REVIEW

OF

LITERATURE
According to the World Health Organization (WHO) overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health (WHO, 2006). Body mass index (BMI), defined as body weight in kilograms divided by the square of height in meters (kg m⁻²), is commonly used in categorizing adult populations and individuals as either underweight, normal weight, overweight or obese. Furthermore, WHO classifies obesity into three classes according to its risk of co-morbidities; from moderate risk to very severe risk (WHO, 2008a). These classifications can be seen in Table 1.

Table 1. The international classification of adult underweight, overweight and obesity according to body mass index (WHO, 2008a).

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal weight</td>
<td>18.5 - 24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0 - 29.9</td>
</tr>
<tr>
<td>Obesity</td>
<td>≥30</td>
</tr>
<tr>
<td>Obesity class I</td>
<td>30.0 - 34.9</td>
</tr>
<tr>
<td>Obesity class II</td>
<td>35.0 - 39.9</td>
</tr>
<tr>
<td>Obesity class III</td>
<td>≥40</td>
</tr>
</tbody>
</table>

Despite its frequent use in classifying people’s physical health, BMI has its limitations since it does not always reflect body composition and its accuracy can be greatly distorted by muscle mass, physical fitness, visceral adiposity, gender, age, ethnicity and bone structure. Hence, a person categorized as obese might not experience a higher risk of co-morbidities if the extra body weight is mainly caused by increased muscle mass due to high level of physical activity. Also, a normal weight person cannot be labeled as healthy because he/she might lead an unhealthy lifestyle and/or have a poor muscle mass and therefore be in increased risk of impaired health. It is well known that obese people store more fat in the abdomen, and since excess visceral abdominal tissue is often accompanied by elevated
triglycerides, reduced high-density lipoprotein (HDL) cholesterol, elevated blood pressure, elevated fasting plasma glucose and/or elevated concentrations of inflammatory cytokines, this increases the risk of developing numerous chronic diseases (WHO, 2006; Despres, 2007). Clinical and epidemiological research has found waist circumference to be the best anthropometric indicator of intra-abdominal fat mass (Guagnano et al., 2007). Therefore it is advisable to include waist circumference, as well as BMI, in the evaluation of the risk of illness caused by overweight and obesity (Janssen et al., 2002).

The distribution of body fat has significant implications for health. Central or visceral adiposity increases the risk for cardiovascular and other diseases, independent of obesity. Individuals with this characteristic are at the highest risk for developing type 2 diabetes, metabolic syndrome and subsequent cardiovascular complications, including retinopathy, nephropathy, neuropathy, macular degeneration and cardiovascular disease (Ribisl, 2004). Risk for such disease progression is caused by excess visceral adipose tissue; simply being overweight is not the culprit. It is not the total amount of body fat that creates this problem, but the location of the body fat. The Gothenberg, Sweden, longitudinal study showed that increased waist size was positively correlated with an increased incidence of myocardial infarction, angina, and stroke independent of age and BMI (Klauer and Aronne, 2002).

Clinicians may use the waist circumference as a measure of central adiposity. According to the US Preventative Task Force, men with a waist circumference greater than 40 inches and women with a waist circumference greater than 35 inches are at increased risk for cardiovascular disease.

In addition, determination of the waist/hip ratio may be useful for assessing some adults, particularly those whose weight or BMI is borderline for classification as overweight and who have personal or family history medical histories placing them at increased health risk. The waist/hip ratio may be a better predictor of the sequelae associated with adult obesity than BMI, can also be measured in the clinical setting. The reliability of the waist/hip ratio is comparable to that of the BMI. A waist/hip ratio greater than 1.0 in men and 0.8 in women has been shown to
predict complications from obesity, independent of BMI, although the waist/hip ratio has not been evaluated in all ethnic groups.

Humans have evolved as a species from hominids that were well-equipped to survive and reproduce in environments that yield an unsteady supply of readily available food. Survival and reproduction were dependent on energy stores of the individual and the species. For evolutionary reasons, human physiology is predisposed to conserve and store weight, not to shed excess amounts. However, in the modern industrial environment that provides easy access to calorically-dense foods and encourages a sedentary lifestyle, the metabolic consequences of these genes are maladaptive (Rosenbaum and Liebel, 1998). The prevalence of childhood obesity has increased by more than 30% over the past decade. The rapid increase in the prevalence of obesity emphasizes the role of environmental factors, because genetic changes could not occur at this rate.

This increasing prevalence of obesity in the United States apparently represents the interaction of genes with an environment that encourages a sedentary lifestyle and consumption of calories. The current relative adiposity is a product of the interaction between genetic predisposition with regard to the storage of body fat and an environment (low physical activity, high availability of calorically-dense foods) that is increasingly permissive to the expression of that genetic tendency. Although there are clearly strong genetic influences on susceptibility to obesity, large changes in the prevalence of obesity over such a short time must reflect major changes in non-genetic factors, providing tacit evidence that some instances or aspects of obesity must be responsive to, or preventable by, manipulation of the environment (eg, diet, physical activity).

In most humans, body fatness is a continuous quantitative trait reflecting the interaction of development and environment with genotype (Rosenbaum and Liebel, 1998). Studies in twins, adoptees, and families indicate that as much as 80% of the variance in BMI is attributable to genetic factors. Genetic influences on body weight are as potent as those on height. Heritability of adipose tissue distribution, physical activity, resting metabolic rate, changes in energy expenditure that occur in
response to over-feeding, certain aspect of feeding behavior, food preferences, lipoprotein lipase activity, maximal insulin-stimulated triacylglyceride synthesis, and basal rates of lipolysis are estimated to be as high as 40% (Rosenbaum and Liebel, 1998).

According to Rosenbaum and Liebel (1998), there is substantial evidence that body weight is regulated by complex signaling systems that provide afferent signals, including glucostatic, lipostatic and aminostatic signals to the CNS about the nutritional state of the organism, which are translated into efferent signals that affect energy intake and expenditure.

1.3 Prevalence of obesity

Obesity has become a healthcare problem today and its prevalence has increased greatly in recent decades in almost every country and all age groups. The major cause in the recent obesity epidemic is a changing environment that promotes excessive calorie intake and discourages physical activity, causing an energy imbalance. According to WHO’s latest projections approximately 1.6 billion adults (age 15+) were overweight worldwide in 2005 and at least 400 million adults were obese. WHO further estimates that by 2015, approximately 2.3 billion adults will be overweight and more than 700 million will be obese (WHO, 2006).

1.4 Etiology and impetus of obesity

Storage of excess calories as fat must ultimately result from a net positive energy balance (energy intake is greater than energy expenditure) over time (Rosenbaum and Liebel, 1998). The rise of global obesity is thought to be a by-product of environmental and behavioral changes linked to economic development, modernization and urbanization. Paradoxically, obesity often coexists with a substantial level of malnutrition (Peterson, 2005).

Increasing evidence suggests that obesity is not a simple problem of will power or self-control, but a complex disorder involving appetite regulation and energy metabolism that is associated with a variety of co-morbid conditions. Although its etiology is not clearly established, genetic, metabolic, biochemical,
cultural and psychosocial factors contribute to obesity (Lyznicki et al., 2001). In most cases, the increasing prevalence of overweight and obesity reflects changes in society and behaviors over the past 20-30 years.

1.3.1 Overconsumption of Calories

Americans live in an environment that promotes obesity. Food is in abundance and portion sizes have increased. US studies showed that of children between 7 and 14 years of age, only 46% met the recommended daily intake for grain, 20% for vegetables, 5% for fruit, 9% for dairy and 26% for meat. Moreover, a large proportion of total caloric intake came from fat and added sugar, accounting for more than 46% of the total calories (Luke et al., 2004). Another trend in nutrition that have attributed to the overconsumption in calories are the increased consumption of soda and juice. Only 2% of school-aged children currently meet the number of servings suggested in the Food Guide Pyramid (Luke et al., 2004). These poor dietary habits follow these children into adolescence and adulthood, leading to overweight and obese adults.

1.3.2 Decreased Physical Activity

While caloric consumption has steadily increased, daily physical activity has significantly declined for several reasons. First, there has been an increased reliance on motor vehicles for transportation. In addition, more workers now have sedentary jobs because of the continual decline in manufacturing and other physically demanding types of labor. The proliferation of modern technology, such as video games and computers, the increase in number of hours people watch television, and our propensity for convenience all contribute to our sedentary lifestyles (Spence-Jones, 2003).

Lifestyle influences promoting excessive caloric intake and sedentary patterns are known to induce a positive energy balance leading to weight gain (Swinburn et al., 2004). Indeed, the current food industries have increased the availability of energy-dense meals, while sedentary patterns facilitated by motorized transport and other common physically inactive pursuits (TV viewing, computer work, etc) have markedly risen in the last decades (Maffeis, 2000).
It is believed that much of the increase in obesity in the last 25 years has resulted from the decreased level of physical activity in everyday life. Worldwide there has been a large shift towards less physically demanding work, and currently at least 31 percent of the world’s population gets insufficient exercise (WHO Physical inactivity, 2011). The prevalence of insufficient activity was highest in the United States, where 50% of women and 40% of men were insufficiently active, while the rate of No Leisure-Time physical activity was 25.4% in 2008 (US Physical activity statistics, 2010; WHO Physical inactivity, 2011). This is primarily due to increasing use of cars instead of walking and fewer physical demands at work or home because of modern technology and conveniences. In children, there appears to be declines in levels of physical activity due to less walking and physical education.

### 1.4.2 Social Influences

Fashion designers and clothing manufacturers, as well as advertising agencies, promote and ideal, often emaciated, body image (Rogge et al., 2004). Women are excessively stigmatized by the disease, given society’s premium of female physical attractiveness (Klauser and Aronne, 2002).

Also, an emerging economic explanation (for obesity) is that the increase in BMI among people in the US may be attributable to technological advances that have reduced job difficulty and increased consumption of mass produced foods. The overall decrease in work-related physical activity, as well as other changes in the ways we use our time, have contributed to the trend toward a higher BMI. Advancing food technology may have accelerated the rate of BMI increase by making it easier for people in the US to consume more high-calorie, prepackaged and snack foods. Although technologic advances have enriched our lives and made things much easier, it has become almost impossible to get a decent amount of exercise (Klauser and Aronne, 2002).

### 1.4.3 Family Influences

Risk factors associated with childhood and adolescent overweight and obesity include high birth weight, maternal diabetes and a family history of obesity. If one parent is obese, there is a three-fold increase for the child to become obese in
adulthood. If both parents are obese, the risk is ten times greater. Before age 3, parental weight is more of a risk factor for developing obesity that the child’s actual weight. Low income, low education, absence of family meals, and sedentary behavior are also linked with the development of overweight and obesity in children (Shepard, 2004).

