides, resistant starches and soluble oligosaccharides. The classification of natural and also some synthetic prebiotic types is listed in Table 2.4. Major prebiotics include fructans and galactooligosaccharides (GOS). Fructans include inulin derived from chicory, whole grains, fruits (e.g., bananas), vegetables (e.g., onions, artichokes) or fructo-oligosaccharides (FOS) hydrolyzed from chicory or enzymatically from sucrose. GOS are made from lactose as a by-product of dairy-food processing (Bai 2014).

**Table 2.4: Classification of Prebiotics**

| Classification | Origin/ Manufacturing process |
|---|---|
| **Disaccharides** | from lactose, synthetic |
| Lactulose | from lactose, synthetic |
| Lacticol | |
| **Oligosaccharides** | Legumes, vegetables, cereals |
| Fructose Oligosaccharides (FOS) | Extraction/hydrolysis |
| Soyabean Oligosaccharides | Soyabean |
| (Trans) Galactooligosaccharides | Extraction/hydrolysis |
| Inulin | From lactose, Synthetic |
| | Legumes, vegetables, cereals |
| | Extraction |
| **Polysaccharides** | Legumes, vegetables, cereals |
| Resistant Starch | Extraction |

Although probiotic and prebiotic approaches are likely to shares common mechanism of action, as their effect is impacted through increase in beneficial colonic bacteria, they differ in composition and metabolism. Prebiotics are found naturally in some plants or are produced enzymatically from sucrose, and often are used in dietary supplements. However, the prebiotic property has been demonstrated adequately for only a few food ingredients. These includes non-digestible carbohydrates, which are often described as soluble fibers, include non-starch polysaccharides, resistant starches and soluble oligosaccharides.

## 2.13 Fructooligosaccharide (FOS) as a Prebiotic

### a) Inulin type fructans: chemistry and nomenclature

Inulin-type fructans are natural components of several edible fruits and vegetables, and the average daily consumption has been estimated to be between 3 and 11 g in Europe (Van Loo J et al., 1995) and between 1 and 4 g in the United States (Moshfegh AJ et al., 1999). The most common dietary sources are wheat, onion, banana, garlic, and leek. Chemically, inulin-type fructans are a linear polydisperse carbohydrate material consisting mainly, if not exclusively, of β-(2)1) fructosyl-fructose linkages (Waterhouse AL and Chatterton NJ 1993). A starting a-D-glucose moiety can be present but is not necessary. GpyFn [glucopyranosyl-(fructofuransoyl)n-fructose] and FpyFn [fructopyranosyl- (fructofuranosyl)n-fructose] compounds are included under that same nomenclature; they are both a mixture of oligomers and polymers that are best characterized by the degree of polymerization (DP), either as the average (DPav) or the maximum (DPmax) value.

The plant that is most commonly used industrially for the extraction of inulin-type fructans belongs to the Composite family, i.e., chicory. Native chicory inulin is a non-fractionated inulin extracted from fresh roots (De Leenheer L 1996). Because of the β-configuration of the anomeric C2 in its fructose monomers, inulin-type fructans resist hydrolysis by human small intestinal digestive enzymes, which are specific for a-glycosidic bonds. They have thus been classified as ‘‘nondigestible’’ oligosaccharides (Sabater-Molina et al., 2009; Femia et al., 2010; Xu et al., 2009;

Delzenne N and Roberfroid MB 1994; Roberfroid MB et al 2000). Structure of inulin and fructooligosaccharide has been displayed in Figure 2.15.

