Chapter II

LITERATURE REVIEW
Chapter II

Literature Review

Obesity is set to be the world’s largest single cause of mortality and morbidity in the 21st Century. The explanation for this grim prediction is that obesity significantly increases the risk of developing various life-threatening diseases, including type II diabetes, hypertension, coronary heart disease, stroke and certain cancers (Cheetham et al., 2004)

Definition

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health (WHO, 2000). It is defined by body mass index (BMI) and further evaluated in terms of fat distribution via the waist-hip ratio. Body mass index (BMI) or Quetelet index is a simple index of weight-for-height that is commonly used in classifying overweight and obesity in adult populations and individuals. It is defined as the weight in kilograms divided by the square of the height in meters (kg/m²). BMI provides the most useful population-level measure of overweight and obesity as it is the same for both sexes and for all ages of adults. BMI is closely related to both percentage body fat and total body fat (Gray and Fujioka, 1991).

The World Health Organization (WHO) defines "overweight" as a BMI equal to or more than 25, and "obesity" as a BMI equal to or more than 30. These cut-off points provide a benchmark for individual assessment, but there is evidence that risk of chronic disease in population’s increases progressively from a BMI of 21.

Table 1: Cut-off points proposed by a WHO expert committee for the classification of overweight and obesity

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>WHO classification</th>
<th>Popular description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>Underweight</td>
<td>Thin</td>
</tr>
<tr>
<td>18.5–24.9</td>
<td>-</td>
<td>‘Healthy’, ‘normal’, ‘acceptable’</td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>Grade 1 overweight</td>
<td>Overweight</td>
</tr>
<tr>
<td>30.0–39.9</td>
<td>Grade 2 overweight</td>
<td>Obesity</td>
</tr>
<tr>
<td>≥40.0</td>
<td>Grade 3 overweight</td>
<td>Morbid obesity</td>
</tr>
</tbody>
</table>
Diabetes and obesity

Diabetes is a serious condition associated with overweight and obesity (Geiss et al., 2006). The incidence of type 2 diabetes increases with age and increasing obesity (particularly visceral or abdominal) and is more common in men than in women. The risk of developing NIDDM increases with a family history of diabetes or cardiovascular disease (particularly hypertension or dyslipidaemia) and lack of physical activity (Ehtesham, 2001). There is an increasing amount of data showing that being overweight during childhood and adolescence is significantly associated with insulin resistance, dyslipidemia, and elevated blood pressure in young adulthood. Weight loss by obese youngsters results in a decrease in insulin concentration and improvement in insulin sensitivity (Steinberger and Daniels, 2003).

Despite the very strong linkage between obesity and type 2 diabetes (80% of NIDDM patients are obese), the molecular link has remained a mystery. Given the high levels of free fatty acid (FFA), products of triglyceride metabolism, in the blood stream in obese people compared to non-obese individuals, along with the ability of FFA to induce insulin resistance in peripheral tissues (Boden, 1997), these biomolecules were naturally suspected as a link between obesity and diabetes. Mutation in the nuclear receptor peroxisome proliferator activating receptor gamma (PPARγ), which is an important regulator of adipocyte differentiation and modulator of intracellular insulin signalling events, has recently been found to predispose people to obesity (Beamer et al., 1998) and hypertension (Barroso et al., 1999).

Epidemiology

As of 2005 the WHO estimates that at least 400 million adults (9.8%) are obese, with higher rates among women than men. WHO further projects that by 2015, approximately 2.3 billion adults will be overweight and more than 700 million will be obese. In the USA, the country with the highest prevalence, more than 30% of adults are now obese (http://www.cdc.gov/nchs). Economic and technological changes promoting a sedentary lifestyle with easy access to low-cost, high-fat food are factors fuelling this epidemic coupled with a “thrifty genotype” that predisposes humans to store excess calories as fat (WHO, 2000).
Current obesity levels range from below 5% in China, Japan and certain African nations, to over 75% in urban Samoa. But even in relatively low prevalence countries like China, rates are almost 20% in some cities. Childhood obesity is already epidemic in some areas and on the rise in others. An estimated 17.6 million children under five are estimated to be overweight worldwide.

According to the US Surgeon General, in the USA the number of overweight children has doubled and the number of overweight adolescents has trebled since 1980. The prevalence of obese children aged 6-to-11 years has more than doubled since the 1960s. Obesity prevalence in youths aged 12-17 has increased dramatically from 5% to 13% in boys and from 5% to 9% in girls between 1966-70 and 1988-91 in the USA. The problem is global and increasingly extends into the developing world; for example, in Thailand the prevalence of obesity in 5-to-12 year olds children rose from 12.2% to 15-6% in just two years (http://www.who.int/nut).

In 1997, an article in the Indian Express dated July 19th stated that the incidence of obesity in India is 7-9 %, though the number of obesity is less as compared to America and the other countries, but it is also a significant due to the sheer size of the population in India. With such large numbers, India has been requested to join the International Congress on Obesity (ICO) for further study on the risk and management of the overweight in a developing economy.

Prevalence of obesity in Indian population is 20% in adults and 10% in children. In Northern India obesity was most prevalent in urban populations (male = 5.5%, female = 12.6%), followed by the urban slums (male = 1.9%, female = 7.2%). Obesity rates were the lowest in rural populations (male = 1.6%, female = 3.8%) (Yadav and Krishnan, 2008). Socioeconomic class also had an effect on the rate of obesity. Women of high socioeconomic class had rates of 10.4% as opposed to 0.9% in women of low socioeconomic class. The National Family Health Survey (NFHS-2, 1998-99) shows that 9 percent women in Delhi are obese and another 25 percent are overweight, which is highest among all the states in country. Punjab comes after Delhi with 21.1 percent overweight and 9.1 percent obese women. Also Haryana
comes third rank in north India with 12.3 percent overweight and 3.9 percent obese women. All together, these three north Indian states comprise 18.5 percent overweight and 7.2 percent obese women (Agrawal, 2002).

In the past 20 years, the rates of obesity have tripled in developing countries that have been adopting a Western lifestyle involving decreased physical activity and overconsumption of cheap, energy-dense food. Such lifestyle changes are also affecting children in these countries; the prevalence of overweight among them ranges from 10 to 25%, and the prevalence of obesity ranges from 2 to 10% (Hossain et al., 2007).

Approximately 85% of people with diabetes are type 2, and of these, 90% are obese or overweight. The growing prevalence of type 2 diabetes, cardiovascular disease, and some cancers is tied to excess weight. The burden of these diseases is particularly high in the middle-income countries of Eastern Europe, Latin America, and Asia, where obesity is the fifth-most-common cause of the disease burden—ranking just below underweight. The high risk of both diabetes and cardiovascular disease associated with obesity in Asians may be due to a predisposition to abdominal obesity, which can lead to the metabolic syndrome and impaired glucose tolerance.

The increase in the prevalence of type 2 diabetes is closely linked to the upsurge in obesity. About 90% of type 2 diabetes is attributable to excess weight. Furthermore, approximately 197 million people worldwide have impaired glucose tolerance, most commonly because of obesity and the associated metabolic syndrome. This number is expected to increase to 420 million by 2025 (Hossain et al., 2007).

The serious cardiovascular complications of obesity and diabetes could overwhelm developing countries that are already straining under the burden of communicable diseases. The risk of cardiovascular disease is considerably greater among obese people, and this group has an incidence of hypertension that is five times the incidence among people of normal weight. Hence, overweight and obesity are contributing to a global increase in hypertension: 1 billion people had hypertension in
2000, and 1.56 billion people are expected to have this condition by 2025 (Kearney et al., 2005).

Obese patients are at higher risk from coronary artery disease, hypertension, hyperlipidemia, diabetes mellitus, cancers, cerebrovascular accidents, osteoarthritis, restrictive pulmonary disease, and sleep apnoea (Calle et al., 2003). The risk of morbidity and mortality increases with an increase in body weight beyond a body mass index (BMI) (weight in kg/height in m²) of 27 and with an increase in waist circumference (as an index of visceral localization of fat). Obesity reduces life expectancy (WHO, 2000).

Pathophysiology

Obesity is characterized by an increase in subcutaneous adipose tissue. Its metabolic consequences, such as insulin resistance, are primarily attributable to increased fat deposition at such as the omentum, liver, and skeletal muscles. Recently, a virus has also been found to be associated with obesity. Human adenovirus Ad-36 causes adiposity in animal models and enhances differentiation and lipid accumulation in human and 3T3-L1 preadipocytes, which may, in part, explain the adipogenic effect of Ad-36 (Vangipuram et al., 2007).

Obesity occurs as a result of imbalance in energy input and expenditure. A number of genes, peptides, neurotransmitters, and receptors in the hypothalamus and neighbouring areas which regulate appetite and body weight (William, 2000).

There are four hypotheses regarding afferent mechanisms involved in appetite regulation. According to lipostatic hypothesis adipose tissue produces a hormonal signal that is proportionate to the amount of fat. Obesity is also said to be an inflammatory condition of the body. A growing list of adipocytokines involved in inflammation (IL-1 beta, IL-6, IL-8, IL-10, IL-18 (Mihai et al., 2006) and TNF-α) and acute phase response (serum amyloid A, PAI-1) have been found to be increased in the metabolic syndrome.
From white adipose tissue, there is release of leptin and resistin which decrease appetite. There is also release of adiponectin and adipocytokines like tumor necrosis factor -α and interleukin-6 (IL-6) which increases appetite. Brown adipose tissue also releases PPAR-γ and uncoupling protein (UCP-1) which are responsible for high metabolic rate and thus, for weight reduction.

Gut hypothesis determines release of peptides like GRP from the stomach. Glucagon and somatostatin from pancreas which decrease appetite and control weight. Some more peptides like CCK and PYY released from intestine and colon also are responsible for appetite and body weight regulation. Polypeptide ghrelin is released from stomach. It exerts orexogenic effect through neuropeptide Y (NPY)/ agouti related peptides (AGRP) pathways in the arcuate nucleus.

Glucostatic hypothesis holds that reduced blood glucose level increases appetite, frequent fasts lead to reduction in basal metabolic rate and increase in adiposity. Thermostatic hypothesis postulates that fall in body temperature below set point stimulates appetite and above set point inhibits (Srivastava et al., 2007).

**Figure 1**: Pathophysiology of obesity and its associated disorders
Factors influencing obesity

Obesity is not a single disorder but a heterogeneous group of conditions with multiple causes. Body weight is determined by an interaction between genetic, environmental and psychosocial factors acting through the physiological mediators of energy intake and expenditure. Although genetic differences are of undoubted importance, the marked rise in the prevalence of obesity is best explained by behavioral and environmental changes that have resulted from technological advances.

