Epidemiology, Causes and Complications of Obesity

Epidemiology of Obesity:

Obesity has reached epidemic proportions globally ***(WHO, 2003)***. It is defined as excess body fat accumulation with multiple organ-specific pathological consequences ***(Haslam et al., 2006)***. Often coexisting in developing countries with under-nutrition, obesity is a complex condition, with serious social and psychological dimensions, affecting virtually all ages and socioeconomic group.

It is the most prevalent metabolic disease in world, with prevalence rates of 20% for males and 25% for females ***(James, 2004)***. The prevalence of overweight and obesity is commonly assessed by using body mass index (BMI), defined as the weight in kilograms divided by the square of the height in meters (kg/m2). A BMI over 25 kg/m2 is defined as overweight and a BMI of over 30 kg /m2 as obese ***(WHO, 2003)***.

Now, more than 1.1 billion adults worldwide are overweight, and 312 million of them are obese. In addition, at least 155 million children worldwide are overweight or obese, according to the International Obesity Task Force, so the prevalence of obesity is increasing to epidemic proportions at an alarming rate around the world ***(WHO, 2004 and Hossain et al., 2007)***.

Factors affecting the prevalence of obesity:

The prevalence of obesity in adults is 10% to 25% in most countries of the worlds, this figure rises to 40% for women in eastern

European and Mediterranean countries, ***(Erem et al.,2004)***. In Arabic countries such as Bahrain, Kuwait, and Jordan, prevalence of obesity was estimated as high as 35% ***(Musaiger and Al-Mannai, 2001)***.

The prevalence of obesity and overweight had increased dramatically in economically developed countries as well as in developing countries ***(Aekplakorn et al., 2004)***. Accordingly, overweight/obesity is one of the leading preventable causes of death in the United States and most industrialized countries ***(Centers for Disease Control and Prevention, 2004)***, and the increasing prevalence of obesity among children and adolescents is also of great concern and suggests a likelihood of worsening obesity trends in future adults ***(Hedley et al.,2004)***.

Increasing age is associated with an increase in obesity ***(Stene et al., 2001)***. Data from large population studies showed that mean body weight gradually increase during most of adult life and reach peak values at 50–59 years of age in both men and women and after the age of 60 years, mean body weight tends to decrease ***(Villareal et al.,2005)***.

In fact, data from longitudinal cohort studies suggested that body weight does not change, or decreases only slightly, in older adults (60–70 y old at study entry). Aging is associated with considerable changes in body composition. After 20–30 y of age, fat-free mass (FFM) (primarily skeletal muscle) progressively decreases, whereas fat mass increases. FFM decreases by up to 40% from 20 to 70 y of age. Maximal FFM is usually reached at ~20 y of age, and maximal fat mass is usually reached at ~60–70 y of age; both fat measures subsequently decline thereafter. Therefore, both FFM and fat mass decrease during old age (>70 y) ***(Fogelholm et al., 2000)***.

These changes in body weight and body composition are attributable, in part, to the natural declines in growth hormone, dehydroepiandrosterone, and testosterone with aging. In addition, reductions in resting metabolism alter energy balance and contribute to weight gain. Also this association between obesity and age can be explained, in part, by a decrease in the degree of physical activity with age in both men and women ***(Martinez-Ros et al., 2001)***.

Gender differences also are apparent in the patterns of weight gain and the development of overweight and obesity ***(Poehlman, 2002)***. Obesity is clearly more prevalent in women worldwide. In a review of 39 surveys from 28 developing countries to determine obesity among women, ***Martorell et al., (2000)*** reported that women in Egypt and Turkey had the highest proportion of overweight (31.7% for both), as well as the highest proportion of obesity (20.1% for Egypt and 18.6% for Turkey).

During the perimenopausal and postmenopausal periods, many women experience alterations in body weight, total body fat and body fat distribution**.** Women are also prone to weight gain during menopause as the loss of the menstrual cycle affects calorie intake and slightly lowers metabolic consumption, although most weight gain has been attributed to a reduction in physical activity. Furthermore, various pregnancy-related circumstances should be considered because body weight has been shown to increase with the number of pregnancies. Therefore, reproductive history (higher parity and earlier age at menarche) had been reported to be related to obesity. Based on the NHANES III data set, approximately 70% of women between 45 and 54 years of age is overweight or obese ***(Racette et al.,2003)***.

Ethnicity could be also related to obesity. Substantial disparities exist among white, black, and Hispanic women in USA, with a higher prevalence of obesity observed among the latter 2 groups. Some of this difference appears to be attributable to lower rates of physical activity among black women and Hispanic women. Interestingly, the health risks associated with obesity also are influenced by race, with Asians at higher risk compared with whites at the same BMI ***(WHO, 2010)***.

Additional factors influencing body weight include income and education level, which are inversely associated with overweight and obesity among adolescents and adults ***(Racette et al., 2003)***. Unlike in Europe and North America, obesity in the Eastern Mediterranean Region is more prevalent in urban areas and those of higher socioeconomic status. In Jordan, for example the prevalence of obesity was 56% in urban areas compared with 44% in rural areas. Similar trends were found in Egypt, the Islamic Republic of Iran, Morocco, Oman, Tunisia and Turkey ***(Musaiger,2004)***.

Obesity had a strong inverse association with the level of education. An association between occupation and employment situation and obesity was observed so as women engaged in domestic duties were more often obese than employed women ***(Martinez-Ros et al., 2001)***.

The marital status was related to obesity and stated that married men or those living as part of a couple are twice as likely to be obese than those living alone. Other researchers using multivariate analysis had reported that the prevalence of obesity in widowed persons is higher than that in single and married subjects ***(Robert and Allison, 2002)***.

The relation between obesity and physical activity was well established as had been reported that prevalence of overweight was

considerably higher in sedentary women (21%) and men (14%) than in physically active women (8%) and men (7%). Other studies had found that obesity is inversely associated with physical activity.

Subjects with a family history of obesity, diabetes, and hypertension have a greater prevalence of obesity compared with those without a family history ***(Lang and Froelicher, 2006)***.

Smoking cessation usually leads to weight gain and changes in adipose cell metabolism, in particular increases in adipose tissue lipoprotein lipase activity**)**. This increase in lipoprotein lipase activity may contribute to the increase in body weight associated with smoking cessation and also, this trend might be due to the effect of cigarettes on depressing the appetite ***(Ferrara et al.,2001)***.

