

Chapter two

Literature review

2.literature Review

2.1 Obesity

Obesity is defined as the accumulation of fat in the human body beyond the amount required for the normal body function. This continuous accumulation has as a result weight gain (Taku *et al.*, 2003). And According to the World Health Organization (WHO), obesity is classified as chronic and severe disease in developed and developing countries, affecting both adults and children.(nilsson *et al.*, 2005) Obesity predisposes an individual to many medical risks and serious diseases (van *et al.*, 2005 and Gonzalez *et al.*, 2008), and adversely affects general health and homeostasis of the body, including the immune system (AlSufyani and Mahassni, 2011). Systems in the body must interact in order to function properly, thus a malfunction in the immune system leads to a malfunction in other systems of the body, and vice versa (Gonzalez *et al.*, 2008).

2.1.2 Diseases associated with obesity

Obesity affects all aspects of human life in a negative way and is associated with many diseases. The scientific data confirm that central obesity is associated with greater health risks compared to the total obesity. In particular, it is associated with increased incidence of hypertension, cardiovascular disease, diabetes mellitus type II, as well as higher rates of sudden death (Taku *et al.*,2003; avito *et al.* .2004).

Obesity is characterized by a pathologic situation with increased total cholesterol and triglycerides, elevated levels of LDL cholesterol and reduced levels of HDL cholesterol. This metabolic profile is common among obese people and especially among people with central obesity. Many studies have shown that there is a strong association between obesity and the metabolic syndrome. Insulin resistance, increased levels of plasma free fatty acids, reduced activity in muscle lipoprotein lipase and reduced effectiveness of the LDL receptor are some of the mechanisms of development of the metabolic syndrome. (Heseker and Schmid, 2000) .

2.1.3 Adipose tissue-induced production of CRP

Two of the first cytokines/adipokines to be associated with low-grade inflammation were interleukin-6 and tumor necrosis factor-alpha, and these have been shown to be up-regulated in obese patients (Winkler *et al.*, 2003) Studies has shown that levels of CRP are

significantly related to levels of IL-6 and TNF- α (Yudkin J S *et al.*, 1999). Interleukin-6 is, as mentioned earlier, the chief stimulator of CRP production. Abdominal adipose tissue, with its increased production of cytokines from both immune cells and adipocytes, is drained directly to the portal circulation. It could be that this direct route to the liver, where CRP is produced, is partly responsible for the increased production of CRP in abdominally obese people (Hajer *et al.*,2008). Weight loss has shown to significantly decrease CRP levels in obese subjects (mayama *et al.*,2012) , which could support the theory that the adipose tissue is actively involved in the low-grade inflammatory state seen in abdominally obese people.

2.1.4 Assessment of obesity

There are two types of body fat, the essential and the storage fat. The essential fat is necessary for the normal functions of the body and is mainly stored in the bone marrow, the heart, the lung, the liver, the spleen and the muscle. The essential fat also includes the female fat, which is stored in the breasts and hips. Storage fat is the fat stored mainly in the subcutaneous tissue as a result of the additional energy received through food. In healthy young adults the total body fat represents the 15-20% of total body weight for men and 20-25% of total body weight for women. The fat distribution differs in Central (Android type) and Regional (or female type). Central obesity is characterized by location of the fat in the upper torso and mainly in the abdomen and is common among the male population. Regional obesity is characterized by deposition of fat in the thighs and hips and it characterizes women (Maria and Evagelia,2009).

2.1.5 Measurements of obesity

Properly assessing body weight and fat distribution using more than one method is important, to be able to determine their effects on the health status of the body.

2.1.5.1 Body mass index (BMI)

The Body Mass Index (BMI) is a very common, easy and reliable way to classify patients into groups and compare them. Although there is a high correlation between BMI and fat percentage, it does not provide information about the weight of the muscle tissue and bones. (Maria and Evagelia,2009). BMI is a mathematical formula that is defined by

dividing the body weight to the second power of the height: $BMI = \text{body weight (Kg)} / \text{height cm.}^2$

Table (2.1.1) BMI classification (WHO,2000)

Classification	BMI
Underweight	<18
Normal weight	18.0-24.9
Over weight	25.0-29.9
Obese class1	30.0-34.9
Obese class 2	35.0-39.9
Obese class3	40.0+

2.1.5.2 Waist Circumference (WC)

provides important information about the accumulation and distribution of the body fat. More specifically, it is considered an adequate tool for assessing central obesity (Kushner, 2003).

