Obesity has come to be recognized as a critical global health issue. Obesity is a medical disorder in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems (Chiara et al., 2012; Shen et al., 2012; Halford, 2006; WHO, 2000; Haslam & James, 2005). Rates of obesity in North America and in most European countries have more than doubled in the last 20 years and over half the adult populations are now either overweight or obese. Obesity is a risk factor for non-communicable diseases such as non-insulin dependent diabetes (NIDDM), cardiovascular disease (CVD) and various types of cancer. Like obesity, the prevalence of obesity-related diseases such as diabetes also continues to rise. The impact of this obesity-associated morbidity and mortality has already had an enormous impact on global health care and welfare systems and this economic burden is only set to increase (Halford, 2006).

A. DEFINITION OF OBESITY

The word "obesity" (from the Latin obesitas), used today in a purely descriptive way, in its etymology, points to the most common behavioral condition leading to obesity, i.e. overeating. In fact, obesitas is the condition of the obesus (i.e., plump), word that, in turn, is composed of ob (i.e., over) and esus, i.e. the past participle of edere (i.e., to eat).

‘Obesity’, defined as excess adiposity for a given body size, results from an imbalance between energy intake and energy expenditure (Kuczmarski et al., 1997).

The World Health Organization (WHO) defines ‘obesity’ in terms of body mass index (BMI). This is a measure derived from dividing body weight in kilograms by the square of height in metres. Individuals with a body mass index between 18.5 and 25 are regarded as being of normal weight. Those between 25 and 30 are regarded as overweight and obesity is defined as a body mass index equal to, or greater than 30 (WHO, 1998).

As per OECD (Organization for Economic Co-operation and Development) ‘Obesity’ is defined as a body mass index (BMI) of 30 kg/m² or more. The BMI is a single number that evaluates an individual's weight status in relation to height (weight/height²), with weight in kilograms and height in metres) (OECD, 2001).

CDC (Centers for Disease Control and Prevention) states that ‘overweight and obesity’ ranges are determined by using weight and height to calculate a number called the "body mass index" (BMI). BMI is used because, for most people, it correlates with their amount of body fat (CDC, 2010).
B. CLASSIFICATION OF OBESITY

Obesity can be classified in several different ways: for example, by BMI intervals and related aggregate risk of mortality, by anatomic phenotypes or by etiologic criteria.

a. Etiopathogenetic

1. Primary obesity is not associated with a demonstrable clinical condition.
2. Secondary obesity is less frequent, associated with an identifiable medical disorder, or drug therapy.

b. Pathologic

1. Hypertrophic obesity shows an increase in the size of the fat cells in the increased adipose tissue mass.
2. Hyperplastic obesity is consist of an increase in the number of fat cells in the increased adipose tissue mass.

c. According to fat distribution

1. Android type (apple shaped) obesity consists of fat localised in trunk and in abdominal cavity, carries an increased risk of DM, AMI, brain ischemia, other deseases of CVS. Android type (apple shaped) obesity is more common in male.
2. Gynoid type (pear shaped) obesity consists of fat localised at gluteal part, at thighs, carries an increased risk of joints damage. Gynoid type (pear shaped) is more common in female.

According to the World Health Organization (WHO), obesity is classified as class I for a BMI between 30 and 34.9 kg/m², class II for a BMI between 35 and 39.9 kg/m², and class III for a BMI ≥ 40 kg/m². In turn, class I obesity is associated with (hence, labeled as) a "moderate risk", class II with a "high risk", and class III with a "very high risk" of mortality (WHO, 2000).

Table 1. Classification of overweight according to BMI (WHO, 2000).

<table>
<thead>
<tr>
<th>Weight status</th>
<th>Body mass index (BMI) (Kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under weight</td>
<td>&lt; 18.5</td>
</tr>
<tr>
<td>Healthy weight</td>
<td>18.5-24.9</td>
</tr>
<tr>
<td>Over weight</td>
<td>25-29.9</td>
</tr>
<tr>
<td>Obesity class I</td>
<td>30-34.9</td>
</tr>
<tr>
<td>Obesity class II</td>
<td>35-39.9</td>
</tr>
<tr>
<td>Obesity class III (extreme obesity)</td>
<td>≥ 40</td>
</tr>
</tbody>
</table>

BMI, body mass index; WHO, World Health Organization.

The most common anatomical characterization refers to a prevalently visceral or a prevalently subcutaneous deposition of fat. The ratio of waist circumference to hip
circumference (WHR) has served the purpose of defining the degree of central (i.e. visceral) vs. peripheral (i.e. subcutaneous) obesity. It is known that visceral adiposity is a major risk factor for metabolic complications of obesity, while subcutaneous fat seems to be much more benign, and in some cases even protective against the development of metabolic complications (Jensen, 2008).

From an etiologic standpoint obesity can be fundamentally classified as primary or secondary. Obesity, in fact, can be iatrogenic, i.e. secondary to pharmacologic treatments, including some antipsychotics, some antidepressants, some antiepileptics, and steroids. An obesity phenotype is also characteristic of some diseases or conditions, including polycystic ovary syndrome, Cushing's syndrome, hypothyroidism, hypothalamic defects, and growth hormone deficiency. On the other hand, as a primary disorder, obesity still has an elusive etiology. While its pathogenesis can be expressed in relatively simple thermodynamic terms, i.e. the excess of body fat storage as a result of a chronic positive energy balance (i.e., surplus of energy intake vs. expenditure), the identification of the primary causes of the chronic energy imbalance remains challenging, while the metabolic, psychological, and behavioral phenotypes leading to "garden variety" obesity are still controversial. In fact, excessive energy intake (or hyperphagia) is considered an obvious phenotype of obesity (Delparigi et al., 2005). However, linking hyperphagia to actual weight gain has proved exceptionally difficult, most likely because it is inherently challenging to measure energy intake in free-living individuals. Other aspects of food intake and their relationship to obesity, such as diet composition (Astrup, 1999), energy density of food (Drewnowski, 2003), rate of meal consumption (Meyer, 1972), taste preferences, eating behavioral style, and sub-phenotypes, have also been explored with somewhat contradictory results (Provencher, 2003).

Not surprisingly, the molecular biology of obesity is also only partially understood. This is likely due to the heterogeneity of "garden variety" obesity and the fact that it is caused, like other complex diseases, not by a single genetic mutation but by multiple allelic defects, which determine susceptibility to environmental factors (Pomp, 2008). Individuals who carry only one or some of these alleles may still not develop the disease, because they either lack another allele (gene-gene interaction) or are not exposed to the precipitating environment (gene-environment interaction). Furthermore, there is controversial evidence for a direct association between genotypes and lifestyle (Holzapfel et al., 2010) or anatomical (Bauer et al., 2009) phenotypes of obesity.
C. EPIDEMIOLOGY

Obesity affects a large proportion of the population, worldwide. However, estimates of its prevalence are not available for all countries, and the available data are not uniformly accurate or comparable (Flegal et al., 2010).

It was not until the 20th century that obesity became common, so much so that in 1997 the World Health Organization (WHO) formally recognized obesity as a global epidemic (Caballero, 2007). As of 2005 the WHO estimates that at least 400 million adults (9.8%) are obese, with higher rates among women than men (WHO, 2000). As of 2008, The World Health Organization claimed that 1.5 billion adults, 20 and older, were overweight and of these over 200 million men and nearly 300 million women were obese. The rate of obesity also increases with age at least up to 50 or 60 years old (Peter, 2005). Once considered a problem only of high-income countries, obesity rates are rising worldwide. These increases have been felt most dramatically in urban settings (WHO, 2000). The only remaining region of the world where obesity is not common is sub-Saharan Africa (Haslam and James, 2005).

According to National Health and Nutrition Examination Survey (NHANES; a nationally representative health examination survey conducted by the National Center for Health Statistics division of the US Centers for Disease Control and Prevention, Atlanta, GA) data for the 2007–2008 period, 68% of adults in the U.S. aged 20–74 years are overweight or obese, with rates of 72% for men and 64% for women. For men, the age-adjusted prevalence of obesity was 32%, while the prevalence for women was 36%. Although these values are high, they may represent a stabilization compared with the obesity trends observed in the 1988–1994 and 1999–2000 periods. The rate of progression of obesity has decreased from 7 to 8 percentage points between 1988 and 1994 and again in 1999–2000 to nearly 2–4 percentage points from 2000 to 2008. This could be an early sign of a plateau in the obesity epidemic. The prevalence of obesity was relatively low and stable from 1960 to 1980, but doubled in the period following 1980, jumping from 15% in 1980 to 34% in 2006 (Selassie and Sinha, 2011). More than 1.6 billion adults worldwide are overweight and at least 400 million are obese an outline which is projected to almost double by 2015 (Herber, 2010) (Figure 1).
Obesity rates among women of different ethnic groups were significantly different, while the prevalence of obesity among men belonging to the same groups was not significantly different (Selassie and Sinha, 2011). Data from NHANES for children aged 2–9 years show that 32% of children had a BMI at or above the 85th percentile of the 2000 CDC BMI-for-age growth charts. Nearly one-fifth (16%) had a BMI at or above the 95th percentile. Similar to the data on adult obesity, obesity trends since 2003 show no significant changes in the prevalence of obesity for children between the ages of 2 and 19 years. This represents a dramatic change from 1980 to 2008, when the overweight prevalence skyrocketed from 6% in 1980 to 16% in 2008 (Flegal, 2006; Hedley et al., 2004).

D. OBESITY STATISTICS IN INDIA

According to The National Family Health Survey (NFHS) which is a large-scale, multi-round survey conducted in a representative sample of households throughout India, as many as 30 million Indians are overweight, and obesity continues rise. Around 20 per cent of school-going children are overweight, as the prevalence of obesity is increasing in epidemic proportions worldwide especially in developed countries, and the problem in India is also increasing, the survey said (NFHS, 2010).

Obesity has reached epidemic proportions in India in the 21st century, with morbid obesity affecting 5% of the country's population. India is following a trend of other developing countries that are steadily becoming more obese. Unhealthy, processed food
has become much more accessible following India's continued integration in global food markets. Indians are genetically susceptible to weight accumulation especially around the waist. While studying 22 different SNPs near to MC4R gene, scientists have identified a SNP (single nucleotide polymorphism) named rs12970134 to be mostly associated with waist circumference (The Hindu, 2007).

In India urbanization and modernization has been associated with obesity. In Northern India obesity was most prevalent in urban populations (male = 5.5%, female = 12.6%), followed by the urban slums (male = 1.9%, female = 7.2%). Obesity rates were the lowest in rural populations (male = 1.6%, female = 3.8%) (Yadav and Krishnan, 2008). Socioeconomic class also had an effect on the rate of obesity. Women of high socioeconomic class had rates of 10.4% as opposed to 0.9% in women of low socioeconomic class (Agrawal, 2002). With people moving into urban centers and wealth increasing, concerns about an obesity epidemic in India are growing.

**E. PATHOPHYSIOLOGY**

Much has been learned in the past decade regarding the regulation of obesity as it relates to the molecular regulation of appetite that affects energy homeostasis, particularly as positive energy balance upsets lipid and glucose metabolism (Schoonjans et al., 1996; Verges, 2004). Furthermore, obesity appears to play a central role in the dysregulation of cellular metabolism that accounts for insulin resistance in diabetes mellitus type (Verges, 2004). Excess adipocytes secrete numerous cytokines that contribute to vascular dysfunction in hypertension and dyslipidemia, as manifested by hypercholesterolemia and triglyceridemia. These conditions eventually contribute to significant atherosclerosis, and when associated with obesity and/or diabetes and insulin resistance, they constitute the metabolic syndrome (Shirai, 2004; Berg and Scherer, 2005). New knowledge related to fatty liver and its association with inflammation, as well as visceral adiposity’s effect on gastroesophageal reflux, gallstone disease, and cancer of the bowel, also make the liver and gut vulnerable to comorbidities of obesity (Berg and Scherer, 2005).

Many possible pathophysiological mechanisms involved in the development and maintenance of obesity (Flier, 2004). This field of research had been almost unapproached until leptin was discovered in 1994. Since this discovery, many other hormonal mechanisms have been elucidated that participate in the regulation of appetite and food intake, storage patterns of adipose tissue, and development of insulin resistance. Since leptin's discovery, ghrelin, insulin, orexin, PYY 3-36, cholecystokinin, adiponectin, as well as many other mediators have been studied. The adipokines are...
mediators produced by adipose tissue; their action is thought to modify many obesity-related diseases. Leptin and ghrelin are considered to be complementary in their influence on appetite, with ghrelin produced by the stomach modulating short-term appetitive control (i.e. to eat when the stomach is empty and to stop when the stomach is stretched). Leptin is produced by adipose tissue to signal fat storage reserves in the body, and mediates long-term appetitive controls (i.e. to eat more when fat storages are low and less when fat storages are high). Although administration of leptin may be effective in a small subset of obese individuals who are leptin deficient, most obese individuals are thought to be leptin resistant and have been found to have high levels of leptin (Hamann and Matthaei, 1996; Rang and Dale, 2005). This resistance is thought to explain in part why administration of leptin has not been shown to be effective in suppressing appetite in most obese people (Rang and Dale, 2005; Flier, 2004).

While leptin and ghrelin are produced peripherally, they control appetite through their actions on the central nervous system. In particular, they and other appetite-related hormones act on the hypothalamus, a region of the brain central to the regulation of food intake and energy expenditure. There are several circuits within the hypothalamus that contribute to its role in integrating appetite, the melanocortin pathway being the most well understood (Rang and Dale, 2005; Flier, 2004). The circuit begins with an area of the hypothalamus, the arcuate nucleus, that has outputs to the lateral hypothalamus (LH) and ventromedial hypothalamus (VMH), the brain's feeding and satiety centers, respectively (Boulpaep, 2003; Rang and Dale, 2005).