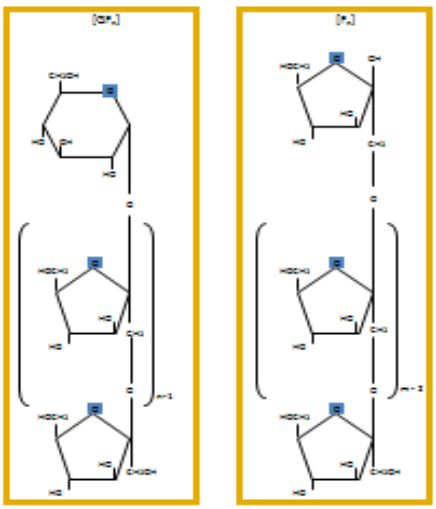

**Figure 2.15: Structure of inulin (left) and Fructooligosaccharide (right)**

**a) Safety and tolerance of Fructooligosaccharide (FOS)**

Fructooligosaccharide and inulin are a significant part of the daily diet of most of the world's population. Daily intakes for the U.S. and Europe have been estimated at up to 10 g, specifically 1–4 g for the 97th percentile in the U.S. Because both inulin and oligofructose are macro-ingredients, it is difficult to apply classical toxicology tests. Although some high dose animal tests have been performed, none have revealed any toxic effects. The safety of inulin and oligofructose for use in foods was evaluated by many legal authorities worldwide. As a result, both inulin and oligofructose are accepted in most countries as food ingredients that can be used without restrictions in food formulations. In the U.S., a panel of experts performed a generally accepted as safe (GRAS) Self-Affirmation Evaluation in 1992 and concluded similarly. At high doses, increased flatulence and osmotic pressure can cause intestinal discomfort. These doses vary widely from person to person and also depend on the type of food in which inulin or oligofructose is incorporated. With regard to labeling, both inulin and oligofructose are gradually being accepted as ''dietary fibers'' in most countries around the world. The mention of their ''*bifidogenic* effect'' on food labels has also been legally accepted in several countries (Coussement 1999).

According to the U.S., FDA notice on GRAS of FOS with notice number GRAS Notice No. GRN 000118, based on the proposed uses FDA estimates that dietary intake of inulin at the 90th percentile level would be approximately 6 grams per day for infants less than one year of age, approximately 15 grams per day for infants one year of age, and approximately 20 grams per day for the general population (i.e., two years of age and older) (Lied et al., 2011; Grabitske and Slavin 2009; Sabater-Molina et al., 2009; Femia et al., 2010; Xu et al., 2009; Pasman 2006).

***c*) Caloric value of fructooligosaccharide (FOS)**

Longer chain native oligosaccharides (Inulin) and shorter chain synthetic fructooligosaccharides (Neosugar)-GF2,GF3,GF4 reach the large intestine virtually intact and, as such, were considered not to be a major source of energy (Oku et al., 1984).

Furthermore, in the rat model, there appear to be no hydrolytic enzymatic adjustments in the small intestine to long-term ingestion of these factors. Nilsson and others (1988 a,b) used oral intubation to give fructans with a DP of about 9 or DP 16 to rats and found that both proceeded as undigested material through the gastrointestinal tract to the colon. However, due to the bacterial fermentation that occurs in the colon, these oligosaccharides do contribute to the energy pool. The caloric value of a fructosyl unit of oligofructose is calculated at 30 to 40% of a digested fructose molecule or between 1-1.5 kcal/g (Roberfroid et al., 1993). Ranhotra and coworkers (1993) reported a caloric value for oligofructose of 1.48 kcal/g. They determined usable energy value based on efficiency of conversion of gross food energy to net energy (carcass energy) using young rats as the test model. Molis et al., 1996 further defined the energy value of fructooligosaccharides (44% GF2; 46% GF3; and 10% GF4) working with six healthy human subjects. Calculated mean energy value of the fructooligosaccharide was 9.5+0.6 kJ/g (range: 8.3-11.7 kJ/g) or about 2 kcal/gram. For nutrition labeling purposes, Roberfoid (1999) recommends that inulin and oligofructose, as well as all nondigestible oligosaccharides that are mostly fermented in the colon, be assigned a caloric value of 1.5 kcal/g (6.3 kJ/g).

**d) Legal classification of fructooligosaccharide (FOS)**

Fructooligosaccharide (FOS) and inulin are legally classified as food or food ingredients, and not as additives, in all countries in which they are used. Although this seems evident if one considers the nutritional properties and the use of both substances, it has not been easy to obtain confirmation of this legal status from many of the legal authorities in the world. As a consequence, neither inulin nor oligofructose are listed as accepted food additives in the standard positive lists from the European Union or from Codex Alimentarius. EU Directive EC 95/2 explicitly lists inulin as a substance that is not an additive. The EU Standing Committee meeting of June 1995 confirmed that oligofructose is a food ingredient. In Europe, both inulin and oligofructose were brought to market long before the Novel Foods Regulation (EC 258/97) came into force. Since 1987, Orafti has applied for authorization as a food ingredient for both substances in all European countries separately. In most countries, the files were submitted to the Superior Health Council (or the corresponding government body) for advice. None of the European countries has ever expressed reservations with regard to the safety of inulin or oligofructose. In all countries, both substances are accepted for food use without limitations. No ADI were fixed. In the U.S., a committee of experts convened by Orafti declared both inulin and oligofructose as generally Recognized as Safe in 1992 (Slavin2013; Kolbye et al., 1992).