2.1.5.3 The waist-to-hip ratio (WHR)

Defines the exact location of fat to differentiate between abdominal (android or male pattern) obesity and lower body (gynoid or female pattern) obesity (Champe, Harvey, & Ferrier, 2005; Rolfes, Pinna, and Whitney, 2006). Android obesity may lead to serious metabolic consequences and increased morbidity and mortality, whereas gynoid obesity carries a better prognosis for health risks and morbidity and mortality (Geissler and Powers, 2005). WHR is used as a measurement of **obesity**, which in turn is a possible indicator of other more serious health conditions. WHR calculate by formula ;waist by cm /hips by cm

Table 2.1.2 WHR classification (Geissler & Powers, 2005)

Classification	Waist to hips ratio	
	Women	Men
Normal weight	<0.80	<0.90
Over weight	0.80-0.84	0.90-0.99
obese	>0.90	>1.00

2.2 high sensitive C reactive protein

C-reactive protein is an well-known unspecific marker of inflammation and tissue damage, although its functions has not yet been fully established. (Pepys and Hirschfield., 2003). CRP is synthesized by the liver in response to factors released by fat cells (adipocyte). It is a member of the pentraxins family of proteins. It is not related to C-peptide or protein C. Creactive protein was the first pattern recognition receptor (PRR) to be identified (Mantovani et al., 2008).

2.2.1 History and nomenclature of CRP

CRP was so named because it was first discovered as a substance in the serum of patient with acute inflammation that reacted with the C- (capsular) polysaccharide of pneumococcus. Discovered by Tillet and Francis in 1930, it was initially thought that CRP might be a pathogenic secretion as it was elevated in people with a variety of illness including cancer; however discovery of hepatic synthesis demonstrated that it is a native protein (Faraj and Salem., 2012)

2.2.2Genetic and biochemistry of CRP

The CRP gene is located on the first chromosome (1q21- q23). CRP is a protein is an annular pentameric disc in shape and a member of the small pentraxins family (Faraj and Salem, 2012).

2.2.3 The structures of CRP

.Structurally, the human CRP molecule is composed of five identical nonglycosylated polypeptide subunits each containing 206 amino acid residues. The

promoters are non-covalently associated in an annular configuration with cyclic pentameric symmetry (Hirschfield *et al.*, 2003)

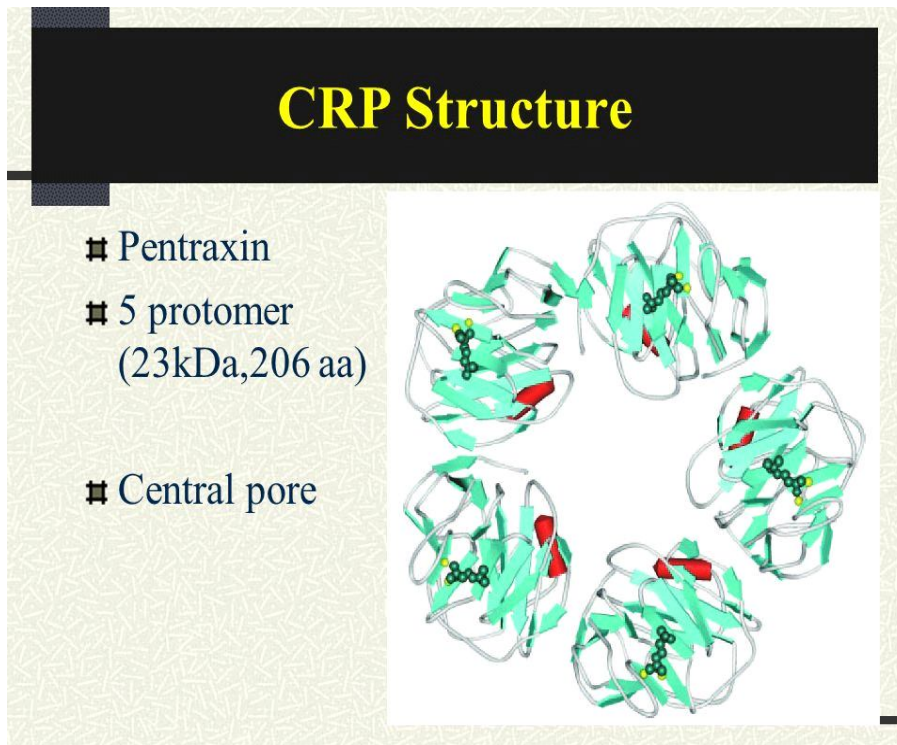


Figure 2.2.1 C-reactive protein structure (Hirschfield *et al.*, 2003)