### 1.3 Pathophysiology of Obesity

The following information concerning the pathophysiology of obesity was found in Kumar et al. (2005), unless otherwise noted. Energy intake from food and energy expenditure from cellular metabolism and exercise are precisely matched over long intervals in healthy adults resulting in stable body fat stores. Energy is continuously expended, and the rate of expenditure varies among persons. The brain and the liver are efficient at controlling nutrient levels based on need. Following ingestion of food, nutrient levels move from the gut into tissues for immediate use or storage. Decreases of plasma fuels below levels to meet tissue requirements are rare in normal, free-feeding individuals. Under homeostatic conditions, the supply of energy in the blood does not decrease to below threshold levels and cause the brain to trigger eating. Even though ample energy is generally readily available, animals and humans still initiate meals.

Prior to initiation of a meal, there is a small decrease in plasma glucose of about 12%. The brain initiates a decline in plasma glucose by eliciting a small increase in plasma insulin via the vagus nerve to the pancreas, which precedes the pre-meal decline in glucose. Small physiologic fluctuations of glucose are hypothesized to provide important signals to the brain to elicit meals. There is also evidence that the liver responds to small fluctuations of fatty acids and their metabolites by sending signals to the brain via the vagus nerve, which in turn stimulates food ingestion.

Other events also predict the onset of meals, such as an increase in body temperature, past experiences of meal initiation, such as the time of day, social factors and others. According to this evidence, individuals do not initiate meals because there is a lack of available energy, but rather the individual eats when it is
adapted to eating. The timing of meals is dictated by the individual’s lifestyle, convenience and opportunity. The timing and frequency of meals are driven more by lifestyle than by immediate need.

Most adult mammals, including humans, maintain a relatively constant level of adiposity over long intervals, and this occurs in spite of the variability of daily energy intake, expenditure and meal patterns.

The central regulation of caloric intake and energy expenditure that contribute to energy balance involves interactions between the peripheral hormonal and neuromodulatory factors and neural pathways. Peripheral signals of hunger and satiety are interpreted in the hypothalamus and distributed to the periphery by the sympathetic nervous system. A positive energy balance or satiety is mediated by increased intestinal distention and other mechanical-chemical changes that induce neural impulses carried by the afferent vagus nerve and by augmentation in the circulating concentrations of glucose, leptin, cholecystokinin, glucagons-like peptide-1 and peptide YY (Konturck et al., 2005).

Leptin is a signal secreted mainly from fat cells that controls food intake and energy homeostasis. The concentration of leptin in the blood is highly correlated with total body fat mass. Excess body fat that results in increased leptin production may actually be a correction for primary or secondary impairment of leptin-induced signal transduction in the hypothalamus. The decrease in body fat that occurs with diet-induced weight loss causes leptin concentrations to decrease and triggers responses that aim to conserve body fat (Halaas et al., 1995).

In addition to stimulating secretion of anorexigenic peptides, leptin decreases expression of orexigenic neuropeptide Y (NPY) and agouti-related protein (AgRP) (Bagnasco et al., 2002). Activation of the melanocortin 4 receptor (MC4R) gene (a receptor site in the “satiety center”) within the hypothalamus not only suppresses food intake, it also increases energy utilization. Thus, loss of function mutations in the propopmelanocortin (POMC) or MC4R lead to hyperphagia and obesity in both experimental animals and humans (Gropp et al., 2005).
When the leptin feedback system is disturbed, such as in animals or humans that either make no leptin or have no leptin receptor sites, there is a chronic bias to overeat and gain weight. These individuals are hyperphagic and extremely obese, and administration of leptin reverses this syndrome (Ahima et al., 1994).

However, leptin alone cannot regulate this energy homeostasis alone. Both insulin and leptin satisfy the criteria to be adiposity signals. The hypothalamus relies upon information from adipose stores in the form of insulin and leptin, as well as information on immediately available energy from the liver and hindbrain, to help control food intake and energy expenditure. Insulin deficient animals are hyperphagic and administration of insulin eliminates their hyperphagia, which suggests the importance of insulin as an adiposity signal (Woods et al., 1998).

Ghrelin stimulates hunger and increases food intake through the stimulation of ghrelin receptors on hypothalamic NPY expressing neurons and AgRP expressing neurons (Wang et al., 2002). Ghrelin suppresses the effects of leptin. Increased ghrelin secretion and activation of ghrelin receptor sites increases expression of NPY and AgRP. Ghrelin increases food intake by inhibiting MC4R, and decreases energy expenditure by lowering the catabolism of fat. Ghrelin also inhibits expression of POMC and other anorexigenic factors. Leptin (an anorexigenic, or appetite-suppressing factor) and ghrelin (anorexigenic, or appetite-stimulating peptide) act in a mutually antagonistic manner through their respective receptors in the hypothalamus and brainstem to regulate caloric intake and energy expenditure (Madan, 2005).

Peptide YY (PYY) signals satiety. PYY is secreted postprandially by endocrine L cells lining the distal small bowel and colon. PYY is secreted in proportion to the calories ingested. The initial release of PYY occurs shortly after food intake. The release of PYY is stimulated by nutrients, particularly carbohydrates and lipids, within the lumen of the small intestine and the colon. PYY inhibits food intake through inhibition of gut motility, causing a sense of satiety and by way of vagal influences on the hindbrain (Hagan, 2002).

In a study conducted by Batterham et al. (2003), a single infusion of PYY, as compared to an infusion of saline, reduces appetite and food consumption by
approximately 30% at an all-you-can-eat buffet lunch provided two hours after the infusion. In obese subjects, the endogenous postprandial PYY response was diminished as compared with that in lean subjects, even though the obese subjects consumed a greater amount of calories (Korner and Leibel, 2003).

The amount of food intake is regulated by signals generated as food is eaten. Cholecystokinin (CCK) is secreted in the intestine in response to ingested food and stretch receptors in the gut. CCK acts to reduce meal size. According to Clegg and Woods (2004) when CCK is administered to animals or humans prior to a meal, meal size is reduced dose-dependently. The availability of meal-generated, pre-absorptive negative feedback signals such as CCK to reduce meal size depends upon estrogen levels. Estrogen increases the satiating action of CCK. Hence, generally eat less food, assuming normal circulating plasma estrogen concentrations (Stephen et al., 2008).

1.6 Co-morbid conditions associated with obesity

Obesity is regarded as the most preventable causes of morbidity and mortality, primarily because of the links to hypertension, coronary artery disease, stroke, diabetes and cancer (Rogge et al., 2004). Obesity is a risk factor for major causes of death, including cardiovascular disease, numerous types of cancer and diabetes. It is also linked with markedly diminished life expectancy (McTigue et al., 2003). Studies suggest that people who are more than 20% overweight have prevalence’s of hyperlipidemia, hypertension and diabetes that are between 1.5 and 3.5 times higher than those people whose weight is normal (Multon, 1998). Other complications associated with obesity include osteoarthritis, joint pain, gallbladder disease, sleep apnea, respiratory impairment, diminished mobility and psychosocial distress.

The American Heart Association has cited obesity as a major modifiable risk factor for coronary heart disease. Compared with their lean counterparts, obese women have an increased mortality risk that rises in proportion to the degree of
Obesity (Klauer and Aronne, 2002). The risk of developing coronary heart disease is increased threefold in women with a BMI greater than 29 compared to BMI less than 21.

Obese persons are likely to have hypertriglyceridemia and a low HDL cholesterol values, and these factors may increase the risk of coronary artery disease. The association between obesity and heart disease is not straightforward, and the linkage may be related to the associated hypertension and diabetes rather than to weight. Observational studies have established a clear association between overweight and hypercholesterolemia and suggest an independent relationship between overweight and coronary artery disease (Klauer and Aronne, 2002).

The mechanisms underlying these associations are complex and are likely to be interrelated. Obesity for instance, is associated with insulin resistance and hyperinsulinemia, important features on type 2 diabetes mellitus. It has been speculated that excess insulin, in turn may play a role in the retention of sodium, expansion of blood volume, production of excess norepinephrine and smooth muscle proliferation that are the hallmarks of hypertension. The prevalence of diabetes and hypertension is three times higher in overweight adults than in those of normal weight.

1.0.2 Diabetes Mellitus

Diabetes is a disorder of the body that occur when there is either an absolute or a relative lack of insulin, the hormone needed to control blood sugar. As of 2010, it is estimated that as many as 25.8 million people in the United States are living with diabetes (National diabetes fact sheet, 2011). The American diabetes association states that 18.8 million people have been diagnosed and the other 7 million are living undiagnosed. Comparison of the 2007 estimates suggests that the net number of people with the diagnosed diabetes is growing by 2 million people per year (National diabetes fact sheet, 2011).

There is strong association between obesity and type II diabetes mellitus, in both genders and all ethnic groups. In addition, weight gain appears to precede the
development of diabetes (Malnick, 2006). The risk of diabetes is increased 53 times the normal rate with severe obesity. In a study completed by the center for Diabetes Control and Prevention in 2002, the prevalence of obesity among adults with diagnosed diabetes was 53% of men and 58% of women (Fiberhardt and Ogden, 2004). Of the diagnosed cases of diabetes, 90% of diabetic are type II. This is generally developed between the ages of 30 - 60 years old. Type II diabetes is almost always associated with lifestyle factors and genetics and appears to be related to substances called cytokines. These hormonal-like substances which are produced in adipose (fat) tissue interfere with the cellular action of insulin and lead to diminished insulin action. In the majority of obese individuals with diabetes, reducing body weight by 10% could eliminate or reduce the need for oral medications or insulin injections (Myers, 2004).

As the prevalence of diabetes continues to grow, the economic burden caused by increased health resources use and lost productivity is outstanding. According to research conducted by the American Diabetes Association, the total estimated cost of diabetes in 2007 is 174 billion, including 116 billion in excess medical expenditures and 58 billion in reduced productivity from work related absenteeism, reduced productivity at work and at work at home, unemployment from chronic disability and premature mortality. In addition to these quantified costs, diabetes inflicts high intangible costs on society in terms of reduced quality of life and the pain and suffering of people with diabetes, their families, and their friends (American diabetes association, 2007).

Medical costs attributed to diabetes include 27 billion for care to directly treat diabetes, 58 billion to treat the portion of diabetes related chronic complications that are attributed to diabetes and 31 billion in excess general medical costs. The large components of medical expenditure generated by diabetes are hospital inpatient care, accounting for 50% of the total cost, diabetes medication and supplies with 12% of the total, retail prescriptions to treat complications of diabetes were estimated at 11%, and physician office visits were calculated at 9% of the total cost (American diabetes association, 2007).
Cancer is a class of diseases in which abnormal cells display uncontrolled growth, invasion and sometimes spread to other locations in the body via lymph or blood (Cancer facts and figures 2010). Cancer accounted for 7.6 million deaths (or around 13% of all deaths) in 2008, making it the leading cause of death worldwide (Sleep apnea, 2010). Cancers are primarily an environmental disease with 90-95% of cases due to lifestyle and environmental factors and 5-10% due to genetics. Common environmental factors leading to cancer death include: tobacco (25-35%), diet and obesity (30-35%), infections (15-20%) radiation, stress, lack of physical activity and environmental pollutants (Anand et al., 2008). These environmental factors cause abnormalities in genetic material of cells. More than 70% of all cancer deaths occurred in low and middle income countries. Deaths from cancer worldwide are projected to continued rising, with an estimated 11 million deaths in 2030 (WHO, 2011).