The arcuate nucleus contains two distinct groups of neurons (Rang and Dale, 2005; Flier, 2004). The first group coexpresses neuropeptide Y (NPY) and agouti-related peptide (AgRP) and has stimulatory inputs to the LH and inhibitory inputs to the VMH. The second group coexpresses pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) and has stimulatory inputs to the VMH and inhibitory inputs to the LH. Consequently, NPY/AgRP neurons stimulate feeding and inhibit satiety, while POMC/CART neurons stimulate satiety and inhibit feeding. Both groups of arcuate nucleus neurons are regulated in part by leptin. Leptin inhibits the NPY/AgRP group while stimulating the POMC/CART group. Thus a deficiency in leptin signaling, both via leptin deficiency or leptin resistance, leads to overfeeding and may account for some genetic and acquired forms of obesity (Rang and Dale, 2005).
Figure 2. Pathophysiology of obesity.
F. FACTORS AFFECTING OBESITY

Obesity is a consequence of an energy imbalance where energy intake has exceeded energy expenditure over a considerable period. However, arguing that obesity results from overindulgence of food or lack of physical activity is an oversimplification. Powerful societal and environmental forces influence energy balance and can overwhelm the physiological regulatory mechanisms. An individual’s susceptibility to these forces is affected by genetic and other biological factors (WHO, 2000). Obesity arises from the interaction between genes, environment and behaviour. As described in the previous section, the prevalence of obesity has increased worldwide during the last few decades, while our genes have hardly changed at all (Gill, 1997). The genetic background of most people is likely not equipped to handle the current abundance of food and a sedentary lifestyle (Filozof and Gonzalez, 2000). Thus, the environment has been suggested to promote obesity-causing behaviours (Egger and Swinburn, 1997; Hill and Peters, 1998). Nevertheless, little is known about factors that may explain the obesity epidemic or the large differences between populations in the distribution of BMI and the prevalence of obesity (Seidell and Flegal 1997; WHO, 2000).

I. Demographic factors

1. Gender: Women generally have a higher prevalence of obesity (BMI ≥ 30 kg/m²), especially after the age of 50 years, whereas men usually have a higher prevalence of overweight (BMI 25-29.9 kg/m²) (Flegal et al., 1998; Stam-Moraga et al., 1999). In addition, in most European countries, the prevalence of obesity in women as compared with men varies much more across countries (Seidell, 1995a).

2. Age: A BMI increase with age has been documented in several cross-sectional studies (Seidell et al., 1995, Flegal et al., 1998). The older the subjects, the higher the mean BMI and the prevalence of obesity in both men and women, at least up to the age of 50-60 years (Rolland-Cachera et al., 1991; Seidell 1995a; Seidell et al., 1995). The BMI increase with age in women tends to continue longer than in men (Seidell et al., 1995, Stam-Moraga et al., 1999). In fact, in a Swiss population, BMI in men did not vary at all across age groups (Morabia et al., 1997).

3. Ethnicity: The prevalence of obesity has been shown to vary across ethnic groups (Flegal et al., 1998). These differences have been suggested to be partly due to a genetic predisposition for obesity, which becomes apparent especially when individuals are exposed to an affluent lifestyle, such as Pima Indians in Arizona or Australian Aboriginals in an urban environment (WHO, 2000).
II. Socio-cultural factors

1. Educational level: The socioeconomic gradient in obesity is amply documented in the literature (Lissner 1997). Especially in women, a strong inverse association between obesity and socioeconomic status (SES), mostly assessed by educational level, has been reported in numerous affluent populations (Wardle and Griffith 2001; Rahkonen et al., 1998; Stam-Moraga et al. 1999).

2. Marital status: Marital status has been found to be associated with BMI and obesity, although this relationship is not well established. A study carried out in the European Union suggests single subjects (data on men and women analysed together) are less likely to be obese than married or previously married subjects (Martínez et al., 1999).

3. Number of children: Childbearing has been suggested to be a contributor to obesity in women, with pregnancy belonging to the vulnerable period for development of obesity (WHO, 2000). The effect of childbearing on body weight may be due to environmental factors rather than being purely biological.

III. Dietary intake, physical activity, alcohol consumption and smoking

It is important to note that weight changes observed in populations over time are generally so small that they are unlikely to be detected by existing methods for measuring energy expenditure and energy intake in populations (Seidell 1997, Heitmann and Garby, 1999). Alcohol consumption and smoking habits are also discussed as lifestyle factors.

1. Food choices and dietary intake: Nutrition is of critical importance in establishing a positive energy balance. Of the nutritional factors related to obesity, dietary fat intake is widely believed to be the primary determinant of body fat (Bray, 2003). High-fat diets have been suggested to promote obesity by increasing energy intake, further increasing the likelihood of a positive energy balance and weight gain (Hill et al., 2000). From epidemiological studies, however, evidence for a high-fat diet promoting a positive energy balance and development of obesity is not definitive (Seidell, 1998). To summarize, numerous dietary factors have been suggested to be associated with obesity.

To date, however, there is no conclusive evidence from epidemiological studies that any special composition diet promotes the development of obesity more than other diets.

2. Physical activity: Physical activity has three main components: occupational work, household chores and leisure-time physical activity (WHO, 2000). This overview is focused mainly on the latter component due to the shortage of epidemiological studies reporting on the role of work and household activities in obesity. In recent reviews,
habitual physical activity has been concluded to play an important role in attenuating age-related weight gain and maintaining body weight (Fogelholm and Kukkonen-Harjula, 2000).

3. Alcohol consumption: Studies on BMI and alcohol consumption have also yielded inconclusive results. Interestingly, in most of the studies reporting a positive association, this finding was restricted to men, whereas in women, the association has usually been the inverse (Westerterp et al., 1999).

4. Smoking habits: Numerous studies have shown that smoking is associated with lower BMI (Istvan et al., 1992; Molarius et al., 1997). The association between smoking status and BMI may be modified by social and behavioural factors, the level of education being a strong confounding factor (Molarius et al., 1997).

G. HEALTH CONSEQUENCES OF OBESITY

Obesity causes or exacerbates many health problems, both independently and in association with other diseases. In particular, it is associated with the development of type 2 diabetes mellitus, coronary heart disease (CHD), an increased incidence of certain forms of cancer, respiratory complications (obstructive sleep apnoea) and osteoarthritis of large and small joints. The Build and Blood Pressure Study has shown that the adverse effects of excess weight tend to be delayed, sometimes for ten years or longer. Life-insurance data and epidemiological studies confirm that increasing degrees of overweight and obesity are important predictors of decreased longevity (Shen et al., 2012; Morrell et al., 2012; Kopelman, 2007).

Obesity constitutes a complex disease associated with a wide spectrum of comorbidities due to a deleterious adipose tissue related metabolic profile and increased physical burdens imposed on various body sites. Thus, even in cases of metabolically “healthy obese” individuals, presenting with a predominantly female type of fat distribution, multiple other parameters such as osteoarthritis, disability and effects on psychological well-being need to be further considered when discussing benefits of weight management interventions.
1. Metabolic syndrome
The constellation of metabolic abnormalities – including centrally distributed obesity (large waist circumference), decreased HDL cholesterol level, elevated triglyceride level, elevated blood pressure (hypertension) and high blood glucose level (hyperglycaemia) – is known as the metabolic syndrome (Calle et al., 1999). It is associated with increases in type 2 diabetes (threefold) and cardiovascular diseases (two folds). At least four definitions of this syndrome are now commonly used, but all of them include central obesity as a criterion. In a recent definition by the International Diabetes Federation, central obesity is the essential feature, and the metabolic syndrome is present if a large waist circumference (defined by cut-off points specific to different ethnic groups) is accompanied by any two of the other components (Klein et al., 2007).

2. Cardiovascular diseases
Obesity is associated with some of the major risk factors for cardiovascular diseases, such as hypertension and low concentrations of HDL cholesterol, but it is also associated with small-particle-sized LDL cholesterol (Snijder et al., 2004). Obesity is associated with accelerated coronary atherosclerosis and long-term longitudinal studies demonstrate that obesity predicts coronary atherosclerosis in an independent manner. The risk for developing coronary artery disease is increased 3.3-fold in American women with a
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BMI over 29 kg/m², in comparison with women with a BMI below 21 kg/m² (Manson et al., 1995).

3. Hypertension

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

4. Type 2 diabetes

Obesity is a well-known risk factor for type 2 (non-insulin-dependent) diabetes mellitus. Men and women with a BMI of 35 kg/m² had about 20 times the risk of developing diabetes of those of normalweight. From several large prospective studies, overweight and obesity (BMI over 25 kg/m²) have been estimated to account for about 65–80% of new cases of type 2 diabetes. The risk is a function of the age of onset and the duration of obesity, and weight gain during adult life. In addition, people with a family history of type 2 diabetes, who are already at greatly increased risk, seem to be more vulnerable to excess fat and accumulation of abdominal fat (Snijder et al., 2004).

5. Obesity and non-alcoholic fatty liver disease

The liver is the largest solid organ in adults constituting 2-3% of the body weight and accounting for 25-30% of the total oxygen consumption. Obesity may cause hyperinsulinemia, hyperglycemia and ectopic fat accumulation in the liver. In turn, this can impair hepatic function and lead to a spectrum of abnormalities, ranging from steatosis and elevation of circulating liver enzyme levels to cirrhosis, liver failure and even liver cancer (Fabbrini et al., 2010; Chávez-Tapia et al., 2009).

6. Obesity and gallbladder disease

Gallbladder disease is a common gastrointestinal disorder in Western countries with cholelithiasis being the most frequent hepatobiliary pathology, primarily with gallstones composed of cholesterol (Shaffer, 2006; Marschall and Einarsson, 2007).
7. Obesity, stress and psychiatric co-morbidities
A growing body of evidence indicates that depression and other common psychological disorders constitute independent risk factors for developing obesity and metabolic syndrome manifestations (Blaine, 2008). In a large community-based cohort of elderly persons, followed for 5 years, baseline depression was associated with increased abdominal fat accumulation, independent of overall obesity, suggesting pathogenetic links between depression and central obesity (Vogelzangs et al., 2008).

8. Obesity and cancer
At relatively low levels of BMI, obesity is already related to some forms of cancer, mainly colon cancer and hormone-related malignancies in the uterus, and cancer of the ovary, breast (post-menopausal) and prostate. When BMI reaches levels higher than 35 kg/m², obesity is related to more cancer sites. The World Cancer Research Fund has estimated that 30–40% of all cancers can be attributed to inappropriate diet, physical inactivity and overweight (American College of Sports Medicine, 1990).

9. Weight-related co-morbidities of the musculoskeletal system and skin
Osteoarthritis (OA) is the most frequent joint disorder worldwide and one of the leading causes of chronic pain and disability in the adult population of Western societies, particularly among the elderly. Obesity is a major risk factor for knee OA, with available data indicating that weight gain can precede the disease onset by several years and that this increased risk begins as early as the third decade of life (Blagojevic et al., 2010).

10. Weight-related co-morbidities of the respiratory system
Increased body weight and fat accumulation in the abdomen and chest wall can have a significant impact on respiratory physiology leading to deterioration of pulmonary function, attributed primarily to increased mechanical pressure on the thoracic cage and trunk. Although the effects on conventional respiratory function tests are often modest until BMI exceeds 40 kg/m², obese patients may exhibit reductions in lung volumes and respiratory compliance, as well as in respiratory efficiency (O'Donnell et al., 2010).

11. Obesity mortality
The impact of obesity on early death seems to be one of the simplest epidemiological relationships, but the relationship between obesity and mortality has been controversial for many decades, and continues to be debated. In the 1970s and 1980s, most of the debate centred on the observation that obesity was not associated with an increased risk
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of mortality once traditional risk factors for cardiovascular diseases, such as hypertension, dyslipidaemia and type 2 diabetes, were taken into account. Manson et al., (Martinez, 1999). The observation that obesity has very little impact on mortality in people without risk factors (such as hypertension and dyslipidaemia) and without type 2 diabetes does not mean that obesity is not related to increased mortality, because most obese people will have at least one of these conditions.

12. Reduced life expectancy

Some studies have calculated the number of reduced years of life expectancy caused by obesity. The Framingham study calculated that obesity (BMI ≥30 kg/m²) at the age of 40 years was related to a loss of 6–7 years of life. Fontaine et al., calculated that a BMI ≥33 kg/m² from age 40 years was related to a loss of 2–3 years (Ruiz, 2006).

13. Mortality in different age groups

The relative impact of obesity on mortality is highest in the youngest age categories (Gutin, 2005). Reasons for small or no statistical associations between BMI and mortality in the elderly may be due to a ceiling effect—the selective survival of obese people with few co-morbidities—or the use of a measure such as BMI, which may be less sensitive to mortality risk than, say, waist circumference. Interestingly, the optimal BMI has been reported to shift upwards with age. The BMI with lowest absolute risk of mortality is somewhere between 18.5 kg/m² and 25 kg/m² for young adults, but has been reported to be around 27 kg/m² in older adults (Ruiz, 2006a).

14. Health consequences of childhood obesity

Attention to childhood overweight and obesity is highly warranted, as overweight and obese children are likely to be obese into adulthood and to have non-communicable diseases at a younger age. Obese children also have a direct, increased risk of disease, and they often suffer from stigmatization (Laaksonen, 2005).

H. BIOMARKERS OF OBESITY

1. Anthropometric measures

BMI (calculated as weight in kg/height² in meters) has been considered the standard measure of adiposity for clinical use and for epidemiological studies for many years. A considerable amount of data based on BMI have been used to show the increased morbidity and mortality associated with obesity and the WHO current definitions of
obesity, still rely predominantly on BMI (Shen et al., 2012; WHO, 1998). However use of BMI as the sole measure of fatness can classify some physically fit, muscular individuals as obese because it does not directly measure body fat or fat distribution. Other simple anthropometric measures that can be used to complement BMI, and may be better markers of some (particularly diabetes and cardiovascular) disease risk include measures of waist circumference and waist–hip ratio (Han et al., 1995).

2. Measures of adiposity

The gold standard measures of body fatness are underwater weighing and double labeled water techniques; the former requires specialist equipment and an awkward technique for both subjects and researchers. Double-labeled water is expensive, and availability is limited by access to isotope (Jebb, 1998). The newer technique of air-displacement plethysmography (“Bod-Pod”) overcomes some of these limitations, and has been reasonably well validated against gold-standard techniques (Noreen and Lemon, 2006). Dual beam X-ray absorbitometry (DEXA) is widely available, and uses a low radiation dose (less than 10% of a standard chest X-ray). Using a three compartment model it provides an accurate estimate of lean body mass, fat mass and body water and an estimate of fat distribution. Subcutaneous and visceral fat area can be measured using CT or MRI scanning.

3. Measures of energy expenditure

The three main components of energy expenditure are the basal resting metabolic rate (RMR), the thermic effect of food, and the energy requirements of voluntary physical activity. Calorimetric methods rely on measurement of oxygen consumption and carbon dioxide production, with a correction for protein metabolism based on measurement of urinary nitrogen excretion. Whole body calorimetry in a sealed room is considered the gold standard, but requires considerable technical support and is expensive to set up and maintain; it can however be used to study subjects over a period of time, and can therefore include the effects of meals and episodes of physical activity. Physical activity can be measured to a reasonable degree of accuracy using modern triaxial accelerometers, but these can only provide estimates of the energy expenditure (Marti et al., 2000).