2.2.4 C-reactive protein and obesity

The pathophysiological mechanisms linking obesity to elevated levels of CRP that Adipose tissue is an active endocrine organ that releases a variety of hormones and cytokines that contributes to CRP elevation (Poirier *et al.*,2006). In obesity, the accumulation of free fatty acid intermediates activates pro inflammatory serine kinase cascades (Rocha and libby ,2009). These cascades promote the secretion of cytokines, such as interleukin-6 (IL-6), which in turn trigger the hepatic synthesis of CRP. The liver is known to play a central role in the expression and release of CRP as it drains visceral adipose tissue, circulating triacylglycerol and free fatty acids to yield elevated cytokine secretion and promote an inflammatory (Brooks *et al.*, 2010) .Researchers have shown

that the level of CRP increases significantly as the BMI and WHR increase in both men and women (Das, 2001; Park et al., 2005; Heilbronn and Clifton, 2002).

2.2.5 The relationship between CRP and the components of the metabolic syndrome

The metabolic syndrome is the concurrence of hyperglycaemia, mild dyslipidaemia, hypertension, and visceral obesity that substantially increases the risk of developing cardiovascular diseases and type 2 diabetes (Alexander CM et al,2003).they must have:Central obesity (defined as waist circumference ≥ 94 cm for men and ≥ 80 cm plus any two of the following four factors:Raised TG level: ≥ 150 mg/dL, Reduced HDL cholesterol: < 40 mg/dL in males and < 50 mg/dL in females,Raised blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mm Raised fasting plasma glucose (FPG) ≥ 100 mg/dL, or previously diagnosed type 2 diabetes Mellitus, Increased levels of CRP has been found in obese people, and patients with metabolic syndrome have been found to have be high-risk levels (Horakova *et al* .,2010; Laurson *et al*.,2011).

2.2.6 CRP and cardiovascular diseases

Inflammatory mechanisms play a central role in all phases of atherosclerosis, from initial recruitment of circulating leukocytes to the arterial wall to the rupture of unstable plaques resulting in clinical manifestations of the disease. CRP may be causally involved in each of these stages by influencing processes such as endothelial dysfunction, monocyte recruitment and activation, lipid-related effects, complement activation, angiogenesis and apoptosis, and thrombosis.

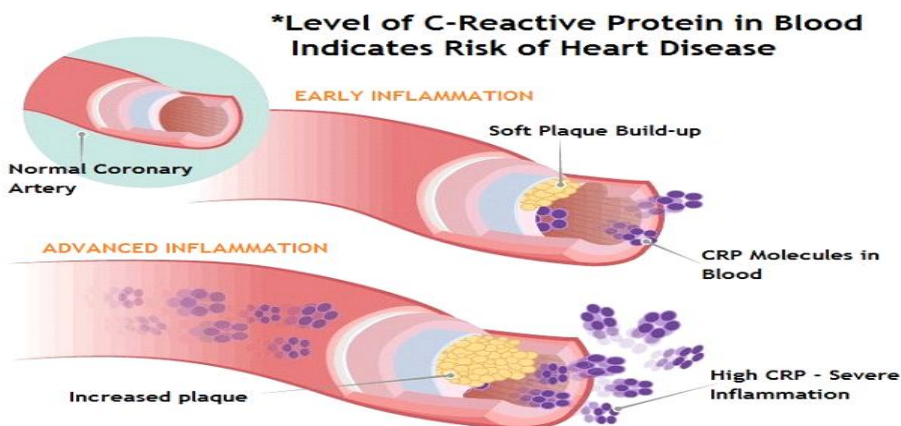


Figure 2.2.2 effect of high level of C-reactive protein on heart vessels(David, 2013)

Arterial damage results from white blood cell invasion and inflammation within the wall. CRP is a general marker for inflammation and infection, so it can be used as a very rough proxy for heart disease risk. Since many things can cause elevated CRP, this is not a very specific prognostic indicator (Lloyd-Jones et al., 2006).

2.3 serum magnesium:

Magnesium is the fourth most common cation found in the body and the second most common intracellular cation. It is important to perform many physiological roles for different body functions like enzyme function, direct enzyme activation including many ATP generating reactions, membrane function, structural function which includes synthesis of RNA, DNA and protein, and acts as calcium antagonist in muscle contraction (Jahnen-Dechent and Ketteler. 2012). It also has important role in cell cycle, mitochondrial integrity, modulating ion transport (Romani, 2011; Swaminathan , 2003).