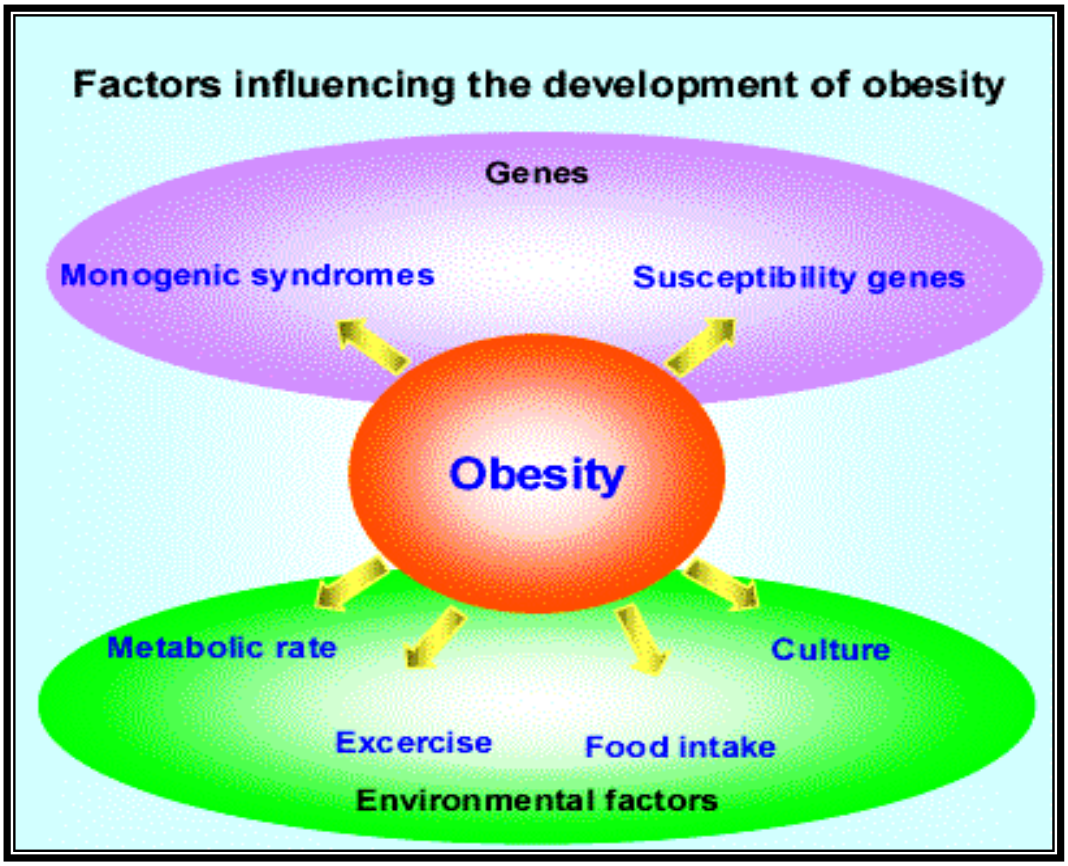


***Fig.* (1): Factors affecting development of obesity *(Ferrara et al.,2001)*.**

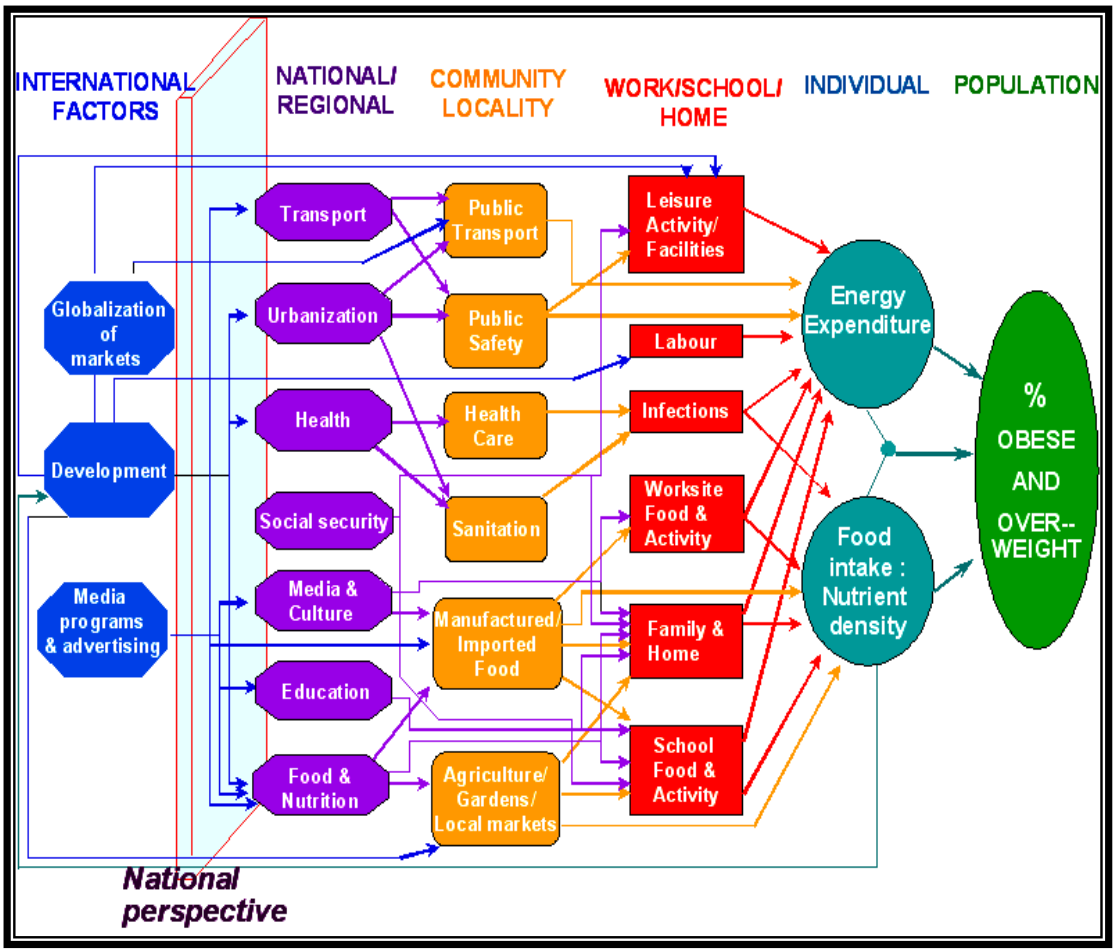


***Fig.* (2): Factors affecting prevelance of obesity *(Atkinson, 2000)*.**

Aetiology of Obesity:

Numerous factors contribute to the etiology of obesity including genetic factors; environmental factors, such as diet, activity, and exercise; familial and ethnic factors; drugs; stress; and endocrine diseases ***(Atkinson, 2000)***.

Most observers consider obesity to be a complex multigenic disorder in which there is an interaction between genes and environment. In a given population, some people are genetically predisposed to develop obesity, but that genotype may be expressed only under certain

adverse environmental conditions, such as high-fat diets and sedentary lifestyles. So the interaction between genetics and environment is very important ***(Hamann and Sharma, 2002)***.

Estimates of the genetic contribution to the variance of obesity in the population vary from about 20% to 70%, with a consensus of about 40%, leaving 60% due to environment as the gene pool could not have changed sufficiently in the last 2 decades to account for the massive surge in prevalence of obesity ***(Tuomo et al.,2006)***.

