T.R.N.C
NEAR EAST UNIVERSITY
INSTITUTE OF HEALTH SCIENCES

PLASMA OMENTIN-1 LEVELS IN OBESITY

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BIOCHEMISTRY PROGRAM

MASTER THESIS

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SYMBOLS / ABBREVIATIONS

%: Percentage

&: And

°C: Degree celsius

µg: Micro gram

µl: Microlitre

µM: Micro molar

Acetyl-CoA: Acetyl co-enzyme

AMP: Adenosine monophosphate

AMPK: AMP-activated protein kinase

ATP: Adenosine triphosphate

BAT: Brown adipose tissue

BMI: Body mass index

cDNA: Complementary DNA

cm: Centimeter

COX-2: Cyclooxygenase-2

CRP: C-reactive protein

CT: Computed tomography

CVD: Cardiovascular disease

DNA: Deoxyribonucleic acid

ELISA: Enzyme-linked immunosorbent assay

FFA: Free fatty acid

GLUT: Glucose transporter

GPI: Gingival periodontal index

HDL: High density lipoprotein

ICAM-1: Intercellular adhesion molecule-1

IGT: Impaired glucose tolerant

IL-6: Interleukin-6

IR: Insulin receptor

IRS: Insulin receptor substrate

kCal: Kilocalorie

kDa: Kilodalton

Kg: Kilogram

LSG: Laparoscopic sleeve gastrectomy

m^2: Meter square

mRNA: Messenger ribonucleic acid

MSCs: Mesenchymal stem cells

NAFLD: Nonalcoholic fatty liver disease

NF-kβ: Nuclear factor kappa beta

NHANES III: Third National Health and Examination Survey

NO: Nitric oxide

P13K: Phosphatidylinositol 3-kinase

PAI-1: Plasminogen activator inhibitor-1

PCOS: Polycystic ovary syndrome

PDK: Pyruvate dehydrogenase kinase

PI-PLC: Phosphatidylinositol-specific phospholipase C

PKB: Protein kinase B

PKC-ζ/λ: Protein kinase C zeta and lambda

PLA: Processed lipoaspirate

REM: Rapid eye movement

SAT: Subcutaneous adipose tissue

SD: Standard deviation

SNP: Single-nucleotide polymorphism

STAT: Signal transducer and activator of transcription

T2DM: Type 2 diabetes mellitus

TG: Triglycerides

TLR: Toll-like receptor

TNF- α: Tumor necrosis factor - Alpha

UCP1: Uncoupling protein 1

US: United state

VAT: Visceral adipose tissue

VCAM-1: Vascular cell adhesion molecules-1

Vs: Versus

WAT: White adipose tissue

WC: Waist circumference

WHO: World Health Organization

WHR: Waist to hip ratio

α: Alpha

β: Beta

γ: Gamma

ζ: Zeta

/λ: Lambda

ABSTRACT

Abdulrahman FH. Plasma omentin-1 levels in obesity. Near East University, Institute of Health Science, Biochemistry, Master Thesis, Nicosia, 2015.

Obesity has reached pandemic proportions and is associated with serious cardiometabolic sequelae including insulin resistance, diabetes, dyslipidemia, hypertension, and cardiovascular disease, where adipose tissue–secreted cytokines, that is adipokines which have been implicated in these processes. Omentin-1 is a novel adipokine preferentially produced by visceral adipose tissue and circulating levels are decreased in obesity. The aim of this study was to investigate the association between omentin-1 levels in obesity in terms of body mass index (BMI) and lipid parameters. Fasting glucose, insulin, HDL cholesterol (HDL-C), triglycerides (TG), total cholesterol (TC), LDL cholesterol (LDL-C) and anthropometric parameters were measured. We determined plasma omentin-1 levels with an enzyme-linked immunosorbent assay (ELISA). Non-obese subjects had significantly higher omentin-1 levels compared to obese subjects. The plasma omentin-1 was significantly correlated with BMI, waist circumference and triglycerides in both obese and non-obese subjects. The results suggest that omentin-1 levels have an association with BMI and waist circumferences. Moreover there is a significant influence on lipid profile both in obese and non-obese subjects.