Genetics

Although obesity had a genetic component, it is not a simple genetic disorder. There is an underlying genetic predisposition to obesity on to which environmental factors are layered. The discovery of 'ob' gene, which was mapped to chromosome, has led to a renewed interest in understanding the patho-biological basis of genetic predisposition in obesity. The 'ob' gene codes a hormone called leptin, a 167 amino acid protein and was supposed to be produced in white and brown adipose tissue and placenta. The leptin receptors are concentrated in hypothalamus and belong to the same class of IL-2 and growth hormone receptors (Auwerx and Stales, 1998). Any mutation of 'ob' gene leads to improper coding of leptin, which further results in obesity. The effects of the 'ob' gene are mediated through effects on both energy intake and energy expenditure. The genes for obesity can be chosen for their possible effects on body fat composition, anatomical distribution of fat, food intake and energy expenditure. Monogenic rodent models of obesity are all characterized by early onset of obesity, hyperinsulinaemia and insulin resistance. The genetic aetiology of obesity in the laboratory-bred ob mouse is well defined. The ob gene is positioned on chromosome 6 and expressed exclusively in adipose tissue in normal mice. The gene product, which is called leptin (derived from Greek leptos, meaning thin), is nonfunctional in mice that are homozygous for the ob mutation (Zhang et al., 1994). Replacement of leptin by intraperitoneal injections in these animals leads to a reduction in body weight, body fat, food intake and serum insulin. Leptin introduced into the lateral or third ventricle of the brain is effective in reducing weight, indicating a probable central effect (Campfield et al., 1995). By contrast, the administration of
leptin to the db/db mouse (an obese mice characterized by high leptin levels) has no effect on appetite, body weight or body fat. These mice have a mutation of the leptin-receptor gene, which gives rise to a nonfunctioning leptin receptor. The initial hypothesis that obesity in humans results from a relative or absolute deficiency of leptin has not been borne out. Paradoxically, most obese humans have high circulating levels of leptin that are raised in proportion to fat mass (Maffei et al., 1995), whereas only a handful of individuals with severe obesity have been identified either with congenital deficiency or a mutation in the leptin-receptor gene.

Several other genes have been associated with human obesity or its metabolic complications. They include receptors that are important in mechanisms of thermogenesis (for example, $\beta_3$-adrenergic- receptor gene and the family of uncoupling proteins) as well as those involved in appetite regulation.

---

**Figure 2: Factors affecting obesity**

**Environmental factors**

Implicit to the susceptible-gene hypothesis is the role of environmental factors that unmask latent tendencies to develop obesity. Predictions about possible interactions...
between genes and the environment are difficult because there may be a delay in an individual’s exposure to an ‘obesogenic’ environment, and/or alteration in lifestyle related to living circumstances and uncertainty about the precise timing of the onset of weight gain.

Energy expenditure
The most variable component of energy expenditure is physical activity, representing 20–50% of total energy expenditure. In developed countries there is a relationship between low levels of physical activity and obesity. A longitudinal Finnish study found that those reporting physical exercise three or more times each week had on average lost weight since a preceding survey. By contrast, those who undertook little physical activity gained weight and had twice the risk of gaining 5 kg or more (Rissanen et al., 1991). Among children in the United States, the relative risk of obesity is 5.3 times greater for children who watch television for 5 hrs or more each day compared with those children who watch for less than 2 h, even after correcting for a wide range of socioeconomic variables (Gormaker et al., 1996).

Energy intake
There is good evidence that individual macronutrients (protein, fat and carbohydrate) exert differing effects on eating behaviour predominantly as a result of their effects on satiety. Fat has a weak satiating capacity, particularly when compared with protein, and subjects in experimental situations readily overeat when presented with high-fat foods (Lawton et al., 1993).

It seems likely that environmental influences act through increasing energy intake and/or decreasing energy expenditure. There is some evidence that high-fat diets are associated with an increased risk of obesity within populations, but cross-cultural dietary studies have failed to show any consistent relationship between nutritional factors and relative weights (Blundell et al., 1997).

Culture
Evidence for the critical role of environmental factors in the development of obesity comes from migrant studies and the ‘westernization’ of diet and lifestyles in
developing countries. The pronounced increase in age-standardized prevalence of obesity (>60% in men and women) in the Naurians in Micronesia and Polynesians in Western Samoa is closely paralleled by alterations in diet and lifestyle (James, 1996). Pima Indians, for example, living in the United States is on average 25 kg heavier than Pima Indians living in Mexico (Ravussin, 1995).

In both men and women, the prevalence of overweight and obesity increases with age until 50 to 60 years; it is particularly apparent between the ages of 20 and 40 years. In industrialized countries, a higher prevalence of overweight and obesity is observed in those with lower educational attainments and low income, although the reverse may be seen in developing countries. There is a tendency for overweight to increase after marriage and with increasing party.

Fetal nutrition
Evidence indicates that undernutrition of the fetus during intrauterine development may determine the later onset of obesity, hypertension and type 2 diabetes independent of genetic inheritance. Such a phenomenon suggests the possibility of long term programming of genetic expression as a consequence of altered intrauterine growth (Barker, 1995).

These adaptations are detrimental when there is a constant supply of nutrition. There are reports showing an inverse correlation between abdominal fatness and birth weight but none which have examined the effect of size at birth and the subsequent incidence of obesity (Kopelman, 2000).

HEALTH CONSEQUENCES OF OBESITY
Obesity is associated with high blood pressure, ischaemic heart disease, stroke, type 2 diabetes, dyslipidemia, social and mental health problems and certain forms of cancer. Apart from these metabolic and cardiovascular disturbances, obese people are frequently suffering from joint diseases and respiratory disorders such as obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS).
Diseases associated with obesity could arise from two mechanisms: from the metabolic changes associated with excess fat, as type 2 diabetes mellitus and cardiovascular disease, or from the increased fat mass itself, as it is clearly the case for joint diseases. In summary, obesity can affect almost all organs and tissues of the body, from the brain to the lower extremities, causing a multitude of clinical problems.

**Insulin resistance and type 2 diabetes mellitus**

The relationship between obesity and insulin resistance applies to all ethnic groups and the full range of body weights. Insulin is a regulator of the adipocyte biology and adipocytes are one of the cells of the body with a higher response to insulin. Insulin fosters the differentiation of preadipocytes to adipocytes, stimulates lipogenesis, and inhibits lipolysis (Kahn and Flyer, 2000).

Insulin resistance is defined as the decreased effect of insulin on glucose uptake, metabolism and storage. There is a diminished insulin-stimulated glucose uptake in skeletal muscle and adipose tissue, and impairment in the suppression of hepatic glucose output. In muscle and adipose tissue of obese humans and rodents there is an increased expression and/or activity of several protein tyrosine phosphatases, which dephosphorylate and terminate signaling propagated through tyrosine phosphorylation (Goldstein et al., 1998).

Additionally, a reduction in the expression of several insulin signaling molecules has been described in skeletal muscle in morbid obesity. Intra-abdominal fat depots are much more strongly linked to insulin resistance than subcutaneous fat depots. Then, subjects with central fat distribution are more prone to insulin resistance. Obesity is accompanied by the production of several cytokines that decrease insulin sensitivity in liver and skeletal muscle. TNF-α has paracrine effects on adipose cells, and reduces insulin action in skeletal muscle (Hotamisligil, 1999).
Free fatty acids (FFA) released from the more lipolytically active intraabdominal adipocytes, increase insulin resistance in liver and skeletal muscle through mechanisms affecting the intracellular insulin signaling cascade (Griffin et al., 1999).

The National Cholesterol Education Program Adult Treatment Panel III has established that the syndrome of insulin resistance exists when three of the five following criteria are abnormal: waist circumference >102 cm (>40 in.) in men and >88 cm (>35 in.) in women; HDL cholesterol <40 mg/dl in men and <50 mg/dl in women; triglycerides ≥150 mg/dl; fasting glucose ≥110 mg/dl; and blood pressure (systolic and diastolic blood pressure) ≥130/≥85 mm Hg (NIH, 2001).

Type 2 diabetes mellitus (DM), accounting for the 90–95% of those persons with diabetes, and previously known as non-insulin dependent diabetes or adult-onset diabetes, refers to individuals who have insulin resistance and insulin levels that frequently appear normal or elevated but are insufficient to compensate for insulin resistance, resulting in high blood glucose levels. Most patients with this form of diabetes are obese, and obesity has been recognized as a significant risk factor for the development of type 2 DM. Although not all obese individuals develop type 2 DM, the increase in the prevalence of obesity has been associated with an increase in its prevalence (Mokdad et al., 2003).

**Dyslipidemia**

It is well established that obesity and insulin resistance state are strongly associated with quantitative and qualitative alterations in plasma lipids. Obesity and obesity-related insulin resistance state are characterized by impaired adipocytes trapping of fatty acids and excessive adipocytes lipolysis. Further to VLDL dysregulation, obesity is also associated with low HDL levels. An impaired lipoprotein lipase activity and enhanced cholesteryl ester transfer protein (CETP)-mediated lipid exchanged contribute to the observed HDL-C reduction in obesity. In addition TG-rich HDL-C constitutes a better substrate for hepatic lipase, further lowering HDL-C levels. Atherogenic dyslipidemia is clinically presented as elevated serum TG levels, increased levels of small dense low-density lipoprotein (sdLDL) particles, and
decreased levels of HDL-C (Vinik, 2005). Indeed evidence suggests that as BMI increases over 21 kg/m², dyslipidemia is progressively developed, and sdLDL is raised. These changes are postulated to increase CHD risk by 3–6 folds (James, 2005).

Hyperuricemia
Hyperuricemia is frequently observed in obese subjects due to the overproduction of uric acid and its impaired renal excretion. Matsuura et al. (1998) reported that purine synthesis and the overproduction of uric acid could be linked to fatty acid synthesis by the liver. On the other hand, hyperinsulinemia has been proposed as a contributing factor to increased levels of uric acid in obesity, due to its renal effect resulting in diminished clearance of urate.

Cardiovascular disease
Obese subjects have increased risk of cardiovascular disease (CVD), and this is true especially for the abdominal or central type obesity. Obese individuals with central fat distribution are at higher risk for heart disease than those with peripheral type of obesity.

Hypertension
Among all the obesity related comorbidities, high blood pressure is, probably, the most well known. In the USA, data from the third National Health and Nutrition Examination Survey (NHANES III) clearly demonstrate a positive and linear association between the values of the BMI and the percentage of people with arterial hypertension. The Health Professionals Follow-up Study shows that among obese men (BMI ≥ 30 kg/m²) around 35% are hypertensive (Baik et al., 2000). Also, in women there is a strong relationship between obesity and hypertension. In the Nurse’s Health Study it is clearly seen that, women with a BMI over 30kg/m² have a four-fold increase in relative risk of having high blood pressure in comparison with those with a BMI of 21kg/m² (Huang et al., 1998).

Two hemodynamic disturbances are commonly seen in obesity-associated hypertension: increase of intravascular volume, and an ‘abnormally normal’
peripheral vascular resistance unable to respond correctly to the enhanced intravascular volume. The primary defect leading to the increase in intravascular volume should be some renal disturbance producing a change in the pressor natriuresis. In fact, obesity-hypertension shows an increase in sodium retention. Moreover, as demonstrated in animal models increased sympathetic activity is commonly found in obese hypertensive humans, which could explain, at least in part, the hemodynamic disturbances (Carlson et al., 2000).

The renin-angiotensin-aldosterone system (RAAS) probably has a key role in obesity hypertension. The RAAS seems to be hyperactivated in obesity, in spite of the increase of intravascular volume and sodium retention. Engeli and Sharma (2001) have demonstrated a direct association between plasma leptin and angiotensin levels suggesting that adipose tissue may contribute to the plasma angiotensin level.

Heart disease

Obesity is associated with several heart abnormalities. In a study of the American population, there was a significant increase in the prevalence of heart disease, diabetes, hypertension and hypercholesterolemia with increasing body weight in all gender, racial and socioeconomic groups (Paerataku et al., 2002).

