INTRODUCTION

The term obesity is derived from the Latin word “obesus” meaning “having eaten until fat”. It describes an excessive accumulation of body fat (adipose tissue), usually caused by the consumption of more calories than the body requires to fuel its energy requirements. The term “overweight” refers to an increase in body weight above an arbitrary standard, usually defined in relation to height (WHO, 1998; Haslam and James, 2005). The excessive fat accumulation quite often leads to health impairment.

According to a global estimate by the World Health Organization (WHO), in 2005 there were about 1.6 billion overweight persons aged 15 years and above and among them at least 400 million adults were obese. WHO further projects that by 2015, approximately 2.3 billion adults will be overweight and more than 700 million will be obese (WHO, 2006). Obesity, a chronic disease and prevalent among all age groups, is on the rise among adults especially the women worldwide in both developed and developing countries (Flegal, 2005). However, its prevalence varies greatly between and with in the countries. In many developing countries, obesity is now rapidly increasing and often co-exists with chronic under-nutrition (Popkin, 2001).

Obesity, an increasingly prevalent and difficult-to-treat condition, affects more women than men. As per van der Merwe (2008), latest prevalence figures for obesity within the European region confirm that in most countries, the number of obese women surpasses the number of obese men, sometimes being double than men. According to Seidell and Flegal (1997), the prevalence of obesity in Europe is probably in the order of 10–20% in men and 15–25% in adult women. Among Asian countries, in Malaysia, the National Morbidity Survey of 1996 reported slightly higher prevalence of overweight amongst women (21.4%) compared to men (20.7%), whereas, the problem of obesity amongst women of Malaysia was reported twice (7.2%) that of men (3.8%) by Lim et al. (2000) and Tee (2002). Similarly, Rampal et al. (2007) also reported that the prevalence of obesity was significantly higher in females (13.8%) as compared to males (9.6%) in Malaysia. High prevalence of overweight men (19.8%) and women (28%) has also been reported for selected rural population groups of Malaysia in a study of the mid-1990s by Khor et al. (1999). Many reports on obesity in India have also confirmed the prevalence...
of obesity to be higher among women than men (Zargar et al., 2000; Misra et al., 2001; Kaluski et al., 2007).

At all ages and throughout the world, women are generally found to have a higher mean body mass index (BMI) and higher rates of obesity than men. The reasons for these differences are probably biological and related to greater ability of men to deposit more lean than fat tissue when energy imbalance occurs with weight gain. This additional lean tissue is metabolically active and increases the basal metabolic rate in men thereby compensating for the discrepancy between intake and output. Women are naturally fatter, with higher level of essential fats and less lean tissue than men. They have to gain far more weight to accrue the additional lean tissue needed to provide the adaptive gain in basal metabolic activity (James and Reeds, 1997; WHO, 2004).

Obesity in itself has negative consequences for women’s health throughout the life cycle. Obesity is associated with more than 30 medical conditions, and scientific evidence has established a strong relationship with at least 15 of those conditions. The growing prevalence of obesity is increasingly recognized as one of the most important risk factors for the development of hypertension, lipid abnormalities and type 2 diabetes mellitus (T2DM), which are known to be independent risk factors for cardiovascular diseases (CVDs) (Ganguly et al., 1997; Hossain et al., 2007; Marinou et al., 2010). The American Heart Association now recognizes obesity as a risk factor for heart attack (NCEP-III, 2001).

The relevance of both hypertension and obesity, as important public health challenges, is increasing worldwide and excess body weight is the fifth most important risk factor ranking just below underweight contributing to the overall burden of disease. The burden of these diseases is particularly high in the middle-income countries of Eastern Europe, Latin America, and Asia (Haslam and James, 2005; Hossain et al., 2007). As per Bravo et al. (2006), obesity is one of the major causes of hypertension and it is observed that about 50% of obese individuals suffer from hypertension. Correia and Haynes (2008) reported that obesity contribute to elevated blood pressure (BP) in over 70% of hypertensive patients in United States. According to Framingham Heart Study, the excess body weight including overweight and obesity, accounted for approximately 26 percent of cases of hypertension in men and 28 percent in women, and for
approximately 23 percent of cases of coronary heart disease (CHD) in men and 15 percent in women (Schmieder and Messerli, 1993).