## 2.14 Fructooligosaccharide (FOS) and its Technological Functions

Nowadays one of the tendencies in food segment is the healthiness and wellness, associated to the growth of food industry in answering the consumer exigencies who is more conscious that an adequate feeding with healthy ingredients are indispensable to a better life wellness to children and adults.

Over the last 20 years, there has been a significant interest, by both consumers and food manufacturers in the production and consumption of prebiotics in daily diet (O'Sullivian 2001; Bruno and Shah 2002). Many researches about of developing food products, involving milk and derivatives, bread, cake, etc., adding value due contain prebiotic ingredients. . It is valid to highlight that these products must positively

answer to the nutritional and sensory characteristics, and remain in appropriate conditions during the processing and storage (Barreto et al., 2003)

Among the prebiotics researched so far fructooligosaccharide and inulin hold the key position in the food industry because of its interesting technological characteristics. Refined native inulin powder from chicory is white, amorphous, and slightly hygroscopic; has a specific gravity of about 1.35 and an average molecular weight of about 1,600. It is neutral in odor and taste. Commercial inulin contributes a marginally sweet taste due to a small amount of naturally occurring mono-and disaccharides. OFS is soluble in water with the solubility dependent on the temperature of the water, degree of polymerization, distribution of the molecular chains, degree of molecular branching and how the molecule is processed. FOS exhibit minimal influence on the organoleptic characteristics of a product and possesses nutritional benefits and health claims.

Sensory analysis is a decisive phase during the food product development (Morais et al., 2014) developed chocolate dairy dessert with addition of prebiotics and replacement of sucrose with different high-intensity sweeteners. The relative sweetness analysis showed that sweeteners had the highest sweetening power compared with the prebiotic chocolate dairy dessert containing 8% sucrose. The study of sweetness in this product is important because consumers desire healthier functional products with no added sugar.

Cruz et al., 2013 aimed to evaluate the effect of increasing concentrations of oligofructose addition on physicochemical, rheological and microbiological characteristics of non-flavored yogurt. The addition of oligofructose showed no influence on the pH, proteolysis or the viability of *Streptococcus thermophilus* or *Lactobacillus bulgaricus* during 28 days of refrigerated storage ($p > 0.05$).

In another study, inulin was supplemented in bread and results are smaller loaves, harder crumb and darker colour. Sensory studies reflected acceptability decreases with inulin content, yeast invertase and dry heat degrade inulin, and fructo-oligosaccharide/inulin fortification in bread at 5% seems achievable (Morris and Morris 2012)

Study to determine the effect of a prebiotic (fructooligosaccharide) on the sensory properties and consumer acceptability of peach-flavored drinkable yogurts was carry out. The yogurts containing the prebiotic were not significantly different from their comparable controls indicating that a prebiotic can be added without impacting acceptance (Gonzalez et al., 2011).

## 2.15 Role of Fructooligosaccharide Fermentation in the Gut

### a. Role of Fructooligosaccharides in enhancing the microflora

The fermentability of FOS and inulin by fecal bacteria has been extensively investigated in several *in vitro* models (Langlands SJ et al., 2004; Vuyst de Luk and Leroy F 2011). Wang and Gibson (1993) determined *in vitro* the prebiotic efficacy of FOS and inulin as compared to a range of reference carbohydrates (starch, polydextrose, fructose and pectin) in 12 h batch cultures with mixed populations of gut bacteria. Bacterial growth data showed preferential fermentation by *Bifidobacteria* while populations of *Escherichia coli* and *Clostridium perfringens* remained at relatively low levels, which showed the Bifidogenic properties of this prebiotic. Shin and coworkers in 2000 cultured two commercial strains of Bifidobacterium spp (Bf-1 and Bf-6) in 12%(w/w) non-fat dry milk containing 0.5, 1.0, 3.0 and 5.0%(w/v) fructooligosaccharide (FOS), galactooligosaccharide (GOS) and inulin. Inoculated samples were incubated anaerobically at $37^0$C for 48 h. Growth and activities of the cultures were determined. Viability of each strain was assessed after 4 weeks of refrigerated storage at $4^0$C. Growth promotion, enhancement of activity and retention of viability were greatest when *Bifidobacteria* Bf-1 and Bf-6 were grown in the presence of FOS followed in a descending order by GOS and inulin. The effects of oligofructose and inulin increased with increasing carbohydrate concentration and was maximal at 5%(w/v).