Obesity is associated with accelerated coronary atherosclerosis and long-term longitudinal studies demonstrate that obesity predicts coronary atherosclerosis in an independent manner. The risk for developing coronary artery disease is increased 3,3-folds in American women with a BMI over 29 kg/m², in comparison with women with a BMI below 21 kg/m² (Manson et al., 1995). Moreover, a WHR of ≥0.92 is associated with a 3-folds increased risk of coronary heart disease (Lakka et al., 2002).

IL-6, a cytokine produced by adipose tissue, seems to play a key role in the development of coronary heart disease associated with obesity through different metabolic, endothelial and procoagulant mechanisms (Yudkin et al., 2000). Left ventricular hypertrophy is frequent in obesity. Obesity can also be the cause of
arrhythmias, and the prolonged QT interval also seen in obesity might be a predisposing factor for sudden death (Eckel, 1997).

**Stroke**
The association between obesity and stroke remains controversial, although most studies have shown a positive relation. In a prospective study of 21,414 US male physicians participating in the Physicians' Health Study, increasing BMI is associated with a rise in the risk of total, ischemic and hemorrhagic stroke independently of the presence of hypertension, diabetes and dyslipidemia.

**Gall bladder disease**
Cholelithiasis is the primary hepatobiliary pathology associated with obesity. Obese women have at least twice the risk of gall bladder disease as compared with normal weight women. The risk of having gall bladder disease is positively associated with the BMI.

Csendes et al. (2003) reported in a prospective study of 125 obese patients a high frequency of gall stones (30.4%). The explanation for the cholelithiasis seems to be the higher excretion of cholesterol through the bile in obese patients, favored by high plasma levels of cholesterol and triglycerides frequently found in obesity.

**Locomotor system**
There are functional locomotor limitations in obese women (Larsson et al., 2001). They have flexibility troubles and frequently pain in performing tasks at floor level such as picking things up, squatting or kneeling. They also move more slowly, and experience more exertion than the control population.

On the other hand, osteoarthritis and other joint problems are more frequent in obese subjects. The first National Health and Nutrition Examination Survey showed that women with a BMI between 30–35 kg/m² had nearly four times the risk of arthritis of the knee than women with a BMI under 25 kg/m² (Anderson and Felson, 1988).
Arthritis develops as a consequence of trauma associated with the excess of body weight in joints such as the knees and the ankles.

**Obesity-related kidney disease**

Obesity is related also to kidney disease. The renal effects of obesity include both structural and functional changes. Both glomerulomegaly and focal segmental glomerulosclerosis have been associated with obesity, not only massive obesity but also class I and II obesity. In relation to functional adaptations, increased glomerular filtration rate, increased renal blood flow and renal hypertrophy are considered to be the most relevant. Clinically, the presentation of obesity-related glomerulopathy is nephritic or sub-nephrotic range proteinuria and renal insufficiency in 44% of cases.

Obesity may have similar effects as diabetes on the kidney, with an initial phase of glomerular hyperfiltration followed by microalbuminuria, with this phase followed by a progressive fall in glomerular filtration rate and a further rise in urinary albumin excretion with the development of proteinuria and, sometimes, end-stage renal failure (Pinto-Sietsma et al., 2002).

**Obesity and cancer**

There is a growing body of evidence that obesity has also some kind of cause-and-effect relationship with many types of cancers. Given the global rising trend in obesity prevalence, even a small added risk of cancer due to obesity should be a major concern. In the USA, an increase in the relative risk of dying from cancer has a clear positive association with the BMI both for men and women. Assigning the risk to people with a normal BMI (18.5-24.9), those with obesity class II have a 1.3-folds relative risk, whereas those with a BMI ≥40kg/m² have a relative risk higher than 1.5-folds (Adami and Trichopoulos, 2003).

**Respiratory disease**

Two of the most common respiratory disturbances found in obesity are: obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS). In severe cases, both diseases can constitute a real threat for the patient’s life.
Obstructive sleep apnea
The association of obesity with OSA is strong, although very variable among the published studies. It is known that around 70% of individuals with OSA are obese and that the prevalence of OSA among obese people is approximately 40% (Resta et al., 2001).

Obese individuals have a narrowing of the upper airway due to an extrinsic soft tissue enlargement because of fat deposits in the posterolateral oropharyngeal area. Patients with central type obesity are more prone to have OSA because of their fat accumulation pattern (visceral and trunk).

Obesity-hypoventilation syndrome
The other respiratory disturbance associated with obesity is the poorly known obesity-hypoventilation syndrome (OHS). This syndrome is characterized by day time hypercapnia and severe hypoxemia (arterial partial oxygen pressure<70 mmHg) in the absence of lung or neuromuscular disease.

Biomarkers of Obesity
Obesity is a major risk factor for cardiovascular diseases, but the mechanisms for increased cardiovascular risk in obesity are still unclear. Inflammation and increased oxidative stress are two potential mechanisms proposed to play a major role in the morbidity associated with obesity. Biomarkers are generally considered to be plasma measurements of molecules, proteins, or enzymes that provide independent diagnostic or prognostic value by reflecting an underlying disease state or condition. The clinical utility of a biomarker depends on its ability to account for a significant proportion of the disease being evaluated; be accurate and reliable; provide good sensitivity, specificity, and predictive value; and be available for widespread application (Tsimikas et al., 2006).

Leptin
Leptin, the product of the ob gene, is a recently discovered single-chain proteohormone with a molecular mass of 16 kDa that is thought to play a key role in
the regulation of body weight (Friedman et al., 1998). Leptin is produced by differentiated adipocytes, although production has been demonstrated in other tissues, such as the fundus of the stomach, the skeletal muscle, the liver, and the placenta (Baratta, 2002). Leptin acts on the central nervous system, in particular the hypothalamus, suppressing food intake and stimulating energy expenditure (Webber, 2003). Leptin is also produced by the brain, which is involved in the regulation of body weight (Eikelis et al., 2004). It is closely associated with obesity and risk factors for CVD such as increased systolic blood pressure (Schutte et al., 2005). One mechanism by which leptin can increase CVD risk is via increased production of inflammatory markers (Eikelis et al., 2004), and it plays a role in the early induction of vascular dysfunction.

It was shown recently in humans that decreasing leptin concentrations in response to food deprivation are responsible for the starvation-induced suppression of the hypothalamic-pituitary-gonadal axes (Veniant et al., 2003) as well as the malfunction of several other neuroendocrine axes. Thus it seems that leptin may act as the critical link between adipose tissue, hypothalamic centers regulating energy homeostasis, and the reproductive system, indicating whether adequate energy reserves are present for normal reproductive function (Chehab et al., 2002).

Adiponectin

It is highly expressed during adipocyte differentiation (Scherer et al., 1995). The protective roles of adiponectin include reduction of tissue triglyceride content and inhibition of insulin resistance in diabetic and obese mouse models (Yamauchi et al., 2001). Adiponectin was reduced in obese rodents (Hu et al., 1996). Plasma levels of adiponectin were inversely associated with body mass index, percentage of body fat, and fasting plasma insulin in different ethnic groups (Kern et al., 2003), and they were increased with a 21 percent reduction in mean body mass index (Yang et al., 2001).
Resistin
Resistin is expressed in adipose tissues and is regulated by nutritional status (McTernan et al., 2003). Although circulating resistin was reported to be increased in obesity, its expression in adipose tissue was unchanged in some murine models of obesity compared with lean animals. In contrast, circulating resistin levels were higher in obese mice compared with lean controls (Lee et al., 2005).

Obesity and Insulin resistance
Obesity is characterized by elevated fasting plasma insulin and an exaggerated insulin response to an oral glucose load. Increasing upper body obesity is accompanied by a progressive increase in the glucose and insulin response to an oral glucose challenge with a positive correlation being observed between increasing upper body obesity and measures of insulin resistance. Post-hepatic insulin delivery is increased in upper body obesity leading to more marked peripheral insulin concentrations that, in turn, lead to peripheral insulin resistance (Kopelman, 2000). Insulin resistance correlates with the degree of obesity, notably abdominal obesity, and is a strong predictor for the development of Type 2 diabetes. The continuing dual epidemics of obesity and diabetes lend support to the notion that insulin resistance is the causal link between the two prevalent conditions (Mokdad et al., 2003).

Lipid profile and obesity
Obesity-associated dyslipidemia plays a crucial role in the development of atherosclerosis and cardiovascular disease in obese subjects, because all the elements of the dyslipidemia normally associated with this disease have been shown to be atherogenic. Obesity, mainly of central fat distribution, is associated with increases in plasma triglycerides, and decreases in HDL cholesterol. In fact, when adjusting for BMI, patients with a higher WHR seem to have higher triglycerides levels and lower HDL cholesterol levels (Dowling et al., 1993).

Interestingly, a change in LDL composition occurs in obese individuals whose LDL particles are smaller and more dense, increasing the risk of cardiovascular disease in individuals with this kind of LDL particles than in those with large LDL particles for
the same level of total cholesterol and, again, associated with a central distribution of the fat (Williams et al., 1997). This obesity-associated pattern of dyslipidemia (high tryglyceride levels, low HDL concentrations, and dense and small LDL particles) is related to insulin resistance.

The primary defect in lipid metabolism in obesity seems to be the overproduction of VLDL by the liver. Besides this increased synthesis, there is a decreased clearance of triglyceride-rich lipoproteins in the circulation due to decreased lipoprotein lipase activity (Miyashita et al., 2002). This impaired triglyceride lipolysis leads to reduced HDL concentrations by decreasing the transfer of apolipoproteins and phospholipids from triglycerides to the HDL compartment. Another characteristic of obesity is the impairment in LDL receptor activity, the most important point of clearance from the circulation of VLDL particles.

**Oxidative Stress**

Reactive oxygen species that lead to increased oxidative stress can be generated in adipocytes (Furukawa et al., 2004) all of which can be a source of increased oxidative stress in obese humans. Increased oxidative stress is independently associated with obesity measures including body mass index and waist-hip ratio (Keaney et al., 2003) and improves upon weight loss of at least 2 percent (Dandona et al., 2001). It is also associated with several CVD risk factors including smoking, blood glucose, and hyperlipidemia (Keaney et al., 2003; Ferroni et al., 2004). Oxidative stress may also promote endothelial dysfunction, atherogenesis (Fumkranz et al., 2005), and coronary heart disease independent of traditional risk factors (Stephens et al., 2006).

**Antioxidants**

Antioxidants are molecules, which can safely interact with free radicals and terminate the chain reaction before vital molecules are damaged. The human body has an elaborate antioxidant defense system. Antioxidants are biosynthesize within the body and can also be extracted from the food humans eat such as fruits, vegetables, seeds, nuts, meats, and oil. There are two lines of antioxidant defense within the cell. The first line, found in the fat-soluble cellular membrane consists of vitamin E, beta-
carotene, and coenzyme Q. Inside the cell water-soluble antioxidant scavengers are present. These include vitamin C, glutathione peroxidase, superoxide dismutase (SOD), and catalase.

**Glutathione (GSH)** Glutathione is synthesized in the erythrocytes and is found in living cells. It has been reported that cellular glutathione has an important function against chemical agents by protecting the cell membrane integrity. GSH constitutes the first line of defence against free radicals in the liver and is also responsible for the maintenance of protein thiols and acts as a substrate for glutathione peroxidase (GPx) and glutathione-S-transferase (GST) (Prakash *et al.*, 2001).