Hypertension has become a major health concern only lately, possible a consequence of the rapid epidemiological transition over the last 2 or 3 decades. The prevalence of hypertension has been increasing, and in year 2000, an estimated 972 million people, out of which 333 million in economically developed and 639 million in economically developing countries, in the world were suffering from this problem. Compared with the year 2000, the number of people with hypertension in economically developed countries is projected to increase by 24% from 333 million to 413 million and a rise of 80% is predicted for economically developing countries from 639 million to 1·15 billion (1·12–1·17 billion) by the year 2025. On the basis of these estimates, almost three-quarters of the world’s hypertensive population will be in economically developing countries by 2025 (Kearney et al., 2005). Subjects with hypertension possess two folds higher risk of developing coronary artery disease (CAD), four times higher risk of congestive heart failure and seven times higher risk of CVD compared to normotensive subjects (King et al., 1998; Abate and Chandalia, 2003). Changing life style environment, industrialization and urbanization has led to increase the prevalence of hypertension in developing countries like India. Although India is the second largest nation, relatively little is known about the actual prevalence of hypertension in India.

T2DM is another obesity related metabolic disorder. The name diabetes mellitus has Greek and Latin roots. “Diabetes” comes from the Greek word for “siphon”, and implies that a lot of urine is made. The second term, “mellitus” comes from the Latin word, “mel” which means “honey”, and was used because the urine was sweet. Diabetes mellitus and CVDs often appear as two sides of a coin; diabetes mellitus has been rated as equivalent to CAD. The increasing prevalence of diabetes is associated with increased rates of overweight and obesity and it has been estimated that 90% of T2DM is attributable to excess weight (Lipscombe and Hux, 2007; Hossain et al., 2007). Diabetes often coexists with obesity, hypertension and dyslipidaemia.

Prevalence of T2DM is rising globally and the impact is most marked in developing countries like India. Asians and Pacific Islanders are at high risk of developing diabetes where it is growing at an alarming rate with 90-95% being type 2
diabetic and it is more prevalent among obese individuals (Haslam and James, 2005). It was observed by Colditz et al. (1990) that the risk conferred by obesity for the development of diabetes was 40 times more in obese women as compared to the slim women. As per Hossain et al. (2007), approximately 197 million people worldwide have impaired glucose tolerance, most commonly because of obesity and the associated metabolic syndrome. This number is expected to increase to 420 million by 2025. WHO has reported that India has the maximum number of diabetic patients than any other country (Wild et al., 2004).

According to World Diabetes Foundation (2010), an estimated 50.8 million people are living with diabetes in India. This is projected to increase to 57 % by 2025 (Bajaj, 2010). Thus, India has become the “Diabetic capital of world” where every fifth diabetic in the world is an Indian (Joshi and Parikh, 2007). A positive association between obesity and the risk of developing T2DM has been consistently observed in many populations (WHO, 2000; Ramachandran et al., 2001). Studies of Everhart et al. (1992) have shown that as obesity continue, the risk of development of T2DM increases at that rate. Subjects who have obesity for over 10 years have a two times greater risk for diabetes than subjects who have obesity for less than 5 years. Snehalatha et al. (1999) have reported that insulin resistance (IR) which is a characteristic feature of Asian Indians is worsened by minor increment in weight. WHO projects that diabetes deaths will increase by more than 50% worldwide in the next 10 years (WHO, 2006).

Diseases of the heart and the blood vessels such as heart attack and stroke have traditionally been considered as a condition predominately affecting men. There is a marked difference in the risk of CHD between men and women of reproductive age but this gap closes with advancing age. Reports are there that women are at less risk of developing CAD than their male counterparts, but this gap is abolished after 60 years of age (Rich-Edward et al., 1995; Carr, 2003; Nedungadi and Clegg, 2009). According to Calhoun and Oparil, (1998), there is difference in BP of men and women, where women with functional ovaries tend to have lower BP than men of their age, but menopause or ovariectomy tends to eliminate the sexual dimorphism and cause women to develop a ‘male pattern of BP’. According to Solimene (2010) women die twice as often as men so far as CHD is concerned, after myocardial infarction and myocardial revascularization
procedures. Similarly, Vital et al. (2006) concluded from their animal studies that females are more susceptible to the rapid development of a more severe form of diabetes than males at all age groups.