According to a recent American Cancer Society report, one in five cancer deaths are linked to obesity (Peterson, 2005). It is noteworthy that obese women, who are at a higher risk of breast and endometrial cancer, undergo screening for breast and cervical cancer less frequently than non-obese women. Obese patients may choose to forego early or preventative healthcare so as to avoid oppressive encounters with clinicians (Rogge et al., 2004).

Obesity predisposes individuals to a wide variety of diseases, and of special concern for women’s health is the association of obesity with breast and endometrial cancers and disorders of reproduction (Klauer and Aronne, 2002). The link with uterine and breast cancer is believed to be due to the increase in estrogen produced by adipose tissue. The link between obesity and breast cancer in postmenopausal women may be related to the amount of visceral fat present. Obesity has also been associated with certain cancers, including those of the colon, rectum, gallbladder, biliary tract, breast, cervix and ovary.
**1.8.1 Cholelithiasis**

Cholelithiasis is six times more common in obese than in lean subjects (Kumar et al., 2005). The mechanism is mainly an increase in total body cholesterol, increased cholesterol turnover, and augmented biliary excretion of cholesterol in the bile, which in turn predisposes to the formation of cholesterol-rich gallstones.

**1.8.2 Osteoarthritis and Degenerative Joint Disease**

Obesity has been identified as the main preventable risk factor for developing osteoarthritis (Powell et al., 2004). It has been speculated that obesity increases subchondral bony stiffness, making bones less adept at coping with impact loads.

People who are overweight have a higher prevalence of osteoarthritis of the knee than those who are not. The risk for osteoarthritis increases by 35% for every 5 kg of excess weight. The relation of osteoarthritis of the knee to obesity is stronger in women than in men for reasons that are unknown. Also, studies have shown that obese women are at a higher risk of osteoarthritis of the hand than women who are thinner. This suggests that the effect of obesity on osteoarthritis is mediated not only by excess loading on the joints, but also by metabolic or inflammatory factors that may accompany obesity. These metabolic factors may have deleterious effects on the joint (Felson, 2004). Arthritis, which typically appears in older persons, is attributed in large to the cumulative effects of wear and tear on the joints. It is reasonable to assume that the greater the bodies burden of fat, the greater the trauma to the joints with passage of time.

**1.8.3 Respiratory Hypoventilation**

Physiological studies have documented that obesity decreases chest wall compliance and increases airway resistance and the work of breathing. Respiratory studies in obese individuals have shown a decrease in forced vital capacity and forced expiratory volume at one second compared with normal weight controls (Castro and Avina, 2002). Hypoventilation syndrome is a constellation of respiratory abnormalities in very obese persons. Hypersomnolence, both at night and during the day, is characteristic, and is often associated with apneic pauses during sleep, polycythemia and eventual right sided heart failure.
Significant associations are seen in reproductive endocrinology between excess body fat and irregular menstrual cycles, reduced spontaneous and induced fertility, increased risk for miscarriage and hormone-sensitive carcinomas. Distinct changes in circulating sex hormones appear to underline these abnormalities (Pasquali et al., 2003). One study cited by Pasquali et al. (2003) found that 43% of women affected by various menstrual disorders, infertility and frequent miscarriages were either overweight or obese. It is also known that the presence of anovulatory cycles, oligoamenorrhea and hirsutism, either separately or in association, were significantly higher in obese than in normal weight women.

Obesity may interfere with many neuroendocrine and ovarian functions, thereby reducing both ovulatory and fertility rates in otherwise healthy women. Obesity is associated with increased risk of hyperandrogenism and an ovulation in women of reproductive age as supported by the strong association between obesity and the polycystic ovarian syndrome (PCOS). Approximately 50% of women with PCOS are overweight (Pasquali et al., 2003). Obesity may be associated with several alterations in the balance of sex hormones. Such alterations involve both androgens and estrogens, and their carrier protein, sex hormone binding globulin (SHBG). Changes in SHBG concentrations lead to an alteration of estrogen and androgen delivery to target tissues. Obesity also affects the metabolism of the androgens not bound to SHBG, leading to increased levels in the blood.

Obesity is a condition of insulin resistance and compensatory hyperinsulinemia. Target tissues, such as the muscles, liver and adipose tissue become resistant to insulin over time. But the ovaries remain responsive to insulin through interaction with its own receptor. Excess insulin has been shown to stimulate steroidogenesis and excessive androgen production from the theca cell system (Pasquali et al., 2003). In addition, by inhibiting SHBG synthesis by the liver, excess insulin further increases the delivery of free androgens to target tissues. The excess in local ovarian androgen production induced by excess circulating insulin may also cause premature follicular atresia, which leads to anovulation. Insulin resistance and hyperinsulinemia, which develop together in the presence of obesity, may play a dominant role in the development of hyperandrogenism in women with PCOS.
The role of adipose tissue is crucial in controlling the balance of sex hormone availability in the target non-fat tissues. Adipose tissue is able to store various lipid-soluble steroids, such as androgens. Most sex hormones appear to be preferentially concentrated in the adipose tissue rather than in the blood. As a consequence, since the amounts of fat in obesity are larger than their intravascular space, and the steroid tissue concentration is much higher than in plasma, the steroid pool in obese individuals is greater than that found in normal-weight individuals (Pasquali et al., 2003). Obesity can also be considered a condition of increased estrogen production. Reduced SHBG concentrations may in turn lead to an increased exposure of target tissues to free estrogens.

As discussed earlier, obesity may represent a condition of leptin resistance. Leptin acts directly on the ovary, in particular on the follicular cells, including the granulosa, thecal and interstitial cells. Leptin may exert a direct inhibitory effect on ovarian function, by inhibiting both granulosa and thecal cell steroidogenesis, probably through the antagonism of stimulatory factors (Pasquali et al., 2003). High leptin concentrations in the ovary may interfere with the development of dominant follicles and oocyte maturation.

Ghrelin levels are negatively correlated with androgen levels, indicating that the gonads may be important targets of ghrelin action. Since ghrelin concentrations are negatively correlated with insulin resistance, it can be speculated that this peptide in some way represents a link between hyperandrogenism and the insulin system in conditions such as obesity and PCOS. It therefore appears that ghrelin, like leptin, may represent a further endocrine factor that is related not only to energy balance and metabolism, but also to gonadal function.

While most rodents tend to become obese on high-fat diets, there can be variable responses in weight gain, glucose tolerance, insulin resistance, triglycerides and other parameters depending on the strain. Some inbred strains are more susceptible to obesity when fed high-fat diets such as the C57Bl6 or AKR mouse (Rossmeis et al., 2003). However, strains that exhibit similar levels of weight gain may show different responses to other parameters. For example, when fed a 58 kcal
% fat diet, C57Bl/6 mice and AKR mice will have similar degrees of weight gain, but C57Bl/6 mice are more glucose intolerant compared to AKR mice (Rossoneis et al., 2003). Other strains are simply more resistant to obesity, such as the SWR/J and A/J mice (Surwit et al., 1995; Prpic et al., 2002). Even within the same strain, different phenotypical responses to high fat diets have been observed between animals bred in different facilities (Pecoraro et al., 2006).

Rat models including out bred Sprague-Dawley and Wistar rats are popular strains to study obesity as they readily gain weight on high-fat diets. In particular, Sprague-Dawley rats have been studied for their ability to show a variable response to a high-fat diet (32 or 45% kcal fat). Some animals rapidly gain weight while others gain only as much weight as those fed a low-fat diet (Levin et al., 1997; Farley et al., 2003), allowing for the study of animals that are prone and resistant to obesity. These animals have been selectively bred over time to study the genetic traits of animals with the obese or lean phenotype.

There has been a growing body of literature using rodents as models of human obesity, even though there are many confounding factors including species, strain and age of the animals, type of diet, level of fat and type of control diet. Fortunately, there is a growing discussion about these issues which will help scientists design studies with tightly controlled conditions and therefore improve our understanding of obesity and related diseases.

1.8.1 Effect of high fat diets on the development of obesity

As early as 1951, Fenton and Carr observed that, when providing diets with increasing fat content to rodents, some strains showed marked weight gains, while others had a much less pronounced response. They reported elevated food utilization with diets high in fat and showed by carcass analysis that the strain responding well to high fat feeding accumulated most of the excess weight as fat (Fenton and Carr, 1951). In 1955, Mickelsen et al. showed for the first time in rats that obesity could be achieved by feeding a diet high in fat and implied that this could be due to an excess consumption of calories (Mickelsen et al., 1955). High fat diets are now
fairly well accepted to model the disorders of human obesity in rodents (Buettner et al., 2007) and have since then been extensively used to induce obesity in animal models. To understand the mechanisms behind the excess storage of energy usually associated with feeding high fat diets, some parameters of the energy balance need to be considered.

1.3.2 High fat diets and hyperphagia

The most obvious, and possibly easiest, parameter to look at is the energy intake, which is simply calculated by measuring the food consumption and multiplying it by the energy density of the diet. High fat feeding has usually been associated with hyperphagia, meaning the group given the high fat diet tended to consume more calories than the control group. This effect has been observed in mice (Mercer and Trayhurn, 1987; West et al., 1995; Gallou-Kahani et al., 2007), rats (Ramirez and Friedman 1990; Shafat et al., 2009) and humans (Lissner et al., 1987). Therefore, it seems that subjects fed a high fat diet are unable to regulate their food intake to meet their needs and develop obesity as a consequence. Interestingly, the hyperphagia associated with high fat diet does not seem to be due to fat itself but rather to the energy density of the diets. Fat is characterised by a high energy density (in kcal per g of macronutrient: fat, 9; carbohydrate, 4; protein, 4) and thus, high fat diets are often high in energy density. Ramirez and Friedman fed rats either a low fat or a high fat diet but presenting the same energy density.

Rats fed the high fat diet then presented increased body weight and energy intake compared to the mice fed the low fat diet (Ramirez and Friedman, 1990). This result has been confirmed by others in rats (Paulino et al., 2008). Therefore, as underlined by Warwick and Schiffman, who reviewed 40 studies comparing the effects of high fat to high carbohydrate diets, when the caloric density of the diets was similar (density of the high fat diet less than 25% greater than high carbohydrate diet), only 5 out of 10 studies observed greater weight gain in high fat fed animals whereas when the high fat diet had an energy density at least 25% greater than the high carbohydrate diet, then 28 out of 30 studies observed a greater weight gain in the high fat fed animals (Warwick and Schiffman, 1992). These findings have been confirmed in humans as well (Stubbs et al., 1995; Prentice, 1998; Rolls, 2000).
Thus, the hyperphagia associated with high fat diet feeding is abolished when the diets provided are matched with respect to caloric density. To summarize, the hyperphagia associated with high fat diet seems to be due to the high energy densities of high fat diets and not because of the fat content of the diet per se. Of note, contradictory results have been reported in rats when using liquid diets (Warwick, 2003).