The degree of polymerisation of oligofructose is also important in affecting the level of growth and viability of bacteria. For instance, in a study β-fructofuranosidase gene from *Bifidobacterium lactis* was identified and characterised. This gene showed high identity with a similar gene in *Bifidobacterium longum*. The deduced enzyme showed maximum activity towards oligofructose, to a lesser extent to inulin and a minimum

activity towards long chain inulin. From this data it appears that the characterized enzyme is highly selective for oligofructose and has a high affinity towards β(2→1) fructosyl-linkages, and that its specificity decreases as the degree of polymerization (DP) of the fructan increases (Janer C et al., 2004).

Experiments with a three-stage continuous culture model of the human colon *(in vivo*) further confirmed the Bifidogenic effect of FOS (Gibson GR and Wang X 1994). Karpinen and coworkers in 2000 compared the fermentability of inulin by human fecal bacteria of the rye, wheat, oat bran in non pH controlled batch cultures. Inulin was the most rapidly fermented of the test substrates giving the highest butyrate production. In a 2 week study upon the effects of 4g/day FOS on 10 healthy individuals, Williams et al., 1994 reported a significant increase in *Bifidobacteria* levels and an increase in *lactobacilli* in six volunteers. In a similar study, Buddington et al., 1996 investigated the influence of FOS supplementation on the fecal microflora composition of 12 healthy adult humans. Subjects were fed a controlled diet for 42 days, which was supplemented with 4g/day FOS. The controlled diet increased *Bifidobacteria* levels but the highest increase was observed during FOS supplementation.

Tuohy and coworkers in 2001 further used fluorescent in situ hybridization (FISH) to investigate the prebiotic efficacy of biscuits delivering 6.6 g/day short chain FOS (scFOS) in a double blind, placebo-control study of 31 healthy adults. A significant increase in *Bifidobacteria* levels was observed at the end of supplementation. Bouhnik et al (1999) assessed the tolerance and threshold dose of scFOS which significantly increased fecal *Bifidobacterial* counts in an 8-day study of 40 healthy human volunteers. Volunteers were divided into six treatment groups each given a treatment between 0 and 20g/day scFOS. They reported that the optimal dose for increased bifidogenesis without significant side effects, such as flatulence, was 10g/day. Most recent both *in vitro* and *in vivo* studies on Bifidogenic properties of FOS on humans also exhibit the similar results of increasing *Bifidobacteria* (Sheth and Assudani 2015; Scott et al., 2014; Mendlik K et al., 2012; Boler BV 2013).

## 2.16 Health Implications of FOS

Recent use of FOS as a food ingredient has stimulated much research to know its functionality and its effects on human health. Thus, its potentially beneficial effects in preventing and controlling some diseases have been extensively discussed (Conterno L et al., 2011).

### a) Effect of fructooligosaccharide in Gastrointestinal tract

The inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis and pouchitis are chronic conditions of unknown etiology characterized by persistent mucosal inflammation at different levels of the gastrointestinal tract (O'Hara Am and Shanahan F 2007). There is evidence showing that the microbiota of patients with IBD differs from healthy subjects. Differences include low biodiversity of dominant bacteria, temporal instability, and changes both in composition and spatial distribution: high numbers of adherent bacteria in the mucus layer and at the epithelial surface (Guarner F 2005; Manichanch C et al., 2006; Ott SJ et al., 2004). Numerous studies have shown that prebiotics like inulin and oligofructose increases saccharolytic activity within the gut and promote the growth of *Bifidobacteria*. By increasing the number of 'friendly' bacteria on the mucosal surface, inulin and oligofructose could improve the barrier function in IBD and prevent mucosal colonization (Guandalini and Cernat 2014). Both human and animal data have shown a powerful impact on improved gastrointestinal tract diseases by inulin type fructans (Vidella 2001; Osman et al., 2006).

FOS has also been given to patients with ulcerative colitis and crohn's disease with different doses ranged from 12g/d to 15g/d for the duration of 3-4 weeks and reported overall improvement and decrease mucosal inflammation in both the gastrointestinal disease conditions (Furrie E et al., 2005; Lindsay JO et al., 2006).