**Glutathione peroxidase (GPx)** Glutathione peroxidase is a major antioxidant defence system against increased oxidative stress. Glutathione peroxidase is present in most mammalian cells including the endothelium. Serum glutathione peroxidase is increased in animal models of obesity (Beltowski *et al.*, 2000).

**Glutathione S-transferase (GST)** is a soluble protein that is located in the cytosol and endoplasmic reticulum of the liver, and catalyses the conjugation of GSH with many xenobiotics and their reactive metabolites to form more water-soluble compounds (Vontas *et al.*, 2001). Ishii *et al.* (2000) showed that expression of GST are regulated by a common “antioxidant response element” and suggested that their gene products play a protective role against oxidative damage in various tissues by neutralizing ROSs.

**Glutathione reductase (GR),** also known as GR, is an enzyme that reduces glutathione disulfide (GSSG) to the sulfhydryl form GSH, which is an important cellular antioxidant. For every mole of oxidized glutathione (GSSG), one mole of NADPH is required to reduce GSSG to GSH. The activity of glutathione reductase is used as indicator for oxidative stress (Mannervik, 1987).

**EXPERIMENTAL MODELS TO INDUCE OBESITY IN RATS**

Obesity results from prolonged imbalance of energy intake and energy expenditure. Animal models have provided a fundamental contribution to the historical development of understanding the basic parameters that regulate the components of our energy balance. Obesity represents major challenges for basic science and clinical research. It is obvious that appropriate animals models are crucial for studies on the
pathogenesis and therapy of this complex metabolic disorder, but it is less clear how exactly to define the term "appropriate." From a scientific and an ethical point of view, it is reasonable to require that not only the phenotype but also the pathogenesis of the animal's condition resembles the human disease examined (Buettner et al., 2007).

The induction of obesity may be performed in animals by neuroendocrine, dietary or genetic changes. The study of these models has shown that it is the central nervous system that regulates energy expenditure and food intake, and it has also identified interrelationships among adrenal glucocorticoids, the autonomic nervous system and dietary behavior in the development of obesity (York, 1996). The great similarity and homology between the genomes of rodents and humans make these animal models a major tool to study obesity.

Some obesity-induction models in rats are found in the literature and among them all, the main ones are feeding on hypercaloric diets (Prunet-Marcassus et al., 2003), a lesion of the ventromedial hypothalamic nucleus (VMH) which can be achieved mainly in two ways (administration of monosodium glutamate or direct electrical lesion) (Shimizu et al., 2003), ovariectomy (Chu et al., 1999), and genetic manipulation for obesity.

**High Fat Diets for Diet-Induced Obesity Models**

This is the simplest obesity-induction model, and possibly the one that most closely resembles the reality of obesity in humans. The first description of a 'high-fat diet' to induce obesity by a nutritional intervention was in 1959 (Masek and Fabry, 1959).

High-fat diets produce a consistent and significant increase in body fat content that is dependent on the amount of fat in the diet and the duration of feeding. The earlier studies by Mickelson et al. (1955) in rats and by Fenton and Carr (1951) and Lemonnier (1972) in mice generally used diets that were extremely high in fat contents with 70-80% of total energy derived from fat. These diets resulted in prodigious obesity. The rats gain weight rapidly and can become quite obese on this
fare, and they tend to select and consume a high proportion of energy from fat (Prats et al., 1989).

Subsequent studies have revealed that high-fat diets promote hyperglycemia and whole-body insulin resistance, and numerous researchers have examined their effects on muscle and liver physiology as well as insulin signal transduction. High-fat diets can be used to generate a valid rodent model for the metabolic syndrome with insulin resistance and compromised β-cell function (Lingohr et al., 2002).

There are several types of diets to induce obesity that have proved effective. Diets based on saturated fatty acids induce the typical high-fat-diet phenotype, whereas diets containing polyunsaturated ω-3 fatty acids exert beneficial effects on body composition and insulin action (Storlien et al., 1996). Hyperphagia might be one important mechanism by which high-fat diets promote obesity. Some studies have been performed with so-called “cafeteria” diets that provide a mixture of commercially available supermarket foods consumed by humans (Rothwell et al., 1988).

A few diets attain hypercaloric values by adding carbohydrates and fats, and most of them vary between 3.7 Kcal/g and 5.4 Kcal/g. All of them are highly palatable and induce obesity. High-fat diets used in laboratory research typically contain about 32 to 60% of calories from fat. From a nutritional perspective, a human diet of 60 kcal% fat would be considered extreme. Diets with 60 kcal% fat are commonly used to induce obesity in rodents since animals tend to gain more weight more quickly (Ghibaudi et al., 2002; Johnston et al., 2007), thereby, allowing researchers to screen their compounds after a shorter period of time.

a) Dose-response relation between dietary fat and body fat content
In rats, there is a clear relation between the age of the rats when an obesity-producing diet is initiated, the duration of the diet, and the degree of body fat increase. That is, the earlier an obesity-producing feeding regimen is begun, the greater the effect on the final body fat content (Peckham et al., 1962), and the longer the duration of an
obesity-producing diet, the greater the increment of bodyweight gain and presumably body fat. The implication of these results is that obesity-producing diets may have a gradual, continuous effect on body fat and therefore, the duration of exposure to the diet is an important variable. Furthermore, there may be no plateau effect of dietary manipulations that promote obesity. Thus, feeding a high-fat diet to experimental animals may not result in rapid accumulations of body fat that then plateau. Instead, there may be a gradual, steady accumulation of body fat that might decelerate as extremes of body fat content are achieved, but weight gain may never plateau.

b) Obesity-Prone and -Obesity Resistant Rodent Strains

Overall, the data from studies in a variety of mammals including nonhuman primates, dogs, pigs, hamsters, and squirrels support the notion that increased amounts of dietary fat are associated with greater body fat content. There also is evidence from these species that there is heterogeneity in the response to dietary fat between different strains or among different species in the same family.

Rats have some advantages over mice when performing metabolic Studies due to their larger size (e.g., catheter techniques, blood drawing, etc.). Due to the large number of reported studies, it seems justifiable to see Wistar and Sprague-Dawley outbreed rats as the standard rodents for this experiment type. These strains are susceptible to diet-induced obesity and insulin resistance with individual variations. Looking at strain differences with respect to HF diet effects, metabolic research has focused on the dietary fat preferring obesity-susceptible Osborne-Mendel rat and the obesity resistant (i.e., the carbohydrate preferring) S5B/Pl rat. The phenotypic variations between these two inbred strains might be due to an altered hypothalamic gene expression (Schaffhauser et al., 2002), leptin sensitivity (Madihe et al., 2000), sympathetic stimulation (Fisler et al., 1984), or epigenetic programming (White et al., 2005). The analysis of strain-dependent diet susceptibility has been performed more extensively in mice. From this, it is known that the inbred mouse strains C57BL/6J, AKR/J, and DBA/2J are more prone to develop obesity and insulin resistance than SWR/J, A/J, and 129S6.
Ventromedial hypothalamic nucleus (VMH) lesion

a) Monosodium Glutamate (MSG)

The administration of monosodium glutamate to newborn rats causes the destruction of the ventromedial hypothalamic and arcuate nuclei, leading the rats to develop obesity due to the lack of control between absorption and energy expenditure. The involvement of enzyme activity of the small bowel in the induction of obesity after the use of MSG and the influence of the adrenal gland has been researched (Guimaraes et al., 2002). MSG caused a drop in the hypothalamic dopamine (Lorden et al., 1986). MSG can be administered subcutaneously or intraperitoneally (Shivshankar and Devi, 2005) at doses that vary by 2-4 mg/g of body weight of the rat during the neonatal period and for periods ranging by 4-10 doses causing obesity (De Carvalho et al., 2002).

b) Electrical VMH Lesion

The VMH lesion was described by Saito et al. (1985) and now, with a few changes, it can be used to induce obesity. A 1.2 mA current lasting 4 seconds, repeated 3 times at 30-second intervals after positioning the electrodes, can cause bilateral destruction of the hypothalamic nuclei, leading to obesity. It is known that the electric lesion of the hypothalamus causes an increased level of leptin, reduction of the total neuropeptide Y, maintaining the fluctuations of the circadian rhythm and there appears to be a loss of the feedback mechanism between insulin and leptin (Dube et al., 1999).

Oophorectomy

The obesity induction model in rats through oophorectomy, on the contrary of the previous ones, results from the observation of women who, after menopause, present a number of metabolic changes, including weight gain. This model is used in order to achieve a better understanding of these modifications in women after the end of their fertile age and also to study interventions that could alter the impact of hormone reduction in a woman. The removal of gonads from female rats causes a drop in the initial leptin levels, which is correlated with a period of hyperphagia and marked weight gain. It is believed that there is a factor responsible for alerting the
hypothalamus to the fact that estrogen production has ceased. A few studies speculate on the participation of neuropeptide Y.

**Genetic models**

The genetic models to study obesity began to be used increasingly in the 1990s because of cloning and identification of the product of five different genes causing obesity. Furthermore, in the last few years, genetically modified or knockout animals have been produced to study new genes that are candidates to influence the rate of Obesity (Marques-Lopes et al., 2004). There are over 50 different types of genetic models of obesity in rodents. The first five monogenic models of obesity were diabetic (db/db), obese (ob/ob) – these two in the same metabolic pathway, Tubby (tub), “Agouti” yellow (Ay) and fat (fat). The “Agouti” rat was described for the first time over a century ago, and it was the first obesity gene to be cloned and characterized at the molecular level in 1992. Today there are over 25 mutations in rodents known with “Agouti”, 5 of them dominant genetic mutations. This rat, also known as yellow rat, expresses a very high amount of agouti protein coded by chromosome. This leads to later obesity and hyperphagia (Good, 2005).

**Seasonal models of obesity**

Many small mammals exhibit annual cycles of body mass and adiposity (Drazen et al., 2002). Most rodents rely on changing day length to trigger these responses (Bartness et al., 2002), which can be readily mimicked in the laboratory by transferring animals between long day (LD) and short day (SD) photoperiods. This makes seasonal mammals attractive for investigations of mechanisms underlying the regulation of body mass (Bartness et al., 2002). Seasonal fat cycles have been studied most extensively in the Siberian or Djungarian hamster (Phodopus sungorus), Syrian or golden hamster (Mesocricetus auratus) and the collared lemming (Dicrostonyx groenlandicus). In the Siberian hamster, both sexes defend a maximal body mass (and adiposity) in the summer (Bartness and Goldman, 1988). The transfer of adult male hamsters (housed at room temperature) from LD (16 h light cycle) to SD (8 h light) results in a gradual weight loss accompanied by reduced food intake.
MANAGEMENT OF OBESITY AND METABOLIC SYNDROME

Obesity is a particularly challenging clinical condition to treat because of its complex pathophysiological basis. Rather than focusing primarily on body weight, many experts are focusing on the so-called "metabolic fitness", which tracks the metabolic health of obese individuals. Metabolic fitness is defined as the absence of biochemical risk factors associated with obesity (elevated fasting concentrations of cholesterol, triglycerides, glucose, or insulin; impaired glucose tolerance; or elevated blood pressure) (Nisoli and Carruba, 2004). Modest weight reduction, in the range of 5-10% of initial body weight, has been shown to improve obesity-related morbidity and mortality (WHO, 2000). In women 40-60 years of age who had never smoked, moderate but intentional weight loss reduced all-cause mortality by 20% and diabetes-associated mortality by 30-40% (Williamson et al., 1995). Modest weight reduction has also been associated with clinically significant improvements in hypertension (Tuck et al., 1981), lipid abnormalities (Dattilo et al., 1992) and glycaemic control (Bosello et al., 1997). Recently, the Finnish Diabetes Program (Tuomilehto et al., 2001) reported that, in overweight patients losing approximately 5% of their body weight and increasing their physical activity the risk of developing type 2 diabetes was reduced by 58%.