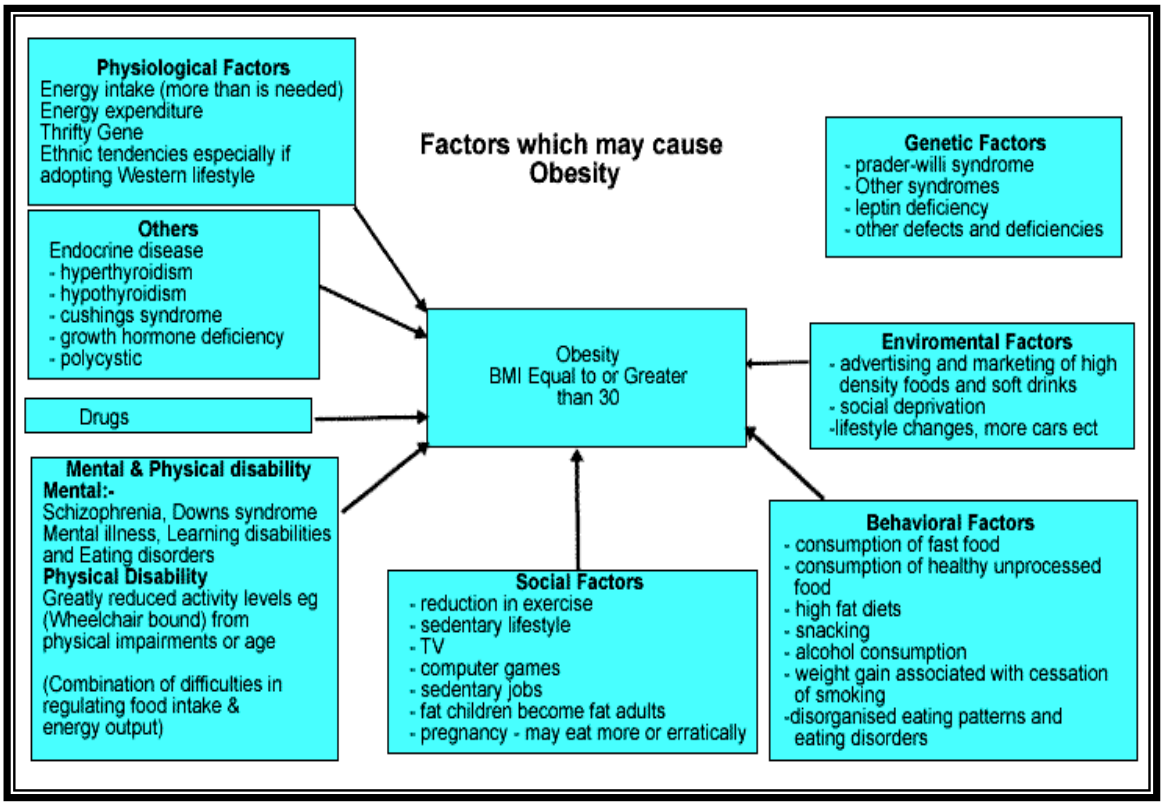


***Fig.* (3): Causes of obesity *(Tuomo et al.,2006)*.**

Environmental factors:

The World Health Organization (2010) concluded that behavioral and environmental factors (ie, sedentary lifestyles combined with excess energy intake) are primarily responsible for the dramatic increase in

obesity during the past 2 decades. Accordingly, the main preventable causes of obesity are lack of physical activity and chronic consumption of excess calories ***(Skidmore and Yarnell ,2004)***.

The development of obesity is dependent on an imbalance between energy intake and energy expenditure during an extended period of time. The cause may be viewed as excess energy intake relative to daily energy expenditure, or as low energy expenditure relative to daily energy intake ***(Racette et al.,2003)***.

An energy intake greater than expenditure promotes oxidation of carbohydrate and storage of triglycerides in adipose tissue. In recent decades the prevalence of snacking and soft drink consumption has increased, these fast foods had assumed a greater role in family eating habits,they tend to be higher in calories and fat than the home-cooked meals and they replaced as the ubiquitous "supersize" option, eg, a double hamburger, large french fries, and jumbo soft drink, may contain 1500 kcal The increasing array of "low fat" and "no fat" foods often are not lower in calories, and the tendency to eat larger portion sizes increases energy intake back to the levels of the high-fat versions ***(Janet et al., 2009)***.

Decreased activity may have contributed to the increased prevalence of obesity. Activity level may be the most important factor contributing to obesity in populations.Labor-saving devices (eg, cellular telephones and television channel changers) reduce the need for movement so that television viewing had increased, particularly in children, and hours of watching television correlated with increasing obesity in children ***(William et al., 2007)***.

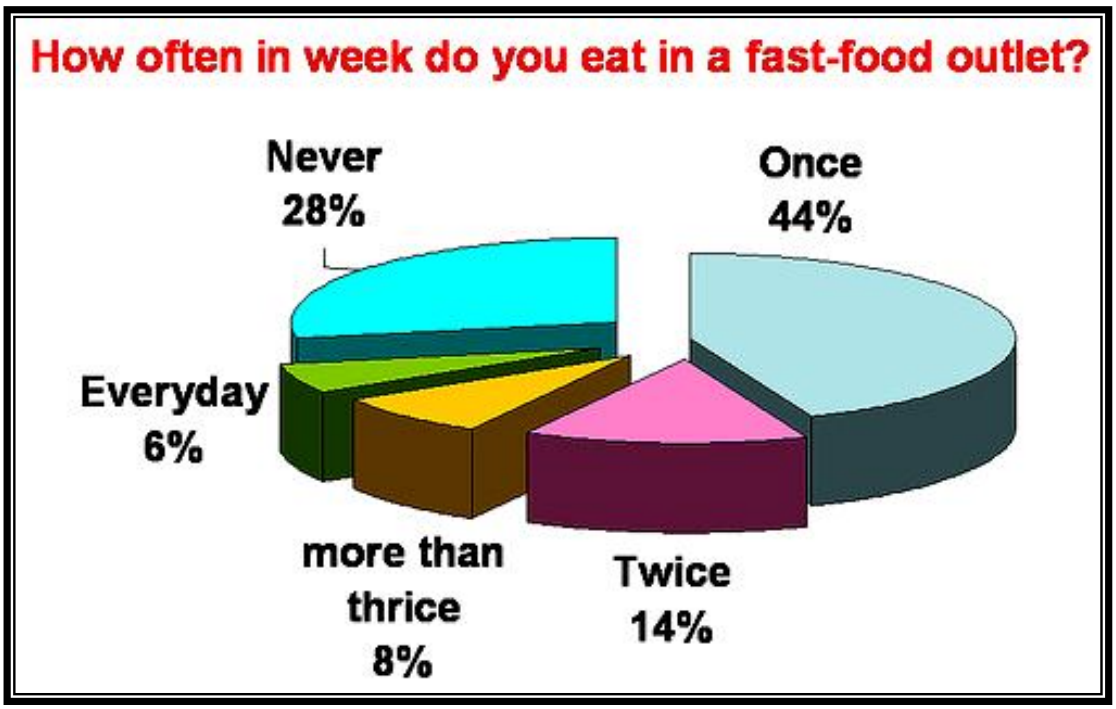


***Fig.* (4): Fast foods *(William et al., 2007)*.**

Genetic considerations:

Identification of several single gene defects that produce obesity in animals focused attention on the genetic causes of obesity. Family, twin, and adoption studies indicate that obesity is highly heritable, with the estimated genetic contribution to BMI ranging from 60% to 84% ***(Miller et al.,2004)***. Most human obesity is polygenic, and more than 200 genes and gene markers are in some way associated with obesity and this number of genes mandate that many different combinations contribute to the obesity phenotype ***(Chagnon et al.,2000)***.

The discovery of 'ob' gene, which was mapped to chromosome 7, has led to a renewed interest in understanding the patho-biological basis of genetic predisposition in obesity. The 'ob' gene codes a hormone called leptin, a 167 amino acid protein and was supposed to be produced

in white and brown adipose tissue and placenta. The leptin receptors are concentrated in hypothalamus. Any mutation of 'ob' gene leads to improper coding of leptin, which further results in obesity. The effects of the 'ob' gene are mediated through effects on both energy intake and energy expenditure ***(Tuomo et at., 2006)***.

Drugs:

Aronne (2002) reported that some drugs could be incriminated in occurance of obesity (Table 1).

***Table* (1): That some drugs could be incriminated in occurance of obesity *(Aronne, 2002)*.**

Drugs that may promote weight gain
Psychiatric/neurologic treatments:
- **Antipsychotics: olanzapine, clozapine, risperidone .**
- **Antidepressants: selective serotonin reuptake inhibitors, tricyclic antidepressants.**
- **Lithium.**
- **Antiepileptic drugs: valproate, gabapentin, carbamazepine.**
Diabetes treatments:
- **Insulin.**
- **Sulfonylureas.**
- **Thiazolidinediones.**
Steroid hormones and miscellaneous agents:
- **Hormonal contraceptives.**
- **Corticosteroids.**
- **Progestational steroids.**
- **Antihistamines.**
- **α-Blockers, β-blockers.**

Stress:

Is associated with obesity. Depression, especially seasonal affective disorder, may produce weight gain. Trauma to the brain is a rare cause of obesity. Hypothalamic damage due to automobile collisions, tumors, surgery, or infection is reported to produce massive obesity. Some obese people stated that they were normal-weight children until after a surgical procedure, usually tonsillectomy ***(Susan et al., 2009)***.