Obesity can result from a minor energy imbalance which leads to a gradual but persistent weight gain over a considerable period. In females, weight gain particularly after menopause seems to be a universal phenomenon. Before the age of 50, majority of women tend to increase their weight slowly, whereas, after menopause there appears to be an accelerated increase in fat mass and a change in preferential fat storage to a central part of body that is abdominal location. The word menopause is derived from Greek words ‘menos’ means ‘month’ and ‘pause’ means ‘to stop’. It is a time in woman’s life when there is pause in menses, a cessation of monthly reproductive function. In the literature menopause is synonymous with “climacteric”. The ‘climacteric’ period is a phase of life when woman changes, mentally and physically from sexual maturity to old age. The term “menopause” is only a mile stone, the last bleeding from the uterus and this must be considered as the counterpart of the first blood loss from the uterus called ‘menarche’.

The reproductive phase of a woman can be divided into three phases: premenopause (when woman is at the peak of her reproductive phase), perimenopause (when woman’s menstrual cycle gets disturbed due to fluctuations of hormonal level) and postmenopause (when her reproductive cycle stops which signals the cessation of woman’s capacity to bear children). Menopause comes midway between the challenges of adulthood and despair of old age, in women’ life during which their lives take a compulsory change of direction. There is permanent cessation of the reproductive cycle some time before the end of their natural lifespan. Millions of follicles are formed in the ovary and prenatally, more than 50% of the follicle pool is lost. Thereafter, atresia slows until women reach their early 40’s, when remaining follicle numbers reach a critical threshold. So, there is progressive decline in ovarian function as the number of ovarian follicles decline with time. Ultimately, women after progressing through this transition phase, reach at a stage when they are left with essentially negligible number of oocytes and cease to have periods (Guyton and Hall, 2008). This marks the end of their reproductive life and a women is said to have attained menopause.
During reproductive period, there is a more gynoid type of fat distribution among women. After the menopause, the more gynoid fat distribution may change towards android type of fat distribution. Genazzani and Gambacciani (2006) suggested that endocrine changes during the menopausal transition, rather than the aging process, are related to changes in body weight and fat distribution in perimenopausal and postmenopausal women. Sharma et al. (2008) also reported the presence of android type of fat distribution in postmenopausal women, whereas, Pasquali et al. (1994) suggested that the menopausal status could slightly but significantly increase body weight, without affecting body fat distribution. Prior to menopause, the majority of women have their body fat concentrated in the areas of their hips and thighs giving them pear-shaped body. This is advantageous because women who have pear-shaped body are at a lower risk of heart diseases and diabetes. Body fat distribution is more important determinant of disease risk than simple increase in body mass. This redistribution of body fat during and after menopause may be attributed to the effects of estrogen deficiency on adipocyte metabolism leading to differential fat patterning. So, menopause apart from defining a biological limit for human reproduction also has profound effect on the health of women because it introduces a period when new health problems emerge.

Majority of adults are becoming increasingly overweight and one of the subgroup in which this prevalence is growing rapidly, is postmenopausal women. Studies have reported that during menopause, weight gain and onset or worsening of obesity is favoured and prevalence of obesity is highest (de Paz et al., 2006; Sharma et al., 2008). It has been reported by Evans and Racette (2006) that seventy percent women of age 45-54 years are over weight or obese. So, it may be concluded that the prevalence of obesity increases in postmenopausal women as compared to premenopausal women. Menopause related changes of body fat distribution are associated with worsening CVD risk factors. It seems likely that some factors of reproductive physiology are responsible for these changes (Chang et al., 2000; Sharma et al., 2008). The incidence of CVD and diabetes rise to approach that for men of similar age after menopause. One-third of women in the age group of 50 to 70 years have CVD which account for more than 50% of all deaths among women annually (Feldstein et al., 2002). The increased risk of CVD after menopause can be attributed to the increased body fat coupled with poor insulin mediated
glucose disposal due to menopause transition (Zamboni et al., 1992; Lindheim et al., 1994).