From these strong experimental and clinical studies it can be concluded that inulin and FOS can offer an opportunity to prevent or mitigate gastrointestinal disease and their symptoms.

**b) Effect of fructooligosaccharide on Obesity and Low Grade Inflammation**

Gut microflora has recently been proposed as an environmental factor responsible for the weight gain and the altered energy metabolism that accompanies the obese state (Moran and Shanahan 2014; Harris et al., 2012). Several studies reported that the gut microflora differs at phylum level depending on weight status (Angelakis et al., 2012; Eckburg PB et al., 2005; Turnbaugh PJ 2006).

Prebiotics are defined as food ingredients that stimulate the growth of a limited number of microbial genus/species in the gut microbiota that are hypothesized to confer health benefits to the host (Guandalini and Cernat 2014; Slavin 2013). The administration of oligofructose to high-fat-fed mice increased the abundance of *Bifidobacterium* and *lactobacilli* (Everard et al., 2013; Slavin 2013) and normalized endotoxaemia (Zhao 2013; Cani et al., 2007; Neves et al., 2013) and the inflammatory tone associated with the high-fat diet (Martin et al., 2009; Million et al., 2013). The administration of oligofructose to genetically obese mice induced increases in the levels of *Lactobacillus*, *Bifidobacterium*, and *C. coccoides*, *E. rectale* , which led to a reduction in intestinal permeability and an improvement in tight junction integrity and inflammatory markers, such as lipopolysaccharides and cytokines (Cani et al., 2007; Million et al., 2013) (Figure 2.16) .

Parnell and Reimer 2009 evaluated the effects of oligofructose supplementation on body weight and concentrations of ghrelin and PYY as a measure of satiety in overweight and obese adults. FOS induced carbohydrate fermentation results in the production of SCFAs, (Xu J and Gordon JI 2003; Samuel et al., 2008; Tolhurst et al., 2012) which ultimately results in the regulation of gut hormones such as glucagon-like peptide (GLP-1) and peptide YY (PYY) (Bomhof et al., 2014; Neyrinck et al., 2012; Conterno 2011; Knauf C et al., 2008; Chaudhri OB et al., 2008) (Figure 2.17). These gut hormones are responsible for satiety through regulating the production and release of digestive enzymes (Baggio and Drucker 2014). The randomized 48 healthy adults (BMI>25 kg/m2) to receive either oligofructose (21 g/daily) or placebo (maltodextrin) for 12 weeks. They found a reduction of 1.03 ±0.43 kg in patients with oligofructose as compared to an increase of 0.45± 0.31 kg (p= 0.01). This led to

conclude that oligofructose supplementation has a potential benefit in promoting weight loss as well as improving glucose regulation in overweight and obese adults (Parekh et al., 2014).

A study reported that oligofructose feeding (20g/d) significantly increased plasma GLP-1 after mixed meal (Piche T et al., 2003). Furthermore, a study demonstrated that in healthy humans, feeding of 16g/day FOS promoted satiety followed breakfast and dinner and reduced hunger after dinner. This was accompanied by a significant 10% lower total energy intake (Cani PD et al., 2006; Bomhof et al., 2014).