Successful weight management implies not only initial weight loss over a short period of time, but also maintenance of reduced weight over a period of years. In most cases, dietary changes, exercise and behavioral modification, either alone or in combination, are generally met with poor long-term outcomes. Pharmacological therapy is an adjunct to the treatment of obesity. Anti-obesity drugs must be used only in the context of a comprehensive management programme that includes the standard model. To date, agents for the management of obesity have been limited and unsatisfactory.

ROLE OF PHARMACOTHERAPY

Any national or global strategy to tackle the prevalence of non-communicable disease must address the current obesity pandemic. Serious reductions in the prevalence of NIDDM, CVD or cancer cannot occur whilst levels of obesity continue to rise.
Obesity has been traditionally challenged with prescribed and self-initiated diets, exercise and behavioral modification (Halford, 2006).

**Current criteria for the evaluation of new anti-obesity drugs**

Both the American Food and Drugs Administration (FDA) and the European agency for the Evaluation of Medicinal Products (EMEA) demand that any anti-obesity drug should produce significantly greater weight loss compared to placebo control over any trial. The FDA specifically demands that placebo-subtracted weight loss (i.e. drug induced weight loss minus placebo) is greater than 5%. Moreover, significantly more individuals in the drug treated group should have lost 5% or more of their initial body weight compared to placebo. The EMEA alternatively demands that the weight loss in the drug group is greater than 10% from baseline. Moreover, significantly more individuals in the drug treated group should have lost 10% or more of their initial body weight compared to placebo. The secondary outcome of anti-obesity drug trials is to ensure that this weight loss in sustained and that it produces a significant reduction in risk factors for a number of obesity related co-morbidities (e.g. fasting blood glucose, HbA1c, insulin, total plasma cholesterol, LDL-cholesterol, triglycerides, uric acid and blood pressure). The FDA also demands that drugs reduce total body fat mass and alter body fat distribution (specific risk factors for ill health). Finally, drug induced weight loss should have a positive impact on health related quality of life (Halford, 2006).

**Drugs currently in use:**

(i) **Orlistat** (Xenical) Orlistat (N-formyl-L-leucine (s)-1-[(2S, 3S)-3-hexyl-4-oxooxetan-2-yl]methyl)dodecyester) is a hydrogenated derivative of a lipostatin isolated from soil bacteria (Streptomyces toxytincini). Reported side effects of orlistat include flatus with discharge, oily spotting and oily stool. Severe problems such as faecal urgency, incontinence and abdominal pain can also occur. Orlistat blocks the digestion of fat in the gut and the availability of fat soluble vitamins (vitamins A, D, E and K), so it is recommended that those taking orlistat should also take vitamin supplements also (Halford, 2006).
(ii) Sibutramine (Meridia, Reductil)

Sibutramine hydrochloride monohydrate 9N-[1-[1(4-chlorophenyl) cyclobutyl]-3-methylbutyl]- N, N-(dimethylamine hydrochloride monohydrate), a beta-phanethylamine, is the only centrally acting anti-obesity compound approved for use in most countries. Cardiovascular side effects include an increase in systolic and diastolic blood pressure, and an increase in heart rate, tachycardia and palpitations and vasodilatation. Sibutramine is a nor-adrenergic and serotoninergic re-uptake inhibitor. The drug, and its active metabolites, have little direct activity at monoaminergic receptors and do not promote NA or 5-HT release. Sibutramine, itself is actually a weak inhibitor of 5-HT and NA in vitro (Halford, 2006).

The stimulatory effect of sibutramine on thermogenesis in rodents is well established (Heal et al., 1998). Central NA and 5-HT reuptake inhibition leads to sympathetic activation of adipose tissue and thermogenesis (Heal et al., 1998). In humans, sibutramine-induced increases in energy expenditure appear less pronounced and less important for the therapeutic efficacy of sibutramine (Seagle et al., 1998).

The weight loss produced by sibutramine has a number of beneficial effects on key risk factors for non-communicable diseases. However, perhaps the most critical issue is cardiovascular function. Sibutramine has been shown to increase heart rate (3–7 beats per minute) and blood pressure (20% patients BP increase of 2–3 mmHg). These adrenergic side effects are a particular concern for patients with hypertension. From a meta-analysis of 21 placebo controlled trials, Kim et al. (2003) concluded that sibutramine significantly, but only slightly, raised blood pressure.

(iii) Rimonabant (SR141716, Acomplia)

Endocannabinoids may be involved in the leptin pathway, which regulates food intake. Rimonabant is a cannabinoid antagonist binding to the CB1 receptor (Di Marzo et al., 2001). Rimonabant has been developed to treat obesity and aid smoking cessation, major risk factors for cardiovascular problems. Rimonabant reduces food intake, hunger and body weight in obese humans over 7 days of treatment (Hesmati et al., 2001). HDL cholesterol increased more than 20%, and triglycerides decreased by more than 15% with the higher dose of rimonabant.
Glucose and insulin also were reduced. Rimonabant also reduced BP in association with the weight loss. Rimonabant produces a dose-dependent reduction in food intake in various rodent models, effects that seem to be both centrally and peripherally mediated. Potential peripheral mechanisms include enhanced thermogenesis via increased oxygen consumption in skeletal muscle, diminished hepatic and adipocyte lipogenesis, augmentation of adiponectin concentrations, promotion of vagally mediated cholecystokinin-induced satiety, inhibition of preadipocyte proliferation, and increased adipocyte maturation without lipid accumulation (Padwal and Majumdar, 2007).

Table 2: Drugs used in the treatment of Obesity

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Mechanism</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of the 19th century</td>
<td>Thyroid hormone</td>
<td>Increase metabolic rate</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>1920s</td>
<td>Dinitrophenol</td>
<td>Mitochondrial uncoupling</td>
<td>Cataracts, neuropathy, cardiac failure</td>
</tr>
<tr>
<td>1930s</td>
<td>Amphetamines (phentermine, diethylpropion, phendimetrazine)</td>
<td>Dopamine-noradrenaline-reuptake inhibitor, releaser, sympathomimetic drugs</td>
<td>Addiction, myocardial infarction, stroke</td>
</tr>
<tr>
<td>1950s</td>
<td>Phenylpropanolamine</td>
<td>Sympathomimetic</td>
<td>Stroke</td>
</tr>
<tr>
<td>1960s</td>
<td>Rainbow pills (mixture of digitalis, amphetamine and diuretics)</td>
<td>Mixed</td>
<td>Fatalities due to narrow therapeutic index of digitalis</td>
</tr>
<tr>
<td>1990s</td>
<td>Fen-phen (mixture of fenfluramine and phentermine)</td>
<td>5-HT-reuptake inhibitor and releasing agent with sympathomimetic</td>
<td>Valvupathy</td>
</tr>
<tr>
<td>Currently used</td>
<td>Sibutramine</td>
<td>5-HT-reuptake inhibitor</td>
<td>Tachycardia, hypertension</td>
</tr>
<tr>
<td>Currently used</td>
<td>Orlistat</td>
<td>Gastric lipase inhibitor</td>
<td>Depressive symptoms</td>
</tr>
<tr>
<td>Currently used</td>
<td>Rimonabant</td>
<td>CB1 antagonist</td>
<td>Depressive symptoms, anxiety</td>
</tr>
<tr>
<td>Currently used</td>
<td>Topiramate</td>
<td>Antiepileptic drug</td>
<td>Memory impairment,</td>
</tr>
</tbody>
</table>
These mentioned drugs remain "symptomatic" and they are not "curative" drugs. Thus, exploring research has been finding new potential drug. Currently available antiobesity drugs are modestly effective, and, in some subjects, they are associated with unacceptable and life-threatening adverse effects. As a result, there is a growing need to find effective, safe, and well-tolerated antiobesity drugs.

Research studies are being carried out to detect and confirm the action of drugs and natural products that yield better and long-lasting results in terms of weight reduction. In this field, medicinal plants play a very important role (Moro and Basile, 2000).

THE ROLE OF PHYTOTHERAPY IN THE TREATMENT OF OBESITY

Due to its complex and multifactorial pathogenesis of obesity, behavioral therapy alone has had limited success in providing meaningful, sustained weight reduction, and pharmacological treatment becoming a challenging research priority. Phytotherapy today avails itself of the extensive knowledge on its active principles and its chemical and pharmacological characteristics (Blumenthal, 1998). Nowadays, it is possible to find formulations that maintain the plant-specific characteristics and which undergo microbiological and analytical tests. It seemed, therefore, reasonable and timely to assess the validity of phytotherapeutic products in the treatment of obesity (Moro and Basile, 2000).
Phytotherapy is becoming increasingly popular both for the results it yields in several pathologies, and for a growing sense of mistrust towards conventional medical treatments.