According to Solimene (2010), heart disease is the first killer of women in the modern era, regardless of age, race and of ethnicity, and its prevalence rises after menopause. According to Upkar et al. (2000), CVD is the leading cause of death in women who have passed the age of menopause. Chandha (2001) also reported that majority of women, less than 65 years of age die of CVD. According to Bush (1990) and Giardina (1998), CVD which include CHD and stroke, not only are the leading cause of death among women; they are more lethal and less aggressively treated in women than in men. Increase in BP increases CVD risk and hypertension is a strong predictor for the development of T2DM has been reported in literature (Conen et al., 2007a,b). According to the Third National Health and Nutrition Examination Survey (NHANES III), about 50% of all hypertensive patients are women, and among elderly women, up to 80% suffer from hypertension (NCHS, 1996). Hypertension is by far the most important risk factor that affects women in the early postmenopausal years. About 30 to 50% of women develop hypertension before the age of 60 and the onset of hypertension can cause a variety of symptoms that are often attributed to menopause (Burt et al., 1995; Wassertheil-Smoller et al., 2000).

As obesity is a problem in postmenopausal women, according to Rosano et al. (2007), postmenopausal obesity complicates the situation leading to increased rates of hypertension, T2DM, CAD and mortality. Coylewright et al. (2008) has also reported that along with endothelial dysfunction, arterial stiffness, rennin-angiotension system, obesity is the major cause of hypertension among postmenopausal women. The association between menopause and IR has been reported by Kalish et al. (2003) which leads to increase in diabetes rate among postmenopausal women. According to Revis and Keene (2007), among diabetic Americans, the large proportion is of postmenopausal women. The prevalence of obesity and related co-morbidities like hypertension and T2DM become higher after menopause (Bhatti et al., 2007; Yadav et al., 2008; Wiklund et al., 2008).
Menopause appears to be associated with adverse changes in blood lipid profile and these changes may speed up the process of atherosclerosis and specially CHD which is the major cause of death and disability in postmenopausal women (Godsland et al., 1987; Igweh et al., 2005). According to Rosano et al. (2007), estrogen withdrawal during menopause brings detrimental effect on metabolism and changes the body fat distribution from a gynoid to an android pattern. They further reported that fall in estrogen level during menopause leads to reduced glucose tolerance, abnormal plasma lipids, increased BP, increased sympathetic tone, endothelial dysfunction and vascular inflammation. Bales (2000) reported that there is also derangement of lipoprotein profile independent of age. Murano et al. (2003), observed 10% increase in total cholesterol (TC), 20% increase in low density lipids (LDL) and 10% decrease in heavy density lipids (HDL) within 2 years after menopause.

A young woman, whose estrogen production is high, has normal serum lipids. But after menopause, abnormal lipid levels and increased incidence of CHD show a possible relationship among estrogen, normal lipid levels and a relative immunity to CVD. According to Feldstein et al. (2002), one possible cause for the increase in CVD in postmenopausal women is the enhanced TC level after menopause. It was further suggested that the rate of elevation of TC results from increase in level of LDL. Igweh et al. (2005) have also suggested the importance of effect of menopause on lipid profile and reported that the level of LDL increases and that of HDL and VLDL, the cardioprotective components falls after menopause. Smith and Lall (2008) reported that hypercholesterolemia, hypertriglyceridemia and lipoprotein are the main lipid abnormalities found in diabetes which increases the risk for CAD. Taskinen (1990) and Goldberg (1981) also suggested that the most characteristic lipid abnormality in diabetics is hypertriglyceridemia, with or without associated increase in plasma cholesterol. Ugwu et al. (2009) observed that the diabetic patients had higher prevalence of high serum cholesterol than the controls, which on the contrary have higher HDL levels, whereas, other studies have reported that low level of HDL-C is a key feature leading to T2DM (Rosenson, 2005, Bitzur et al., 2009).
As estrogen levels fall at menopause, risk factors for CHD become more apparent, especially hypertension (Mass and Franke, 2009) and diabetes (Revis and Keene, 2007). The decline in the level of estrogen at menopause in women has been found to bring metabolic changes that cause changes in amount and distribution of fat (Bjorkelund et al., 1996). Decrease in estrogen in menopausal women increases body fat (Shimizu et al., 1997). It is yet unclear whether the menopausal transition itself leads to weight gain, but Dubnov-Raz et al., (2007) suggests that the physiological withdrawal of estrogen, together with no physical activity brings about changes in fat distribution and probably prove the major cause of obesity. Previous studies (Svendsen et al., 1993; Pasquali et al., 1997) have reported that estrogenic depletion after menopause, results in lower sex hormone binding globulin, relatively higher androgenicity and higher activity of lipoprotein lipase in the abdominal subcutaneous adipose tissue in postmenopausal women as compared to premenopausal subjects. Revis and Keene (2007) have also reported that lower levels of the hormones estrogen and progesterone, and human growth hormone contribute to lower metabolism and obesity which is the major cause of T2DM. The decrease in these hormones may explain the rapid increase of fat and these physiological changes may result in a more male like central adipose tissue distribution after menopause among postmenopausal women which may further complicate the situation (Tchernof and Poehlman, 1998; Freeman et al., 2010).