4. Insulin resistance and systemic inflammation

Other biomarkers of CV and metabolic risk may also be measured, although their usefulness in routine clinical practice is not yet proven. Improvements in insulin
resistance are expected with effective weight loss and it is helpful to demonstrate that this improves, especially as insulin resistance may precede and usually co-exists with type 2 diabetes. Several methods exist—the simplest involve measurement of fasting insulin and glucose, such as the HOMA (homeostasis model assessment) and QUICKI, but these are probably less accurate than the hyperinsulinemic euglycemic clamp or frequently sampled intravenous glucose tolerance tests (Matthews et al., 1985).

5. Adipocytokines
Adipocytes and adipose tissue produce a wide range of hormones and cytokines involved in glucose metabolism (e.g. adiponectin, resistin), lipid metabolism (e.g. cholesteryl ester transfer protein, CETP), inflammation (e.g. TNF-a, IL-6), coagulation (PAI-1), blood pressure (e.g. angiotensinogen, angiotensin II), and feeding behaviour (leptin) thus affecting metabolism and function of many organs and tissues including muscle, liver, vasculature, and brain. In pathological conditions, excessive adipose tissue development depends on hyperplasia (increase in several adipocytes by cell proliferation associated with the recruitment of new adipose cells from precursors) and hypertrophy (increase in adipocyte size because of fat storage). Hypertrophy and hyperplasia induce a loss of adipose tissue heterogeneity associated with a dramatic disturbance to its structure and function (Trayhurn et al., 2001). This endocrine tissue is able to express and secrete numerous molecules and biologically active proteins called adipocytokines or adipokines including leptin, TNFa, IL-6, IL-1b, PAI-1, TGFb, angiotensinogen, adipin, resistin, acylation-stimulating protein (ASP) and Adiponectin (Guerre-Millo et al., 2002).

6. Leptin
Leptin was named from the Greek root “leptos” because it suppresses food intake and decreases body weight in mice. Leptin was originally cloned as the protein product of the ob gene (Halaas et al., 1995). The murine ob gene encodes a 4.5-kb messenger RNA (mRNA) transcript with a highly conserved 167-amino-acid open reading frame. Detailed information on the leptin gene, its protein structure and biological functions, has been summarized in a recent review (Ahima and Flier, 2000). Adipocytes secrete leptin in direct proportion to adipose tissue mass as well as nutritional status. Plasma leptin concentrations positively correlate with subcutaneous, rather than intra-abdominal, fat tissue mass (Cnop et al., 2002). Leptin expression and protein levels in circulation are increased during the development of obesity. Obese persons have higher leptin mRNA and protein levels than lean individuals. Leptin expression is stimulated upon feeding; plasma leptin level declines rapidly during fasting. Insulin is a
potent activator of leptin mRNA expression and protein secretion and is the major
mediator of increased postprandial leptin concentration (Vicennati et al., 2002). Potential
modifiers of leptin concentrations are energy-yielding nutrients such as fatty acids,
carbohydrates, proteins and alcohol (Perusse et al., 1997). Leptin is also regulated by
steroid hormones. Leptin plays a very important role in maintaining energy homeostasis.
Leptin acts both centrally and peripherally, with a major role in the regulation of food
intake, body weight and energy balance (Friedman et al., 2004). Leptin inhibits appetite
and weight gain by decreasing orexigenic and increasing anorexigenic peptide
expression in the hypothalamus (Trayhurn et al., 1999) and reduces the level of
intracellular lipid in skeletal muscle and liver. Reduced leptin levels promote energy
intake and limit the high-energy cost of reproduction, thyroid thermogenesis and immune
response. The mutation of the ob gene leads to massive obesity in ob/ob mice. While the
leptin-mediated adaptation to energy deficiency is likely to have been beneficial in times
of food shortage, this tendency towards efficient energy metabolism may have
contributed to the current epidemic of obesity in an environment where food is abundant
(Flier, 1998).

7. Adiponectin
Adiponectin inhibits hepatic glucose production while it may enhance glucose uptake in
muscle, increases fatty acid oxidation in both liver and muscle, and augments energy
expenditure in vitro, presumably by enhanced uncoupling of adenosine triphosphate
generation in mitochondria. Interleukin-6 (IL-6) may induce energy expenditure
(including thermogenesis) and inhibit feeding behaviour at the level of the central
nervous system (Wallenius et al., 2002).

8. Insulin
Obesity is associated with elevated basal insulin levels and resistance to the metabolic
effects of insulin (Lichtenstein and Schwab, 2000; De Ferranti and Mozaffarian 2008).
Independent of obesity, high-fat feeding itself contributes to impaired glucose tolerance
and insensitivity to the blood glucose lowering effect of insulin (Lichtenstein and
Schwab 2000; Riccardi et al., 2004). Mechanisms of the hyperinsulinemia and insulin
resistance with high-fat diets and obesity are discussed in reviews by Lichtenstein and
Schwab (Lichtenstein and Schwab, 2000), and Riccardi et al., (Riccardi et al., 2004).
These authors suggested that decreases in insulin receptors, glucose transport and
metabolism are involved, plus reduction in liver and muscle glycogen synthase activity
and storage of glucose as glycogen (Lichtenstein and Schwab, 2000; Riccardi et al.,
2004). Excessive amounts of adipose tissue (hypertrophy and hyperplasia) stress the endoplasmic reticulum, resulting in secretion of cytokines and decrease in the responsiveness of the cells to insulin (De Ferranti and Mozaffarian, 2008). Differences among dietary fatty acids affect the composition of the cell membranes and this in turn influences the affinity of receptors for insulin and so its action on the cell (Lichtenstein and Schwab 2000; Riccardi et al., 2004).

9. Ghrelin

Ghrelin is a peptide released by cells in the fundus of the stomach that stimulates the release of growth hormone from the pituitary and was identified by Kojima and colleagues in 1999 (Kojima et al., 1999). Ghrelin rises before and falls after each ad libitum meal and increases food intake (Tschop et al., 2000). In humans ghrelin levels peak in the morning (8:00), at noon (12:00-13:00) and in the evening (17:00-19:00) and fall after each peak (Natalucci et al., 2005). Obese people have lower fasting ghrelin levels than lean people and reduced suppression of ghrelin secretion after a meal (Reinehr et al., 2005).

10. Tumor necrosis factor-α (TNF-α)

TNF-α was recognized as the first cytokine that could induce IR (Moller, 2000) and was proposed to represent a molecular link between obesity and IR (Hotamisligil et al., 1993). Both human and animal studies showed that TNF-α expression in adipose tissue is highly induced by obesity (Hotamisligil et al., 1993). Expression of TNF-α mRNA was increased and was strongly correlated to the degree of obesity and the level of IR in obese animal models and humans (Kern et al., 2003). Therefore, TNF-α may partially contribute to IR in obesity. In obese individuals and subjects with IR and T2D, TNF-α levels are raised and correlated with high plasma insulin levels and decreased insulin sensitivity. In adipose tissue of obese humans, there is a strong inverse correlation between secretion of TNF-α and insulin-stimulated glucose metabolism (Arner, 2005).

11. Interleukin-6

IL-6 is secreted by many types of cells. IL-6 is also produced by fat cells and stromal-vascular cells in adipose tissue. Since about 30% of systemic IL-6 is secreted by adipose tissue, this protein is also an adipocytokine. Elevated plasma levels of IL-6 are strongly linked to IR IL-6 concentrations at baseline independently predict future risk of developing T2D (Pradhan et al., 2001). Weight loss significantly decreases IL-6 levels in both adipose tissue and serum. IL-6 has direct effects on insulin signaling in adipocytes
and hepatocytes. It impairs insulin signaling in primary mouse hepatocytes and 3T3-L1 adipocytes with decreased activation of IRS-1 and PI3-kinase, as well as impaired insulin-induced glycogenesis in hepatocytes (Senn et al., 2002). Administration of recombinant IL-6 in rodent models and humans induces hepatic gluconeogenesis that, in turn, leads to hyperglycaemia and compensatory hyperinsulinaemia (Tsigos et al., 1997).

12. Resistin
Resistin is an approximately 12-kDa polypeptide that belongs to a unique family of cysteine-rich C-terminal domain proteins called resistin-like molecules. It was discovered as a novel mRNA induced during adipocyte differentiation but down-regulated by TZDs in vitro (Steppan et al., 2002). Resistin was subsequently identified by other groups. It is also known as ADSF (adipose tissue-specific secretory factory) and FIZZ3 (found in inflammatory zone 3). The resistin polypeptide is expressed and secreted by mature adipocytes. However; human resistin is also expressed in macrophage at a much higher level compared with adipocyte (Patel et al., 2003).

13. Lipid profile
Cholesterol metabolism is significantly altered in both obesity and metabolic syndrome in that cholesterol synthesis is increased and absorption reduced. As patients become more obese, more insulin resistant and acquire a high TG and low HDL-C, cholesterol absorption decreases and synthesis increases (Hoeing et al. 2007). Obesity is always accompanied by excess lipid accumulation, impaired glucose tolerance, and elevated serum triacylglycerol concentration; thus, it is positively associated with the progression of various chronic diseases such as type 2 diabetes mellitus, cardiovascular diseases, and cancers (Chang et al., 2011). In epidemiological studies, human obesity is clearly associated with the increased risk for atherosclerosis, contributing to the early onset of coronary artery disease. Visceral obesity in particular increases the risk of atherosclerosis owing to both insulin resistance and dyslipoproteinemia (Chan et al., 2004). Visceral obesity is associated with dyslipidemia and may account for the increased risk of CVD (Chan et al., 2010). Visceral obesity is frequently associated with high plasma triglycerides (TGs) and low plasma high density lipoprotein-cholesterol (HDL-C), and with high plasma concentrations of apolipoprotein-B (apo-B)-containing lipoproteins (Chan et al., 2004). Further, it may involve increased hepatic secretion of very-low-density lipoprotein (VLDL) and impaired catabolism of VLDL, intermediate-density lipoprotein (IDL), and low density lipoprotein (LDL) apo-B. These abnormalities may be
consequent on insulin resistance which is very much associated with obesity (Chan et al., 2010).

14. Oxidative stress

Oxidant stress in obesity may be an important pathogenic mechanism in the obesity-associated metabolic syndrome, which includes the coexistence of several risk factors for atherosclerosis, including hyperglycemia, dyslipidemia, and hypertension (Vincent et al., 2007). Numerous research studies have recommended that obesity is associated with enhanced oxidant stress i.e. enhanced free radical production and/or depleted cellular antioxidant defense systems. Possible mechanisms contributing to the obesity associated oxidant stress include augmented oxygen consumption and subsequent radical production via mitochondrial respiration, diminished antioxidant capacity, elevated fat deposition and cell injury causing amplified rates of radical formation such as O$_2^-$ and OH$^-$ (Keaney et al., 2003; Vincent et al., 2007). In addition, hyperglycemia, hypertension, and hyperleptinemia are also possible sources of increased oxidant stress in the obese state. It is not known whether obesity-associated oxidant stress is related to excess adipose tissue accumulation or is a consequence of obesity-related diseases i.e., hypertension, hyperlipidemia, hyperleptinemia, and hyperglycemia (Stephens et al., 2006; Ferroni et al., 2004; Furnkranz et al., 2005).

An antioxidant is a molecule capable of inhibiting the oxidation of other molecules. Obesity has been shown to be one of the conditions that reduce antioxidant capacity by lowering the levels of antioxidant enzymes predominantly catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GR) (Carmiel-Haggai et al., 2005). The enzymatic antioxidants such as superoxidase dismutase (SOD), CAT or GPx, can scavenge reactive oxygen species and free radicals or stop their formation (Husain et al., 2005).

15. Glutathione (GSH) estimation

Glutathione (GSH) is a tripeptide that contains an unusual peptide linkage between the amine group of cysteine (which is attached by normal peptide linkage to a glycine) and the carboxyl group of the glutamate side-chain. It is an antioxidant, preventing damage to important cellular components caused by reactive oxygen species such as free radicals and peroxides. GSH represents the first line of defense against free radicals and is also responsible for the maintenance of protein thiols and acts as a substrate for GPx and glutathione-s-transferase (GST) (Prakash et al., 2001). GPx activity is considered to
symbolize the initial protective response required for adjusting the H$_2$O$_2$ concentration under physiological condition, as well as after oxidative insult (Izawa et al., 1996).

16. Glutathione peroxidase (GPx)
Glutathione peroxidase (GPx) is the general name of an enzyme family with peroxidase activity whose main biological role is to protect the organism from oxidative damage. The biochemical function of glutathione peroxidase is to reduce lipid hydroperoxides to their corresponding alcohols and to reduce free hydrogen peroxide to water (Vincent et al., 2007).

17. Superoxide dismutases (SOD)
Superoxide dismutases (SOD) are a class of enzymes that catalyze the dismutation of superoxide into oxygen and hydrogen peroxide. As such, they are an important antioxidant defense in nearly all cells exposed to oxygen. One of the exceedingly rare exceptions is Lactobacillus plantarum and related lactobacilli, which use a different mechanism. The superoxide anion (O$^{-2}$) is a key peroxidative molecule. The chief scavenger of superoxide anions is the cellular antioxidant enzyme SOD, which catalyzes the dismutation of superoxide to hydrogen peroxide that in turn is removed by another antioxidant enzyme, GPx (Juul et al., 2004).

I. ANIMAL MODELS OF OBESITY
It is widely agreed that obesity occurs from a prolonged imbalance between the level of energy intake and the level of energy expenditure, with the resultant surplus being stored as body lipids, predominantly in adipose tissue. Our understanding of the regulation of food intake and food choice behaviour, and the physiological basis of differences in energy expenditure owes in large part to studies made on animals. Animals models have not only contributed to our understanding of the physiological and genetic basis of obesity, but have been a cornerstone of studies into environmental effects, such as epigenetics, responses to high-fat and low-calorie diets and the identification and the development of several pharmaceutical agents for the treatment of obesity.

a. Murine models of obesity
Obesity and diabetes are syndromes quite often linked in patients (maturity onset diabetes) and hereditary animal models. A survey on hypothalamic and genetic obesity in experimental animals was given by Bray and York (1979). The inheritance of obesity in animal models of obesity was discussed by Festing (1979). Cawthorne (1979) discussed the use of animal models in the detection and evaluation of compounds for the treatment
of obesity. The regulation of body weight in animals by leptin was reviewed by Friedman and Halaas (1998).