Table 3: Medicinal plants used to treat obesity

<table>
<thead>
<tr>
<th>Medicinal plant</th>
<th>Active principle</th>
<th>Therapeutic indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Amorphophallus konjac</em> Koch (Araceae)</td>
<td>Fiber</td>
<td>Obesity, lipid and glucose metabolism alterations</td>
</tr>
<tr>
<td><em>Ananas sativus</em> Schult. f. (Bromeliaceae)</td>
<td>Bromelain</td>
<td>Cellulite, edema, hemorrhoids</td>
</tr>
<tr>
<td><em>Betula alba</em> L. (Betulaceae)</td>
<td>Flavonoids, saponin, essential oils</td>
<td>Cellulite, water retention, hypertension, altered protein metabolism</td>
</tr>
<tr>
<td><em>Camellia thea</em> Link. (Theaceae)</td>
<td>Caffeine, theine, theobromin, theophylline, tannic acid</td>
<td>Obesity, protein metabolism alterations, cellulite</td>
</tr>
<tr>
<td><em>Carica papaya</em> L. (Caricaceae)</td>
<td>Papain</td>
<td>Obesity, cellulite, digestive problems</td>
</tr>
<tr>
<td><em>Citrus aurantium</em> L. (Rutaceae)</td>
<td>Adrenergic amines (sympathomimetic)</td>
<td>Obesity</td>
</tr>
<tr>
<td><em>Citrus decumana</em> Murr. (Rutaceae)</td>
<td>Fiber, flavonoids, phenylalanine</td>
<td>Obesity, cellulite</td>
</tr>
<tr>
<td><em>Filipendula ulmaria</em> Max. (Rosaceae)</td>
<td>Salicylic acid derivatives, flavonoids (spiroside, quercitin)</td>
<td>Cellulite, hyperuricemia, goiter, arthritis, arthrosis, water retention</td>
</tr>
<tr>
<td><em>Fucus vesiculosus</em> L. (Fucaceae)</td>
<td>Iodine, mucilage, phytochemicals, tetraterpenes</td>
<td>Obesity, cellulite</td>
</tr>
<tr>
<td><em>Garcinia cambogia</em> Desr. (Clusiaceae)</td>
<td>Hydroxycitric acid</td>
<td>Obesity, altered lipid and glucose metabolism, weight maintenance</td>
</tr>
<tr>
<td><em>Gelidium amansii</em> Lamour. (Algae)</td>
<td>Agar-agar</td>
<td>Obesity, constipation, irritable colon, diverticulitis, gastritis</td>
</tr>
<tr>
<td><em>Ginkgo biloba</em> L. (Ginkgoaceae)</td>
<td>Bioflavonoids flavone glycosides (quercitin, luteolin)</td>
<td>Cellular aging, vascular diseases, hemorrhoids, varicose veins</td>
</tr>
<tr>
<td><em>Gymnema sylvestre</em> R. Br. (Asclepiadaceae)</td>
<td>Gymnemic acid</td>
<td>Obesity, lipid and glucose metabolism alterations</td>
</tr>
<tr>
<td><em>Hieracium pilosella</em> L. (Asteraceae)</td>
<td>Polyphenolic acids (caffeic, chlorogenic), tannins, flavonoids</td>
<td>Obesity, cellulite, water retention, hypertension</td>
</tr>
<tr>
<td>Plant Name</td>
<td>Key Ingredients</td>
<td>Health Benefits</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Hydrocotyle asiatica</strong> L. (Apiaceae)</td>
<td>Asiatic acid, madecassic acid, phytosterols, flavonoids, triterpenes, tannic acid</td>
<td>Cellulite, varicose veins, capillary fragility, hemorrhoids</td>
</tr>
<tr>
<td><strong>Ortosiphon stamineus</strong> Benth. (Lamiaceae)</td>
<td>Lipophylic flavones, potassium, glucoside Ortosiphonine</td>
<td>Obesity, weight maintenance, water retention, goiter</td>
</tr>
<tr>
<td><strong>Passiflora incarnata</strong> L. (Passifloraceae)</td>
<td>Flavonoids, alkaloids, sterols, hydroxycoumarine</td>
<td>Stress, anxiety, agitation, distress, insomnia, asthma, neurovegetative dystonia</td>
</tr>
<tr>
<td><strong>Paullinia sorbilis</strong> Mat. (Sapindaceae)</td>
<td>Caffeine, catechin, choline, tannic acid</td>
<td>Obesity, asthenia, improved physical performance and mental concentration</td>
</tr>
<tr>
<td><strong>Phaseolus vulgaris</strong> L. (Fabaceae)</td>
<td>Fiber</td>
<td>Obesity, weight maintenance, altered lipid and glucose metabolism</td>
</tr>
<tr>
<td><strong>Plantago ovata</strong> Forsk. (Plantaginaceae)</td>
<td>Mucilage</td>
<td>Obesity, lipid and glucose metabolism alterations, Constipation</td>
</tr>
<tr>
<td><strong>Rheum officinale</strong> Baill. (Polygonaceae)</td>
<td>Bitter compounds, tannic acid, glucosides Anthraquinones</td>
<td>Constipation, hemorrhoids, bile and liver diseases</td>
</tr>
<tr>
<td><strong>Taraxacum officinale</strong> Weber. (Asteraceae)</td>
<td>Taraxicine, inuline, p-hydroxyphenylacetic acid, 3-4 dihydroxycinamic acid, sterols, triterpenes, flavonoids, carotenoids</td>
<td>Cellulite, lipid and glucose metabolism alterations, constipation, liver diseases</td>
</tr>
</tbody>
</table>


**Gymnema sylvestre** R. Br. (Asclepiadaceae)

**Description**

*Gymnema sylvestre* is a woody, climbing plant, native to India. The leaves of this plant have been used in India for 2,000 years to treat madhu meha, or “honey urine,” an early term for glucosuria detected by pouring the patients urine onto the ground and observing whether or not insects were attracted to it. Chewing the leaves also destroys the ability to discriminate “sweet” taste, giving it its common name, gurmar or “sugar destroyer.”

(a) Classification:

<table>
<thead>
<tr>
<th><strong>Kingdom:</strong></th>
<th>Plantae</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Division:</strong></td>
<td>Angiospermae</td>
</tr>
<tr>
<td><strong>Class:</strong></td>
<td>Dicotyledoneae</td>
</tr>
<tr>
<td><strong>Order:</strong></td>
<td>Contortae</td>
</tr>
<tr>
<td><strong>Family:</strong></td>
<td>Asclepiadaceae</td>
</tr>
<tr>
<td><strong>Genus:</strong></td>
<td>Gymnema</td>
</tr>
<tr>
<td><strong>Species:</strong></td>
<td>sylvestre R.Br</td>
</tr>
</tbody>
</table>

(b) Botanical synonym:

*Asclepias geminata* Roxb.

*Periploca sylvestris* Retz.
(c) Vernacular name:

- English: Periploca of the woods
- Hindi: Gudmar, Gurmar
- Kannada: Kadhasige
- Malayalam: Cakkarakkolli, Madhunasini
- Tamil: Sirukurunkay, Sakkaraikkolli
- Sanskrit: Meshashringi
- Telugu: Podapatra

(d) Part used: Leaves

(e) Botanical description:

Large climbers, rooting at nodes, leaves elliptic, acuminate, base acute to acuminate, glabrous above sparsely or densely tomentose beneath; Flowers small, in axillary and lateral umbel like cymes, pedicels long; Calyx-lobes long, ovate, obtuse, pubescent; Corolla pale yellow campanulate, valvate, corona single, with 5 fleshy scales. Scales adnate to throat of corolla tube between lobes; Anther connective produced into a membranous tip, pollinia 2, erect, carpels 2, unilocular; locules many ovuled; Follicle long, fusiform.

(f) Geographical distribution:

Throughout India, in dry forests upto 600 m, common throughout the district from January to November. Distributed in Asia, Tropical Africa, Malaysia and Srilanka (Keshavamurthy and Yoganarasimhan, 1990).

(g) Traditional uses:

Sushruta describes Gymnema sylvestre, as a destroyer of madhumeha (glycosuria) and other urinary disorders. On account of its property of abolishing the taste of sugar it has been given the name of gur-mar meaning 'sugar destroying' and it is believed, therefore, that it might neutralize the excess of sugar present in the body in Diabetes mellitus. The plant is also reported to be bitter, astringent, acrid, thermogenic, anti-inflammatory, anodyne, digestive, liver tonic emetic, diuretic, stomachic, stimulant, anthelmenthics, laxative, cardiotonic, expectorant, antipyretic and uterine tonic. It is
useful in dyspepsia, constipation, jaundice, haemorrhoids, renal and vesical calculi, cardiopathy, asthma, bronchitis, amenorrhoea, conjunctivitis and leucoderma (Nadkarni, 1993).

**Phytochemistry of *G. sylvestre***

*G. sylvestre* leaves contain triterpene saponins belonging to oleanane and dammarenene classes. Oleanane saponins are gymnemic acids and gymnemasaponins, while dammarenene saponins are gymnemasides. Besides this, other plant constituents are flavones, anthraquinones, hentri-acontane, pentatriacontane, α and β-chlorophylls, phytin, resins, dquercitol, tartaric acid, formic acid, butyric acid, lupeol, β- amyrin related glycosides and stigmasterol. The plant extract also tests positive for alkaloids. Leaves of this species yield acidic glycosides and anthroquinones and their derivatives (Dateo and Long, 1973).

**Chemical Constituent**

The major phytoconstituents are Gymnemic acids, Gurmarin, a polypeptide of 35 amino acids and Saponins. Other chemical constituents include resins (one soluble in alcohol), tartaric acid, calcium oxalate, glucose, stigmasterol, quercitol, and the amino acid derivatives betaine, choline and trimethylamine.

**Plant bases** Choline, Betaine etc

Leaves Contains several O-iso-propylidene derivatives of gymnemagenin, a Hexahydro -terpene, crystalline gymnemagenin, gymnestrophenol, 2 and gymnemic acid (the antisweet principle), which is a complex mixture of at least nine closely related acidic glycosides.
Basic molecular structure of gymnemic acid, the active ingredient in Gymnema sylvestre

Mechanism of action
There are some possible mechanisms by which the G. sylvestre exert its effects are: 1) it increases secretion of insulin, 2) it promotes regeneration of islet cells, 3) it increases utilization of glucose: it is shown to increase the activities of enzymes responsible for utilization of glucose by insulin dependent pathways, an increase in phosphorylase activity, decrease in gluconeogenic enzymes and sorbitol dehydrogenase, and 4) it causes inhibition of glucose absorption from intestine.

Pharmacological studies of Gymnema sylvestre

Rachh et al. (2010) have investigated Gymnema sylvestre R. Br. leaf extract on high cholesterol fed diet rats. Hyperlipidemia was induced in rats by high cholesterol diet (2% cholesterol, 1% sodium cholate and 2% coconut oil) for 7 days. Oral treatment with hydroalcoholic extract of Gymnema sylvestre leaves (200 mg/kg) significantly
decreased TC, TGs, LDL-C, VLDL-C and increased the HDL-C in hyperlipidemic rats and was comparable with that of standard atorvastatin.

**Rachh et al. (2009)** have determined *in-vitro* antioxidant activity of *Gymnema sylvestre* R. Br. leaf extract. The antioxidant activity was studied in *in-vitro* antioxidant models like DPPH radical scavenging activity, superoxide radical scavenging activity, ferric reducing power and hydrogen peroxide scavenging activity. The *Gymnema sylvestre* R. Br. alcoholic leaf extract showed antioxidant activity by inhibiting DPPH, scavenging superoxide and hydrogen peroxide.

**Liu et al. (2009)** have characterized the insulinotropic activity of an aqueous extract of *Gymnema Sylvestre* in mouse β-cells and human islets of langerhans.

**Khanna and Kannabiran (2009)** reported the anticancer-cytotoxic activities of isolated saponins, gymnemagenol from *Gymnema sylvestre* and dasyscyphin C from *Eclipta prostrata* leaves were tested under *in vitro* conditions in HeLa cells. The gymnemagenol and dayscyphin C at 50 g/ml showed a good cytotoxic activity in HeLa cells.

**Daisy et al. (2009)** have reported that a novel dihydroxy gymnemic triacetate isolated from *Gymnema sylvestre* possessed normoglycemic and hypolipidemic activity on STZ-induced diabetic rats by reducing plasma glucose, insulin, glycated hemoglobin (HbA1c), tissue glycogen, lipid parameters such as TGs, TC, LDL-cholesterol, HDL-cholesterol and activities of hepatic marker enzymes, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and acid phosphatase (ACP).

**Malik et al. (2008)** have investigated that the aqueous extract of *Gymnema sylvestre* leaves showed significant anti-inflammatory activity in rats in carrageenan-induced paw oedema and cotton pellet method.
Raju et al. (2006) have reported an improved high-performance thin-layer chromatographic (HPTLC) method for the standardization of Gymnema sylvestre. The method involves the initial hydrolysis of gymnemic acids, the active ingredients, to a common aglycone followed by the quantitative estimation of gymnemagenin.

Gholap and Kar (2005) have investigated that intraperitoneal administration of gymnemic acids (GA) from the leaves of Gymnema sylvestre, R. Br. regulates dexamethasone-induced hyperglycemia in mice by altering the changes in hepatic lipid peroxidation (LPO), superoxide dismutase (SOD), and catalase (CAT) activity.