2.3.1 Magnesium intake

Magnesium concentration depends on the magnesium intake from food and drinking water. Whole seeds, unmilled grains, green leafy vegetables (rich in magnesium containing chlorophyll) legumes and nuts are the most important sources of dietary magnesium. Meat, fish, fruits are also good sources of magnesium. Drinking water especially hard water is also one of the sources of magnesium which might account for almost 10% of daily magnesium intake. (Shils *et al.*, 2006)

2.3.2 Homeostasis of magnesium

depends on its intake, efficiency of intestinal and renal absorption and also excretion and many other relevant factors like hormones. Two pathways that is paracellular and trans cellular pathways are involved in the absorption of Mg^{2+} Paracellular pathway which is a passive mechanism absorbs Mg^{2+} through small spaces between epithelial. The trans cellular pathway involves movement of Mg^{2+} to the blood through the interior of epithelial cell. Around 30 to 40% of normal dietary intake of magnesium is absorbed through intestine. Jejunum and ileum are the important sites where magnesium absorption takes place. After 1 hour of ingestion the absorption begins and continues for 2 to 8 hours.

After 12 hours the ingested material reaches large bowel in human where little or no absorption takes place (Shils *et al.*, 2006; Baaij *et al.*, 2012).

2.3.3 Hypomagnesia

The level of magnesium in our body might not always be the same. Hypomagnesia indicates depletion of body magnesium. It is defined as hypomagnesia when the serum magnesium is less than 1.8mg/dl (<0.74mmol/l). Most of the cases of hypomagnesia are asymptomatic. Symptomatic cases are seen only when serum magnesium falls below 1.2mg/dl (Assadi 2010). Magnesium deficiency or hypomagnesia can occur due to various reasons and mechanisms. Some of the reasons for magnesium deficiency are redistribution of magnesium, reduction in dietary intake and intestinal absorption, renal loss, endocrine causes, diabetes mellitus, alcohol, drugs (Swaminathan, 2003).

2.3.4 Hypermagnesia

Hypermagnesia, the excess of magnesium in body may be the result of high intake of magnesium salt or magnesium containing drugs which is mostly seen in people with renal failure or reduced renal function. Occurrence of hypermagnesia is very rare but it may result in various neuromuscular, cardiovascular manifestation and hypocalcaemia. Higher level of magnesium also leads to cardio toxicity (Swaminathan 2003). Chronic kidney disease or end stage kidney disease is the only strong clinical predictor for hypermagnesia and net positive magnesium balance. Dialysis patients have higher magnesium level (Spiegel, 2011).

2.4 Lipids

Lipids are defined as organic compounds that are poorly soluble in water but miscible in organic solvents. Lipids play a critical role in almost all aspects of biological life they are structural components in cells and are involved in metabolic and hormonal pathways. The importance of having a knowledge of lipid disorders cannot be overstated, not least because they are common in clinical practice and, in some cases associated with atherosclerosis such as coronary heart disease (Martin, 2012)

2.4.1 Classification of lipid:

2.4.1.1 Tri acylglycerols or triglycerides

Triglycerides is the most common type of lipid formed in animals it contain three fatty acid molecules attached to one molecule of glycerol by ester bond and containing saturated fatty acid which do not have kinks in their structure, pack together more closely and tend to be solid at room temperature. In contrast triglycerides containing cis unsaturated fatty acid with bends in their structure, typically from oils at room temperature (Bishop., 2004).

2.4.1.2 Lipid Cholesterol

Cholesterol is an unsaturated steroid alcohol containing 4 rings (A, B, C and D) it has single C-H side chain tail similar to fatty acid in the physical properties. It is oriented in lipid layers, and can exist in an esterified form called cholesterol ester (CE). Cholesterol has three types low-density lipoprotein (LDL-C) often called “bad” cholesterol because it carries cholesterol to the tissues of the arteries, causing plaque to build up and the blood vessels to narrow, high-density lipoprotein (HDL-C) it called “good” cholesterol because it helps to keep cholesterol from building up inside your blood vessels and keeps them from getting blocked higher levels of HDL can reduce the risk of cardiovascular disease and very-low density lipoprotein (VLDL-C) this form contains the highest amount of triglyceride like LDL, this is considered “bad cholesterol.” A value less than 32 mg/dl is desirable. VLDL is usually not measured directly and it can be calculated from the other lipoprotein concentrations (Bishop *et al.*, 2004).