Murine models resemble human being in several organ functions, nutrition and sensitive to most of the drugs. To investigate the effects of obesity on endocrine function and metabolism, genetic or dietary mouse and rat models of obesity are used. Studies with these obese animals revealed that insulin resistance accelerated by obesity resulted in disturbed metabolism of glucose and lipids (Ishii et al., 2010).

1. Experimental obesity

1.1 Food-induced obesity

Diet is one of the main environmental factors that contribute to the obesity. High-fat diets produce a consistent and significant increase in body fat content that is dependent on the amount of fat in the diet and the duration of feeding. The consumption of high-fat diet led to obesity because it facilitates the development of a positive energy balance, leading to an increase in visceral fat deposition; this led to abdominal obesity in particular (Azman et al., 2012). Human studies have shown that increased fat intake is associated with body weight gain which can lead to obesity and other related metabolic diseases (Buettner et al., 2006). Animal rodent models are therefore useful tools for studying obesity as they will readily gain weight when fed high-fat diets (Sashidhara et al., 2012; Woods et al., 2003). Obesity can be induced in rats by offering a diet containing corn oil and condensed milk. Scalfani and Springer (1976) induced obesity in adult female rats by adding a variety of supermarket foods to lab chow (“cafeteria diet”). In behavioral tests, the authors found similarities to hypothalamic and human obesity syndromes. Rothwell et al., (1982) compared the effects of feeding a cafeteria diet on energy balance and diet-induced thermogenesis in four strains of rats. Stock and Rothwell (1979) discussed the influence of various forms of feeding, high-fat diets, insulin injections, tube-feeding, and cafeteria feeding on energy balance in laboratory animals.

Several studies have shown that the intake of a high-fat diet increases insulin resistance as well as serum leptin, adipose mass and inflammation (Panchal et al., 2012). Panchal et al., (2012) reported that feeding of high fat diet for 8 weeks significantly increases the body weight, food consumption, visceral organs weight, and the levels of triglycerides, total cholesterol, low-density lipoproteins, very low-density lipoproteins, atherogenic index and glucose in high fat diet-induced obese rats. Azman et al., (2012) reported that
feeding with high fat diet for 10 weeks produces an increase in plasma leptin and fatty acid synthase (FAS) activity and decreased the efficiency of the antioxidant defense system with the concomitant enhancement in the levels of plasma total cholesterol, low-density lipoprotein (LDL), and triglyceride, and decrease in high-density lipoprotein (HDL). Moreover, induction of high fat diet obesity was confirmed by increased body weight, adipose tissue weights, as well as increasing the degree of hepatic steatosis in the high fat fed rats. Ishii et al., (2010) reported that rat models of obesity are used to investigate the effects of obesity on endocrine function and metabolism. Studies with these obese animals revealed that insulin resistance accelerated by obesity resulted in disturbed metabolism of glucose and lipids. Rolls et al., (1980) found persistent obesity in rats following a period of consumption of a mixed, high energy diet. When the high energy foods were withdrawn after 90 days and just chow was available, the obese rats maintained their elevated body weights. Hill et al., (1992) studied the influence of amount and composition of dietary fat on development of obesity in rats. Adult male Wistar rats were fed high fat (HF; 60% of calories) or low fat (LF; 20% of calories) diets for 28 weeks. Half of the rats in each condition received diets with saturated fat (lard) or with polyunsaturated fat (corn oil). There was some indication that unsaturated fat diets were associated with greater accumulation of fat in subcutaneous tissue depots than saturated fat diets. The effects of the type of fat were less than those of the amount of dietary fat.

1.2 Hypothalamic obesity
Hyperphagia in rats has been reported after hypothalamic lesions. Surgical techniques were described by Leibowitz et al., (1981), Vander et al., (1985). Sclafani and Aravich (1983) adapted adult female Sprague Dawley rats to a macronutrient self-selection regimen which allowed them ad libitum access to separate sources of protein, carbohydrate, and fat. The rats were then given either ventromedial hypothalamic lesions, paraventricular hypothalamic lesions, parasagittal knife cuts through medial hypothalamus or sham lesions. Following surgery, all lesioned rats overate and became obese as compared to sham operated controls. The group with parasagittal knife cuts through medial hypothalamus gained more weight than the groups with ventromedial hypothalamic lesions and paraventricular hypothalamic lesions. Enhanced expression of rat obese (ob) gene in adipose tissue of ventromedial hypothalamus (VMH)-lesioned rats was described by Funahashi et al., (1995). Elmquist
et al., (1999) discussed the role of leptin and other peptide hormones in different areas of the hypothalamus in controlling food intake and body weight.

1.3 Goldthioglucose-induced obesity

Intraperitoneal or intramuscular injection of goldthioglucose induces obesity in mice. The effect is related to destruction of hypothalamic and extrahypothalamic areas of the brain (Perry and Liebelt 1961). Debons et al., (1962, 1968, 1977) administered 800 mg/kg goldthioglucose by a single intraperitoneal injection to female CBA mice. Obesity was induced in rats by implants of goldthioglucose in the hypothalamus (Smith and Britt 1971; Smith 1972). Several other compounds produce obesity concomitantly with brain lesions.

1.4 Monosodium glutamate-induced obesity

Adiposity can be induced in mice by repeated subcutaneous injections of monosodium-L-glutamate at an early stage of life (Olney 1969). Tokuyama and Himms-Hagen (1986) studied brown adipose tissue thermogenesis, torpor, and obesity in glutamate-treated C57B1/6J mice offered either normal chow or a cafeteria diet and found that the high metabolic efficiency and obesity of the glutamate obese animals are principally a consequence of their maintenance of a hypothermic torpid state for more than 50% of the time.

2. Genetically obese animals

2.1 Spontaneously obese rats

The occurrence of spontaneous obesity has been reported in several strains of rats:

2.1.1 WBN/KOB rat: Spontaneous hyperglycemia, glucosuria and glucose intolerance have been observed in aged males of an inbred Wistar strain, named the WBN/Kob rat (Koizumi 1989). These animals exhibit impaired glucose tolerance and glucosuria at 21 weeks of age. Obvious decreases in the number and size of islets are found already after 12 weeks of age. Fibrinous exudation and degeneration of pancreatic tissue are observed in the exocrine part, mainly around degenerated islets and pancreatic ducts in 16 weeks old males.

2.1.2 Zucker-Fatty rat: The Zucker-fatty rat is a classic model of hyperinsulinemic obesity (Zucker 1965). Obesity is due to a simple autosomal recessive (fa) gene and develops at an early age. Obese Zucker rats manifest mild glucose intolerance, hyperinsulinemia, and peripheral insulin resistance similar to human NIDDM. However, their blood sugar level is usually normal throughout life (Bray 1977; Abadie et al., 1993; Alamzadeh et al., 1993; Kasim et al., 1993).
2.1.3 WDF/TA-FA rat: The WDF/Ta-fa rat, commonly referred to as the Wistar fatty rat, is a genetically obese, hyperglycemic rat established by the transfer of the fatty (fa) gene from the Zucker rat to the Wistar Kyoto rat (Velasquez et al., 1990). The Wistar fatty rat exhibits obesity, hyperinsulinemia, glucose intolerance, hyperlipidemia, and hyperphagia similar to Zucker rats being, however, more glucose intolerant and insulin resistant than Zucker rats. Hyperglycemia is usually not observed in females but can be induced by addition of sucrose to the diet.

2.1.4 OLETF rat: A spontaneously diabetic rat with polyuria, polydipsia, and mild obesity was discovered in 1984 in an outbred colony of Long-Evans rats. A strain of rats developed from this rat by selective breeding has since been maintained at the Tokushima Research Institute (Otsuka Pharmaceutical, Tokushima, Japan) and named OLETF. The characteristic features of OLETF rats are: (1) late onset of hyperglycemia (after 18 weeks of age), (2) a chronic course of disease, (3) mild obesity, (4) inheritance by males, (5) hyperplastic foci of pancreatic islets, and (6) renal complications (nodular lesions). The clinical and pathological features of disease in OLETF rats resemble those of human NIDDM.

2.1.5 Obese SHR rat: The strain of obese SHR rats was developed by Koletsky (1975) by mating a spontaneous hypertensive female rat of the Kyoto-Wistar strain with a normotensive Sprague Dawley male. After several generations of selective inbreeding, these obese SHR exhibited obesity, hypertension, and hyperlipidemia. In addition, some rats developed hyperglycemia and glucosuria associated with giant hyperplasia of pancreatic islets.

2.1.6 JCR: LA-corpulent rat: Several substrains were developed from obese SHR rats, such as the JCR: LA-corpulent rat which exhibits a syndrome characterized by obesity, hypertriglyceridemia and hyperinsulinemia with impaired glucose tolerance and is susceptible to vascular arteriosclerotic lesions (Russell et al., 1994). Compared to fatty Zucker rats, the JCR: LA corpulent rats have higher levels of the insulin releasing hormone gastric inhibitory polypeptide and higher insulin levels (Pederson et al., 1991).

2.1.7 Growth hormone-deficient dwarf rat: Clark et al., (1996) described the obese growth hormone-deficient dwarf rat as a new model of obesity.

2.2 Spontaneously obese mice

2.2.1 Yellow obese (AYA) mouse: The yellow obese mouse in the only example of obesity inherited through a dominant gene. It is located on chromosome 2 at linkage group 5, the agouti locus (Bateson 1903). Since the genes controlling obesity and the
agouti coat colors are so closely linked, the obesity is associated with a change of pigmentation from black to yellow. Such an association allows the early identification of pre-obese mice as soon as the coat hair begins to grow.

2.2.2 KK-AY mouse: Iwatsuka et al., (1970) reported on yellow KK mice (also named KK-Ay mice), carrying the yellow obese gene (Ay). These mice develop marked adiposity and diabetic symptoms in comparison with their littermates, black KK mice. Blood glucose and circulating insulin levels as well as HbA1c levels were increased progressively from 5 weeks of age. Degranulation and glycogen infiltration of B cells were followed by hypertrophy and central cavitation of islets. Lipogenesis by liver and adipose tissue were increased. Insulin sensitivity of adipose tissue was more remarkably reduced than in black KK mice to its complete loss at 16 weeks of age. Renal involvement is uniquely marked by early onset and rapid development of glomerular basement membrane thickening (Diani et al., 1987).

2.2.3 Obese hyperglycemic (ob/ob) mice: Ingalls et al., (1950) observed hereditary diabetes in genetically obese mice. The obese hyperglycemic mice were glycosuric, the non-fasting blood sugar levels were about 300 mg %, but neither ketonuria nor coma were observed. One of the most interesting features was insulin-resistance; doses as high as 400 IU/kg had little effect on blood sugar. The serum insulin-like activity was high, the islands of Langerhans were hypertrophic, their insulin content was increased and the liver glycogen stores were decreased. Kidneys and other organs did not show pathological changes. Obviously, the diabetic condition of this and other strains of obese hyperglycemic mice is different from that of the human diabetic patient.

2.2.4 BL/6 obese mice: An obese mutation occurred in a noninbred stock (Ingalls et al., 1950) but was established later, and has been maintained, in the C5BL/6J (BL/6) strain. BL/6 obese mice are characterized by marked obesity, hyperphagia, transient hyperglycemia and markedly elevated plasma insulin concentrations associated with an increase in number and size of beta cells in the islets of Langerhans (Coleman and Hummel, 1973). The mutation is autosomal recessive and homozygous mutants of both sexes are infertile. Obese mutants are obtained by mating known heterozygotes. A primary metabolic disturbance in the adipocyte has been postulated since increased adipocyte size has been observed as early as 14 days of age well before any obesity or hyperinsulinemia are observed (Joosten and van der Kroon, 1974).

2.2.5 NZO mouse: The New Zealand obese (NZO) mouse was first described in 1953 by Bielschowsky and Bielschowsky (1953). The strain was developed by selective
inbreeding of obese mice from a mixed colony, beginning from a pair of agouti mice, which also gave rise to the NZB black strain (Melez et al., 1980). NZO mice develop obesity, mild hyperglycemia, glucose intolerance, hyperinsulinemia, and insulin resistance. The adult NZO mouse normally attains a body weight of 50–70 g by 6–8 months, although weight gain continues slowly after this age (Herberg et al., 1970). Hyperglycemia and glucose intolerance increase continuously with advancing age of the animals.

2.2.6 Diabetes obesity syndrome in CBA/CA mice: A spontaneous maturity onset diabetes obesity syndrome occurs in a small proportion (10–20%) of male CBA/Ca mice. Inbreeding can increase the incidence to 80%. It occurs at 12–16 weeks of age, and is characterized by hyperphagia, obesity, hyperglycemia, hypertriglyceridemia, hyperinsulinemia, and an impaired glucose tolerance. The mice are also resistant to exogenous insulin. Female mice remain normal except for a slight increase in serum insulin. The male obese diabetic mice have a normal life expectancy.

2.2.7 FAT/FAT mice: Fat mice carry an autosomal recessive mutation and display a range of abnormalities, including progressive adult onset obesity, hyperinsulinemia and infertility (Coleman and Eicher 1990). The mutant allele of fat was identified and shown to be a missense (serin→proline) mutation in carboxypeptidase E which abolishes enzyme activity in a variety of neuroendocrine tissues (Naggert et al., 1995). Carboxypeptidase E is required for both sorting and proteolytic processing of a variety of prohormones including proinsulin and POMC (Cool et al., 1997). As carboxypeptidase E is expressed in the CNS, defective processing of a variety of hypothalamic neuropeptides—such as POMC and MCH—may trigger obesity in these animals (Rovere et al., 1996).

2.2.8 Tubby mice: Tubby is an autosomal recessive mutation in mice (Coleman and Eicher, 1990) which display a tripartite phenotype of blindness, deafness and maturity onset obesity. In response to weight gain, these mice gradually increase their food intake in proportion to body weight and increase plasma insulin levels thereby maintaining normoglycemia. The progressive retinal degeneration in tubby mice results from apoptotic loss of photoreceptor cells, with abnormal electrotetinograms detected as early as 3 weeks of age (Heckenlively et al., 1955). The mouse obesity gene tubby has been identified and characterized (Noben-Trauth et al., 1996; Kleyn et al., 1996).
3. **Transgenic animals**

Transgenic animals will offer a new approach to study development of obesity and therapeutic possibilities. Lowell *et al.*, (1993) used a transgenic toxigene approach to create transgenic mice with primary deficiency of brown adipose tissue. The potential for inserting new genetic material into mammals has produced numerous transgenic mice with increased or decreased quantities of body fat (Bray and Bouchard 1997). Jensen *et al.*, (1997) reported prevention of diet-induced obesity in transgenic mice overexpressing skeletal muscle lipoprotein lipase. The authors hypothesized that the potential to increase lipoprotein lipase activity in muscle by gene or drug delivery may prove an effective tool in preventing and/or treating obesity in humans.