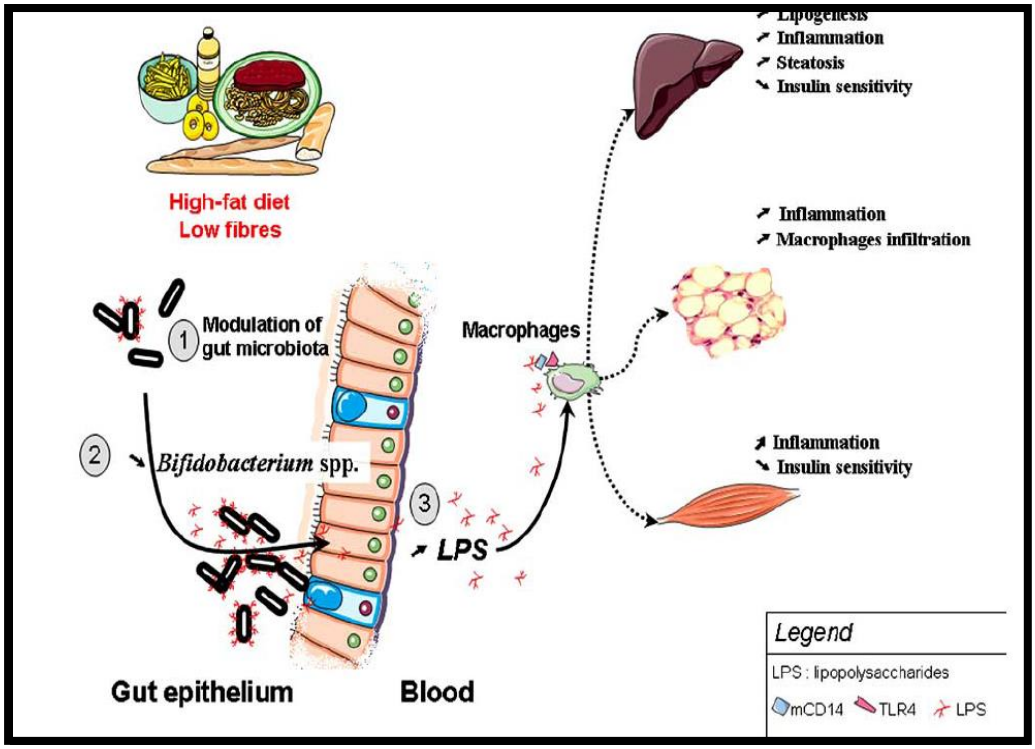


**Figure 2.16: High fat feeding diet changes the gut microflora, promote endotoxemia and obesity.** (1) High-fat diet feeding changes gut microbiota in a complex way and (2) specifically decreases *Bifidobacterium* spp. (3) This phenomenon is associated with a higher plasma LPS content (metabolic endotoxemia), a LPS-dependent secretion of pro-inflammatory cytokines. High fat feeding and LPS promotes low-grade inflammation-induced metabolic disorders (insulin resistance, diabetes, obesity, steatosis, adipose tissue macrophages infiltration). ***(Source**: PD and Delzenne NM 2009)*