1. INTRODUCTION

1.1. Obesity

Obesity is a disease that adversely affects the health by accumulating excess fat in the body. Obesity is linked to storing fat as energy excessively due to the imbalance between the level of intake and expenditure of energy and it is considered as a worldwide health risk in developed and industrialized countries (James et al., 2001).

Obesity has become the most important worldwide health problem. A complex interaction among factors such as genetics, environment and human behaviour leads to this problem (Sfar et al., 2013) (Nguyen & El-Serag, 2010). According to the World Health Organization, obesity appears to be due to an overabundant accumulation of body fat when instability occurs between intake and expenditure of energy in the body destroying the periodic balance of the positive energy (WHO, 2000). According to distribution of excess body fat, obesity can be divided into such types android obesity which is located in upper portion of body, gynoid obesity that located in lower portion of body (Ofei, 2005) and one more type that excess body fat has distributed equally from head to toe (Patidar, 2013). Obesity and being overweight can be most commonly identified by body mass index (BMI) "which is derived from the weight of the individual in kilograms divided by the square of the height in meters (kg/m2)" (Ofei, 2005). World Health Organization (WHO) states that individuals are considered as underweight if BMI <18.5kg/m2, as normal if 18.5-24.9 kg/m2 and as overweight or pre-obese if 25-29.9kg/m2. In addition, WHO sub-categorizes the obese group as obese class I (30-34.9kg/m2), obese class II (35-39.9kg/m2) and obese class III (>40kg/m2) (WHO, 2000). A 28kg/m2 or higher BMI is linked to more dangerous morbidity because of CVDs (Cardiovascular Disease) and T2DM (Type 2 Diabetes Mellitus) compared to the general population (Ofei, 2005).

Abdominal fat accumulation and possibilities of catching more dangerous morbidity depend on the waist: hip ratio or the waist circumference measurement and the measurement is made between the lower rib cage and the iliac crest (WHR). The region around the abdomen bigger than 98 cm (35 inches) for women and 108 cm (40 inches) for men or a WHR > 0.85 and 1.0 in women and men respectively show that the

excessive abdominal fat accumulates leading to a metabolic problems (WHO, 2000 & Ofei, 2005).

1.1.1. Types of Obesity According to Distribution of Excess Fat in Body

1.1.1.1. Android Type (Apple Type)

Android is a kind of obesity that is equivalent to an apple shape of the body of individuals. Swellings are found on the face, neck, shoulders, arms, chest and upper part of the abdomen (Ofei, 2005 & Patidar, 2013). The stomach, shoulders, arms and breasts are in a thick and stiff appearance. The back is straight and erect whereas the chest looks inflated and the neck is shorter and compressed. The hips, thighs and legs are thinner compared to the upper section of the body. People with apple type obesity are likely to suffer from the vital organs such heart, liver, lungs and kidneys. Both males and females suffer from the android obesity even though it is observed more in males. Females with menstrual irregularities who take hormone treatment or after labor are likely to have this type of obesity. In addition, females would suffer from this sort of obesity during the period of menopause due to malfunctioning of the thyroid organ. People with this type of obesity are under the high danger of suffering from heart diseases and heart damages due to high cholesterol (Patidar, 2013).

1.1.1.2. Gynoid Type (Pear Type)

In gynoid type of obesity, the lower part of the body is thicker than the upper part. In this kind of obesity, females are more inclined although it is common for both genders (Patidar, 2013). The shape of the body is like a pear in the gynoid type of obesity (Ofei, 2005 & Patidar, 2013). The abdomen, thighs, backsides and legs are droopy more or less depending on the amount of fat. The face and neck generally have a similar appearance. Even sometimes , the cheeks might be tight. By these people get older, the body transforms into a stooping posture as well as the spine never becoming erect due to the fatty hips and thighs. The vital organs such as kidneys, intestines, uterus, bladder and bowls are generally influenced. People with gynoid type obesity will not lose weight easily by dieting or doing exercises (Figure 1.1.) (Patidar, 2013).