The pathophysiological mechanisms responsible for body weight regulation or obesity were incompletely understood until leptin was discovered in 1994. Leptin (Greek word leptos meaning thin), a 16 kDa protein hormone, 167 amino acid long, is a multifunctional hormone produced mainly by the adipose tissue that plays a key role in regulating food intake, energy expenditure including appetite and metabolism, energy balance, obesity and reproductive functions. Leptin is believed to be an anti-obesity hormone also. In addition to its effects on food intake and energy expenditure, leptin also influences Follicle Stimulating Hormone (FSH), Luteinizing Hormone ( LH), Adreno-Cortico Trophic Hormone (ACTH), cortisol, and Growth Hormone (GH) secretion (Ahima et al., 1996; Barash et al., 1996; Licinio et al., 1998). Leptin is one of the most important adipose derived hormones and the product of obese (ob) gene (Brennan and Mantzoros, 2006) and was originally cloned in the ob/ob mouse (Zhang et al., 1994). The
Ob (Lep) gene (Ob for obese, Lep for leptin) is located on chromosome 7 in humans (GreGreen et al., 1995). It has been reported that the leptin gene is expressed in adipose tissue, gastric epithelium, and placenta (Zhang et al., 1994; Masuzaki et al., 1997; Bado et al., 1998; Zhang et al., 2005). Increase in body fat is strongly linked to adipokine production, especially leptin. It is suggested that leptin’s effects on body weight are mediated through its effects on hypothalamic centre that control feeding behavior and hunger, body temperature and energy expenditure (Havel, 2000; Cnop et al., 2003).

Although administration of leptin may be effective in a few obese individuals who are leptin deficient but most of the obese individuals are thought to be leptin resistant and have been found to have high levels of leptin (Bravo et al., 2006; Correia and Haynes, 2008). As leptin is expressed predominantly by adipocytes, serum leptin concentrations have been found related directly to body fat contents and correlate with BMI (Havel et al., 1996; Liuazzi et al., 1999; Bednarek-Tupikowska et al., 2006). Recently, Ritland et al. (2008) have also confirmed the relationship between measures of central obesity and leptin in postmenopausal women. Sexual dimorphism is observed for the levels of leptin. Scientists have reported that leptin levels differ between males and females and its amount has been reported 2-4 times higher in females than males (Rosenbaum et al., 1996; Ostlund et al., 1996; Ram and Malathi, 2007). Further, many recent studies have reported that leptin controls obesity and plays a significant role in causing hypertension and T2DM (Passaro et al., 2001; Imatoh et al., 2008; Sabatier et al., 2008).

A link between sex steroids like estradiol and leptin production has also been suggested in humans (Haffner et al. 1997; Mannucci et al., 1998; Ram and Malathi, 2007). However, there are contradictory findings regarding the relationship between estradiol and leptin concentrations. According to Hadji et al. (2000), the significant differences in leptin concentrations in pre- and postmenopausal women are influenced by BMI and there in no relation between menopausal status and leptin concentrations, whereas, Shimizu et al. (1997) observed 33% higher leptin concentrations during luteal phase of menstrual cycle as compared to follicular phase and estradiol concentrations were found two times higher during the earlier phase. It is predicted that estradiol raises leptin levels in females, so premenopausal women have higher leptin level than postmenopausal women. Few previous studies have either investigated only
postmenopausal women or premenopausal women or included small sample size leading to conflicting results (Rosenbaum et al., 1996; Ostlund et al., 1996; Hicky et al., 1998).