Adenovirus 36:

Was first isolated in 1978, about the time of the increased prevalence in worldwide obesity. It was shown that obese humans had a higher prevalence of adenovirus 36 antibodies than do lean people, and presence of adenovirus antibodies correlated positively with BMI ***(Charles et al., 2010)***.

Endocrine diseases:

Endocrine diseases associated with obesity:

Obesity is associated with several endocrine diseases, including common ones such as hypothyroidism and polycystic ovarian syndrome to rare ones such as Cushing's syndrome, central hypothyroidism and hypothalamic disorders. The mechanisms for the development of obesity vary in according to the endocrine condition. Hypothyroidism is associated with accumulation of hyaluronic acid within various tissues, additional fluid retention due to reduced cardiac output and reduced thermogenesis. The pathophysiology of obesity associated with polycystic ovarian syndrome remains complex as obesity itself may simultaneously be the cause and the effect of the syndrome. Net excess

of androgen appears to be pivotal in the development of central obesity. In Cushing's syndrome, an interaction with thyroid and growth hormones plays an important role in addition to an increased adipocyte differentiation and adipogenesis ***(Jolanta, 2008)***.

Hypothyroidism

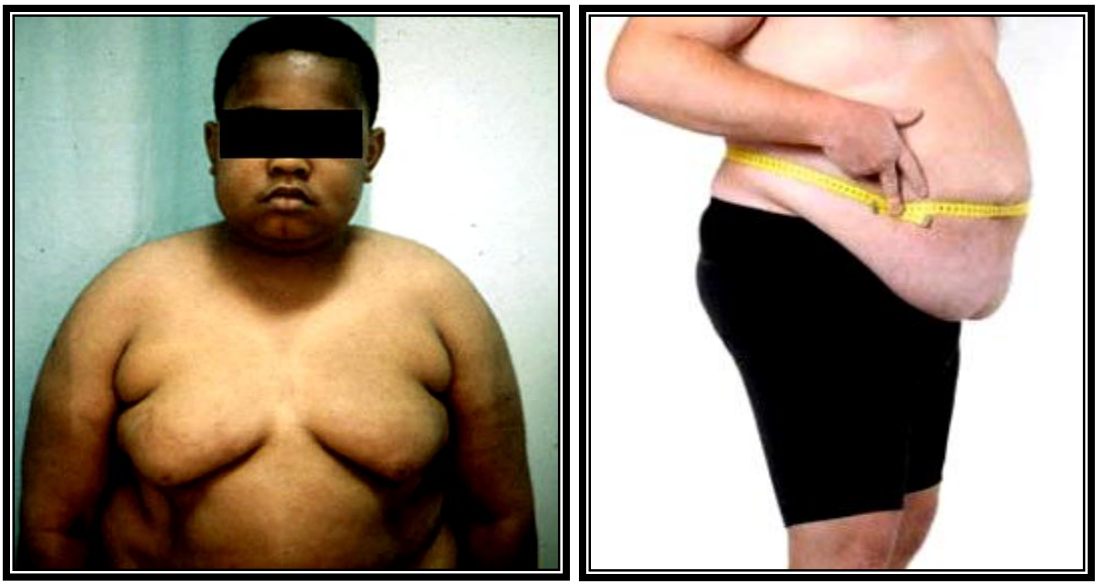
Although hypothyroidism is believed to be a frequent cause of obesity, there is rarely an increase in body fat. Most of the weight gained in hypothyroidism is due to water retention; this condition is reversible after thyroid hormone treatment. Resting energy expenditure is influenced by thyroid hormone levels. Low levels of thyroid hormones decrease and high levels increase, resting energy expenditure. The decrease may cause some degree of weight gain, because even small decreases in thyroid hormone levels decrease resting energy expenditure. In a study of hypothyroid patients who were treated with thyroxin, there was a significant negative correlation between resting energy expenditure and TSH levels, even if TSH changes were within the normal range. This chronic slight decrease in resting energy expenditure may contribute to weight gain in patients who have clinical or subclinical hypothyroidism ***(Panagoitis and Xavier, 2003)***.

Cushing's syndrome

Cushing's syndrome is a disease that often is associated with central obesity. The cause of Cushing's syndrome is a pituitary tumor that oversecretes ACTH (Cushing's disease), an adrenal tumor that oversecretes cortisol, or ectopic ACTH production. Obesity is the most common feature of Cushing's syndrome; weight gain is one of the earliest symptoms. The classic fat distribution in Cushing's syndrome is central without affecting the extremities. Fat usually accumulates in the

abdomen, the trunk, and the neck. Fat accumulation in the face results in moon facies, whereas fat accumulation in the neck results in buffalo hump. In children who have Cushing's syndrome, obesity usually is generalized. Weight loss usually occurs when the syndrome is cured. It can be difficult to establish the diagnosis of the syndrome and differentiate between it and simple obesity.

Several tests, either suppressive or stimulatory, have been used, including the overnight and the low-dose dexamethasone suppression tests, the CRH and desmopressin tests, or a combination (CRH after low-dose dexamethasone suppression) ***(Jolanta, 2008)***.



Cushing diseases **Steroids exess**

***Fig.* (5): Endocrinal diseases and obesity *(Jolanta, 2008)*.**

Growth hormone deficiency

In children or adults who are deficient in GH, there is an increase in body fat, especially abdominal fat, and a decrease in lean body mass. GH administration usually restores normal body fat distribution in adults who are GH deficient ***(Panagoitis and Xavier, 2003)***.

Hypogonadism:

Low levels of testosterone in males may result in increased body fat and decreased lean tissue. Testosterone treatment in hypogonadic men restores body fat distribution. Aging is accompanied by a gradual decrease in free testosterone levels and an increase in body fat. Testosterone administration may decrease body fat and increase lean body mass ***(Panagoitis and Xavier, 2003)***.

Polycystic ovarian syndrome:

Obesity is one of the characteristic features of the polycystic ovarian syndrome. This syndrome is presented in detail elsewhere in this issue ***(Panagoitis and Xavier, 2003)***.

Insulinoma

Patients who have insulinoma may present with increased body weight. The main reason for the gain is the increased amount of food that is consumed to avoid hypoglycemic symptoms. Treatment of insulinoma generally results in weight loss ***(Panagoitis and Xavier, 2003)***.

Traumatic hypothalamic obesity:

Lesions in the ventromedial region of the hypothalamus may produce a syndrome that is characterized by hyperphagia that can result in obesity. Injuries, neoplasms, systemic diseases, or previous radiation treatment can cause lesions in this region. Hypothalamic obesity is more frequent in children; craniopharyngioma is the tumor that is most often associated with hypothalamic obesity in this group of patients. The syndrome also may cause headaches, visual field impairment, endocrine deficiencies, neurologic symptoms, and alterations in body temperature ***(Panagoitis and Xavier, 2003)***.

The hypothesis:

The hypothesis of "fetal origins of disease," which is supported by a number of observational epidemiologic studies, postulates that early (intrauterine or early postnatal) undernutrition causes an irreversible differentiation of metabolic systems, which may, in turn, increase the risks of certain chronic diseases in adulthood. For example, a fetus of an undernourished mother will respond to a reduced energy supply by switching on genes that optimize energy conservation. This survival strategy causes a permanent differentiation of regulatory systems that result in an excess accumulation of energy (and consequently of body fat) when the adult is exposed to an unrestricted dietary energy supply. Because intrauterine growth retardation and low birth weight are common in developing countries, this mechanism may result in the establishment of a population in which many adults are particularly susceptible to becoming obese ***(Caballero,2005)***.