Ogawa et al. (2004) have conducted a 52-week study of oral-repeated-dose toxicity for the extraction powder of Gymnema sylvestre (GS), Indian-native genus, Metaplexis japonica, in both genders of Wistar rats. The rats were administered a graded dose of GS at 0.01, 0.10 and 1.00% of basal powder diet, along with a group fed solely with the basal powder diet without GS, for 52 weeks. None of the animals died in the period up to 52 weeks. No exposure-related changes in body-weight, in the food consumption, in the hematological examinations, or in the serum biochemical examinations were recognized. No histopathological alterations were seen. Thus, it was concluded that there was no toxic effect in rats treated with GS at up to 1.00% in the diet for 52 weeks. The no-observable-effect level from this study is 1.00% GS, i.e., 504mg/kg/day for male and 563mg/kg/day for female as mean daily intake, for 52 weeks.

Preuss et al. (2004) have determined the efficacy of a novel, natural extract of (−) hydroxycitric acid (HCA-SX) and a combination of HCA-SX, niacin-bound chromium and Gymnema sylvestre extract for weight loss in moderately obese subjects by monitoring changes in body weight, body mass index (BMI), appetite, lipid profiles, serum leptin and serotonin levels, and enhanced excretion of urinary fat metabolites.
Satdive \textit{et al.} (2003) have demonstrated antimicrobial activity of an ethanolic extract of \textit{Gymnema sylvestre} leaves against \textit{Bacillus pumilis}, \textit{B. subtilis}, \textit{Pseudomonas aeruginosa} and \textit{Staphylococcus aureus}.

\textbf{Shigematsu \textit{et al.} (2001a)} have evaluated the extract of \textit{Gymnema sylvestre} leaves was administered to rats receiving either a high fat diet or normal fat diet for 10 weeks to investigate its influence on plasma and liver lipids and on visceral fat accumulation. The extract suppressed body weight gain, accumulation of liver lipids, intraperitoneal fat and fat drop vacuoles on the epithelium of renal tubules, were scattered by administration of the extract.

\textbf{Shigematsu \textit{et al.} (2001b)} have investigated the influence of extract of \textit{Gymnema sylvestre} R. Br leaves (GE) to rats fed a high fat diet or normal fat diet for 3 weeks on lipid metabolism. The apparent fat digestibility was significantly decreased by GE in both diet groups for the last 2 weeks of the experimental period, though not the apparent protein digestibility. In addition, the excretion of neutral sterols and acid steroids into feces was increased by GE in both diet groups. Furthermore, GE decreased the total cholesterol and triglyceride levels in serum. On the other hand, blood lecithin-cholesterol acyltransferase (LCAT) activity was increased by GE.

\textbf{Maji \textit{et al.} (2000)} have reported that water soluble portion of the alcoholic extract of \textit{Gymnema sylvestre} (Asclepediaceae) leaves administered intra-peritonially to normal, glucose fed hyperglycaemic and adrenaline induced hyperglycaemic rats. The extract has a significant glucose lowering effect compared to standard hypoglycaemic agents.

\textbf{Sugihara \textit{et al.} (2000)} have investigated the antihyperglycemic action of a crude saponin fraction and five triterpene glycosides (gymnemic acids I-IV and gymnemasaponin V) derived from the methanol extract of leaves of \textit{Gymnema sylvestre} R. BR. (Asclepiadaceae) in streptozotocin (STZ)-diabetic mice. The saponin fraction (60 mg/kg) reduced blood glucose levels 2 4h after the intraperitoneal administration. Gymnemic acid IV, not the other 4 glycosides at doses of 3.4-
13.4 mg/kg reduced the blood glucose levels by 13.5-60.0% 6h after the administration comparable to the potency of glibenclamide, and did not change the blood glucose levels of normal mice. Gymnemic acid IV at 13.4 mg/kg increased plasma insulin levels in STZ-diabetic mice.

Katsukawa et al. (1999) have reported that there is an induction of salivary gurmarin-binding proteins in rats fed Gymnema-containing diets.

Nakamura et al. (1999) have showed that oral administration of gymnemic acids contained in Gymnema sylvestre leaves increased fecal cholesterol and cholic acid-derived bile acid excretion in rats.

Persaud et al. (1999) have reported that an alcoholic extract of G. sylvestre (GS4) stimulates insulin secretion from rat islets of Langerhans and several pancreatic β-cell lines by increasing cell permeability.

Chattopadhyay (1998) have reported possible mechanism of antihyperglycemic effect of Gymnema sylvestre leaf extract. In glucose fed rats, the leaf extract lowered the glycogen content of the tissue significantly and this was further lowered when both exogenous insulin and leaf extract was administered.

Sahu et al. (1996) have reported the presence of gymnemic acid, quercitol, lupeol, amyrin, stigma sterol etc. from Gymnema sylvestre. Three new oleanane triterpene glycosides i.e. beta-O-benzylsitakisogenin 3-O-beta-D-glucopyranosyl (1-3)-beta-D-glucuronopyranoside, the potassium salt of longispinogenin 3-O-beta-D-glucopyranosyl (1-3)-beta-D-glucuronopyranoside and the potassium salt of 29-hydroxylongispinogenin 3-O-beta-D-glucopyranosyl (1-3)-beta-D-glucuronopyranoside along with the sodium salt of alternoside II were isolated from an isolated from an ethanol extract of leaves of G. sylvestre.

Diwan et al. (1995) have reported that the aqueous extract of Gymnema sylvestre leaves (GSE) tested on various inflammatory models showed anti-inflammatory
activity by significantly inhibiting carrageenan-induced rat paw oedema and peritoneal ascites in mice. GSE elevated liver enzymes (e.g. γ-glutamyl transpeptidase (γ-GT) and Superoxide dismutase (SOD) showing a protective mechanism against the release of slow-reacting substances and free radicals.

Bishayee and Chatterjee (1994) reported that leaf extract of Gymnema sylvestre at a dosage of 25-100 mg/kg administered orally to experimentally induced hyperlipidaemic rats for two weeks reduced the elevated serum triglyceride (TG), total cholesterol (TC), very low density lipoprotein (VLDL) and low density lipoprotein (LDL)-cholesterol in a dose dependent manner. The ability of the extract at 100 mg/kg to lower TG and TC in serum and its antiantherosclerotic potential were almost similar to that of a standard lipid lowering agent clofibrate.

Fushiki et al. (1992) have studied the inhibitory effects of an extract of Gymnema sylvestre and purified gymnemic acid on gastric inhibitory peptide (GIP) release in rats. The GIP release into the portal vein in response to duodenal infusion of D-glucose in presence of leaf extract of Gymnema sylvestre at a dosage of 0.5ml/kg. The results suggested that a glucose receptor which interacted with the leaf extracts of Gymnema sylvestre and purified Gymnemic acid. The inhibition of GIP release by Gymnemic acid observed was attributed to the interaction with the glucose receptor for GIP release which was similar in specificity to the active glucose transport system.

Okabayashi et al. (1990) have studied the effect of Gymnema sylvestre, R.Br. (G. sylvestre; GS4) on glucose homeostasis in rats. The acute effect of GS4 was examined in both non-diabetic and streptozocin (30 mg/kg)-induced mildly diabetic rats. Two weeks after the induction of diabetes, the rats were divided into two groups that had similar impairment of glucose tolerance assessed by an oral glucose loading test. The rats were fed for 32-35 days with either a control diet or a diet supplemented with GS4. After 4 weeks, GS4 showed a tendency to reduce the serum glucose concentrations in the fed state and to improve the glucose tolerance. Gain in body weight, food intake, pancreas weight and the pancreatic contents of immunoreactive insulin (IRI), protein, amylase and trypsinogen were unaltered in the GS4-treated
group compared with the control. These results suggest the usefulness of *G. sylvestre* in the treatment of certain classes of non-insulin-dependent diabetes mellitus.

Shanmugasundaram *et al.* (1990) have tested two water soluble extracts, GS3 and GS4, obtained from the leaves of *Gymnema sylvestre*, in streptozotocin treated rats for their effects on blood glucose homeostasis and pancreatic endocrine tissue. In the diabetic rats, fasting blood glucose levels returned to normal after 60 days of GS3 and after 20 days of GS4 oral administration. GS3 and GS4 therapy led to a rise in serum insulin to levels closer to normal fasting levels. In diabetic rat pancreas, both GS3 and GS4 were able to double the islet number and beta cell number. This herbal therapy appears to bring about blood glucose homeostasis through increased serum insulin levels provided by repair/regeneration of the endocrine pancreas.

Shanmugasundaram *et al.* (1990) have reported that GS4, a water-soluble extract of the leaves of *Gymnema sylvestre*, administered (400 mg/day) to 27 patients with insulin-dependent diabetes mellitus (IDDM) on insulin therapy. Insulin requirements came down together with fasting blood glucose and glycosylated haemoglobin (HbA1c) and glycosylated plasma protein levels. While serum lipids returned to near normal levels with GS4 therapy, glycosylated haemoglobin and glycosylated plasma protein levels remained higher than controls.

Baskaran *et al.* (1990) have investigated the effectiveness of GS4, an extract from the leaves of *Gymnema sylvestre*, in controlling hyperglycaemia in 22 Type-2 diabetic patients on conventional oral anti-hyperglycaemic agents. GS4 (400 mg/day) was administered for 18-20 months as a supplement to the conventional oral drugs. During GS4 supplementation, the patients showed a significant reduction in blood glucose, glycosylated haemoglobin and glycosylated plasma proteins, and conventional drug dosage could be decreased. Five of the 22 diabetic patients were able to discontinue their conventional drug and maintain their blood glucose homeostasis with GS4 alone. These data suggest that the beta cells may be regenerated/ repaired in Type 2 diabetic patients on GS4 supplementation. This is
supported by the appearance of raised insulin levels in the serum of patients after GS4 supplementation.

The present study was designed to investigate the antiobesity potential of *Gymnema sylvestre* extract in high fat diet-induced obesity and associated metabolic disorders using normal healthy Wistar rats and streptozotocin induced diabetes in obese Wistar rats.
RIMONABANT

Rimonabant, a selective cannabinoid-1 receptor (CB 1) blocker, has been shown to reduce body weight and improve cardiovascular risk factors in obese patients.

Rimonabant (SR 141716) is a neurokinin-3 antagonist and selective cannabinoid (CB1) receptor antagonist. The chemical name is N-piperino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide. Rimonabant is the first in a new class of agents that act by selectively blocking the cannabinoid-1 receptors with resultant central and metabolic peripheral effects, thereby decreasing food intake. Evidence currently exists for two types of cannabinoid receptors: CB1 and CB2. CB1 receptors are present both in the CNS as well as in certain peripheral tissues. Rimonabant is reported to possess a 1000-fold higher affinity for the CB1 receptor than CB2 receptor. It shows high affinity for the centrally located cannabinoid receptor, while displaying low affinity for the peripherally located receptor (Singh and Budhiraja, 2006). Rimonabant also inhibits the enzymes involved in lipogenesis (Cota et al., 2003). Many rodent model studies have demonstrated a memory enhancing effect due to rimonabant (Coizer et al., 1998).
A Review of work done on Rimonabant for antiobesity potential

Trillou et al. (2003) reported that rimonabant resulted in 48% reduction of food and 20% reduction in body weight as well as insulin resistance in high fat diet fed mice.