### 1.3.3 Diet-induced Thermogenesis

Diet-induced thermogenesis (DIT) has been shown to have a significant effect on the regulation of energy balance (Himms-Hagen, 1985) and mainly takes place in the brown adipose tissue in rodents (Rothwell and Stock, 1979; Cannon and Nedergaard, 2004). Mercer and Trayhurn showed that mice fed a high fat diet rich in corn oil, meaning a high content of PUFA, exhibited increased energy expenditure, as revealed by an enhanced total thermogenic activity of the BAT, compared to mice fed a low fat diet (Mercer and Trayhurn, 1987). Interestingly, the mice fed a high fat diet rich in beef tallow, meaning a high content of SFA, did not show any evidence for an increased DIT which could partly explain why they displayed greater body weight compared to the 2 other groups. Differences in DIT could also partly account for the differences in energy assimilation efficiencies since mice fed the corn oil diet retained only 18% of the excess energy intake in the carcass whereas mice fed the beef tallow diet retained 77%, despite similar total energy intakes. A decrease in DIT induced by a diet rich in SFA as compared to diets rich in MUFA or PUFA has been confirmed in rats as well (Takeuchi et al., 1995).

Altogether, these results point at differences in DIT as a function of the fat amount or possibly the total energy intake since DIT has been associated with over feeding and the fatty acid composition of the diet which influences the obesity state as well (Corbett et al., 1986). BAT has long been thought to be of negligible importance in humans, based on its mass and activity, and its role in the energy balance has been neglected until recently where positron emission tomography demonstrated that adult humans had significant depots of metabolically active BAT (Cypess et al., 2009; Saito et al., 2009; van Marken Lichtenbelt et al., 2009; Virtanen et al., 2009). Therefore, there is currently a renewal of interest for the role of the BAT in obesity in humans.
The term high fat diet actually encompasses a fairly wide spectrum of diets. In a 1992 review, Warwick analyzed 40 studies comparing the effects of high fat and high carbohydrate diets (Warwick and Schifman, 1992) and reported differences in fat content of the diets used ranging from 28 to 84% of total energy. The diets were also characterized by different fat sources (corn oil, lard, tallow and others, hence providing quite different fatty acid profiles). Therefore, an analysis of feeding trials with animals on high fat diets has to take into account not only the energy density and the fat content but also the role of the fatty acids provided on the development of obesity.

The fat content of the diet has been shown to be a major determinant of body weight in mice fed ad libitum (West et al., 1995). In this study, the authors fed two strains of mice, AKR/J and SWR/J, with increasing levels of fat (15, 30 and 45% kcal) and observed that dietary fat content was strongly associated with body weight gain and a very marked increase in the weight of adipose tissue depots. However, these effects did not become obvious in the SWR/J mice, addressing the importance of genetic predisposition on the development of obesity. Boozer et al. fed rats increasing amounts of dietary fat (12, 24, 36 and 48% energy) in quantities matched energetically (Boozer et al., 1995). They did not observe a significant increase in total body weight (although the diet by time interaction was significantly different) but, the absolute weights of the white adipose tissue correlated with the amount of dietary fat. The authors concluded that dietary fat promoted adiposity, independently of the energy intake. Pair-feeding studies are the gold-standard to determine the relative contributions of hyperphagia versus metabolic effects of dietary fat in inducing obesity. Although some studies reported that animals fed an isocaloric high fat diet had greater body weight gain than animals fed a control or low fat diet (Wade, 1982; Oscai et al., 1987), other data led to the conclusion that there was no difference (Woods et al., 2003).
Diets high in fat not only differ with respect to total fat content but also in their fat sources and thereby their fatty acid profiles. For example, beef tallow, butter fat or pork lard are rich in SFAs, coconut oil is rich in medium-chain SFAs, olive oil is rich in MUFAs, corn oil is rich in omega-6 PUFAs and fish oil is rich in omega-3 PUFAs. Therefore, it is difficult to determine the effects of fat quality (SFA, MUFA, PUFA) on the development of obesity, as the fat sources used always consist of a mixture of different fatty acids. Moussavi et al. reviewed the possible association between types of fatty acids in diets and weight change (Moussavi et al., 2008). In animal studies, diets rich in SFA (beef tallow and lard) seem to initiate a greater weight gain, as reported for mice (Buebner et al., 2006) and for rats (Mercer and Trayhum, 1987; Takeuchi et al., 1995). Only a few epidemiological studies have been carried out in humans and the results are still contradictory with regard to the quality of the dietary fatty acid patterns provided in the diet and the effects on obesity development (Moussavi et al., 2008).

In the early days of rodent diet-induced obesity research, some scientists used what is known as the cafeteria diet. In this model, the animal self-selects from highly palatable, readily available foods including cookies, candy, cheese, and processed meats. These foods contain a substantial amount of salt, sugar, and fat and are meant to simulate the human Western diet. However, the nutritive and non-nutritive components of these foods are not well defined. In addition, the animal may choose a different selection of foods each day. Therefore, these diets cannot be accurately replicated for future a study, which makes this type of diet a poor choice for scientific research (Moore, 1987).

It appears more sensible to induce obesity not only by increasing the amount of dietary fat but also by inducing hyperphagia. Cafeteria diets have been introduced in this respect: animals are offered a choice of several palatable food items of varied composition, appearance and texture in addition to their non-purified diet (Sclafani
These diets have been shown to induce obesity in a very efficient manner, driven by hyperphagia, in rats and mice (Sclafani and Springer, 1976; Rothwell and Stock 1988). For example, Rothwell and Stock reported an 80% increase in energy intake in rats fed a cafeteria diet compared to animals on control diets, although the weight gain was only 27% greater than that of the control animals. (Rothwell and Stock, 1979) This paradox was explained by an increase in DIT in the cafeteria-fed animals, which could thus partly compensate for the excess energy ingested (Rothwell et al., 1985). If rats are given a simple high-sugar or high-fat option to regular chow, they overeat by 15% to 30% compared to rats given only regular chow (Sclafani, 1989), suggesting that elevated sugar and fat content are important components to the hyperphagia induced by a cafeteria diet. The effect of diet management on average energy intake percent of control diet consumed and days to achieve hyperphagia. In addition to fat and sugar content, the degree of hydration also appears important. Hydrated food produces a greater degree of hyperphagia than dry pelleted food (Naim et al., 1985; Sclafani, 1989). Therefore, if the investigator decides to vary the components of the diet presented in this unit, it is important to keep the fat and sugar content increased by 25% to 30%, and to make sure that the foods of choice have at least some liquid content.

Rats fed on variety of foods will eat more than counterparts given only one choice, even if that single choice is very palatable or contains high caloric value. The reason for this variety effect is still not understood. When high-sugar/high-fat pellets are given in a variety of flavors and presented in a choice format, rats eat more than if the pellets are one flavor and presented as a single option to regular chow (Naim et al., 1985). It is commonly observed that if rats are given a choice of foods, they will eat more than if they are given one type of food alone, regardless of the energy value or nutrient composition of the food given alone (Sclafani, 1989). However, if rats are given just one option to chow and it happens to be a "supermarket" item (such as cheese, chocolate, or bread) rats will overeat by as much as 50% to 70% (Sclafani, 1989). Wistars, Long-Evans, Sprague-Dawley and Fischer rats all show hyperphagic responses to cafeteria diet regimens, although outbred strains do show variability in terms of response magnitude (Ramirez, 1991).
In a 1987 article in the Journal of Nutrition, Moore critically assessed the use of cafeteria diets for studies on thermogenesis (Moore, 1987). As cafeteria foods are low in vitamins and minerals and the animals tended not to consume enough of the nutritionally adequate non-purified diet, the animals could face deficiencies. Moreover, the animals usually did not eat the same items and therefore the composition of the diet could greatly differ from one animal to another, which could affect the outcomes of the study since the diet factor was not fully controlled. In a subsequent issue of the Journal of Nutrition, Rothwell and Stock, the most prolific users of the cafeteria diet, convincingly dismissed Moore's criticisms, reporting a 20% energy intake from the non-purified diet and similar coefficients of variation for the different macronutrients in both control and cafeteria fed animals. Nonetheless, they acknowledged that "the major drawbacks of the cafeteria diet are the variations in nutrient composition and the poor control over this factor" (Rothwell and Stock, 1988). Controlling this factor is actually possible, albeit painstaking and tedious (Shafat et al., 2009).

1.9 PHYSIOLOGICAL EFFECTS OF HIGH FAT DIETS

Liver is a major metabolic important organ as a target for ectopic fat accumulation in obesity. Clinically, this accumulation is called nonalcoholic fatty liver disease (NAFLD). In a sense, intensity varies from steatosis through steatohepatitis to fibrosis, and even cirrhosis (Angulo, 2002). Factors that promote fatty liver are FFA flux to the liver, de novo lipogenesis in the liver and dietary factors stimulating lipogenesis (Weiss, 2007). The balance between lipogenesis and lipolysis in the liver is mainly determined by the insulin glucagon ratio. When insulin resistance occurs, FFA flux to the liver is increased, leading to increased hepatic glucose output stimulating further insulin secretion.

Increased insulin secretion further accelerates de novo lipogenesis in the liver, thus creating a vicious cycle. Elevated alanine transaminase (ALT) levels are a marker of fatty liver and are usually associated with insulin resistance, elevated
levels of FFA and hypertriglyceridaemia. A deterioration of glucose and lipid metabolism was already observed in patients with ALT levels in the upper half of normal range (18–35U/l). Also, it was shown that the prevalence of metabolic syndrome was significantly greater in patients with NFD (Burgert et al., 2006).

### Hepatic steatosis

High fat diet-induced obesity in animals is associated with the development of hepatic steatosis (also known as NAFLD, non-alcoholic fatty liver disease), characterized by large vacuoles of triacylglycerides accumulating in hepatocytes (Clarke et al., 1977; Yaqoob et al., 1995). In humans, an increase in intrahepatic triacylglycerides (IHTG) has been associated with hepatic and peripheral insulin resistance (Hwang et al., 2007; Korenblat et al., 2008) and is considered a major determinant of the metabolic syndrome (Marchesini et al., 2003). Recently, Fabbrini et al. demonstrated that IHTG content, but not visceral adipose tissue size, was a marker of obesity related metabolic alterations in humans (Fabbrini et al., 2009). To date, the mechanisms underlying ectopic fat distribution are not known.