Pathophysiology of Obesity:

Identification of polygenic determinants of obesity in the general population is complex. However, significant advances in understanding the appetite regulation system had occurred through the study of individuals with severe obesity inherited in a Mendelian pattern including pleiotropic syndromes such as Bardet–Biedl syndrome, Albright's hereditary osteodystrophy, fragile X and the commonest syndromal cause of human obesity is Prader-Willi syndrome, caused by lack of the paternal segment of a section of chromosome 15 ***(Farooqi and O'Rahilly, 2005)***. Also understanding the neuropeptide and hormone-mediated control of feeding is considered important in developing new or more specific treatment of obesity ***(Cremonini et al., 2005)***.

Appetite and Energy Homeoestasis:

A complex physiological system balances energy intake and expenditure, comprising afferent signals and efferent effectors. Hunger leads to initiation of eating. When a meal is ingested, satiety hormones contribute to digestion and a feeling of fullness. Central circuits in the brain integrate satiety signals and signals of long term energy status to produce a coordinated response to the change in nutritional status ***(Druce and Bloom,2006)***.

Central Regulation:

The nuclei of the hypothalamus (shown in fig 1) and brain stem are important regions for regulation of energy homoeostasis ***(Wynne et al., 2005)***. The arcuate nucleus (ARC) can access signals from the periphery. The signals act on two distinct neuronal populations. One population co-expresses the orexigenic agouti-related peptide (AgRP) and neuropeptide Y (NPY). The other population releases cocaine and amphetamine regulated transcript (CART) and proopiomelanocortin (POMC), both of which inhibit feeding. Both of these populations project to the paraventricular nucleus (PVN) and other nuclei involved in energy regulation ***(Druce and Bloom,2006)***.

Defects in neuropeptide appetite circuits can deregulate energy homoeostasis, resulting in obesity. The POMC molecule is the precursor for several cleavage products known as melanocortins. The most important of these in the ARC is α-melanocyte-stimulating hormone (α-MSH) which inhibits food intake ***(Challis et al., 2002)***. So homozygous mutations in the POMC gene cause early onset obesity, adrenal insufficiency, and red hair pigmentation in humans; while heterozygous mutations in POMC may cause more subtle defects contributing to inherited obesity ***(Krude et al.,2003)***.

The receptors for the POMC cleavage product play a role in energy balance. Melanocortin (MC) receptors, such as the MC4 (and MC3) receptors, are found only in the brain ***(Proietto et al., 2000)***. Stimulation of MC4 receptors normally results in inhibition of feeding. In fact, impaired MC4 activity through MC4 receptor mutations has been described to account for 0.5% to 5.8% of severe cases of obesity ***(Damcott et al.,2003)***. On the other hand, AgRP blocks α-MSH 's effects on MC4 receptors, resulting in weight gain. The role of the MC3 receptor is less clear, but mutations of this receptor have also been found in humans with morbid obesity ***(Farooqi and O'Rahilly,2005)***.

Accordingly, MC4R agonists are in development as an obesity therapy ***(Heid et al.,2005)***. Also, inhibiting the antagonist effects of AgRP might be a promising target in the development of antiobesity agents ***(Bays,2004)***.

Various hypothalamic nuclei other than the ARC also play a role in the control of appetite and body weight in which several neuropeptides are involved, including melanin concentrating hormone (MCH) and the orexins, also the brain stem is important in the control of food intake ***(Wynne et al.,2005)***.

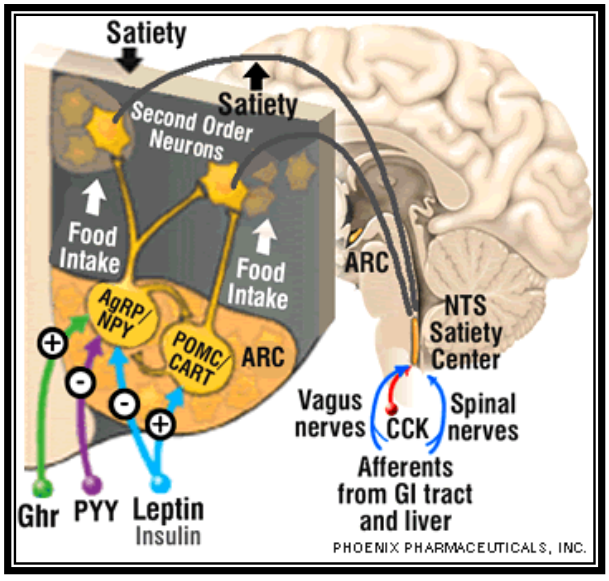


***Fig.* (6): Central regulation *(Wynne et al.,2005)*.**

Peripheral Regulation:

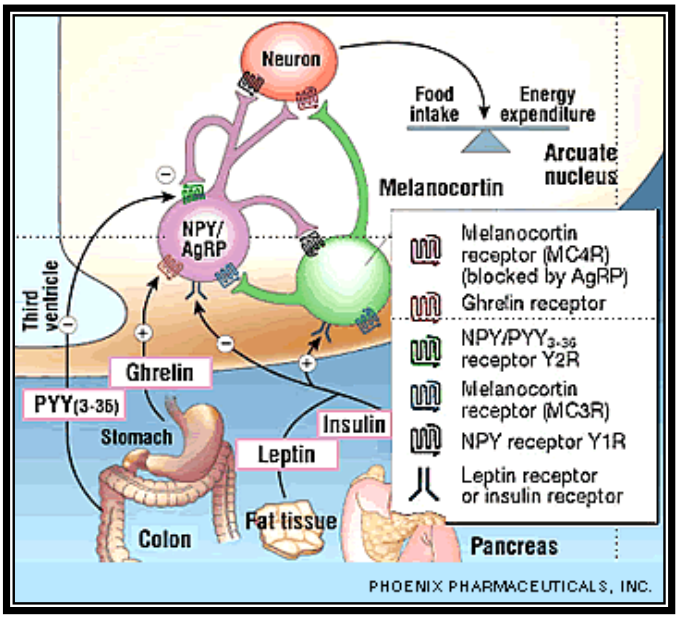


***Fig.* (7): Pereferal regulation *(Wynne et al., 2005)*.**

Gut hormones:

Several gut hormones (summarised in fig 3) are released in response to a meal. These optimise digestion and signal a change in energy status, with subsequent influence on both physiology and behaviour of food intake ***(Druce and Bloom,2006)***.

Ghrelin:

Ghrelin is produced by stomach, intestine, placenta, pituitary, and possibly in the hypothalamus ***(Horvath et al., 2001)***. Ghrelin administration was found to strongly stimulate GH secretion in both rodents ***(Wren et al., 2000)*** and humans ***(Takaya et al., 2001)***, and rat serum ghrelin concentrations were increased by fasting and reduced by re-feeding ***(Nakazato et al., 2001)***. Chronic ghrelin administration induces adiposity ***(Tschop et al., 2000)***, and CNS injection of anti-ghrelin antibodies inhibits the normal feeding response after fasting ***(Nakazato et al., 2001)***.

Human data support a role for ghrelin in appetite regulation, plasma levels are high in the fasted state and fall after eating**,** and exogenous infusion of ghrelin increased food intake by 28% compared with saline control ***(Cummings et al., 2002)***. Ghrelin levels are lower in obese subjects compared to lean, and weight loss results in an increase in ghrelin level, which may contribute to difficulties in maintaining the reduced weight ***(Lindeman et al.,2002)***. Food fails to suppress ghrelin levels in obese humans, which again could impair postprandial satiety and contribute to overeating ***(English et al.,2002)***. Indeed individuals with Prader–Willi syndrome have grossly increased ghrelin levels, and this could be a cause of their hyperphagia ***(Wynne et al.,2005)***.