**b. Monkeys as animal model of obesity**

Spontaneous obesity and overweight have been noted to occur in several species of nonhuman primates, most notably in macaque and rhesus monkeys. The related literature was reviewed by Kemnitz (Kemnitz, 1984). Obesity in captive monkeys generally occurs in adults and is under the control of a variety of factors, especially food availability and social status. About 10–15% of macaque and rhesus monkeys in captivity will become spontaneously obese with aging when maintained on a relatively low fat (< 10% of energy), *ad libitum* diet. Spontaneous obesity also was observed in “wild” monkeys that were contained on an island at a higher than normal population density through the provision of food (Kemnitz, 1984). Thus, limitation in physical activity arising from caging appears not to be a serious factor in producing spontaneous obesity in monkeys. Obesity is less common in monkeys in their natural environment, probably because of limited food availability and selection pressures from predators.

Spontaneous obesity occurs with a relatively low frequency in captive monkeys fed a low-fat diet. Although limited, data from at least two species (rhesus and squirrel monkeys) indicate that a high-fat diet is associated with increased energy intake and, when maintained over a long period of time, an increase in body fat content.

**c. Dogs as animal model of obesity**

It has certainly been noted that obesity is a significant problem among companion animals, especially dogs, with 25–44% of pet dogs being obese (Hand *et al.*, 1989). A significant amount of veterinary literature has addressed the treatment of obesity in companion animals, along with the incidence and treatment of obesity-related diseases in dogs. However, little is actually known regarding the etiology of obesity in pet dogs, although it is often attributed to low levels of physical activity and highly palatable diets.
It has been observed that specific breeds present at veterinary clinics with obesity more frequently than others (Edney et al., 1986). The results from studies conducted in dogs suggest that increased dietary fat content is associated with greater body fat accumulation. The magnitude of this effect may be strain dependent.

d. Pigs as animal model of obesity

Pigs generally respond to increased dietary fat by increasing their body fat. For example, Pond et al (Pond et al., 1985) fed both genetically obese and lean castrated male pigs a low-fat diet and the same diet supplemented with beef tallow (11% by weight) and dried egg yolk (1%) for a 16-mo period beginning at age 7 wk. The animals were initially fed ad libitum for 4 mo and were then maintained on 1.82 kg diets daily until age 16 months. Restricted feeding of pigs is important in nutrient manipulation studies because pigs will become markedly obese with low-fat diets when given ad libitum access to food. Back fat thickness was not affected by diet in the genetically obese pigs; however, in the lean pigs back fat thickness was 4.4 cm in the high-fat diet group and 3.5 cm in the low-fat control group. In a similar study by Diersen-Schade et al. (Diersen-Schade et al., 1985), young pigs were given liberal access (<90% of ad libitum intake) or restricted access to soy-oil or beef-based diets containing 40–50% of energy from fat, or given a conventional diet containing <8–9% fat. With liberal access to food, the effect on body fat of the high-fat diets was even greater. Earlier studies in both young and growing pigs also found that increasing dietary fat increased fat accumulation (Allee et al., 1971; Frobish et al., 1970).

J. HIGH FAT DIET (HFD)-INDUCED OBESITY MODEL

In animal models as in humans, obesity can be assessed by criteria based on (1) gain of body weight or the Lee obesity index and/or (2) increase of body fat content. However standard thresholds for obesity have not been developed like body mass index (BMI) in human beings. In most studies, the degree of obesity has been evaluated by comparing body weight (or fat) of the experimental group fed high-fat/energy-dense diet with control animals that show normal growth while fed chow or low fat diets. Researchers that have attempted to do so differed in the values that are 10%-25% greater body weight than age-matched control rats fed chow (normal pattern of body weight gain) as moderate obesity (Harrold et al., 2000; Woods et al., 2003) and greater than 40% as severe obesity (Harrold et al., 2000; Ghibaudi et al., 2002; Woods et al., 2003).

The Lee index for assessing obesity in rats is similar to BMI in humans. It was defined by Lee in 1929 (Lee 1929) as the cube root of body weight (g) divided by the naso-anal
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length (cm) and multiplied by 1000. Lee considered values greater than 310 as an indicator of obesity. Since then some researchers have used Lee index to assess the levels of obesity in rats (Sun et al. 2002; Li et al., 2004). Reliable correlations were found in some studies between the Lee index and fat content of the body (Rogers and Webb 1980).

In rats fed diets high in fat, a linear increase in body fat with increasing body weight has been shown. However results of the study of Woods et al. (Woods et al., 2003) showed that measuring body fat is a more sensitive criterion for assessing obesity in animals since rats fed a high-fat diet (40% of energy) for 10 weeks displayed a 10% increase in total body weight but a 35-40% increase in total body fat compared to the animals fed a low-fat diet. In models of dietary obesity, animals are classified to prone and resistant based on their body weight, body weight gain, body fat, or norepinephrine (NE) concentrations in urine. Tulipano et al. (2004) categorized Sprague-Dawley rats fed high-fat diet based on their final body weight, with rats in the highest quartile designated as obesity prone and those in the lowest quartile assigned as obesity resistant. In some studies upper (prone) and lower (resistant) tertiles of body weight gain (Levin and Dunn-Meynell 2002; Huang et al., 2004) or body fat of the animals fed high-fat diets have been used for this classification. Prior to developing obesity while fed with chow, prone and resistant animals have also been identified based on high and low levels of urinary NE, respectively (Hassanain and Levin 2002). Dietary fat intake often has been claimed as responsible for the increase in adiposity. Human studies have shown that high-fat diets (≥ 30% of energy from fat) can easily induce obesity (French and Robinson 2003).

1. Composition of high fat diet (HFD)
Composition of a standardized high fat diet (HFD) from NIN, Hyderabad: Casein 1.71 kg; Cystine 15 gms; Starch 0.860 kg; Sucrose 0.860 kg; Cellulose 0.250 kg; G. N. oil 0.125 kg; Tallow 0.950 kg; Mineral Mix (AIN) 0.175 kg; Vitamin Mix (AIN) 0.05 g.

2. Role of ingredients in the composition of high fat diet (HFD)
Casein: Casein has cholepoietic effect and increase the efficacy of fat absorption (Magee et al., 1953).

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

Tallow: Tallow has include about 42% saturated fatty acids and only 1% unsaturated fatty acids. High tallow level decreased feed intake, poor fat digestion (Sedeghi and Tabiedian, 2005).
Sucrose, Starch & Cellulose: These are carbohydrates and provide energy. The excess energy intake causes body fat accumulation, and lead to obesity if energy expenditure is not increased. High intake of simple sugars is generally seen as a detrimental factor in the etiology of both obesity and insulin resistance. Sucrose feeding produces a major impairment of insulin action, predominantly because of an effect at the liver. Free access to sugar solutions in rat experiments leads to rapid weight gain and increased adiposity. The combination of high intakes of dietary fat and sucrose could be particularly potent in the etiology of both diabetes mellitus and obesity (Storlien, 1988). Rats fed high-sucrose or high-starch diets exhibited similar body weight gains and visceral fat accumulation. Both the high-sucrose and the high-starch fed rats accumulated ~35% more visceral fat in 4 weeks than the chow-fed controls (Chun et al., 2010).

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

Mineral Mix and Vitamin Mix: The vitamins and minerals replenish the energy requirements of the body by acting co-enzyme and by participating in metabolic processes e.g. Thiamine and Niacin are essential for protein and carbohydrate metabolism as well as release the energy from carbohydrates. Intake of vitamins plays an important role in avoiding obesity (e.g. vitamin B2, B3, B5, B6 and vitamin C). Manganese involved in the metabolism of carbohydrates, fats and proteins (Srinivasan and Pugalendi, 2000).

K. MONOSODIUM GLUTAMATE (MSG)-INDUCED OBESITY MODEL
MSG is a salt derivation of the amino acid glutamic acid, or glutamate, that is commonly found in Asian cuisine associated with Chinese restaurants and now frequently found in the Western diet (Shi et al., 2010). Because MSG is both an additive and a chemical in natural foods, exposure to this substance is worldwide. Glutamate is an amino acid that is vital in metabolism specifically involved in the breakdown of protein (Matyskova et al., 2007). MSG, like salt in the United States and other Western nations, is one of the most common food additives and flavor enhancers in Asian food. MSG is commonly found in high fat foods associated with unhealthy eating (Collison et al., 2010).
Glutamate is an important aspect of metabolism, as well as a neurotransmitter that relays signals between the brain, nervous system, and digestive system, the amount of consumption of MSG could play a role in weight gain (Shi et al., 2010). Many studies will suggest that the scarring of the arcuate nucleus of the hypothalamus indirectly contributes to the increase in adiposity and body mass measured in rats and humans, as well as facilitating leptin resistance and the level of food consumption (Pepino et al., 2005, Sasaki et al., 2009). The arcuate nucleus contains neuron bundles that are associated with neuroendocrine functioning, specifically human growth hormones, as well as subject to the effects of leptin and insulin inhibition that is known to affect appetite and the amount of food consumption. Leptin is a protein hormone involved in the regulation of appetite and metabolism. Leptin is produced mainly by white adipose tissue and its levels are related to the amount of adipose tissue and affects both food consumption and hunger. Adiposity refers to the amount of fat found in adipose tissue (Matyskova et al., 2007).

Research suggests a relationship between consumption of MSG and weight gain and obesity in humans, but the exact mechanism and level of neurotoxic activity underlying negative health implications is relatively unexplored. As in many cases involving human research, it is necessary to explore animal research with MSG, both orally and neonatally ingested, to understand the possible mechanisms of MSG-induced weight gain and the validity of previous studies’ claims that MSG consumption leads directly to weight gain and obesity. In order to more closely assess issues of obesity, weight gain, adiposity, leptin resistance, food consumption, and their interaction, this review presents studies that differ in their methods of inducing MSG consumption in animals (Collison et al., 2010).

While Collison et al., (2010) assessed spatial memory in addition to weight gain, Sasaki et al., (2009) sought to assess the effects of MSG consumption on diseases more closely linked to weight, such as diabetes mellitus and steatohepatitis of the liver. As MSG consumption has a possible connection to severe obesity, urinary glucose, hyperinsulinemia, and a decrease in both glucose tolerance and insulin sensitivity, Sasaki et al., (2009) looked to understand further the relationship between MSG consumption (at varying dosage levels), weight, and the aforementioned diseases.

L. MANAGEMENT OF OBESITY

Antiobesity medication or weight loss drugs refer to all pharmacological agents that reduce or control weight. These drugs alter one of the fundamental processes of the
human body, weight regulation, by either altering appetite, metabolism, or absorption of calories. It is common for them to be tried and if there is little or no benefit from them to discontinue treatment (National Institute for Health and Clinical Excellence, 2006). Lifestyle interventions including changes in diet and physical activity remain the cornerstone of treatment for overweight and obese individuals. However, lifestyle modifications have not been effective in providing lasting weight loss success. Studies reveal that behavioral interventions aimed at reducing calorie intake and increasing calories expended in daily physical activities can result in 9-10% total body weight loss during the first six months of treatment. However, data shows that one-third to two-thirds of lost weight is regained within one-year following end of treatment, and that almost all weight is regained within 5 years post treatment (Foster, 2006).

Overlapping physiological systems aimed at maintaining fat mass as a survival measure, as well as several environmental obstacles in our "obesigenic" environment have been identified as promoting weight regain (Korner and Aronne, 2003). More aggressive treatment of obesity appears necessary. The National Heart, Lung and Blood Institute of the National Institutes of Health, recommends that for Individuals who fail to respond to lifestyle interventions after 6 months of treatment, and have a BMI of > 30 kg/m², or a BMI of > 27 kg/m² and present with weight-induced comorbidity may have weight loss medication added to their treatment plan (National Institutes of Health, National Heart, Lung, and Blood Institute, 2002).

Health care professionals should be familiar with the basic principles regarding the pharmacotherapy of obesity. The goal of treatment is not only to reduce weight, but more importantly to improve the comorbid conditions associated with obesity, such as hyperglycemia, hyperlipidemia, and heart disease.

M. PHARMACOLOGICAL TREATMENT OF OBESITY

It has only been within the past 10-15 years that our improved understanding of the endogenous systems influencing body weight regulation has been elucidated. Research and development of medications targeting these systems are on the horizon. Given the increasing burden of disease associated with obesity, and steadily increasing evidence on the benefits of weight loss, there is a clear medical need for effective treatment. Pharmacological agents are often used in the treatment of obesity. After withdrawal of sibutramine by different countries viz. Australia, Canada, China, the European Union (EU), Hong Kong, India, Mexico, Thailand, the UK, and the United States in 2010-2011 due to its cardiac toxicity (heart attack, stroke and death), orlistat is the only Food and
Drug Administration (FDA)–approved long-term-use antiobesity drug though its use is often associated with gastrointestinal side effects (oily, loose stools and fecal incontinence) (Pagotto et al., 2008; Lee et al., 2009).