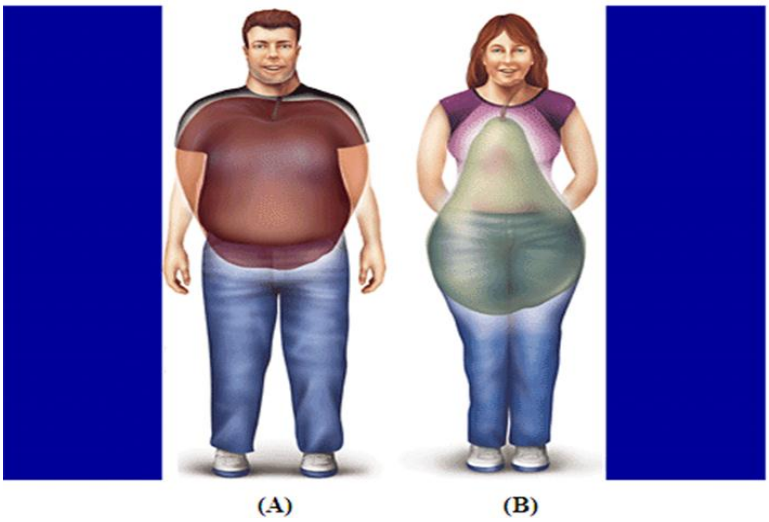

Figure 1.1. Types of obesity according to distribution of excess fat in body. Android type (A) and Gynoid type (B).

1.1.1.3. The Third Type

Another type of obesity exists other than android and gynoid. It is not always necessary that people belong to android and gynoid types of obesity. The whole body from head to toe resembles a barrel. Their gait is more similar rolling as opposed to walking. The fat tissues in their body impede the movement of all the internal organs; therefore their brisk functioning is highly affected. Doing any exercise will not be easy for this kind of people as they have an enormous sized body. Thus, these people must follow a strict diet and do a lot of exercise (Patidar, 2013).

1.1.2. Causes of Obesity

Obesity is not a single disorder only; it happens due to many reasons on the basis of a group of conditions. Body weight changes mainly based on environmental, genetic and psychosocial factors affected by the physiological mediators of energy input and consumption (Figure 1.2.). Despite the significant importance of the genetic differences on the condition of obesity, behavioural and environmental changes as a result of technological developments can be considered as the key factors causing the increase in the predominance of obesity (Locke et al., 2015).

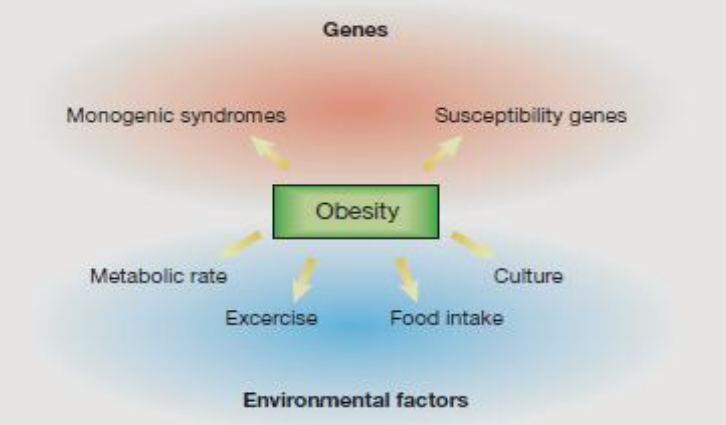

Figure 1.2. Factors influencing the development of obesity.

Obesity is very common in families but it is not always caused by genetic factors; the increase or decrease of the aetiology of obesity affected by the genotype may sometimes depend on nongenetic factors. The susceptibility genes are also influenced by the genes other than obesity related syndromes that are not often encountered. These genes lead to an increase in the tendency towards developing obesity but they do not necessarily develop a disease on their own. The susceptible-gene hypothesis is supported by a study of twins conducted on a number of pairs of twins tested under certain exposure to a balance between positive and negative energies. The differences in the rate of weight gain, the gained weight distribution and the fat deposition place are found to be similar within pairs compared to among pairs. This would prove that the differences in terms of genetics of humanbeings determine the sensitivity towards obesity under certain environmental conditions (Locke et al., 2015).