Peptide YY (PYY):

PYY is produced by the L-cells of the gastrointestinal tract, especially in the distal intestine, and is released into the circulation after meals in proportion to calories ingested ***(Batterham et al.,2002)***. Administration of the active form, PYY 3–36, causes marked inhibition of food intake in rodents and man. It appears to inhibit appetite by acting directly on the Y2 receptor in the ARC (a presynaptic inhibitory receptor) ***(Halatchev et al.,2004)***. Obese subjects have a lower fasting basal PYY and a diminished postprandial rise, but remain sensitive to the inhibitory effects on appetite following exogenous administration. Thus PYY 3–36 might constitute a candidate target for anti-obesity therapy ***(Batterham et al.,2003)***.

Glucagon-like peptide 1 (GLP-1):

GLP-1 is produced by processing of the proglucagon gene in the gut and brain. The active form of the peptide is GLP-1 amide. GLP-1 is released into the circulation after eating in proportion to the amount of

food consumed and acts on the pancreas to release insulin**.** GLP-1 secretion is reduced in obese subjects, and weight loss normalises the levels ***(Verdich et al.,2001)***.

In rodents, peripheral and central administration of GLP-1 inhibits food intake, while administration of the GLP-1 receptor antagonist, exendin 9–39, increases food intake. In humans, GLP-1 inhibits food intake in healthy individuals, diabetics, and non-diabetic obese men ***(Wynne et al., 2005)***. So reduced secretion of GLP-1 could therefore contribute to the pathogenesis of obesity and agonists of the GLP-1 receptor are potential obesity treatments ***(Naslund et al., 2004)***.

Oxyntomodulin (Oxm):

Like GLP-1, Oxm is produced by processing of preproglucagon in the gut and brain, and is released after eating in proportion to nutrient ingestion. CNS administration of Oxm inhibits food intake in the rat. The anorectic actions are blocked by co-administration of exendin 9–39, suggesting a mechanism of action via the GLP-1 receptor ***(Dakin et al.,2001)***. In humans, intravenous infusion of oxyntomodulin significantly reduced food intake at a free-choice meal ***(Cohen et al.,2003)***. Chronic administration over a month leads to an significant reduction in body weight, while the place of Oxm in physiological weight regulation is not clear, these findings show its therapeutic potential ***(Parikh et al.,2005)***.

Cholecystokinin (CCK):

CCK is rapidly released from the gastrointestinal tract postprandially. There are two types of cholecystokinin receptors: type A predominates in the gastrointestinal system, and type B predominates in the brain. It stimulates gall bladder contraction, pancreatic secretion, and gut motility, and also inhibits food intake via the brain stem in humans

and rodents. Cholecystokinin is also synthesized in the brain, and intracranial administration of CCK results in a feeling of satiety. However, its therapeutic potential is limited by its short half-life ***(Beglinger, 2002)***.

Pancreatic polypeptide (PP):

Pancreatic polypeptide is produced in the pancreatic islets and distal gut and released postprandially in proportion to calories ingested. Evidence from rodents suggests a role for PP in appetite control ***(Asakawa et al.,2003)***. In humans, levels of PP are lower in obese subjects. PP administration reduces food intake in normal weight individuals and in obese subjects with Prader–Willi syndrome. Further investigations may indicate potential as a therapy for other obese subjects ***(Wynne et al.,2005)***.

Hormones released by adipose tissue:

Fat tissue is increasingly viewed as an active endocrine organ with a high metabolic activity. Adipocytes produce and secrete several proteins that act as veritable hormones, responsible for the regulation of energy intake and expenditure ***(Mora and Pessin,2002)***. Many of these hormones, collectively called adipokines, These include tumor necrosis factor (TNF-α), leptin, interleukin (IL), angiotensinogen, plasminogen activator inhibitor-1, adiponectin and resistin have been described as secretory products of the adipose tissue ***(Vendrell et al.,2004)***.

Leptin:

Leptin is, a 167-amino acid protein, an important signal in the regulation of adipose-tissue mass and body weight which operates by inhibiting food intake and stimulating energy expenditure ***(Baratta,2002)***. Leptin is produced by the white adipose tissue which provides a long-term fuel reserve that can be mobilized during food

deprivation with the release of fatty acids for oxidation in other organs ***(Trayhurn and Beattie, 2001)***. It downregulates some orexigenic neuropeptides, such as the neuropeptideY, melanin-concentrating hormone, orexins, and agouti-related peptide. Leptin up-regulates anorexigenic neuropeptides such as α-melanocyte stimulating hormone, which acts on the MC4R, cocaine and amphetamine-regulated transcripts, and corticotrophin releasing hormone ***(Jequier,2002)***.

Leptin is expressed in the adipocytes: both its expression and its secretion are highly correlated with body fat and adipocyte size. However, the study of serum leptin levels in relation to several measures of adiposity demonstrated that obesity was not characterized by leptin deficiency but rather by hyperleptinemia; in fact, leptin levels had been found to be elevated in obese patients. The inability of such elevated leptin levels to alter the obese state of these persons may be related to ‘‘leptin resistance’’ which is an inability of leptin to enter the cerebral spinal fluid to reach the hypothalamus regions that regulate appetite ***(Lan et al.,2008)***.

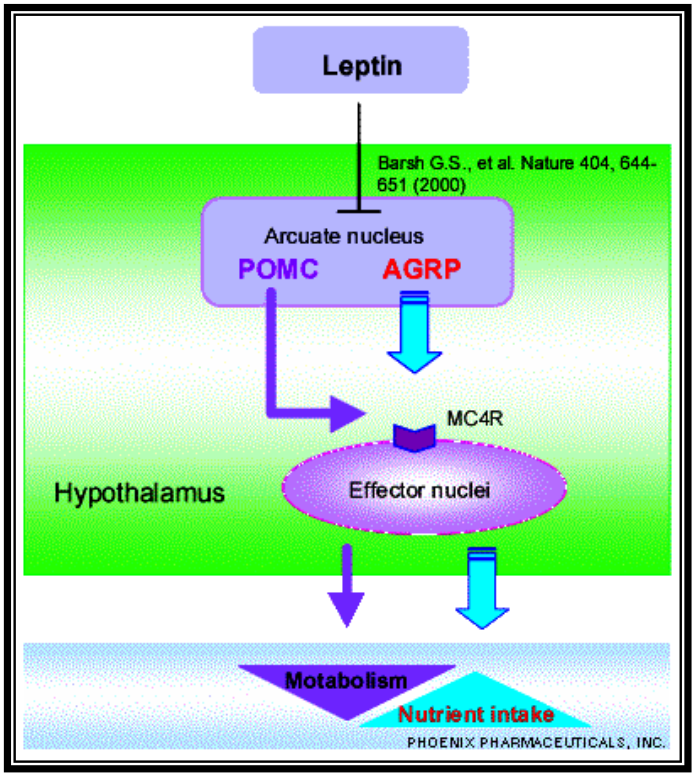


***Fig.* (8): Action of leptin *(Lan et al.,2008)*.**

Resistin:

Resistin is an adipocyte-secreted molecule induced during adipocyte differentiation and down-regulated in mature adipocytes ***(Steppan et al.,2001)***. Initial studies on the regulation of resistin indicated that mRNA expression and protein production were reduced by fasting and rapidly increased on refeeding ***(Kim et al.,2001)***. Conflicting results were obtained in genetically and diet-induced animal models of obesity; in fact, ***Steppan et al., (2001)*** found an increase in resistin serum concentration, whereas ***Le Lay et al., (2001)*** observed a decrease in resistin mRNA level.

In humans, it has been found that resistin is undetectable or weakly expressed in subcutaneous adipose tissue biopsies from lean subjects ***(McTernan et al.,2002)***, and consistently present only in morbidly obese subjects ***(Milan et al.,2002)***. The resistin gene was reported to be highly expressed in human preadipocytes ***(Janke et al.,2002)***, but no relationships between adipocyte resistin expression and body weight, insulin sensitivity, and other metabolic parameters were observed ***(Nagaev and Smith,2001)***.