Table 2. Review of medications for weight loss

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA approval status</th>
<th>Mechanism of action prompting weight loss</th>
<th>Side- effects</th>
<th>Placebo-corrected weight loss (Pooled Data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sibutramine</td>
<td>FDA approved for weight loss in 1997 and withdrawn in 2010</td>
<td>Appetite suppressant: Combined norepinephrine and serotonin reuptake inhibitor</td>
<td>Modest increase in heart rate and blood pressure, nervousness, insomnia</td>
<td>-4.45 kg</td>
</tr>
<tr>
<td>Phentermine</td>
<td>FDA approved for short-term weight loss in 1959</td>
<td>Appetite suppressant: Sympathomimetic amine</td>
<td>Cardiovascular, gastrointestinal</td>
<td>-3.6 kg</td>
</tr>
<tr>
<td>Orlistat</td>
<td>FDA approved for long-term weight loss in1999</td>
<td>Lipase inhibitor</td>
<td>Diarrhea, flatulence, bloating, abdominal pain, dyspepsia</td>
<td>-2.75 kg</td>
</tr>
<tr>
<td>Bupropion</td>
<td>FDA approved for depression</td>
<td>Appetite suppression: Mechanism unknown</td>
<td>Paraesthesia, insomnia, central nervous system effects</td>
<td>-2.77 kg</td>
</tr>
<tr>
<td>Toprimate</td>
<td>FDA approved for epilepsy and migraine treatment</td>
<td>Mechanism unknown</td>
<td>Paraesthesia, taste aversion</td>
<td>-6.5%</td>
</tr>
<tr>
<td>Rimonabant</td>
<td>FDA approval not received</td>
<td>Appetite suppressant: Decreases endocannabinoid system action by blocking cannabinoid-1 receptors</td>
<td>Depression, anxiety, headache, nausea, vomiting, diarrhea</td>
<td>-5 %</td>
</tr>
<tr>
<td>Tesofensine (NS-2330)</td>
<td>Phase 2</td>
<td>5-HT, NE, and DA inhibitor</td>
<td>Nausea, constipation, dry mouth</td>
<td>-</td>
</tr>
<tr>
<td>Cetilistat (ATL-962)</td>
<td>Phase 3</td>
<td>GI and pancreatic lipase inhibitor</td>
<td>Flatulence, steatorrhea, increased stool frequency, fecal incontinence, oily fecal discharge</td>
<td>-</td>
</tr>
</tbody>
</table>

The obesity epidemic continues to grow at an alarming rate. Pharmacotherapy has been shown to be effective in promoting weight reduction and improvement of comorbid conditions. As our understanding of obesity grows so too will our armamentarium to combat this disease. There are several promising medications currently in clinical trials
that induce weight loss through several separate mechanisms. Ultimately obesity will most likely be treated with combinations of medications, similar to other chronic diseases such as heart disease, hypertension, and diabetes.

1. Orlistat

Orlistat (Xenical) reduces intestinal fat absorption by inhibiting pancreatic lipase. Originally available only by prescription, it was approved by the FDA for over-the-counter sale in February 2007 (National Institute for Health and Clinical Excellence, 2006). Orlistat may cause frequent, oily bowel movements (steatorrhea), but if fat in the diet is reduced, symptoms often improve.

2. Sibutramine

Sibutramine (Reductil or Meridia) is an anorectic or appetite suppressant, reducing the desire to eat. Both drugs have side effects. Sibutramine may increase blood pressure and may cause dry mouth, constipation, headache, and insomnia.

3. Rimonabant

Rimonabant (Acomplia) is a recently developed anti-obesity medication not in use. It is cannabinoid (CB1) receptor antagonist that acts centrally on the brain thus decreasing appetite. It may also act peripherally by increasing thermogenesis and therefore increasing energy expenditure (Akbas et al., 2009). Due to safety concerns, primarily psychiatric in nature, the drug has not received approval in the United States or Canada.

4. Metformin

In people with Diabetes mellitus type 2, the drug metformin (Glucophage) can reduce weight (George et al., 1999).

5. Exenatide

Exenatide (Byetta) is a long-acting analogue of the hormone GLP-1, which the intestines secrete in response to the presence of food. Among other effects, GLP-1 delays gastric emptying and promotes a feeling of satiety. Some obese people are deficient in GLP-1, and dieting reduces GLP-1 further (de Luis et al., 2007). Byetta is currently available as a treatment for Diabetes mellitus type 2. Some, but not all, patients find that they lose substantial weight when taking Byetta. Drawbacks of Byetta include that it must be injected subcutaneously twice daily, and that it causes severe nausea in some patients, especially when therapy is initiated. Byetta is recommended only for patients with Type 2 Diabetes. A somewhat similar drug, Symlin, is currently available for treating diabetes and is in testing for treating obesity in non-diabetics.
6. Pramlintide

Pramlintide (Symlin) is a synthetic analogue of the hormone Amylin, which in normal people is secreted by the pancreas in response to eating. Among other effects, Amylin delays gastric emptying and promotes a feeling of satiety. Many diabetics are deficient in Amylin. Currently, Symlin is only approved to be used along with insulin by Type 1 and Type 2 diabetics. However, Symlin is currently being tested in non-diabetics as a treatment for obesity. A drawback is that Symlin must be injected at mealtimes.

N. CURRENT CRITERIA FOR EVALUATION OF NEW ANTIOBESITY DRUGS

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

O. STATINS

Statins (or HMG-CoA reductase inhibitors) are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. Increased cholesterol levels have been associated with cardiovascular diseases (Shiu et al., 2012; Lewington et al., 2007), and statins are therefore used in the prevention of these diseases. Evidence has found that they are most effective in those with cardiovascular disease (secondary prevention), with questionable benefit in those without previous CVD but with elevated cholesterol levels (Taylor 2011).
In 1971, Akira Endo, a Japanese biochemist working for the drug company Sankyo, began the search for a cholesterol-lowering drug. Research had already shown that cholesterol is mostly manufactured by the body in the liver, using an enzyme known as HMG-CoA reductase (Simons and John, 2003). Endo and his team reasoned that certain microorganisms may produce inhibitors of the enzyme to defend themselves against other organisms, as mevalonate is a precursor of many substances required by organisms for the maintenance of their cell wall (ergosterol) or cytoskeleton (isoprenoids) (Simons and John, 2003). The first agent they identified was mevastatin (ML-236B), a molecule produced by the fungus Penicillium citrinum.

1. **Mechanism of action of statins**

Statins act by competitively inhibiting HMG-CoA reductase, the first committed enzyme of the HMG-CoA reductase pathway. Because statins are similar to HMG-CoA on a molecular level they take the place of HMG-CoA in the enzyme and reduce the rate by which it is able to produce mevalonate, the next molecule in the cascade that eventually produces cholesterol, as well as a number of other compounds. This ultimately reduces cholesterol via several mechanisms. By inhibiting HMG-CoA reductase, statins block the pathway for synthesizing cholesterol in the liver. This is significant because most circulating cholesterol comes from internal manufacture rather than the diet. When the liver can no longer produce cholesterol, levels of cholesterol in the blood will fall. Cholesterol synthesis appears to occur mostly at night (Miettinen, 1982), so statins with short half-lives are usually taken at night to maximize their effect. Studies have shown greater LDL and total cholesterol reductions in the short-acting simvastatin taken at night rather than the morning (Saito et al., 1991; Wallace et al., 2003), but have shown no difference in the long-acting atorvastatin (Cilla et al., 1996).

Liver cells sense the reduced levels of liver cholesterol and seek to compensate by synthesizing LDL receptors to draw cholesterol out of the circulation (Ma et al., 1986). This is accomplished via protease enzymes that cleave a protein called "membrane-bound sterol regulatory element binding protein", which migrates to the nucleus and causes increased production of various other proteins and enzymes, including the LDL receptor. The LDL receptor then relocates to the liver cell membrane and binds to passing LDL and VLDL particles (the "bad cholesterol" linked to disease). LDL and VLDL are drawn out of circulation into the liver where the cholesterol is reprocessed into bile salts. These are excreted, and subsequently recycled mostly by an internal bile salt circulation.
2. Pleiotropic effects of statins
Statins not only have lipid-lowering effects, but also have been shown to present a variety of beneficial “pleiotropic”, vasculoprotective effects, including cardiovascular disease, improved endothelial function, reduced oxidative stress, less platelet adhesion and atherosclerotic plaque stabilization (Yoshioka et al., 2010).

3. Adverse effects of statins
The most common adverse side effects are raised liver enzymes and muscle problems. Rare reactions include myositis and myopathy, with the potential for rhabdomyolysis (the pathological breakdown of skeletal muscle) leading to acute renal failure.

4. Drug interactions of statins
Combining any statin with a fibrate or niacin, another category of lipid-lowering drugs, increases the risks for rhabdomyolysis to almost 6.0 per 10,000 person-years (Graham et al., 2004). Most physicians have now abandoned routine monitoring of liver enzymes and creatine kinase, although they still consider this prudent in those on high-dose statins or in those on statin/fibrate combinations, and mandatory in the case of muscle cramps or of deterioration in renal function.

5. Available forms of statins
The statins are divided into two groups: fermentation-derived and synthetic. They include, along with brand names, which may vary between countries:

<table>
<thead>
<tr>
<th>Statin</th>
<th>Brand name</th>
<th>Derivation</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Lipitor, Torvast</td>
<td>Synthetic</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>Lipobay, Baycol.</td>
<td>Synthetic</td>
<td>various CYP3A isoforms</td>
</tr>
<tr>
<td></td>
<td>(Withdrawn from the market in August, 2001 due to risk of serious Rhabdomyolysis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Lescol, Lescol XL</td>
<td>Synthetic</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Mevacor, Altocor, Altoprev</td>
<td>Naturally-occurring compound. Found in oyster mushrooms and red yeast rice.</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Mevastatin</td>
<td>Compactin</td>
<td>Naturally-occurring compound. Found in red yeast rice.</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Pivastatin</td>
<td>Livalo, Pitava</td>
<td>Synthetic</td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Pravachol, Selektine, Lipostat</td>
<td>Fermentation-derived. (A fermentation product of bacterium Nocardia autotrophica).</td>
<td>Non CYP</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Crestor</td>
<td>Synthetic</td>
<td>CYP2C9 and CYP2C19</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Zocor, Lipex</td>
<td>Fermentation-derived. (Simvastatin is a synthetic derivate of a fermentation product of Aspergillus terreus.)</td>
<td>CYP3A4</td>
</tr>
</tbody>
</table>
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LDL-lowering potency varies between agents. Cerivastatin is the most potent, (withdrawn from the market in August, 2001 due to risk of serious Rhabdomyolysis) followed by (in order of decreasing potency), rosuvastatin, atorvastatin, simvastatin, lovastatin, pravastatin, and fluvastatin (Shepherd et al., 2003). The relative potency of pitavastatin has not yet been fully established.

6. Statins in obesity

Statins are thought to have additional benefits beyond cardiovascular disease, such as in type 2 diabetes, hypertension, dementia, cancer, and bone metabolism (Rosenson, 2008). This diversity of effects makes it likely that statins can affect numerous cell types and tissues, either through their lipid-lowering properties or through alternative mechanisms. The liver is the primary target of statins due to its important role in the regulation of cholesterol biosynthesis and LDL turnover. However, the additional benefits that statins display suggest important effects in nonhepatic tissues and cell types as well. Adipose tissue is a good candidate tissue to further explore statin action due to its unique ability for bulk cholesterol storage (Angel and Farkas, 1974). Although most cell types use cholesterol predominantly to maintain the structure of their cell membrane, adipocytes are unique for their storage capacity of very large quantities of cholesterol, accounting for as much as 25% of whole-body cholesterol. Adipocytes have a relatively low de novo cholesterol synthesis rate, accounting for less than 10% of total systemic cholesterol production. Most adipocyte cholesterol is in a free, nonesterified form and is localized to lipid droplets (Le, 2004). In addition, the adipocyte plasma membrane is extremely rich in lipid raft and caveolar structures. Both rafts and caveolae are microdomains highly enriched in cholesterol and are very sensitive to even modest changes in cellular cholesterol levels.

A growing body of evidence shows that statins, HMG–CoA reductase enzyme inhibitors, reduce cardiovascular-related mortality in patients (Sattar, 2003). Statins have a lipid-lowering effect that acts on both total cholesterol and triglyceride (TG) levels (Kasim et al., 1992). The decrease in total cholesterol levels was accompanied by a decrease in the progression of atherosclerosis and cardiovascular disease (Nakamura, et al., 2006). Previous studies have demonstrated that a decrease in serum TG levels could have resulted in the alteration of glucose and lipid homeostasis, which is characteristic of metabolic syndrome (Palomo et al., 2006).

The improvements in lipid profile and atherosclerotic process due to statin use are the result, partly, but importantly, of statin induced enhancement of the adipocyte functions.
Prevention of cardiovascular complications in patients with obesity and/or metabolic syndrome frequently requires statins (3-hydroxy-3-methylglutaryl-Co-A reductase inhibitors) to treat coexisting dyslipidemia. However, their effects on adipose function and insulin resistance underlying these pathologic conditions vary among the different statins (Ishihara et al., 2010).

Statin namely pravastatin is shown in a large clinical trial to have a protective role against the development of hyperlipidemia and related metabolic disorder. Moreover, a recent clinical study revealed that pravastatin treatment ameliorated the insulin sensitivity of metabolic syndrome (Güçlü et al., 2004). Several clinical observations support routine statin therapy for patients with type 2 diabetes resulting from metabolic syndrome (Takano et al., 2006).

7. Current research status of statins on lipid and non lipid metabolic disorders

Koutaro et al. (2008) compare the efficacy and safety of pitavastatin and atorvastatin in Japanese patients with hypercholesterolemia. Pitavastatin 2 mg and atorvastatin 10 mg are equally effective in improving the lipid profile and were well tolerated in Japanese patients with hypercholesterolemia. They concluded that, both pitavastatin 2 mg and atorvastatin 10 mg were well tolerated, lowered non-HDL-C and improved the lipid profile to a comparable degree in Japanese patients with hypercholesterolemia. Non-HDL-C lowering by atorvastatin was more prominent in lean than in obese patients, suggesting the effects of a statin may be influenced by an individual’s metabolic background.

Michael et al. (2007) reported a 12-week, prospective, open-label analysis of the effect of Rosuvastatin on triglyceride-rich lipoprotein metabolism in patients with primary dyslipidemia. Results showed that the baseline TG levels were the most important independent variable associated with the TG lowering effect of Rosuvastatin.

Park et al. (2005) performed a randomized, open-label study to evaluate the efficacy and safety of Pitavastatin compared with Simvastatin in Korean patients with hypercholesterolemia. The HMG-CoA reductase inhibitor Pitavastatin was found to be non inferior to Simvastatin in terms of reducing LDL cholesterol, total cholesterol, and triglyceride levels, and increasing HDL cholesterol levels, in Korean patients with hypercholesterolemia after 8 weeks of treatment.

Watts et al. (2003) reported the effect of Atorvastatin, a statin, on cholesterol synthesis and absorption and VLDL-apoB metabolism in obese men with the metabolic syndrome.
Compared with placebo, Atorvastatin significantly decreased total cholesterol, triglyceride, LDL-cholesterol and VLDL-apo-B. In obesity, atorvastatin inhibits cholesterogenesis but increases intestinal cholesterol absorption. The increased cholesterol absorption may counteract the inhibitory effect on hepatic VLDL-apo-B secretion, but it does not apparently influence enhanced catabolism of VLDL-apo-B. Although there have been a number of clinical reports indicating that statins have an effect on insulin sensitivity, this is far from being an accepted fact in the field, with almost an equal number of reports arguing against a direct impact on any parameters with respect to carbohydrate metabolism. Much of the variability is likely due to differences in the type of statins used, length of treatment, and/or differences in patient populations. In addition, many studies examine statin effects using \textit{in vitro} models, which are not always an accurate reflection of normal physiological conditions \textit{in vivo}.