2.4.1.3 Lipid lipoprotein

Lipoproteins are large macromolecular complexes that transport hydrophobic lipids (primarily triglycerides, cholesterol, and fat-soluble vitamins) through body fluids (plasma, interstitial fluid, and lymph) to and from tissues. Lipoproteins play an essential role in the absorption of dietary cholesterol, long-chain fatty acids, and fat-soluble vitamins; the transport of triglycerides, cholesterol, and fat-soluble vitamins from the liver to peripheral tissues; and the transport of cholesterol from peripheral tissues to the liver. (Daniel *et al.*, 2012).

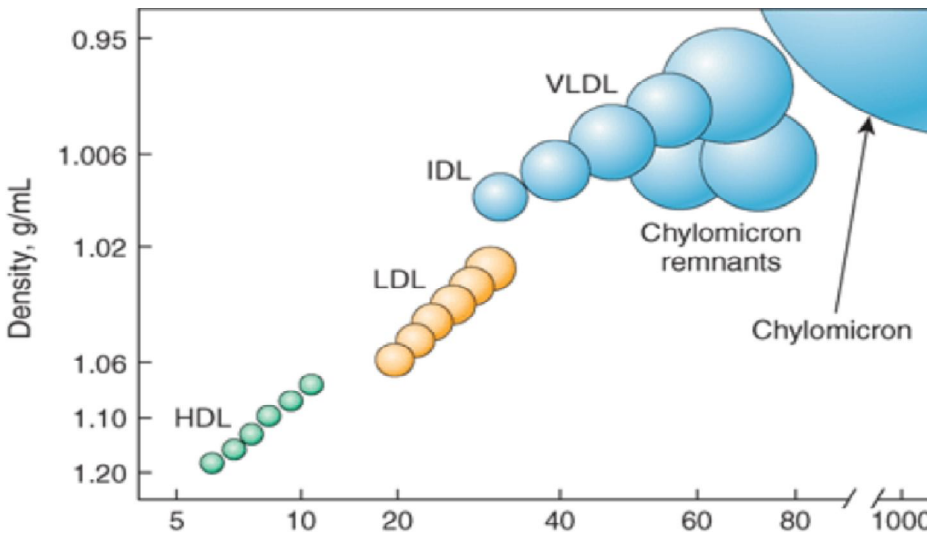


Figure (2.4.1) classification of lipoprotein according to their density .(Daniel et al.,2012:p333).

2.4.1.3.1 Four major groups of plasma lipoproteins

a) Chylomicrons

Chylomicrons, which contain apo B-48, are the largest and the least dense of the lipoprotein particles, Because of their large size, they reflect light and account for the turbidity of postprandial plasma. Because they are so light, they also readily float to the top of stored plasma and form a creamy layer, which is a hallmark for the presence of chylomicrons. it produced by the intestine, where they are packaged with absorbed dietary lipids. (Michael *et al.*, 2010).

b) Very low-density lipoproteins (VLDL)

is produced by the liver and contains apo B-100, apo E, and apo Cs; like chylomicrons , they are also rich in triglycerides. They are the major carriers of endogenous (hepatic-derived) triglycerides and transfer triglycerides from the liver to peripheral tissue. Like chylomicrons, they also reflect light and account for most of the turbidity observed in fasting hyperlipidemic plasma specimens, although they do not form a creamy top layer like chylomicrons, because they are smaller and less buoyant. Excess dietary intake of carbohydrate, saturated fatty acids, and trans fatty acids enhances the hepatic synthesis of triglycerides, which in turn increases VLDL production. .(Michael *et al.*, 2010).

c) Low-density lipoproteins (LDL)

primarily contains apo B-100 and is more cholesterol rich than other apo B-containing lipoproteins. They form as a consequence of the lipolysis of VLDL. LDL is readily taken up by cells via the LDL receptor in the liver and peripheral cells. In addition, because LDL particles are significantly smaller than VLDL particles and chylomicrons, they can infiltrate into the extracellular space of the vessel wall, where they can be oxidized and taken up by macrophages through various scavenger receptors. Macrophages that take up too much lipid become filled with intracellular lipid drops and turn into foam cells. (Michael *et al.*, 2010).

d) High-density lipoproteins (HDL)

HDL, the smallest and most dense lipoprotein particle, is synthesized by both the liver and intestine. HDL can exist as either disk-shaped particles or spherical particles. Discoidal HDL typically contains two molecules of apo AI, which form a ring around a central lipid bilayer of phospholipid and cholesterol. The ability of HDL to remove cholesterol from cells, called reverse cholesterol transport. HDL is highly heterogeneous separable into as many as different subfractions. There are two major types of spherical HDL based on density differences: HDL2 and HDL3. HDL2 particles are larger in size and richer in lipid than HDL3 and may reflect better efficiency in delivering lipids to the liver (Michael *et al.*, 2010).