A number of factors like BMI, adipose tissue mass (Mahabir et al., 2007) and menopausal status (Rosenbaum et al., 1996) have been suggested to regulate plasma leptin levels. Bravo et al. (2006) suggested that serum leptin levels are elevated in obese individuals due to increased amount of adipose tissue. In another study of weight loss programme, Ahima (2008) found that leptin levels were reduced during weight loss and suggested that leptin may act as a critical factor linking reduced energy stores and eating behaviour. Insulin has also been considered as a potential regulator of leptin. According to Mohiti et al. (2009), although insulin and leptin show opposing effects on some of the metabolic processes, both the hormones exert a concerted action especially on central nervous system in the regulation of food intake. Previous studies have also shown that hyperinsulinemia increases plasma leptin levels and gene expression by white adipose tissues (Vidal et al., 1996; Koopmans et al., 1998; Saad et al., 1998). It is well recognised that an increased body weight is often associated with metabolic disorders (hyperinsulinemia and glucose intolerance), as well as increased BP.

Higher leptin levels are associated not only with obesity but with hypertension also (Agata et al., 1997; Suter et al., 1998; Schorr et al., 1998; Correia and Haynes, 2008; Thomopoulos et al., 2009). Increased leptin concentrations accelerate BP in obese individuals by activating sympathetic nervous system (Correia and Haynes, 2008). It has been suggested by Sarkar et al. (2009) that hyperinsulinemia and leptin released from adipocytes play key roles in causing hypertension in obesity. Work done by Dunbar et al. (1997) demonstrated that intracerebroventricular administration of leptin progressively increases mean arterial pressure. According to Bravo et al. (2006), leptin plays a very important role in obesity induced hypertension as leptin influences nitric oxide production and along with sympathetic activation, it leads to sodium retention, systemic vasoconstriction and BP elevation. These studies suggested that leptin plays important role in the development of hypertension in obesity. The association between obesity and hypertension suggests that the adipose mass may serve as an important tissue in the regulation of BP although the mechanisms underlying this are not yet evident.
Some investigators (Ceddia et al., 1999; Muoio and Lynis Dohm, 2002) have demonstrated that leptin plays a role in the regulation of insulin secretion from the pancreatic islet cells. There are conflicting results in literature regarding the role of leptin in controlling diabetes (Haffner et al., 1996; Widjaja et al., 1997; Clement et al., 1997). Role of insulin has also been proposed in the aetiology of IR, T2DM and hypertension. Work done by Feldstein et al. (2002) demonstrate that hyperinsulinemia correlates with ambulatory systolic BP, thus IR may possibly be involved as a pathogenic factor in lean, postmenopausal hypertensive women. The work done by Bano et al. (2004) has concluded that serum insulin levels are significantly higher among hypertensive individuals and significantly correlated with serum cholesterol levels compared to controls. Sarkar et al. (2009) suggested that insulin and leptin increases sympathetic tone which leads to sodium retention and hyper-responsiveness of blood vessels.

Obesity is known to have negative consequences for women’s health and further onset of menopause appears to be associated with adverse changes in blood lipid profile and hormone levels especially leptin, which may contribute in the aetiology of hypertension, type 2 diabetes mellitus and cardiovascular diseases. Till date no comprehensive study has been done on the relationship between leptin and hypertension and type 2 diabetes mellitus in pre- and post-menopausal women in the state of Punjab. The present study was designed to gain further insight into the relationship between leptin and menopausal status in normal (normotensive/ non-diabetic), hypertensive and diabetic pre- and postmenopausal women. The study was carried out on pre- and postmenopausal women with similar values of BMI, so as to assess the actual effect of the menopausal status with respect to the hormonal levels. Overall, the study was done to meet the following objectives:

- To find the incidence of overweight and obesity in pre-and post menopausal women of Jalandhar (Punjab, India).
- To study the association between obesity and occurrence of hypertension and T2DM in pre- and postmenopausal women.
- To further study the lipid profile and levels of hormones like, leptin, insulin and estradiol, in selected pre- and post menopausal women and assess their correlation with obesity related disorders such as hypertension and T2DM.