Two novel statins—rosuvastatin and pitavastatin are currently under clinical investigations. Preliminary data of rosuvastatin and pitavastatin suggest that these compounds are even more powerful than other statins and therefore are sometimes called “superstatins” (Igel \textit{et al.}, 2002).

**P. ROSUVASTATIN**

**Rosuvastatin** (marketed by AstraZeneca as Crestor & marketed by Abbott Healthcare Pvt. Ltd. in India as 'R2') is a member of the drug class of statins, used to treat high cholesterol and related conditions, and to prevent cardiovascular disease. It was developed by Shionogi. Rosuvastatin has been shown to reduce LDL-C in a dose-dependent fashion by 46% to 55%, and has a similar safety profile to other statins. Compared with other statins, however, the terminal half-life of rosuvastatin is relatively long at approximately 18 to 20 h, its prolonged survival and hydroxy-methyl-glutaryl (HMG) CoA reductase inhibition (Li \textit{et al.}, 2012).

**1. Mechanism of action of rosuvastatin**

Rosuvastatin is a competitive inhibitor of the enzyme HMG-CoA reductase, having a mechanism of action similar to that of other statins. Its approximate elimination half life is 19 hours and its time to peak plasma concentration is reached in 3–5 hours following oral administration (Nissen \textit{et al.}, 2006).

Putative beneficial effects of rosuvastatin therapy on chronic heart failure may be negated by increases in collagen turnover markers as well as a reduction in plasma coenzyme Q10 (CoQ10) levels in patients with chronic heart failure (Ashton \textit{et al.}, 2010).
2. Adverse effects of rosuvastatin

As with all statins, there is a concern of rhabdomyolysis, a severe undesired side-effect. The FDA has indicated that "it does not appear that the risk [of rhabdomyolysis] is greater with Crestor than with other marketed statins", but has mandated that a warning about this side-effect, as well as a kidney toxicity warning, be added to the product label (FDA Aler 2005).

Table 4. Properties of rosuvastatin (RSV)

<table>
<thead>
<tr>
<th>Rosuvastatin</th>
<th>Systematic (IUPAC) name</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(3R,5S,6E)-7-[4-(4-fluorophenyl)-2-(N-methylmethanesulfonamido)-6-(propan-2-yl) pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid.</td>
</tr>
<tr>
<td></td>
<td>[Rosuvastatin has structural similarities with most other synthetic statins, e.g., atorvastatin, cerivastatin, pitavastatin, but rosuvastatin unusually also contains sulfur]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical data</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade names</td>
<td>Crestor</td>
</tr>
<tr>
<td>Routes</td>
<td>Oral</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacokinetic data</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>20%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Liver</td>
</tr>
<tr>
<td>Half-life</td>
<td>19 h</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urine / Faeces</td>
</tr>
</tbody>
</table>

Rosuvastatin (RSV) seems to be the most potent in terms of LDL-C-lowering capacity and exhibits a substantial triglycerides (TGs)-lowering effect as well (Kostapanos et al., 2007). The effects of RSV on lipid metabolic disorders, predominantly hyperlipidemia and cardiovascular disorders have been reported in various research studies (Kostapanos et al., 2007). RSV has been reported to have antioxidant property in management of diabetes and cardiovascular disease (CVD) (Miersch et al., 2007). Christos et al. reported the effects of rosuvastatin combined with Olmesartan, Irbesartan, or Telmisartan on indices of glucose metabolism in Greek adults with impaired fasting glucose, hypertension, and mixed hyperlipidemia in a 24-week, randomized, open-label, prospective study. They found that rosuvastatin had favorable effects on homeostasis model assessment of insulin resistance (HOMA-IR), fasting serum insulin, and C-reactive protein compared with Greek adults having impaired fasting glucose, mixed hyperlipidemia, and stage 1 hypertension (Christos et al., 2010). Insulin resistance, mild
hyperglycemia, hyperleptinemia and hypertension are the prominent indicators of obesity (Srinivasan et al., 2005; Considine et al., 1996).

3. Current research status of rosuvastatin

Li et al. (2012) evaluated the potential efficacy of alternate-day dosing of 10 mg rosuvastatin compared with daily dosing of 10 mg rosuvastatin with regarding to lipid and inflammatory markers in patients with dyslipidemia. Thirty-seven patients were randomly divided into the 2 groups: alternate-day group (rosuvastatin 10 mg every other day, n=19) and once-daily group (rosuvastatin 10 mg every day, n=18) for 6 weeks. They concluded that alternate-day dosing of rosuvastatin could be effective comparable with once-daily dosing of rosuvastatin in Chinese patients in improving not only lipid profile but also inflammatory markers, which may provide some cost savings and increase the compliance of patients.

Agapakis et al. (2011) evaluated the effect of rosuvastatin on D-d levels in patients with uncontrolled primary dyslipidemia and elevated body mass index (BMI). 37 patients with uncontrolled primary dyslipidemia under hypolipidemic diet treatment, included in the study. They concluded that their data support that beyond the hypolipidemic effect rosuvastatin also possesses significant anti-coagulation properties and could play a role in reducing thromboembolic complications in primary hyperlipidemic obese patients.

Christos et al. (2010) reported the effects of rosuvastatin combined with olmesartan, irbesartan, or telmisartan on indices of glucose metabolism in Greek adults with impaired fasting glucose, hypertension, and mixed hyperlipidemia in a 24-week, randomized, open-label, prospective study. They found that the RT (rosuvastatin + telmisartan;) combination had favorable effects on homeostasis model assessment of insulin resistance (HOMA-IR), fasting serum insulin, and C-reactive protein compared with the RI (rosuvastatin + irbesartan) and RO (rosuvastatin + olmesartan) combinations in Greek adults with impaired fasting glucose, mixed hyperlipidemia, and stage 1 hypertension.

Wingard et al., (2009) hypothesized that regulatory aspects of short-term statin therapy involve the alteration of the RhoA/Rho-kinase signaling cascade and will reverse the erectile dysfunction seen in a rat. They concluded that their results support a hypothesis that short-term statin therapy may lower RhoA/Rho-kinase expression levels and improve cavernosal blood pressure response to Rho-kinase inhibition and voltage-stimulation, and reversing an augmented vasoconstricted state associated with diabetes and/or hypertension.
Laumen et al. (2008) investigated the effect of rosuvastatin on the regulation of plasminogen activator-1 (PAI-1) gene expression in human adipocytes. They concluded that their data suggest that rosuvastatin inhibits PAI-1 expression and release from human adipocytes.

Michael et al. (2007) reported a 12-week, prospective, open-label analysis of the effect of rosuvastatin on triglyceride-rich lipoprotein metabolism in patients with primary dyslipidemia. Result showed that the baseline TG levels were the most important independent variable associated with the TG lowering effect of rosuvastatin.

Chong et al. (2006) evaluated the effect of rosuvastatin on hepatic production of apolipoprotein B-containing lipoproteins in an animal model of insulin resistance and metabolic dyslipidemia. Their study suggested that the assembly and secretion of VLDL particles in hamster hepatocytes can be acutely inhibited by rosuvastatin in a process involving enhanced apo-B degradation. This appears to lead to a significant amelioration of hepatic VLDL-apo-B overproduction observed in the fructose-fed, insulin-resistant hamster model.

ter Avest et al. (2005) evaluated the effect of rosuvastatin on serum lipids and insulin sensitivity in nondiabetic subjects with familial combined hyperlipidaemia (FCH), a population characterized by decreased insulin sensitivity. Their study concluded that despite marked improvements in lipid and lipoprotein values, low-grade inflammation and oxidative stress, a relatively high dose of rosuvastatin did not change insulin sensitivity in subjects with FCH.

Timo et al. (2004) performed a twelve-week, multicenter, randomized, open-label comparison of the effects of Rosuvastatin 10 mg/d and Atorvastatin 10 mg/d in high-risk adults: a discovery study. In this study of selected patients at high risk for CHD and with primary hypercholesterolemia, Rosuvastatin 10 mg/d for 12 weeks was associated with significantly greater reductions in LDL-C and TC levels compared with Atorvastatin 10 mg/d. Furthermore, significantly more patients receiving Rosuvastatin achieved the 1998 and 2003 JTF-recommended lipid targets compared with those receiving Atorvastatin. Both agents were well tolerated.

Christie et al. (2003) performed an exploratory analysis of data from 5 trials to study the effects of rosuvastatin 10 mg on lipid levels and ratios in hypercholesterolemic patients (LDL cholesterol >160 mg/dL and < 250 mg/dL) who met a modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition of the metabolic syndrome. Of 580 patients completing 12 weeks of treatment with
rosuvastatin 10 mg, 194 (33%) met the definition of the metabolic syndrome by exhibiting >3 of the following: body mass index >30; triglycerides >150 mg/dL; high-density lipoprotein (HDL) cholesterol <40 mg/dL in men and <50 mg/dL in women; blood pressure >130/>85 mm Hg or receiving current medication for hypertension; and fasting blood glucose >110 mg/dL. In patients with the metabolic syndrome, rosuvastatin 10 mg improved LDL cholesterol (47%), non-HDL cholesterol (43%), non-HDL cholesterol/HDL cholesterol ratio (47%), apolipoprotein B (37%), apolipoprotein B/apolipoprotein A-I ratio (40%), triglycerides (23%), apolipoprotein A-I (7%), and HDL cholesterol (10%)—in a manner similar to that in hypercholesterolemic patients who did not meet these criteria. Among patients who met the metabolic syndrome criteria and who had triglycerides >200 mg/dL, 64% met their ATP III non-HDL goals.

Jones et al. (2002) examined the possible effects of a novel 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, rosuvastatin, on endothelial nitric oxide (NO) production and myocardial ischemia-reperfusion injury. Wild-type mice (n = 158) were subjected to 30 min of regional myocardial ischemia and 24 h of reperfusion. They concluded that data of the present study demonstrate that rosuvastatin increases vascular endothelial NO production and attenuates myocardial necrosis following ischemia and reperfusion in mice.

Olsson et al. (2001) conducted 2 dose-ranging studies. In the first study, after a 6-week dietary run-in, 142 moderately hypercholesterolemic patients were randomized equally to receive double-blind placebo or rosuvastatin 1, 2.5, 5, 10, 20, or 40 mg or open-label atorvastatin 10 or 80 mg once daily for 6 weeks; in the second study, conducted to extend the rosuvastatin dose range, 64 patients were randomized to double-blind, once-daily placebo or rosuvastatin 40 or 80 mg (1:1:2 ratio) for 6 weeks. Over 6 weeks, rosuvastatin produced large, rapid, dose-dependent LDL cholesterol reductions and was well tolerated in hypercholesterolemic patients.

**Q. PITAVASTATIN**

Pitavastatin, previously named Itavastatin or Nisvastatin (Noji et al., 2002), is a new, totally synthetic HMG-CoA reductase inhibitor, which has a potentially stronger cholesterol-lowering action compared with other statins (Saito et al., 2002). Pitavastatin (usually as a calcium salt) is a member of the medication class of statins (Kajinami et al., 2003), marketed in the United States under the trade name Livalo. It has been available in Japan since 2003, and is being marketed under licence in South Korea and in India. It is likely that pitavastatin will be approved for use in hypercholesterolaemia (elevated...
levels of cholesterol in the blood) and for the prevention of cardiovascular disease outside South and Southeast Asia as well (Mukhtar et al., 2005).

Pitavastatin (previously known as itavastatin, itabavastin, nisvastatin, NK-104 or NKS-104) was discovered in Japan by Nissan Chemical Industries and developed further by Kowa Pharmaceuticals, Tokyo (Mukhtar et al., 2005). Pitavastatin was approved for use in the United States by the FDA on 08/03/2009 under the trade name Livalo. Pitavastatin has been also approved by the Medicines and Healthcare products Regulatory Agency (MHRA) in UK on 17 August 2010. Pitavastatin is 6.8- and 2.4-fold more potent in inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in a concentration-dependent manner than Pravastatin and Simvastatin, respectively (Park et al., 2005).

1. Mechanism of action of pitavastatin

Like other statins, it is an inhibitor of HMG-CoA reductase, the enzyme that catalyses the first step of cholesterol synthesis.

2. Side-effects of pitavastatin

Common statin-related side-effects (headaches, stomach upset, abnormal liver function tests and muscle cramps) were similar to other statins. However, pitavastatin seems to lead to less muscle side effects than other statins, since coenzyme Q10 is not significantly reduced.

Table 5. Properties of pitavastatin (PTV)

<table>
<thead>
<tr>
<th>Pitavastatin</th>
<th>Systematic (IUPAC) name</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(3R,5S,6E)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxyhept-6-enoic acid</td>
</tr>
</tbody>
</table>

[Unlike other statins, pitavastatin has cyclopropyl group allowing only a small degree of clinically insignificant metabolism by CYP2C9]

<table>
<thead>
<tr>
<th>Clinical data</th>
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<td>Routes</td>
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</table>

Pharmacokinetic data

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>60%</td>
</tr>
<tr>
<td>Protein binding</td>
<td>96%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>minimally CYP4502C9</td>
</tr>
<tr>
<td>Half-life</td>
<td>11 hours</td>
</tr>
<tr>
<td>Excretion</td>
<td>Faeces</td>
</tr>
</tbody>
</table>
3. Metabolism and interactions of pitavastatin

Most statins are metabolised in part by one or more hepatic cytochrome P450 enzymes, leading to an increased potential for drug interactions and problems with certain foods (such as grapefruit juice). Pitavastatin appears to be a substrate of CYP2C9, and not CYP3A4 (which is a common source of interactions in other statins). As a result, pitavastatin is less likely to interact with drugs that are metabolized via CYP3A4, which might be important for elderly patients who need to take multiple medicines (Mukhtar et al., 2005).

Pitavastatin (PTV) has a potentially stronger cholesterol-lowering action compared with other statins (Saito et al., 2002). Pitavastatin is 6.8- and 2.4-folds more potent in inhibiting HMG-CoA reductase in a concentration-dependent manner than pravastatin and simvastatin, respectively (Park et al., 2005). PTV was reported to enhance plasma adiponectin in patients with hyperlipidemia and diabetes mellitus (DM) to the level in non-DM patients, suggesting its beneficial adipotropic actions. Pitavastatin was reported to increase plasma adiponectin in patients with hyperlipidemia and diabetes mellitus (DM) to the level in non-DM patients, suggesting its beneficial adipotropic actions (Ishihara et al., 2010).