A candidate gene is a DNA molecule part which controls the synthesis of a particular polypeptide chain in linkage with a specific disease. The genes of obesity can be searched on a multifaceted approach which includes the analysis of potential candidate genes taken from animals, humans who suffer from obesity and a genome-wide search by using microsatellites on all the genome of humanbeings. The possible effects of candidate genes of obesity on composition of the body fat, anatomical fat proportion, food input and energy consumption highly contribute towards choosing the obesity candidate genes. Early onset of obesity, hyperinsulinaemia and insulin resistance characterizes monogenic rodent models of obesity. The *ob* mouse produced

in the laboratory has a well defined genetic aetiology of obesity. The *ob* gene is found on chromosome 6 and it is found in mice particularly in adipose tissue. Leptin (derived from Greek *leptos*, meaning thin) which is a gene product is not functional in homozygous mice in terms of *ob* mutation. When intraperitoneal injections replace leptin in mice, a decrease is observed in the weight and fat of body, food input and serum insulin. In the event that leptin is put into the lateral or third ventricle of the brain, it shows a probable central effect in reducing weight. Despite this fact, when leptin is introduced to the *db/db* mouse (an obese mice identified by high leptin levels) any effect is not observed on appetite, weight or fat of the body. The leptin-receptor gene of this type of mice suffered a mutation that created a nonfunctioning leptin receptor. Any initial hypothesis such as a relative or absolute deficiency of leptin causes obesity in humans results from was not reached. Contradictorily, the majority of obese people have high leptin circulating levels which increase proportionally with the fat mass, but only a limited amount ot extremely obese people suffer from congenital deficiency or a leptin-receptor gene mutation. The children with early-onset obesity who are dealt with subcutaneous leptin injections exposed to detailed examination have lost weight importantly and impressively without changing anything in terms of energy expenditure over 24 hours, the basal metabolic rate decreased but it was equalized by increasing the physical activities. Leptin contributes to inducing the weight loss by affecting the food intake. Several candidate genes were found to be linked with obesity or its metabolic problems in humanbeings which contain significant receptors for thermogenesis mechanisms (e.g. _3-adrenergic- receptor gene and a group of uncoupling proteins) for appetite controlling (Locke et al., 2015).

Environmental conditions directly influence the energy intake. As a result of processing, storage, distribution and many more food technologies, the type and amount of consumed food is highly controlled by the food industry. An increase was observed in terms of food package and portion size. It has been proven that the energy intake depends on the intake amount of food. In addition, in the last 20 years, food has become easily available in developed societies. More food with higher calories increases the body weight when the amount of exercise is low in developed countries (Nestle, 2001).

Meal times, food preferences and portion sizes mainly depend on the habits and beliefs of individuals. Fast food is preferred in industrialized countries rather than foods

prepared at home. Moreover, social context has a direct effect on the food preference and consumption on the basis of daily life pace. As a result, individuals gradually tend to eat without being based on physiological needs (de Souza Batista et al., 2007).

1.1.3. Prevalance of Obesity

The prevalence of obesity has increased and reached epidemic levels (WHO, 2014). Approximately 200 million obese adults existed around the world in 1995 and this number was higher than 300 million in 2000. 115 million people suffer from obesity associated complications in developing countries (Ofei, 2005). In addition, it is stated that obesity develops in the childhood (Ofei, 2005). Around 1.6 billion adults suffer from being overweight and around 400 million suffer from obesity all around the world. WHO reported that it is expected to have an increase in overweight adults up to 2.3 billion in 2006 and up to 700 million in obese adults by 2015. In 2014, according to the data by WHO, the rate of obesity has increased up to more than double all around the world since 1980. At least 1.9 billion adults, 18 years and above, were overweight. 600 million of them were obese (WHO 2014). According to the third National Health and Examination Survey (NHANES III) that took place in the US in 2004, the rates of obesity based on age was 65.1% for the adults who were overweight and 16.0% for overweight children (Vincent & Taylor, 2006). The United Kingdom pertains 65.7% of men and 61.9% of women as overweight or obese by being one of the countries with highest levels of overweight and obesity in Western Europe. The Scottish Heath Survey has demonstrated similar data in 2003 which shows that 65.4% of Scottish males and 59.7% of Scottish females are either overweight or obese (Wrieden et al., 2013). In contrary, despite the fact that Scottish men tend to be overweight (43.0% vs. 33.8%), Scottish women pertain the prevalence of obesity (22.4% vs. 26.0%), morbid obesity (1.6% vs. 3.4%) or raised waist-to-hip ratio (WHR) and WC (28.8% and 28.0% vs. 37.1% and 38.9%) (Wrieden et al., 2013). High WC and WHR levels which are risk factors for obesity-associated co-morbidities and mortality would cause abdominal fat distribution have several implications (Wrieden et al., 2013). The ratio of overweight men in 1980 throughout the world was 28.8% (UI 28.4–29.3) which raised to 36.9% (36.3–37.4) in 2003, and the ratio of overweight women increased from 29.8% (29.3–30.2) to 38.0% (37.5–38.5). The rise in developed countries and developing countries has shown differences in accordance with the sex patterns. Women tend to be