### Hepatic insulin resistance

The association of NAFLD and hepatic insulin resistance has been shown in diet induced obese animals. Using the hyperinsulinemic-euglycemic clamp technique, it was demonstrated that the insulin-stimulated suppression of hepatic glucose production was drastically impaired in rats fed a high fat diet (Storlien et al., 1986; Anai et al., 1999; Li et al., 2006). The mechanisms for insulin resistance in the liver upon high fat feeding seem to be different from those encountered in the muscle and adipose tissue since neither the insulin receptor substrate 1 and 2 (IRS-1 and -2) protein levels, nor their phosphorylation status, are altered. However, phosphoinositide-3-kinase activity, acting downstream of IRS-1 and -2 to translate insulin receptor activation into metabolic responses, is increased (Anai et al., 1999).

### Hepatic triglyceride content

As shown by Lavau et al. (1979) in adipocytes, glucose incorporation into fatty acids was also decreased in the liver of rats given a high fat diet when compared to rats given a control diet. This difference was even more marked when
the incorporation was stimulated with insulin, suggesting a generalized decreased capacity for de novo hepatic lipogenesis (Storlien et al., 1986). Clarke et al. showed that this reduction of de novo hepatic lipogenesis was more pronounced in rats receiving a PUFA-rich rather than a SFA-rich diet (Clarke et al., 1977).

19.5 High-fat oxidative stress

High fat diet leads to an increase in oxidative stress levels (Vijayakumar et al., 2004). High-fat diets have been reported to increase hepatic oxidative stress and decrease antioxidative enzyme activity (Milagro et al., 2006; Du et al., 2010). It is also believed that oxidative stress is induced by reactive oxygen species (ROS) as its primary factor in aerobic organisms. ROS formed during normal metabolic processes can easily initiate the peroxidation of membrane lipids, leading to the accumulation of lipid peroxides (Stocker and Keaney, 2004).

19.6 Hepatic histology

High-fat feeding rats cause remarkable fat accumulation and infiltration of a mixed population of inflammatory cells in the liver, as well as ballooning degeneration of hepatocytes characterized by cell swelling with empty intracellular content, indicating cell necrosis (Wang et al., 2008). Altunkaynak, showed that high-fat diet causes mononuclear cell infiltrations, foci of necrosis, vascular dilatation, an increase in hepatic connective tissue, hepatocellular steatosis and
shrinkage, additional cytoplasmic acidophilia and nuclear density in the hepatocytes were determined. Finally, it was observed that fat-rich diet (30%) had caused a liver damage (Altunkaynak, 2005). Hepatic histological photograph was shown in rats fed a high fat diet distinguishable hepatic cells, central vein, and portal triad and formation of lipid droplets (Du et al., 2010).

1.9. Adipose tissue

Adipose tissue is connective tissue in which energy in the form of fat is stored. Feeding a high fat diet induces a weight gain and most of this excess weight is based on accumulated fat. However, this fat accumulation has a variety of physiological effects, since not only does the adipose tissue expand but this organ also secretes a large number of endocrine and paracrine factors.

1.9. Remodeling of the adipose tissue

High fat feeding elicits an increase in adipocyte size (hypertrophy) and number (hyperplasia) (Faust et al., 1978; Berke and Kaplan, 1983; Corbett et al., 1986). This hyperplasia is not affected by food restriction, contrary to the adipocyte size, which might indicate permanent deleterious effects of high fat diets on body weight (Rolls et al., 1980). The consequences of this remodeling are also linked to the capacity of the adipose tissue for the secretion of adipokines and cytokines (Huber et al., 2006).

1.9.2. Lipoprotein lipase activity

Lipoprotein lipase (LPL) is the enzyme catalyzing the release of free fatty acids and triacylglycerol from circulating triacylglycerides-rich lipoproteins to adipose tissue and muscle. LPL activity has been shown to be enhanced in high fat fed mice in inguinal and mesenteric fat pads but lipase activity did not show any association with insulin levels (Surwit et al., 1995). Rossmeisl et al. observed an increase in LPL activity in the epididymal fat depots of mice fed a high fat diet for 12 weeks. LPL activity showed a 2-fold increase per unit of weight of tissue and a 4-fold increase if the entire depot was considered (Rossmeisl et al., 2005). This increase in lipoprotein lipase activity could promote the storage of excess lipids in adipose tissue.
The main function of adipose tissue has long been thought to be solely its energy storage capacity. However, during the past years, considerable advances have been made in defining its functions as an endocrine organ (Zhang et al., 1994; Kershaw and Flier, 2004). Leptin was the first adipokines discovered (Zhang et al., 1994) and was shown to inhibit food intake and stimulate energy expenditure (Havel 2000). In mice fed a high fat diet, leptin levels were elevated and positively correlated with body weight (Ahren, 1999; Bullen et al., 2007). Adiponectin is the only adipokines currently known to be negatively correlated with body mass and its decrease has been associated with the progression of metabolic syndrome (Hauner, 2005). The effects of high fat diet feeding on adiponectin secretion are still controversial since adiponectin plasma levels have been reported to be either unaffected upon high fat diet feeding or elevated (Barnea et al., 2006; Bullen et al., 2007; Lee et al., 2009). Resistin, at least in rodents, has been shown to counteract insulin activity (Steppan et al., 2001) and its secretion has been shown to be increased in mice fed a high fat diet (Steppan et al., 2001; Rajala et al., 2004).

Dietary fat has long been implicated as a driver of insulin resistance. A decreased glucose uptake in high fat fed rats, but far less marked and only restricted to the epididymal fat pad when stimulated by insulin, has been reported by Storlien et al. (Storlien et al., 1986). Maegawa et al. also presented data on a decreased glucose uptake but only upon insulin stimulation in high fat fed rats (Maegawa et al., 1986). Wilkes et al. did not observe any effect of a high fat diet with a balanced fatty acid profile but a decrease of the insulin-stimulated glucose uptake at high insulin concentrations was seen with a high fat diet rich in PUFA (Wilkes et al., 1998). The adipose tissue is generally considered to develop a mild insulin resistance upon high fat feeding but very little is actually known on the impairments in the underlying insulin signaling mechanism in the adipocyte (Park et al., 2005).
Analysis of gene expression levels using microarray in adipose tissue of mice fed a high fat diet identified numerous genes significantly up-regulated that belong to inflammatory pathways (Moraes et al., 2003). Indeed, it was shown with immune histochemical methods that mice fed a high fat diet showed an increased infiltration of macrophages into their adipose tissues, forming aggregates named Crown-like structures (CLS), and their number was significantly correlated to the adipocyte size (Weisberg et al., 2003). This infiltration has been associated with increased levels of secretion of the monocyte chemotactic protein-1 (MCP-1), a chemo attractant specific for monocytes and macrophages (Takahashi et al., 2003; Chen et al., 2005). Interestingly, this macrophage infiltration seems to be prevented by a diet containing fish oil, rich in omega-3 PUFA (Todoric et al., 2006).

Modern medicine offers the following methods of treatment of obesity: non-pharmacological (diet therapy, increasing physical activity, behavioral therapy), medication and surgery. The most optimal is a comprehensive approach -- a combination of non-medicinal methods of weight loss and pharmacotherapy.

According to the U.S. Preventative Services Task Force, counseling is more effective in helping people lose weight if combined with behavioral interventions that assist them in developing skills, motivation, and support systems. Primary care clinicians have an important role in diagnosing and in either providing intensive counseling and behavioral interventions or referring patients to receive these services. "Physician counseling is effective in changing certain health risk behaviors, and there is evidence that patients are more likely to lose weight when counseled by a physician" (Nawaz et al., 1999).

The health benefits of modest weight loss include: decreased blood glucose and insulin levels; decreased blood pressure; decreased LDL and triglyceride levels; increased HDL levels; decreased severity of sleep apnea; reduction in symptoms associated with degenerative joint disease; and improvement in gynecologic
conditions (Klauer and Aronne, 2002). Intentional weight loss of 0.5-9.0 kg in overweight women with disorders related to obesity was associated with a 20% reduction in all-cause mortality (Mulrow, 1998).

Basic treatment of overweight and obese patients requires a comprehensive approach involving diet and nutrition, regular physical activity and behavioral change, with an emphasis on long-term weight management rather than a short-term extreme weight reduction. The clinician should obtain a history, perform a physical examination, and conduct a laboratory work-up with attention to the complications of obesity.

Medications should be reviewed and consideration given to changing those that cause weight gain. These include antidepressants, antiepileptics, antipsychotics, lithium, glucocorticoids, progesterational hormones, antihistamines, sulfonylureas, insulin, thiazo-lidinediones and β-blockers, among others (Klauer and Aronne, 2002). The patient should be thoroughly examined for evidence of an endocrine disorder that may be the cause for obesity.

Endocrine problems that are associated with the development of overweight and obesity include hypothyroidism, Cushing’s disease, and primary hyperinsulinemia (Shepard, 2004). Eating disorders, particularly bulimia and binge-eating disorder should be considered. Other differential diagnoses must include: hyperinsulinemia, polycystic ovarian syndrome, hypothalamic state, and growth hormone deficiency.

Women who should not be treated for overweight or obesity include women who are pregnant or nursing or plan to become pregnant, women who have a history of anorexia nervosa, and women with terminal or unstable medical or psychiatric illnesses. Women who have osteoporosis or cholelithiasis must be warned that these conditions may be aggravated by weight loss.

Advising a patient on weight reduction involves balancing and weighing the risks of obesity against the risks and benefits of weight loss, and setting that in context of treatment possibilities with those risks and benefits (Mulrow, 1998).
The use of self-recorded food diary allows a qualitative assessment of the diet. In addition, it can be used to help the patient identify perceptions and beliefs about emotional eating behavior (cognition) and eating habits (behavior). Dietary advice should encourage healthy eating and emphasize the need to increase consumption of grain, cereals, and fiber as well as vegetables and fruits, and to substitute low-fat dairy products and meats for high-fat alternatives (Dansinger et al., 2007; Pirozzo et al., 2002).

The energy content of low-calorie diets (LCD) presented as a total diet composed of meal replacements is specified as between 800 and 1,200 kcal/day (Greenwald, 2006). Diets providing 1,200 kcal/day or more are classified as hypocaloric balanced diets (HBD) or balanced deficit diets (WHO, 1998). Diets providing less than 1,200 kcal/day (5,000 kJ/day) might yield micronutrient deficiencies, which could exert untoward effects not only on nutritional status but also on the weight management outcome. Meal replacement diets (substitution of one or two daily meal portions by VLCD) may contribute to nutritionally well-balanced diet and weight loss maintenance (Greenwald, 2006).

Calculating daily caloric requirements can assist the health care provider in counseling patients about caloric needs to maintain weight. One way to determine how many calories a woman should consume each day is calculating the patient's basal metabolic rate (BMR), or the energy required for involuntary physiologic functions to maintain life, including respiration, circulation, and maintenance of muscle tone and body temperature. The BMR accounts for 65-70% of the body's energy requirement. It is calculated by 10 x ideal weight (lbs) = kcal needed for BMR daily.