Adiponectin:

Adiponectin, a collagen-like plasma protein, is secreted exclusively by adipocytes and has been linked to glucose, lipid, and cardiovascular regulation ***(Ahima,2006)***. Despite that adiponectin is produced only by adipose tissue, plasma levels was found to be decreased in obese patients and type 2 diabetic patients ***(Weyer et al.,2001)***. Body weight reduction increased circulating adiponectin, suggesting that its production is under feedback inhibition in obesity ***(Yang et al.,2001)***. Hypoadiponectinemia may contribute to insulin

resistance and accelerated atherogenesis associated with obesity ***(Kubota et al., 2002)***. So adiponectin treatment appears to improve insulin sensitivity and inhibit vascular inflammation ***(Lyon et al.,2003)***.

Hormones released by other tissues:

Insulin:

Insulin is essential for the development of obesity ***(Schwartz et, al., 2000)***. It plays a key role in lipogenesis and inhibition of lipolysis. Destruction of the beta cells in experimental forms of obesity slows or arrests the development of obesity. Absence of insulin, seen in type 1 diabetics, is associated with nearly normal body weight. Treatment of diabetics with insulin or drugs that increase insulin secretion from the beta cell increase body fat relative to other forms of treatment for diabetes ***(Bray,2002)***.

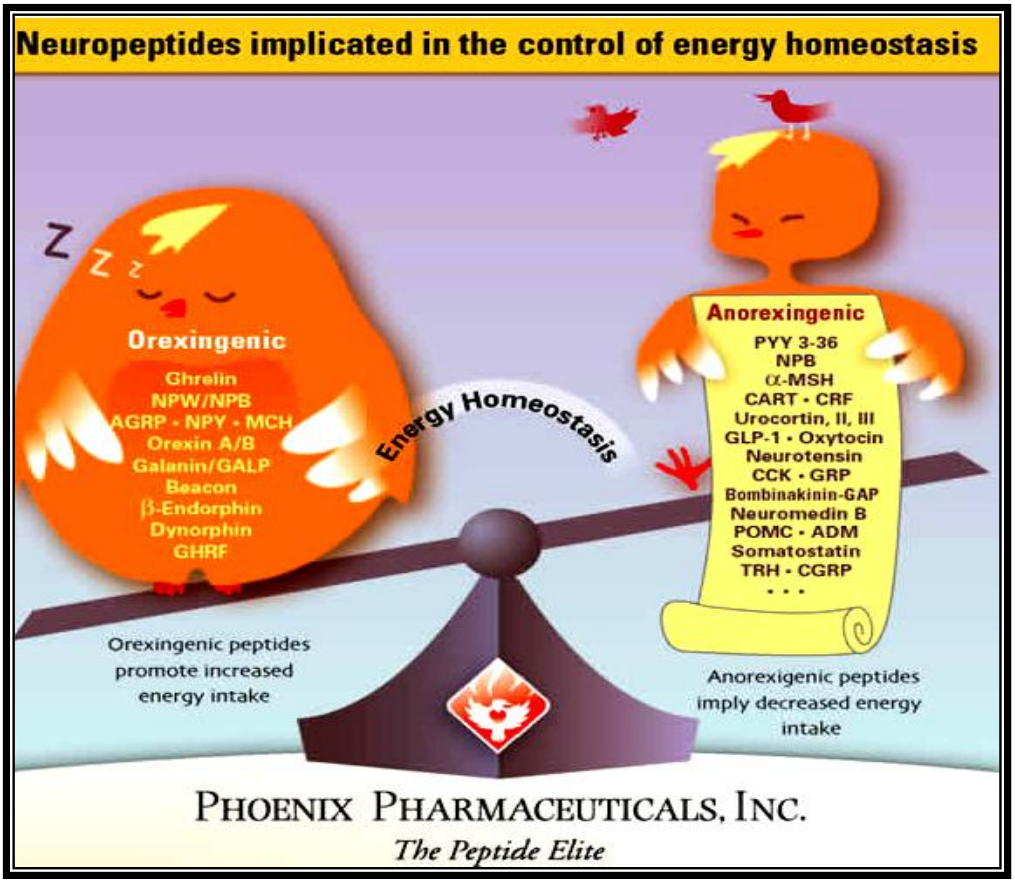


***Fig.* (9): Energy homeostasis *(Bray,2002)*.**

Complication of Obesity:

Kushner and Roth, (2003) reported that obesity leads to, or significantly increases the risk of, comorbidities involving various body systems including:

1. Cardiovascular (hypertension, congestive cardiomyopathy, varicosities, pulmonary embolism, coronary heart disease (CHD)).
2. Neurological (stroke, idiopathic intracranial hypertension).
3. Respiratory (dyspnea, obstructive sleep apnea, hypoventilation syndrome, Pickwickian syndrome).
4. Musculoskeletal (immobility, degenerative osteoarthritis, low back pain).
5. Skin (striae distensae or "stretch marks," venous stasis of the lower extremities, lymphedema, cellulitis, intertrigo, carbuncles, acanthosis nigricans, skin tags).
6. Gastrointestinal (gastro-esophageal reflux disorder, nonalcoholic fatty liver/steatohepatitis, cholelithiasis, hernias, colon cancer).
7. Genitourinary (stress incontinence, obesity-related glomerulopathy, breast and uterine cancer).
8. Psychological (depression and low self-esteem, impaired quality of life).
9. Endocrine (metabolic syndrome, type 2 diabetes, dyslipidemia, hyperandrogenemia in women, polycystic ovarian syndrome, dysmenorrhea, infertility, pregnancy complications, male hypogonadism).

So obesity related illnesses range from non-fatal, but debilitating, complaints like respiratory difficulties and musculoskeletal problems, to life threatening conditions such as stroke, heart disease and cancer ***(Bray, 2003)***.

Hypertension:

Blood pressure is clearly and strongly correlated with BMI. Roughly 30% of cases of hypertension may be attributable to obesity, and in men under the age of 45 years, this figure may be as high as 60% . In the Framingham Offspring Study, 78% of cases of hypertension in men and 64% of cases in women were attributable to obesity, and obesity was noted to be the single best predictor of hypertension incidence ***(Su et al.,2003)***.

Moreover, weight gain in adulthood is in itself an important risk factor for the development of hypertension. A 10-kg higher body weight is associated with a 3.0-mm Hg higher systolic and a 2.3-mm Hg higher diastolic blood pressure ***(Kearney et al.,2005)***. Hence, overweight and obesity are contributing to a global increase in hypertension and it is about 6 times more frequent in obese subjects than in lean men and women ***(Poirier et al.,2006)***.

Type 2 Diabetes:

Evidence from several studies indicated that obesity and weight gain are associated with an increased risk of diabetes**.** Apart from degree of overweight, the distribution of adipose tissue is also strongly associated with diabetes risk; increased abdominal fat mass increases the risk of diabetes at any BMI value ***(Resnick et al.,2000)***.

A strong link between obesity and diabetes is now well established as 70% of diabetic people present as overweight ***(Eckel and Zimmet, 2005)***. About 90% of type 2 diabetes is attributable to excess weight. Furthermore, approximately 197 million people worldwide have impaired glucose tolerance, most commonly because of obesity and the associated metabolic syndrome. This number is expected to increase to 420 million by 2025 ***(Hossain et al.,2007)***.

Cardiovascular Disease Risk:

Coronary Heart Disease:

Obesity is a powerful risk factor for cardiovascular disease (CVD)had reported that overweight, obesity, and excess abdominal fat are directly related to cardiovascular risk factors, including high levels of total cholesterol, LDL cholesterol, triglycerides, blood pressure, fibrinogen and insulin, and low levels of HDL-cholesterol. Plasminogen activator inhibitor-1 causing impaired fibrinolytic activity is elevated in persons with abdominal obesity ***(Surabhi et al., 2010)***.