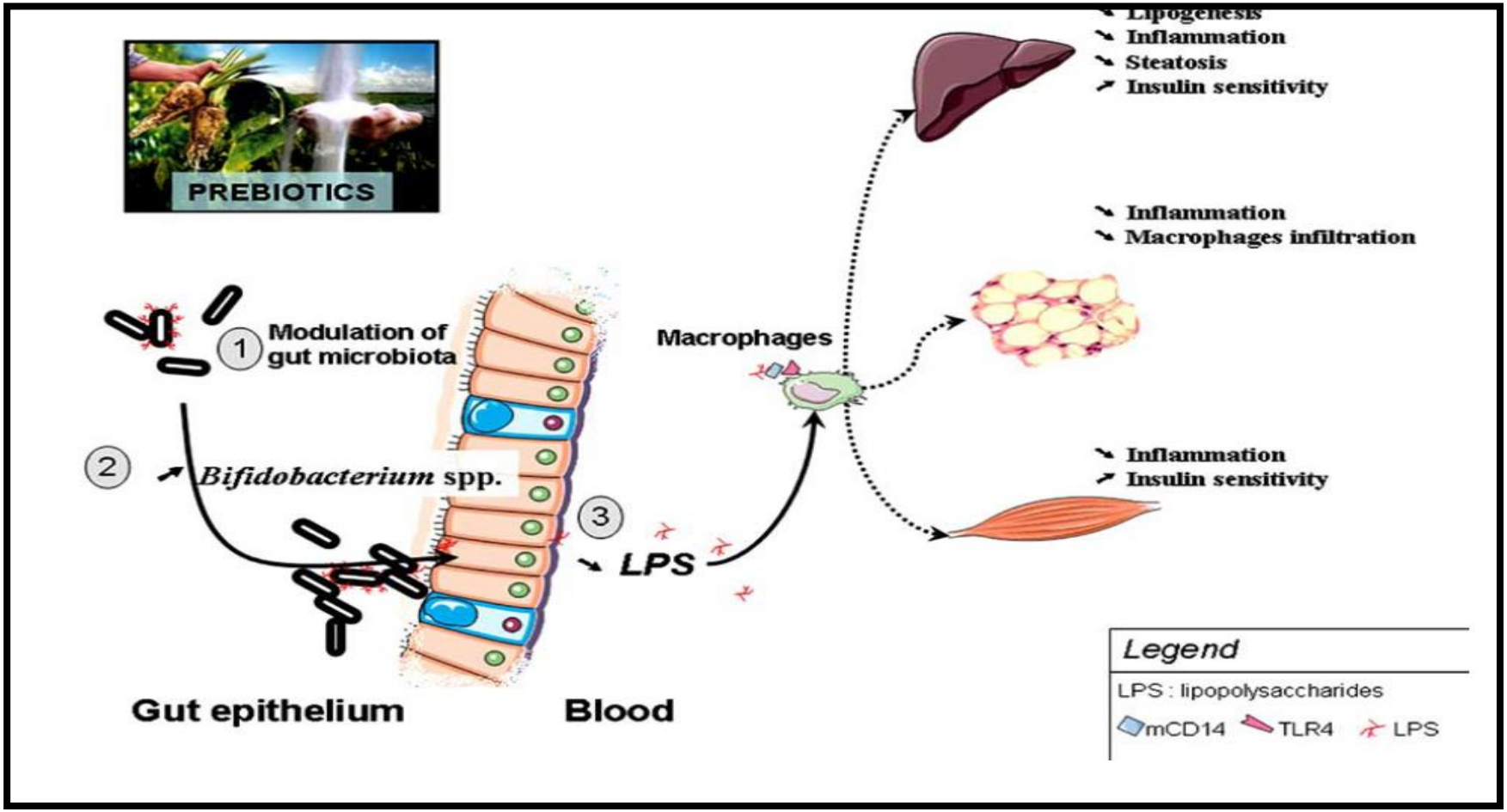


**Figure 2.17: Change in gut microflora by prebiotic (FOS) and decrease in LPS activity.** Prebiotic treatment increases *Bifidobacterium*-spp., decreases plasma LPS levels and improved insulin sensitivity, steatosis, and normalized low-grade inflammation (decreased endotoxemia, plasma and adipose tissue proinflammatory cytokines). *(**Source**: Cani and Delzenne 2009)*

# SCOPE OF INVESTIGATION

The present study entitled **"Sensory evaluation of Fructooligosaccharide (FOS) added foods and its impact on gut health and biochemical parameters in obese industrial employees of rural Vadodara"** was undertaken with following working hypothesis:

- FOS will blend well with many routinely consumed Indian food products.
- Daily intake of 12 g of FOS for 8 weeks will improve satiety, plasma GLP-1 and colonization of beneficial fecal gut microflora (*LAB and Bifidobacteria*) in fecal samples of obese adults.
- Daily intake of 12 g of FOS will bring about a reduction in body weight, endotoxemia (LPS) and colonization of Enteric pathogens.

To authenticate the above mentioned hypothesis present study was undertaken with the following objectives-

**PHASE I – Sensory evaluation of FOS added popular Indian food products**

- Effect of adding varying levels of FOS in the popular Indian food products i.e. buttermilk*, lemon juice,* milk*,* soup*, potato curry, dal, kadi, kheer* and *khichdi* on their organoleptic qualities.

**PHASE II – Comparative analysis of obese and normal weight subjects of an industry for their anthropometric parameters, nutrient intake, fecal gut microflora, GLP-1, LPS, hunger and satiety**

- Collecting data on baseline information in terms of socio-economic status, lifestyle history and medical history of normal weight and obese subjects.
- Assessing anthropometric measurements of the normal weight and obese subjects.
- Assessing the nutrient intakes, food frequency in normal weight and obese subjects.

- Determining biochemical parameters *viz* gut incretin-Glucagon like peptide-1 (GLP-1) and LPS (Lipopolysaccharide) levels of the normal weight and obese subjects.

- Analyzing fecal samples of normal weight and obese subjects by enumeration of gut microflora in terms of *Bifidobacteria, Lactic acid bacteria* and Enteric pathogen.

- Assessing any possible correlations of BMI with hunger and satiety score, dietary intake, serum LPS, GLP-1, gut flora.

**PHASE III- Anthropometric and metabolic responses of obese subjects to supplementation of FOS**

- Studying the effect of FOS supplementation on anthropometric parameters, dietary intake, hunger and satiety scale of obese subjects.

- Assessing the effect of FOS supplementation on serum LPS and gut incretin (GLP-1) levels in obese adults.

- Determining prebiotic effect of FOS supplementation on fecal microbial counts (*Lactobacilli, Bifidobacteria* and Enteric pathogen) in obese adults.