A more efficient way to calculate caloric needs is by calculating the resting energy expenditure. Resting energy expenditure is the estimated kilocalorie requirements for the basal metabolic rate plus additional kilocalories needed for thermogenesis, voluntary activities, and any increased need from catabolic or anabolic processes. The first step is to estimate the recommended individual caloric requirement (kcal per day) by calculating the resting energy expenditure (REE). For
adult women the formula for calculating REE is: $\text{REE} = 10 \times \text{weight (kg)} + 6.25 \times \text{height (cm)} - 5 \times \text{age (years)} - 161$. Then, multiply the REE by an activity factor (AF) of 1.5 for women who engage in light activity or 1.6 for women who engage in higher activity to estimate caloric need.

A useful application of this formula is $\text{REE} \times \text{AF} = \text{estimated caloric need (kcal)}$ to maintain current weight (Lyznicki et al., 2001). It can be inferred then, that by either increasing the energy expenditure, decreasing the caloric need values, or both, weight loss should occur.

Daily physical exercise is basic to health. The benefits of regular exercise are well-documented and include positive effects on mind, bone, lipid profile, endothelial function, risk for cancer, glucose tolerance and insulin sensitivity, and quality of life. The Nurse’s Health Study documented a lower incidence of cardiovascular disease, including both coronary heart disease and stroke (Klauer and Aronne, 2002). Even a moderate-intensity exercise such as walking is associated with a lower risk of disease. The recommendation for aerobic activity is thirty minutes on most, if not all, days of the week. This is the minimum recommendation; those wishing to lose weight should aim to exceed this (Klauer and Aronne, 2002).

The patient should be advised to gradually increase her energy expenditure through changes to her daily routine (e.g., climbing stairs rather than riding the elevator, parking farther from a destination if safe) and the incorporation of regular exercise likely to be continued over the long-term.

Behavior therapy is a useful adjunct to diet and physical activity. The clinician should assess patient motivation and readiness to implement the weight management plan and take steps to motivate the patient for treatment. Behavior strategies to promote diet and exercise should be used routinely, as they are helpful in achieving weight loss and maintenance.
All weight reduction programs should incorporate some form of behavioral modification. The best programs aim to help the patient identify the cause of the weight gain and thereby gain better control over situations that cause overeating. Goals for treatment include identification of situations that trigger eating, improving exercise habits, food shopping with awareness, and recognition of hunger versus craving. Behavior modification alone provides weight losses of ten percent (Klauer and Aronne, 2002). Key techniques include self-monitoring (such as keeping a food diary), stimulus control (mindful eating), reinforcement, and relapse prevention (social support).

Weight loss and maintenance therapy should involve a combination of low-calorie diets, increased physical activity and behavior therapy. The combination of a reduced caloric diet and increased physical activity has been shown to produce weight loss, decrease abdominal fat and increase cardio respiratory fitness (Lynicki et al., 2001).

Surgical interventions can be considered for patients with a BMI greater than 40 who fail other methods of treatment, particularly if serious obesity-related complications are present. Surgery is the most effective treatment for morbid obesity in terms of long-term weight loss (Ridley, 2005; Levy et al., 2007), improves co-morbidities and quality of life (Sjostrom et al., 2007), and in the long term decreases overall mortality (Adams et al., 2007). Surgery should be considered for patients in age groups from 18-60 years with a BMI ≥ 40.0 or with BMI between 35.0 and 39.9 kg/m2 and co-morbidities in whom surgically induced weight loss is expected to improve the disorder such as type 2 diabetes and other metabolic disorders, cardio respiratory disease, severe joint disease and obesity-related severe psychological problems (Fried et al., 2008).

A laparoscopic technique should be considered as the first treatment choice in bariatric surgery (van Dielen et al., 2005). In all situations the bariatric surgeon’s experience is a key issue for a successful outcome.
Today, the most common surgical techniques are:

- Food limitation operations (restrictive procedures) such as adjustable gastric banding (AGB), proximal gastric bypass (GBP) and sleeve gastrectomy (SG),
- Operations limiting absorption of macronutrients (limiting energy absorption) such as biliopancreatic diversion (BPD),
- Combined operations such as biliopancreatic diversion with duodenal switch (BPD-DS) or distal gastric bypass.

The expected average weight loss and long-term weight maintenance is increasing with the following procedures: AGB, SG, GBP, BPD-DS, BPD (Levy et al., 2007). However, the surgical complexity and potential surgical and long-term nutritional risks of the procedures increase in the same order (Ridley, 2005).

Current and putative antiobesity drugs share the same fundamental principles as treatment in adults, that is, to decrease caloric intake and increase energy expenditure, miming the effects of some anorectic neuropeptides or contrasting the orectic ones in order to regulate energy balance. However, the primary goal of overweight/obesity treatment (i.e., weight reduction or deceleration of weight gain) and the recommended way of intervention are variable and dependent on the child's age and level of overweight, among other considerations (Lorenao et al., 2011).

A recent guideline suggests considering pharmacotherapy in (1) obese children only after failure of a formal program of intensive lifestyle modification; (2) overweight children only if severe co-morbidities persist despite intensive lifestyle modification, particularly in children with a strong family history for type II diabetes or premature cardiovascular disease. Pharmacotherapy should be provided only by clinicians who are experienced in the use of anti-obesity agents and aware of the potential for adverse reactions.

Up to now, only two drugs have been reported to reduce weight and/or body mass index (BMI) in adolescents: (1) Sibutramine, a neurotransmitter reuptake
inhibitor which enhances satiety by inhibiting the reuptake of serotonin, norepinephrine, and dopamine, (2) Orlistat, a pancreatic lipase inhibitor which reduces fat absorption. At present, there are only few drugs approved by the Food and Drug Administration (FDA) for the treatment of adult obesity. The most important ones are sibutramine and orlistat. The FDA in the US approved the latter drug in 2003, and it has recently been approved by the European Union for the treatment of adolescents (Lorenzo et al., 2011).

Orlistat, approved since 1998, is an inhibitor of pancreatic lipase reducing dietary fat absorption. The compound is a partially hydrated derivative of an endogenous lipstatin produced by Streptomyces toyotamicus (Ballinger and Peikin, 2002). Orlistat binds irreversibly to the active sites of lipase through covalent binding. Approximately one-third of triglyceride intakes does not undergo digestion and is not absorbed by small intestine, crossing the GI tract and being eliminated. Because of low systemic absorption and first-pass metabolism, the bioavailability of orlistat is <1%; most of the drug being excreted remains unchanged with stools (Fried et al., 2008).

In adults, orlistat has a good safety profile, is generally well tolerated, has minimal systemic absorption, and determines clinically meaningful and sustained decreases in weight and BMI when combined with a mildly hypocaloric diet and exercise. It is approved for weight management in overweight and obese adults in more than 120 countries, and to date more than 22 million patients have received this drug.

Orlistat should be avoided in patients with chronic diarrhea (Branca, 2007). Moreover, it can reduce the absorption of amiodarone (NIH, 2000), and ciclosporin (Lau et al., 2007) and can increase warfarin’s action (Fried et al., 2008). Systemic adverse effects are minimal because of the lack of systemic absorption.

Sibutramine was originally developed as an antidepressant, and it is a centrally acting monoamine reuptake inhibitor that mainly acts to increase satiety (Kyrou et al., 2006). Its most important mechanism of action is to block norepinephrine and 5-HT reuptake, but it also stimulates thermogenesis that plays a minor role in weight reduction (Ailhaud, 2006). Sibutramine undergoes extensive
first pass metabolism, mainly by hepatic cytochrome P450 3A4 enzymes, to activate primary and secondary amine metabolites that are more potent than the parent compound. The drug and its active metabolites are mainly excreted through the kidney (Fried et al., 2008).

The most common adverse effects found in adolescents taking sibutramine was tachycardia, even if generally it was not a reason to withdraw from treatment. Other common side effects include insomnia, elevation of blood pressure, headache, dizziness, dry mouth and constipation. Long-term data on the effect of sibutramine on major obesity related morbidity are lacking. However, the ongoing Sibutramine Cardiovascular Out-comes trial (SCOUT) is evaluating the efficacy of sibutramine in reducing myocardial infarction, stroke, and cardiovascular mortality in 9000 obese and overweight patients (Adams et al., 2006).

Medicinal plants are one of the most important sources of drugs and their medicinal use has a long history. Literature reviews indicate that therapeutic use of plants goes back to 4000–5000 B.C. (Prakash and Gupta, 2005). Plants also play a principal role in the introduction of new therapeutic agents (Kumar et al., 2008).

Herbs are staging a comeback and herbal ‘renaissance’ is happening all over the globe. The herbal products today symbolise safety in contrast to the synthetics that are regarded as unsafe to human and environment. Although herbs had been priced for their medicinal and aromatic qualities for centuries, the synthetic products of the modern age surpassed their importance, for a while. However, the blind dependence on synthetics is over and people are returning to the naturals with hope of safety and security. More than three quarters of the world population relies mainly on plant extracts and plant metabolites for health care.

It has been estimated that in developed countries such as United States, plant drugs constitute as much as 25% of the total drugs, while in fast developing countries such as China and India, the contribution is as much as 80%. Thus, the economic importance of medicinal plants is much more to countries such as India than to rest of the world. These countries provide two third of the plants used in ...
modern system of medicine and the health care system of rural population depend on indigenous systems of medicine.

Plants, especially used in Ayurveda can provide biologically active molecules and lead structures for the development of modified derivatives with enhanced activity and/or reduced toxicity. The small fraction of flowering plants that have so far been investigated have yielded about 120 therapeutic agents of known structure from about 90 species of plants. Some of the useful plant drugs include vinblastine, vincristine, taxol, podophyllotoxin camptothecin, digitoxigenin, gitoxigenin, digoxigenin, tubocurarine, morphine, codeine aspirin, atropine, pilocarpine, capsicicine, allicin, curcumin, digitoxigenin, digoxigenin, tubocurarine, curcumin, artenicinin and ephedrine among others. In some cases, the crude extract of medicinal plants may be used as medicaments. On the other hand, the isolation and identification of the active principles and elucidation of the mechanism of action of a drug is of paramount importance.

Herbal remedies have been used for medical treatment since the dawn of civilization. In recent years, “Non-traditional” or “alternative” treatments using plant extracts and herbal supplements have become extremely popular worldwide fueled by a relentless effort to improve the wellbeing and combat chronic conditions resistant to conventional pharmacologic treatments such as obesity and diabetes mellitus (Wheatley, 2004).

At present, because of dissatisfaction with high costs and potentially hazardous side effects, the potential of natural products for treating obesity is under exploration, and this may be an excellent alternative strategy for developing future effective, safe anti-obesity drugs (Mayer et al., 2009; Nakayama et al., 2007). A variety of natural products, including crude extracts and isolated compounds from plants, can induce body weight reduction and prevent diet-induced obesity. Therefore, they have been widely used in treating obesity (Han et al., 2005a; Rayalam et al., 2008).