Obesity is associated with increased risk for developing coronary heart disease (CHD), presumably by way of its impact on risk factors, including hypertension, dyslipidemia, impaired glucose tolerance, and type 2 diabetes. However, evidence from long-term observational studies demonstrated that overweight and obesity are predictive of cardiovascular disease, independent of its effects on traditional risk factors ***(Yan et al., 2006)***.

Congestive Heart Failure:

Overweight and obesity have been identified as important and independent risk factors for congestive heart failure (CHF). CHF is a

frequent complication of severe obesity and a major cause of death; duration of the obesity is a strong predictor of CHF. Since hypertension and type 2 diabetes are positively associated with increasing weight, the coexistence of these conditions facilitates the development of CHF ***(Finn et al., 2005)***.

The Metabolic Syndrome:

Metabolic syndrome is characterized by central obesity, hypertension, insulin resistance (Type 2 diabetes), and atherogenic disorders ***(Eckel and Zimmet, 2005)***. It is accepted that the distribution of body fat is an important determinant of metabolic abnormalities, possibly more than the degree of excess weight as measured by BMI. In particular, intra-abdominal obesity or visceral fat is strongly associated with metabolic disturbances and insulin resistance. In addition the metabolic syndrome may be associated with pro-thrombotic and pro-inflammatory states. As obesity has become more common ***(National Task Force on the Prevention and Treatment of Obesity, 2000)***, the prevalence of the metabolic syndrome has increased, and these trends are likely to continue ***(Ford,2004)***.

Complications (GIT):

<u>Nonalcoholic fatty liver disease:</u>

Obesity is associated with a spectrum of liver abnormalities, referred to as nonalcoholic fatty liver disease. Patients with fatty liver disease have moderately elevated liver enzymes, 1–4 times the upper limit of normal;elevation of the alanine aminotransferase level is usually higher than that of aspartate aminotransferase. Bilirubin, albumin and prothrombin abnormalities may develop in later stages. The natural

history varies among patients. Hepatic steatosis is frequently characterized by a benign course without histologic progression. Nonalcoholic steatohepatitis (NASH), however, may become associated with increasing fibrosis and ultimately cirrhosis ***(Hramiak et al.,2006)***.

Gastro-oesophageal reflux:

Over weight and obesity are risk factors for symptoms of gastroesophageal reflux disease ***(El-Serag et al., 2005)***. ***Jacobson et al., (2006)*** suggested that the risk of symptoms of gastroesophageal reflux disease rises progressively with increasing BMI. This seems true for all degrees of severity and duration as well as nocturnal symptoms.

Cancer:

Obesity is associated with an increased risk of several types of cancer that occur more commonly in older than in young adults, including breast, colon, gallbladder, pancreas, renal, bladder, uterine, cervical, and prostate cancers ***(Villareal et al.,2005)***. In one study, the incidence of breast cancer in older obese women (≥ 60 y of age, BMI ≥ 30) was higher than the expected incidence of breast cancer in all older women ***(Wolk et al.,2001)***.

Mortality:

Obesity is associated with decreased survival ***(Villareal et al.,2005)***. Data from the Framingham Heart Study found that adults who were obese (BMI ≥ 30) at age 40 y lived 6–7 years less than did their normal weight counterparts ***(Peeters et al.,2003)***. Men and women who have a BMI ≥ 30 are considered obese and generally have a higher mortality risk than do those who are considered overweight (BMI: 25.0 – 29.9). The absolute mortality risk associated with increased BMI

increases with age, up to the age of 75 years, because of the marked increase in mortality with advancing age. Therefore, from a clinical standpoint, the health complications associated with obesity increase linearly with increasing BMI until the age of 75 years ***(Villareal et al.,2005)***.

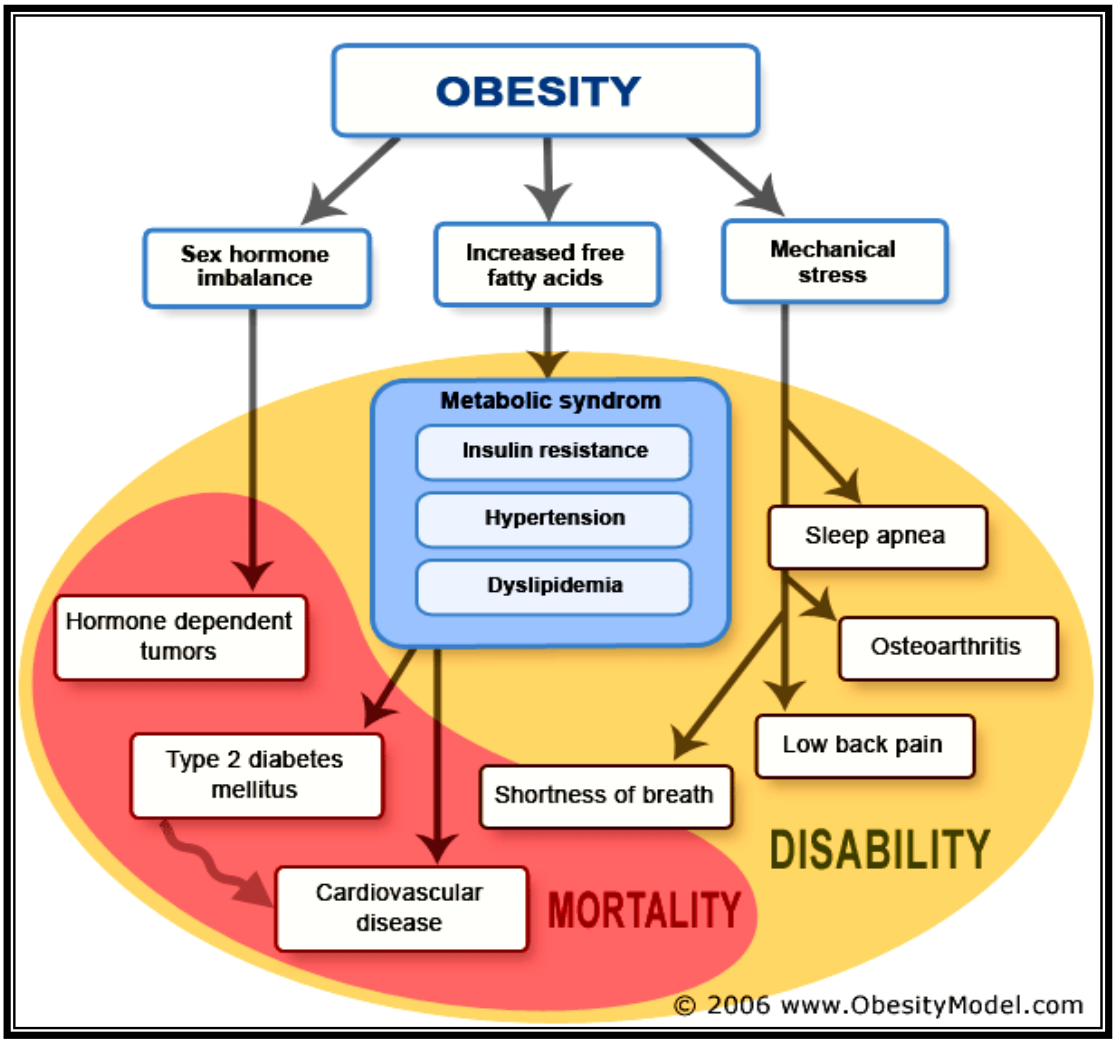


***Fig.* (10): Complications of obesity *(Villareal et al.,2005)*.**