Wiley et al. (2005) demonstrated that CB1 antagonist rimonabant dependently decreased food consumption at doses which did not affect motor activity in mice.

Despres et al. (2005) reported that selective CB1-receptor blockade with rimonabant significantly reduces body weight and waist circumference and improves the profile of several metabolic risk factors in high-risk patients who are overweight or obese and have an atherogenic dyslipidemia.

Pi-Sunyer et al. (2006) reported that treatment with 20 mg/d of rimonabant plus diet for 2 years promoted modest but sustained reductions in weight and waist circumference and favorable changes in cardiometabolic risk factors.

Herling et al. (2008) reported that weight-reducing effect of rimonabant (10 mg/kg/p.o.) was due to continuously elevated energy expenditure based on increased fat oxidation driven by lipolysis from fat tissue as long as fat stores were elevated. When the amount of endogenous fat stores declined, rimonabant induced increased energy expenditure was maintained by a re-increase in food intake.

Van Gaal et al. (2008a) reported that 20 mg/day rimonabant produced weight loss and significant improvements in multiple cardiometabolic risk factors such as waist circumference, A1C, HDL cholesterol, and triglycerides in overweight/obese patients.

Van Gaal et al. (2008b) reported that rimonabant 20 mg produced clinically meaningful weight loss and improvements in serum lipid, glucose, and insulin levels, which were maintained over 2 years with favorable safety and tolerability in patients without a history of severe depressive disorder or severe anxiety.
Verty et al. (2008) reported that rimonabant (10 mg/kg IP) was administered for 21 days to rats significantly reduced body weight, food intake and elevation in energy expenditure.

Schafer et al. (2008) report that rimonabant administered orally (10mg/kg) for up to 6 months attenuates weight gain in obese Zucker rats, an experimental model of insulin resistance/metabolic syndrome and, in older rats, also prevents type-2 diabetes (T2D).

Di Marzo and Szallasi (2008) reported that the synthetic cannabinoid CB1 receptor antagonist rimonabant (10 mg/kg/p.o.) was reported to improve the profile of cardiovascular risk factors in obese patients with the metabolic syndrome, a cluster of metabolic disorders that often precedes the onset of type II diabetes. Rimonabant is shown to attenuate weight gain in Zucker rats, an experimental model of insulin resistance. Neutrophil and monocyte counts were lowered by rimonabant administration.

**Benefit risk analysis of rimonabant**

Risk-benefit analysis is the comparison of the risk of a situation to its related benefits. For research that involves more than minimal risk of harm to the subjects, the investigator must assure that the amount of benefit clearly outweighs the amount of risk.

Singh and Budhiraja (2006) reported that the results of early human trials with rimonabant treatment showed an excellent tolerance among patients, except for some mild gastrointestinal adverse effects at the highest dose administered. Safety data from the preliminary results of the RIO (Rimonabant in obesity) -Lipids, RIO-Europe, and RIO-North America trials revealed that rimonabant is well tolerated among patients. The most frequently reported adverse effects are nausea, dizziness and upper respiratory infections. Diarrhoea was seen most commonly in the RIO-Europe trial (2.3%, 5.8% and 7% for placebo, rimonabant 5 mg/day and 20 mg/day, respectively).
Pi-Sunyer et al. (2006) reported that 20 mg of rimonabant plus a standard dietary intervention produced sustained, clinically meaningful weight loss and favorable changes in cardiometabolic risk factors over 1 year and prevented weight regain in year 2 with favorable effects compared with placebo on fasting serum levels of HDL cholesterol and triglycerides in the RIO-North America trial. Compared with patients who had received 20 mg of rimonabant in year 1 and were then reassigned to receive placebo in year 2, those treated with 20 mg of rimonabant for 2 years maintained weight loss and differences from patients receiving placebo in multiple cardiometabolic risk factors, reflecting the potential effectiveness of long-term rimonabant therapy.

Gadde and Allison (2006) reported that the strengths of rimonabant are as follows:
(1) In 4 well-designed studies with >6600 overweight and obese patients, rimonabant has demonstrated consistent efficacy with regard to weight reduction. (2) Rimonabant offers a novel mechanism of action, which may make it well suited as an alternative for people who do not respond well to other agents and for combination treatment with other antiobesity agents. (3) Weight loss achieved with rimonabant also appears to improve some features of metabolic syndrome. (4) Its pharmacokinetic profile appears to be favorable in general. (5) Most side effects appear to be mild and transient. (6) No evidence of any significant cardiovascular adverse effects exists.

Van Gaal et al. (2008a) reported that treatment with the first selective CB1 blocker, rimonabant was associated with clinically meaningful weight loss, a reduction in abdominal obesity (as measured by waist circumference), and improvements in insulin resistance, lipid profile, and glucose metabolism in a large population of at-risk overweight/obese patients. Furthermore, rimonabant was generally well tolerated in the four pooled Rimonabant in obesity and related metabolic disorders (RIO) studies with a defined safety profile. The occurrence of recurrent depression requires special attention. Rimonabant is therefore a potentially effective new treatment for the improvement of multiple cardiometabolic risk factors in patients with abdominal obesity.
PIOGLITAZONE

Pioglitazone selectively stimulates the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ). Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptor proteins that function as transcription factors regulating the expression of genes (Michalik et al., 2006). PPARs play essential roles in the regulation of cellular differentiation, development, and metabolism (carbohydrate, lipid, protein), and tumorigenesis of higher organisms. PPAR-γ modulates the transcription of the insulin-sensitive genes involved in the control of glucose and lipid metabolism in the muscle, adipose tissue, and the liver. Pioglitazone reduces insulin resistance in the liver and peripheral tissues; increases the expense of insulin-dependent glucose; decreases withdrawal of glucose from the liver; reduces quantity of glucose, insulin and glycated haemoglobin in the bloodstream (Pi-Jung et al., 2008).

Molecular Formula: $C_{19}H_{20}N_2O_3S$

Mol. mass: 356.44 g/mol

Pharmacological studies of pioglitazone

Miyazaki et al. (2002) reported that pioglitazone treatment is associated with improvements in hepatic and peripheral tissue sensitivity to insulin.
Dobrian et al. (2004) showed that pioglitazone treatment prevented hypertension and renal oxidative stress both by reducing free-radical production and by increasing nitric oxide production/availability.

Srinivasan et al. (2004) reported that treatment with pioglitazone (30 mg/kg p.o.) once daily for 2 weeks significantly ameliorated changes in basal plasma insulin, triglycerides and total cholesterol, and reversed oral glucose intolerance to normal in HFD-fed rats, suggesting its potential in the treatment of insulin resistance and glucose intolerance associated with abnormal lipid metabolism.

Ding et al. (2005) have reported that treatment with pioglitazone improves insulin sensitivity in low-dose STZ and high sucrose-fat diet induced obese rats. The insulin sensitizing effect may be associated with ameliorating lipid metabolism, reducing hyperinsulinemia, inhibiting gluconeogenesis, and increasing insulin receptor substrate-1 (IRS-1) and glucose transporter 4 (GLUT4) protein expressions in insulin-sensitive tissues.

Rodriguez et al. (2006) have reported that pioglitazone prevents cardiac remodeling in high-fat, high-calorie-induced Type 2 diabetes mellitus.

Majithiya et al. (2006) reported that pioglitazone (10 mg/kg) administration reduced oxidative stress, which prevented the breakdown of nitric oxide and increased nitric oxide levels, thereby restoring the endothelial function in aorta of STZ-diabetic rat. Hence, pioglitazone administration in STZ-diabetic rats lowers blood pressure, protects against oxidative stress, and restores endothelial function.
COMPOSITION OF HIGH FAT DIET

High fat diet (HFD) used to induce obesity which was procured, standardized and designed by National Centre for Laboratory Animal Sciences (NCLAS), National Institute of Nutrition (NIN), Hyderabad, Andhra Pradesh, India. HFD (5 kg) contains:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casein</td>
<td>1.71 kg</td>
</tr>
<tr>
<td>Cystine</td>
<td>15 gms</td>
</tr>
<tr>
<td>Starch</td>
<td>0.860 kg</td>
</tr>
<tr>
<td>Sucrose</td>
<td>0.860 kg</td>
</tr>
<tr>
<td>Cellulose</td>
<td>0.250 kg</td>
</tr>
<tr>
<td>G. N. oil</td>
<td>0.125 kg</td>
</tr>
<tr>
<td>Tallow</td>
<td>0.950 kg</td>
</tr>
<tr>
<td>Mineral Mix (AIN)</td>
<td>0.175 kg</td>
</tr>
<tr>
<td>Vitamin Mix (AIN)</td>
<td>0.05 g</td>
</tr>
</tbody>
</table>

ROLE OF INGREDIENTS IN THE COMPOSITION OF HIGH FAT DIET

Casein has cholepoietic effect and increase the efficacy of fat absorption (Magee et al., 1953).

Cystine exerted a positive effect on the accumulation of fat in the liver (Evelyn et al., 1950).

Tallow has include about 42% saturated fatty acids and only 1% unsaturated fatty acids. High tallow level decreased feed intake, poor fat digestion (Sedeghi and Tabiedian, 2005).

Sucrose, Starch & Cellulose: These are carbohydrates and provide energy. The excess energy intake causes body fat accumulation, and lead to obesity if energy expenditure is not increased. High intake of simple sugars is generally seen as a detrimental factor in the etiology of both obesity and insulin resistance.

Sucrose feeding produces a major impairment of insulin action, predominantly because of an effect at the liver. Free access to sugar solutions in rat experiments leads to rapid weight gain and increased adiposity (Kanarek and Orthen-Gambrill, 1982). The combination of high intakes of dietary fat and sucrose could be
particularly potent in the etiology of both diabetes mellitus and obesity (Storlien, 1988).

Rats fed high-sucrose or high-starch diets exhibited similar body weight gains and visceral fat accumulation. Both the high-sucrose and the high-starch fed rats accumulated ~35% more visceral fat in 4 weeks than the chow-fed controls (Chun et al., 2010).

In diets specifically designed for obese dogs and cats, fiber is considered important to reduce energy density and therefore energy intake. Fiber level in the diets is achieved by adding cellulose (Dobenecker and Kienzle, 1998).

Groundnut oil contains 46 and 32 percent of monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA), respectively (Rasmussen et al., 1993). Fresh and thermally oxidized sesame, groundnut and coconut oils were fed to different groups of rats, as high fat diet (20%). Feeding fresh and thermally oxidized oils increased the levels of total cholesterol, low density lipoprotein cholesterol (LDL-C), and phospholipids but high density lipoprotein cholesterol (HDL-C) decreased in all the experimental animals (Srinivasan and Pugalendi, 2000).

Mineral Mix and Vitamin Mix

Vitamins and minerals are beneficial to the bodybuilders. These nutrients replenish the energy requirements of the body by acting co-enzyme and by participating in metabolic processes e.g. Thiamine and Niacin are essential for protein and carbohydrate metabolism as well as release the energy from carbohydrates. Intake of vitamins plays an important role in avoiding obesity (e.g. vitamin B2, B3, B5, B6 and vitamin C).

Manganese involved in the metabolism of carbohydrates, fats and proteins. Chromium is important in cholesterol metabolism and essential for proper utilization of sugar.