A wealth of information indicates numerous bioactive components from nature are potentially useful in obesity treatments. A good example of such is the
polyphenols, flavonoids and saponins. These show strong anti-obesity activity and include apigenin, genistein and catechins (Rayalam et al., 2008; Thielecke and Boschmann, 2009). Seven years later, Han et al. 2005a reviewed the anti-obesity effects of natural products from more diverse sources. More recently, anti-obesity phytochemicals by Rayalam et al. (2008) focused on adipocyte life cycle regulation. A growing body of evidence indicates that natural products having anti-obesity effects can be arranged into five categories based on their distinct mechanisms; they produce (1) decreased lipid absorption, (2) decreased energy intake, (3) increased energy expenditure, (4) decreased pre-adipocyte differentiation and proliferation, or (5) decreased lipogenesis and increased lipolysis. Therefore, we addressed naturally occurring compounds possessing antiobesity activity addressed by categorizing them per these mechanisms.

Among treatments for obesity, one of the most promising strategies in the effort to reduce energy intake through gastrointestinal mechanisms, without altering the central mechanisms, is the development of nutrient digestion and absorption inhibitors (Birari and Bhutani, 2007). Dietary fat is not directly absorbed by the intestine unless the fat has been subjected to the action of pancreatic lipase. Therefore, pancreatic lipase is one of the most widely studied mechanisms for determining natural products’ potential efficacy as anti-obesity agents (Birari and Bhutani, 2007).

Pancreatic lipase is a key enzyme in dietary triacylglycerol absorption, hydro-lyzing triacylglycerols to monoacylglycerols and fatty acids. Only a few substances interact directly with the lipases themselves. One example is tetrahydrolipstatin (orlistat), a derivative of the naturally-occurring lipase inhibitor produced from lipase inhibition mechanism acts through a covalent bond to the lipase’s active site serine (Hadvary et al., 1991; Tsujita et al., 2006). Although this pancreatic lipase inhibitor is clinically approved for obesity treatment, orlistat has certain unpleasant gastrointestinal side effects (Karamadoukis et al., 2009; Thurairajah et al., 2005). These side effects result from orlistat mode of action and
include oily spotting, liquid stools, fecal urgency or incontinence, flatulence and abdominal cramping (Chaput et al., 2007). Therefore, researchers are screening novel inhibitors, derived from plants sources that lack some of these unpleasant side effects (Birari and Bhutani, 2007).

Natural products provide a vast pool of pancreatic lipase inhibitors with potential for being developed into clinical products. Birari and Bhutani, 2007 reviewed various extracts and secondary metabolites, derived from plants, that have pancreatic lipase inhibitory activity. Drug development programs should focus on these extracts and metabolites.

A wide variety of plants possess pancreatic lipase inhibitory effects, including *Panax japonicus* (Han et al., 2005b), *Platycodi radix* (Han et al., 2000), *Salacia reticulata* (Kishino et al., 2006), *Nelumbo nucifera* (Ono et al., 2006), *Argyreia speciosa* (Kumar et al., 2011) and *Gymnema sylvestre* (Reddy et al., 2012). These pancreatic lipase inhibitory phytochemicals include mainly saponins, polyphenols, flavonoids, and caffeine (Kim and Kang, 2005; Han et al., 2006).

Body weight regulation through appetite control is a multifactorial event resulting from neurological and hormonal interrelationships. A line of evidence indicates that serotonin, histamine, dopamine, and their associated receptor activities are closely associated with satiety regulation. These receptors may enable researchers to better target their searches for drugs that treat obesity through energy intake reduction (Chantre and Lairon, 2002).

Any changes a potential appetite suppressant induces should be considered in terms of: (1) the psychological experience and behavioral expression of appetite, (2) metabolism and peripheral physiology, and (3) the CNS neural pathways' functioning (Halford and Blundell, 2000). In general, natural appetite suppressants are dietary supplements that aid in appetite control. Appetite suppressant mechanisms of action typically affect hunger control centers in the brain, resulting in a sense of fullness. However, in animals and humans, ghrelin secretion in the
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stomach may increase with decreased food intake, stimulating increased intake. Therefore, ghrelin antagonism may decrease or blunt the increased appetite that potentially occurs with decreased feeding, and, thus, may be a potential adjunctive treatment for obesity (Bays, 2004). MCH receptor antagonism may also prove an important target for obesity treatment through appetite regulation.

One clear example of a natural appetite suppressant is Hoodia gordonii, a leafless, spiny, succulent plant growing in some South African countries (van Heerden, 2008). Despite its popularity there is insufficient clinical information on H. gordonii to provide efficacy. However, the consensus now is that H. gordonii regulates appetite and can significantly reduce calorie intake and boost weight loss (Lee and Balick, 2007; van Heerden, 2008). There are currently more than 20 international patents on compounds originating in H. gordonii, and many Hoodia containing commercial preparations are available on the market (van Heerden, 2008). However, there has been no confirmation that these preparations actually contain hoodia. A common and noteworthy problem with the commercialization of botanicals is that commercially-available products often lack botanical or active ingredients.

Reportedly, other plant extracts and herbal supplements, including Korean red ginseng (Kim et al., 2005), Garcina cambogia (Saito et al., 2005), Camellia sinensis (Moon et al., 2007), Caralluma fimbriata (Kuriyan et al., 2007), ephedra (Fleming, 2007), Citrus aurantium (Klontz et al., 2006), Phaseolus vulgaris (Celleno et al., 2007), Robinia pseudoacacia (Baintner et al., 2003), Cissus quadrangularis (Oben et al., 2007), Argyreia speciosa (Kumar et al., 2011) possess appetite-suppressive properties. Although research has identified several active constituents in these substances possessing appetite suppressive capabilities (e.g. glycosides, saponin and flavonoids), the ways in which they work to suppress appetite are unclear; they are thought to amplify signaling in the basal hypothalamus’s energy-sensing function. Many other natural appetite suppressants mediate the reduced expression of hypothalamic neuropeptide Y (NPY) or serum leptin levels (Kim et al., 2005). For instance, Kim et al. (2005) proved that, in HFD-induced obesity in rats, a crude saponin of Korean ginseng effectively regulated serum leptin and NPY expression in the rat hypothalamus.
The simplest scheme divides energy expenditure into three categories: (1) physical activity, (2) obligatory energy expenditure and (3) adaptive thermogenesis. To regulate body weight and energy expenditure, mammalian Brown adipose tissue (BAT) establishes non-shivering thermogenesis through dissipation of excess energy as heat (Cannon and Nedergaard, 2004). BAT plays an important role in obesity control by controlling energy balance. The key player in this process is UCP1, which discharges the proton gradient generated in oxidative phosphorylation, thereby dissipating energy as heat. Thus, searching for substances that upregulate UCP1 gene expression may be a worthy strategy for achieving obesity control through increased energy expenditure (Kumar et al., 1999). An example is the ethanolic extract of Solanum tuberosum, which activated the expression of UCP3 in BAT and the liver and significantly reduced fat weight in HFD-fed rats (Yoon et al., 2008). Extracts of Pinellia ternate (Kim et al., 2006d) and Panax ginseng (berry) (Attele et al., 2002) also show activity for increasing energy expenditure. The ethanolic extract of Ilex paraguariensis ameliorated HFD-induced obesity through enhanced β-oxidation of fatty acids, increasing AMPK activation in visceral adipose tissue and subsequently reducing ACC activity (Pang et al., 2008). Activated AMPK phosphorylates (inactivates) ACC and lowers levels of intracellular malonyl-CoA, which is the fatty acid synthesis substrate. At the same time, malonyl-CoA inhibits CPT-1, the rate-limiting enzyme in mitochondrial fatty acid oxidation. Accordingly, these processes lead to the promotion of fatty acid oxidation (Pang et al., 2008).

Adipocytes play a central role in the maintenance of lipid homeostasis and energy balance, by storing triglycerides and releasing free fatty acids in response to changing energy demands. Because adipocyte tissue growth can be due to both hyperplasia and hypertrophy of adipocytes, several studies screening for antiobesity materials have focused on the processes of adipocyte proliferation and differentiation (Kim et al., 2006a). In this search, 3T3-L1 pre-adipocytes cells are currently used as an in vitro model for the study of obesity, because such cells
accumulate triglycerides upon differentiating in culture (Cowherd et al., 1999). This is due to the expression of adipocyte specific genes, such as PPAR-γ and C/EBP-α (Lefterova and Lazar, 2009). For this reason, natural products that specifically target adipogenesis inhibition had been considered promising with regard to their potential in treatment of obesity. However, current research suggests that inhibiting adipogenesis or adipose tissue expansion is unhealthy, leading to type II diabetes and other metabolic diseases, such as atherosclerosis (Lefterova and Lazar, 2009).

The pharmacological targeting of lipolysis can be envisaged in two different ways. The first strategy entails stimulating triglyceride hydrolysis in order to diminish fat stores, thereby combating obesity. This option requires the associated oxidation of the newly released fatty acids and led to the development of the β3-adrenergic agonists (Langin, 2006). However, considering that excessive lipolysis contributes to high circulating fatty acid levels and development of dyslipidemia (as seen in metabolic syndrome), a blockade of such a fatty acid release may be of therapeutic interest (Langin, 2006). Some examples of the natural compounds involved in β-adrenergic receptor activation are the various flavonoids in the leaves of Nelumbo nucifera. Through this pathway, NN extract dietary supplementation resulted in significant suppression of body weight gain in A/J mice fed a HFD (Ohkoshi et al., 2007).

Aqueous extract of Salacia oblonga root (active main component, magniferin) has demonstrated PPAR-α activator properties, which then improved postprandial hyper-lipidemic and hepatic steatosis in a genetic-obesity animal model (Huang et al., 2006b). Additionally, a mixture of three herbal extracts improved lipid metabolism by increasing hepatic mRNA levels of PPAR-α, the target enzyme responsible for fatty acid β-oxidation (Lee et al., 2008a).

As mentioned above, many extracts and secondary metabolites show anti-obesity activities of varying mechanisms. Perhaps the recommended approach to researching more efficient obesity treatments and achieving the synergistic effects of extracts and secondary should be to seek treatments using multiple products or
products having multiple activities (Rayalam et al., 2008). Some natural biomaterials possessing multi-functional antiobesity activities have been discovered. Green tea and *Garcina cambogia* are good examples. *G. cambogia* is widely known for its anti-obesity activity (Kim et al., 2004a). Its commercially available extract is derived from the dried fruit of the *G. cambogia* tree, which grows in the forests of South India and Southeast Asia. Its main active ingredient is (-) hydroxycitric acid (Kim et al., 2004a). *G. cambogia* prevents the metabolism of carbohydrates into fats by inhibiting lipogenesis, burning excess fats, and suppressing appetite (Kim et al., 2004a).