The US Food and Drug Administration approved Pitavastatin for use on August 3, 2009, on the basis of results of 5 clinical trials demonstrating its safety and efficacy compared with current statins on the market. Pitavastatin is currently indicated for patients with primary hyperlipidemia and mixed dyslipidemia to reduce total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo-B), triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C), in addition to diet. Pitavastatin is well tolerated; as such, Pitavastatin shows distinctive pharmacokinetic and clinical profiles that should help a greater proportion of dyslipidaemic patients attain their treatment goals (Ose, 2010).

4. Current research status of pitavastatin

Moller et al. (2012) reported that pitavastatin enhances antiviral efficacy of standard pegylated interferon plus ribavirin in patients with chronic hepatitis C: A prospective randomized pilot study A total of 42 CHC patients diagnosed with genotype 1b and with a viral load >5.0 Log IU/ml, who were treated with PEGIFN- 2b at 1.0–1.5 lg/kg/week, plus ribavirin at 800–1400 mg/day or 48 weeks were randomly assigned to receiving pitavastatin (1–2 mg/day) or no additional therapy for 48 weeks. Addition of pitavastatin
to standard antiviral therapy appears to be a promising option to increase SVR in patients with CHC, which will justify larger prospective clinical trials.

Nagashima et al. (2011) determined whether a statin might have an effect on postprandial hypertriglyceridemia, and thereby on endothelial function in obese subjects. Twenty-four obese male subjects were recruited for this study. They were randomly assigned to receive pitavastatin (2 mg/day) or placebo for 2 weeks. Pitavastatin might prevent endothelial dysfunction caused by postprandial hypertriglyceridemia within 2 weeks of therapy in obese subjects.

Ose et al. (2010) reported long-term treatment with Pitavastatin is effective and well tolerated by patients with primary hypercholesterolemia or combined dyslipidemia. Pitavastatin 4 mg once daily was effective and well tolerated during 52-weeks treatment in patients with primary hypercholesterolemia or combined dyslipidemia. HDL-C levels rose continually during follow up, while changes in other efficacy parameters were sustained over the year-long study.

Miyashita et al. (2009) evaluated the effect of pitavastatin on cardio-ankle vascular (CAVI) in type 2 diabetic patients. Forty-five type 2 diabetes mellitus patients with low-density lipoprotein cholesterolemia were enrolled and treated with pitavastatin 2 mg/day for 12 months. In type 2 diabetic patients, pitavastatin may have an oxidative stress-reducing effect, especially in a state of enhanced oxidative stress, and CAVI may be useful as a routine test for the diagnosis and therapeutic monitoring of atherosclerosis.

Koutaro et al. (2008) compare the efficacy and safety of pitavastatin and atorvastatin in Japanese patients with hypercholesterolemia. Both pitavastatin 2 mg and atorvastatin 10 mg were well tolerated, lowered non-HDL-C and improved the lipid profile to a comparable degree in Japanese patients with hypercholesterolemia. Non-HDL-C lowering by atorvastatin was more prominent in lean than in obese patients, suggesting the effects of a statin may be influenced by an individual’s metabolic background.

Inami et al. (2007) investigated the effects of treatment with pitavastatin on inflammatory and platelet activation markers and adiponectin in 117 patients with hyperlipidemia to determine whether pitavastatin may prevent the progression of atherosclerotic changes in hyperlipidemic patients. The data of the study suggested that pitavastatin possesses an adiponectin-increasing effect in patients with hyperlipidemia and this effect is influenced by intensive platelet activation.

Park et al. (2005) performed a randomized, open-label study to evaluate the efficacy and safety of Pitavastatin compared with simvastatin in Korean patients with
Chapter II

LITERATURE REVIEW

hypercholesterolemia. The HMG-CoA reductase inhibitor pitavastatin was found to be non inferior to simvastatin in terms of reducing LDL cholesterol, total cholesterol, and triglyceride levels, and increasing HDL cholesterol levels, in Korean patients with hypercholesterolemia after 8 weeks of treatment.

Fan et al. (2004) examined to establish whether pitavastatin affects bile acid synthesis and if so, to determine a possible molecular mechanism. HepG2 cells were cultured in serum-free Dulbecco’s modified Eagle medium for 18h before drug treatment. Pitavastatin increased the mRNA levels of CYP7A1 in HepG2 cells, suggesting that increased conversion of cholesterol to bile acids may be the mechanism for its potent low-density lipoprotein cholesterol lowering effects.

Aoki et al. (2003) investigated the influence of pitavastatin (CAS 147526-32-7), a potent 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor, exerted on fecal and biliary excretion of sterols and bile acids using guinea pigs. The bile acid excreting efficacy of pitavastatin was relatively high as compared with atorvastatin or simvastatin. It is suggested that this action may contribute to the powerful cholesterol lowering action of pitavastatin.

Noji et al. (2002) reported the clinical efficacy and safety of Pitavastatin, a novel HMG-CoA reductase inhibitor, during long-term treatment, were examined in 25 patients with heterozygous familial hypercholesterolemia (FH). Total cholesterol (TC) decreased by 31% from the initial value of 3409/57 to 2379/40 mg/dl at week 8. The effects of Pitavastatin on TC and LDL-C were stable during long treatment of patients with heterozygous FH could conclude that long-term Pitavastatin therapy is effective and safe for FH patients.

R. ORLISTAT

Orlistat (Xenical by Roche, Alli by GlaxoSmithKline), also known as tetrahydrolipstatin, is a drug designed to treat obesity (Bodkin et al., 2003). Its primary function is preventing the absorption of fats from the human diet, thereby reducing caloric intake. It is intended for use in conjunction with a physician-supervised reduced-calorie diet. Orlistat is the saturated derivative of lipstatin, a potent natural inhibitor of pancreatic lipases isolated from the bacterium Streptomyces toxytricini. However, due to simplicity and stability, orlistat rather than lipstatin was developed into an anti-obesity drug (Pommier et al., 1995).

Orlistat is notorious for its gastrointestinal side effects (sometimes referred to as treatment effects), which can include steatorrhea (oily, loose stools). These decrease with
time, however, and are the most frequently reported adverse effects of the drug. In the United States, the European Union, and Australia, orlistat is available for sale without a prescription. Over-the-counter approval was controversial in the United States, with consumer advocacy group Public Citizen repeatedly opposing it on safety and efficacy grounds (Schmid et al., 2007). Generics of orlistat are available in India and Russia.

1. Indications of orlistat
Orlistat is used for the treatment of obesity. The amount of weight loss achieved with orlistat varies. In one-year clinical trials, between 35.5% and 54.8% of subjects achieved a 5% or greater decrease in body mass, although not all of this mass was necessarily fat. Between 16.4% and 24.8% achieved at least a 10% decrease in body mass. After orlistat was stopped, a significant number of subjects regained weight—up to 35% of the weight they had lost. The incidence of type 2 diabetes in an obese population over four years is decreased with orlistat (6.2%) compared to placebo (9.0%) (Torgerson et al., 2004). Long-term use of orlistat also leads to a modest reduction in blood pressure (mean reductions of 2.5 and 1.9 mmHg in systolic and diastolic blood pressure respectively) (Siebenhofer et al., 2009).

Table 6. Properties of orlistat

<table>
<thead>
<tr>
<th>Orlistat</th>
<th>Systematic (IUPAC) name</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(S)-(S)-1-((2S,3S)-3-hexyl-4-oxooxetan-2-yl) tridecan-2-yl) 2-formamido-4-methylpentanoate</td>
</tr>
</tbody>
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<table>
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<tr>
<th>Clinical data</th>
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<td>Metabolism</td>
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<td>Half-life</td>
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<td>Excretion</td>
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</table>

2. Contraindications of orlistat
Orlistat is contraindicated in malabsorption, hypersensitivity to orlistat, reduced gallbladder function (e.g. after cholecystectomy), pregnancy and breastfeeding.

3. Side effects of orlistat
The primary side effects of the drug are gastrointestinal-related, and include steatorrhea (oily, loose stools with excessive flatus due to unabsorbed fats reaching the large
interestine), fecal incontinence and frequent or urgent bowel movements. GlaxoSmithKline recommends that all users be cautious of the possible side effects until they "have a sense of any treatment effects". To minimize these effects, foods with high fat content should be avoided; the manufacturer advises consumers to follow a low-fat, reduced-calorie diet. Oily stools and flatulence can be controlled by reducing the dietary fat content to somewhere in the region of 15 grams per meal (FDA Approves alli, 2007). The manual for Alli makes it clear that orlistat treatment involves aversion therapy, encouraging the user to associate eating fat with unpleasant treatment effects.

According to Roche, side effects are most severe when beginning therapy and may decrease in frequency with time; this is supported by the results of the XENDOS study, which found that only 36% of people had gastrointestinal adverse effects during their fourth year of taking orlistat, whereas 91% of study subjects had experienced at least one GI-related side effect during the first year of treatment (Torgerson et al., 2004). It has also been suggested that the decrease in side effects over time may be associated with long-term compliance with a low-fat diet (Mancini et al., 2006).

4. Interactions with orlistat
Orlistat may reduce plasma levels of ciclosporin (also known as "cyclosporin" or "cyclosporine", trade names Sandimmune, Gengraf, Neoral, etc.), an immunosuppressive drug frequently used to prevent transplant rejection; the two drugs should therefore not be administered concomitantly. Orlistat can also impair absorption of the antiarrhythmic amiodarone.

5. Mechanism of action of orlistat
Orlistat works by inhibiting gastric and pancreatic lipases, the enzymes that break down triglycerides in the intestine. When lipase activity is blocked, triglycerides from the diet are not hydrolyzed into absorbable free fatty acids, and are excreted undigested instead. Only trace amounts of orlistat are absorbed systemically; the primary effect is local lipase inhibition within the GI tract after an oral dose. The primary route of elimination is through the feces. At the standard prescription dose of 120 mg three times daily before meals, orlistat prevents approximately 30% of dietary fat from being absorbed, and about 25% at the standard over-the-counter dose of 60 mg. Higher doses do not produce more potent effects (Parker-Pope and Tara, 2007).

6. Current research status of orlistat
Koiou et al. (2012) assessed serum lipocalin-2 levels in polycystic ovary syndrome (PCOS) and the effects of weight loss or metformin on these levels. PCOS per se is not
associated with elevated lipocalin-2 levels. Weight loss induces a significant reduction in lipocalin-2 levels in overweight/obese patients with PCOS.

**Nimalie et al (2011)** reported the use of the intestinal lipase inhibitor, orlistat, as a novel therapeutic approach to a complex disorder; Refsum’s disease. Study reported that the effect of the intestinal lipase inhibitor, orlistat, which led to significant reduction of mean preplasma pheresis phytanic acid levels with retardation of the progression of most of their dermatological and neurological symptoms.

**Liu et al. (2010)** evaluated the effects of orlistat-assisted weight loss on endothelium-dependent vasodilation by ultrasonography in obese Chinese subjects with hypertension. Orlistat can effectively reduce body weight and blood pressure and improve endothelium-dependent FMD in obese Chinese hypertensives.

**Metwally et al., (2009)** aimed to compare the effects of metformin and orlistat for improving ovulation in obese anovulatory women. Both metformin and orlistat show a similar effect on weight loss, ovulation rates and androgen concentrations. However, the effects on ovulation rates need to be confirmed in larger studies. The presence of a low baseline serum LH was found to be the most important predictor of ovulation.

**Panidis et al. (2008)** investigated the combined effect of diet and orlistat, for 24 weeks, on anthropometric features, hormonal parameters, and indices of insulin resistance in obese women with polycystic ovary syndrome (PCOS) and in obese women without the syndrome. There appears to be a trend during the first 12-week period for greater improvement of metabolic and hormonal parameters in women with PCOS.

**Woo et al. (2007)** examine the efficacy of a lifestyle modification programme in weight maintenance for obese subjects after cessation of treatment with Orlistat. A specially designed nutritionist-led lifestyle modification programme for obese subjects is effective in weight maintenance after treatment with Orlistat, in the absence of which the benefits of drug treatment were lost. The magnitude of the effect of lifestyle modification is comparable to that observed with Orlistat.

**Owen and Svacina, (2006)** evaluated 32 patients with Type 2 diabetes who underwent such course of treatment, with view of establishing whether the interruption has any detrimental effect on the success of the therapy in terms of weight loss and diabetes compensation. The treatment was well tolerated, producing statistically significant decrease in BMI and triglyceride levels during the first year, which was maintained in the second year. Fasting glucose levels were improved at nearly-significant level. The interruption in treatment between the first and second year had no marked detrimental
effect, although the relative failure of the second treatment year to bring further benefits to the patients can certainly be at least partially attributed to this treatment gap.

Filippatos et al. (2005) assessed the effect of orlistat and fenofibrate treatment, alone or in combination on reversing the diagnosis of the MetS (metabolic syndrome; primary end-point) as well as on anthropometric and metabolic parameters (secondary end-points) in overweight and obese patients with MetS but no diabetes. The combination of orlistat and micronised fenofibrate appears to be safe and may further improve metabolic parameters in overweight and obese patients with MetS compared with each monotherapy.

Czerwieńska et al. (2004) evaluated the effect of orlistat therapy on carbohydrate, lipid, vitamin and hormone plasma levels in obese subjects. 13 obese and 15 non-obese subjects were examined. In spite of significant changes (in opposite direction) in leptinemia and serum NPY level observed in obese subjects treated with orlistat, presence of a functional relationship between these hormones could not be confirmed.

Sekuri et al. (2003) determined the acute effect of gastrointestinal lipase inhibitor on brachial flow-mediated vasodilatation and hemodynamic parameters in young obese women. The study population was composed of 42 female obese patients (mean age 29 +/- 4 years, age range between 18 and 34 years). Flow-mediated endothelial-dependent vasodilatation was assessed in the brachial artery in response to reactive hyperemia using high-resolution ultrasound. Brachial artery diameter (3.46 +/- 0.72 mm to 3.82 +/- 0.84 mm) and flow-mediated vasodilation (7.6 +/- 0.8% to 9.8 +/- 1.6%) changed significantly after 12 weeks of therapy (p < 0.001). Brachial artery flow was not changed (124 +/- 92 ml/min to 148 +/- 14 ml/min, p > 0.05). The results of this study demonstrate that orlistat improved endothelial function, weight, body mass index and systolic and diastolic blood pressure in young women.

The current obesity epidemic and its severe consequences for health provide a strong rationale for developing safe and effective drugs to help management of obesity.