The aqueous extract of *Hibiscus sabdariffa* (containing mainly anthocyanins) has exhibited many potential antiobesity mechanisms, including anti-hyperglycemic effects, plasma cholesterol level reduction, gastric and pancreatic lipase inhibition, thermogenesis stimulation, inhibition of lipid droplet accumulation in fat cells (without affecting adipose conversion), and fatty acid synthase inhibition (Alarcon-Aguilar et al., 2007). *G. cambogia* extract (active component, hydroxycitric acid) has also displayed multi-functional antiobesity effects. Research has shown that it inhibits adipocyte differentiation, reduces fatty acid synthesis, lipogenesis and epididymal fat accumulation through reducing ATP-citrate lyase activity, and suppresses appetite (Kim et al., 2004a; Saito et al., 2005). It has been on the market over 10 years with no adverse side effects (Ohia et al., 2002; Saito et al., 2005).

Pomegranates extract (active components, ellagic acid and tannic acid) also has dual anti-obesity effects, in that it inhibits pancreatic lipase activity and suppresses energy intake. Its effect on energy intake was similar to sibutramine, but with a different mechanism (Lei et al., 2007). In obese rats, supplementation with aqueous extract of *Pinellia ternate* induced increased thermogenesis in BAT (i.e., increased UCPI expression) and fatty acid oxidation (activated PPARα) in WAT (Kim et al., 2006d). Green tea extracts also exert anti-obesity activities in two ways: lipase inhibition and thermogenesis stimulation (Chandre and Lairon, 2002).

Peanut (*Arachis hypogaea*) shell extract contribute to inhibiting fat absorption in the digestive tract, activating lipid metabolism in the liver, and reducing adipocyte lipolysis (Moreno et al., 2006). The *Nelumbo nucifera* leaf
possesses multiple anti-obesity activities, including inhibition of lipid and carbohydrate absorption and acceleration of lipid metabolism and energy expenditure (Ono et al., 2006). One study found an Indian herb; Salacia met multiple obesity reduction targets by both modulating PPARα-mediated lipogenic gene transcription and angiotension II type 1 receptor signaling and also inhibiting α-glucosidase and pancreatic lipase (Li et al., 2008b).

Saponins are a major family of secondary metabolites that occur in a wide range of plants species (Sparg et al., 2004). These compounds have been isolated from different parts of the plants, including the roots, rhizomes, stems, bark, leaves, seeds and fruits. Occasionally, the whole plant has been used (Vincen et al., 2007). These types of plant secondary metabolites are found to inhibit PI. and, thus, may represent potential effective treatments for obesity and related disorders (Slane et al., 2009). One example is different saponins isolated from tea (Han et al., 2001) or ginseng (Karu et al., 2007). Plants rich in saponins include.

Ginseng is one of the most popular medicinal herbs and is commonly consumed as powder, a beverage or a food supplement. Roots of Panax ginseng contain high levels of ginsenosides, which are steroidal saponins that show beneficial effects on lipid metabolism. Saponins from ginseng roots suppress the expected increase in body weight and plasma triacylglycerols in mice following a high-fat diet, which was probably mediated by inhibiting pancreatic lipase (Karu et al., 2007).

The rhizomes of Panax japonicus (Japanese ginseng) are used in folk medicine for the treatment of arteriosclerosis, hyperlipidemia, hypertension and diabetes mellitus. Chikusetsusaponins prevent the increase in body weight and parametrial adipose tissue weight induced by a high-fat diet and inhibited the elevation of postprandial plasma triacylglycerols due to their inhibitory action of PI. on dietary fat (Han et al., 2005).
Platycodi radix, widely used in traditional Oriental medicines as a remedy for respiratory disorders, is rich in saponins, which are responsible for a diversity of effects including antiinflammation, antiallergy, antitumor, and immunostimulation (Zhao et al., 2005). Given its inhibitory action on P1, (Xu et al., 2005), with platycodin D as the most efficient compound (Zhao et al., 2004) it ameliorated high fat-induced obesity in mice (Han et al., 2002) and rats (Zhao et al., 2005). SK1 is an edible saponins-rich compound from Platycodi radix that is able to reduce body weight and fat accumulation by increasing fecal lipid outputs in high-fat fed mice (Kim et al., 2009).

At least three kinds of tea (oolong, green and black) have been used as healthy drinks. Teasaponins suppress the increases in body and parametrial adipose tissue weights and adipocyte diameters induced by a high-fat diet in mice by inhibiting P1, and also reduce the elevation in plasma triacylglycerol levels after oral administration of a lipid emulsion (Han et al., 2001). Thus, the crude saponin fraction from the flower buds of Chinese tea plant exhibits accelerating effects on gastrointestinal transit in mice and inhibitory effects against porcine P1, and the floraltheasaponins (A-C) showed inhibitory effects on serum triglyceride elevation (Yoshikawa et al., 2005).

The Japanese horse chestnut (Aesculus turbinata) is a medicinal plant widely used in East Asia. The saponin mixture extracted from the seeds is called escins and has a strong inhibitory activity on P1 (Kimura et al., 2006). In mice fed a high-fat diet, total escins suppressed the increase in body weight, adiposity and liver fat, and increased triglyceride level in the feces, whereas it decreased plasma triglycerides after the oral administration of a lipid emulsion (Kimura et al., 2008).
1.12.6 Gymnema sylvestre R.Br

*Gymnema sylvestre* R. Br., belonging to the Aselepiadaceae family, is a native plant in the southwest of India, Australia and tropical Africa. From ancient times, *G. sylvestre* has been used in Indian traditional medicine, and is considered to be antiviral, diuretic, antiallergic, hepatoprotective, hypoglycemic, hypolipidemic and to be effective in improving urination, digestion, and obesity (Anonymous, 2006).

- **Botanical name**: *Gymnema sylvestre* R. Br
- **Kingdom**: Plantae
- **Division**: Magnoliophyta
- **Class**: Magnoliopsida
- **Order**: Gentianales
- **Family**: Aselepiadaceae
- **Genus**: Gymnema
- **Species**: Sylvestre

*G. sylvestre* is a large, more or less pubescent, woody climber. It is occasionally cultivated as medicinal plant. Leaves are opposite, usually elliptic or ovate (1.25-2.0 inch, 0.5-1.25 inch). Flowers are small, yellow, in umbellate cymes. follicles are terete, lanceolate, up to 3 inches in length.
G. sylvestre leaves contain triterpene saponins belonging to oleanane and dammarenene classes. Oleanane saponins are gymnemic acids and gymnemamasaponins, while dammarenene saponins are gymnemasisides. Besides this, other plant constituents are flavones, anthraquinones, hentriacontane, pentatriacontane, α and β-chlorophylls, phytin, resins, quercetin, 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). Gymnemic acids have antidiabetic, antisycteptene and anti-inflammatory activities. The antidiabetic array of molecules has been identified as a group of closely related gymnemic acids after it was successfully isolated and purified from the leaves of G. sylvestre (Liu et al., 1992). Later, the phytoconstituents of G. sylvestre were isolated, and their chemistry and structures were studied and elucidated (Sinsheimer and Subbarao, 1971; Yoshikawa et al., 1989).

The total saponin fraction of the leaves, commonly known as gymnemic acid has an anti-sweetening effect (wein-cai et al., 2000). The triterpenoid saponin contain several acylated (tigloyl, methylbutyroyl etc.) derivatives of decacylgymnemic acid which is 3-O-b-glucuronide of gymnemagenin (3b, 16b, 22a, 23, 28-hexahydroxy-olean-12-ene). The individual gymnemic acids (saponins) include gymnemic acids I-VII, gymnemosides A-F, gymnemosides A-F, gymnemamasaponins etc. (Gurav et al., 2007).
G. sylvestre leaves have been found to cause hypoglycemia in laboratory animals and have found a use in herbal medicine to help treat adult onset diabetes mellitus (NIDDM). When Gymnema leaf extract is administered to a diabetic patient, there is stimulation of the pancreas by virtue of which there is an increase in insulin release (Kanetkar et al., 2004). These compounds have also been found to increase fecal excretion of cholesterol (Persaud et al., 1999), but further studies to prove clinical significance in treating hypercholesterolemia (high serum cholesterol) are required. Other uses for Gymnema leaf extract are its ability to act as a laxative, diuretic, and cough suppressant. These other actions would be considered adverse reactions when Gymnema is used for its glucose lowering effect in diabetes. Gymnema leaf extract, notably the peptide ‘Grumarin’, has been found to interfere with the ability of the taste buds on the tongue to taste sweet and bitter. Gymnemic acid has a similar effect. It is believed that by inhibiting the sweet taste sensation, people taking it will limit their intake of sweet foods and this activity may be partially responsible for its hypoglycemic effect (Nakamura et al., 1999).

Gymnemic acid formulations have also been found useful against obesity, according to recent reports (Yoshikawa et al., 1993). This is attributed to the ability of gymnemic acids to delay the glucose absorption in the blood. The atomic arrangement of gymnemic acid molecules is similar to that of glucose molecules. These molecules fill the receptor locations on the taste buds thereby preventing its activation by sugar molecules present in the food, thereby curbing the sugar craving. Similarly, Gymnemic acid molecules fill the receptor location in the absorptive external layers of the intestine thereby preventing the sugar molecules absorption by the intestine, which results in low blood sugar level (Sahu et al., 1996).

Sugihara et al. (2000) reported that the antihyperglycemic action of a crude saponin fraction and five triterpene glycosides (gymnemic acids I-IV and gymnema-saponin V) derived from the methanol extract of leaves of G. sylvestre in streptozotocin (STZ) induced-diabetic mice. The saponin fraction reduced blood glucose levels 24 hr after the intra peritoneal administration. Gymnemic acid IV, not
the other 4 glycosides reduced the blood glucose levels by 13.5-60.0% 6 h after the administration comparable to the potency of glibenclamide, and did not change the blood glucose levels of normal mice.

There are some possible mechanisms by which the leaves and especially gymnemic acids from G. sylvestre exert its hypoglycemic effects are: a) it increases secretion of insulin, b) it promotes regeneration of islet cells, c) 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 gluconegic enzymes and sorbitol dehydrogenase and d) it causes inhibition of glucose absorption from intestine. The gymnemic acid components are believed to block the absorption of glucose in the small intestine, the exact action being unknown. It could be involve one or more mechanisms (Nakamura et al., 1999).

G. sylvestre R. Br leaf extract was orally administered a dose dependent increase in fecal cholesterol and cholic acid derived bile acid excretion has been demonstrated in rats. Three weeks study showed a decrease in apparent fat digestibility and an increase in excretion of neutral sterols and acidic steroids in rats fed on a normal or high-fat diet. Total serum cholesterol and triglycerides also were decreased significantly Shigematsu et al. (2001). In addition long term administration of Gymnema leaves was administered to rats receiving either a high fat diet or normal fat diet for 10 weeks. The extract suppressed body weight gain and accumulation of liver lipids and plasma triglycerides and total cholesterol levels were decreased significantly Shigematsu et al. (2001). Rachh et al. (2010) reported that hydro alcoholic extract of G. sylvestre R. Br leaves significantly decreased serum total cholesterol, triglycerides, LDL, VLDL and increased the high density lipoproteins in hyperlipidemic rats and were comparable with that of standard atorvastatin.