overweight and obese more than men in developing countries whereas men have more tendencies to being overweight and obese compared to women in developed countries (Ng et al., 2014). The level of overweight and obesity was at the peak between 1992 and 2002, but it decreased at a certain amount especially in developed countries in the past decade. In 2010, 3.4 million died, people lost 4% of their life duration and 4% suffered from a life of disability around the world occurred due to being overweight and obesity (Ng et al., 2014). WHO announces that Nauru, Micronesia, the Cook Islands, Tonga, Niue, United States, Kiribati, Samoa, Palau, Dominica, Australia, Egypt, Greece, Kuwait, Argentina, Belarus, Mexico and United Kingdom had the peak levels of obesity and overweight in 2010 which means the individuals in these countries have a BMI index of more than 25.

1.1.4. Treatment and Prevention of Obesity

In order to treat and prevent the obesity, the ways in order to restore balance between energy intake and expenditure should be found and maintained. In other terms, these ways can include diet arrangements, increasing physical activities and some clinical interventions (Pi-Sunyer, 2003).

The main aim of the alterations in diet is to allow a reduction in terms of energy intake. It is demonstrated that overweight individuals who were put on a low-calorie diet (800-1500 Kcal / day) lost approximately 8% of their body weight over 3-12 months. Certains studies have shown that this method would also work in children and adolescents. Many diets are advertised in order to lose weight. Some popular diets have well effects on individuals in a short term but they are not healthy as they are not nutritionally balanced diets. Therefore, these diets make it easier for the individuals to lose weight but increases the chances of formation of other health problems (de Souza Batista et al., 2007).

The increase in physical activity of individuals would help them to spend more energy and balance the calorie intake. This method does not only help to increase the level of energy that body uses when practicing physical exercises, but the rate of basal metabolism is also increased so it increases the use of body energy all the day. Adults and children can exercise physically to lose weight but it should be always under medical supervision. Furthermore, physical activity provides many other mental and physical benefits other than weight loss. It improves self-confidence and mood, and

decreases cardio-vascular diseases (independent of weight loss) and the risk of drug use. However, physical exercises on its own without the help of diet does not create high effects in terms of weight loss, both methods should be carried out at the same time so as to obtain good results (Pi-Sunyer, 2003).

Pharmacological and surgical therapies are included in clinical interventions. Pharmacological therapies are categorized in three groups as decreasing the food input by increasing the feeling of indulgence; modifying the metabolism by preventing the intestinal digestion and fat absorption; and raising the energy consumption which leads to losing weight. Recent controlled experiments have shown that obese people lost between 2-10 Kg when pharmacological treatments were used for 6-12 months together with changes in the life style. Nevertheless, this is only recommended to people with risks of obesity due to the side effects of these medications. On the other hand, the gastrointestinal capacity is changed by surgical interventions in order to limit food consumption. Gastric bypass causes considerable weight loss; however, this method is recommended for individuals who cannot succeed the other described interventions (de Souza Batista et al., 2007).

The medical practitioners should have a stronger background in nutritional knowledge as well as the interventions on balancing energy intake and expenditure to lose weight. Any training on this issue is not available in many medical schools at the moment. Therefore, the medical practitioners are not trained enough to give recommendations to their patients to change their life styles. More generally, education on health and nutrition would create powerful solutions so as to change the life styles. The nonsmoking campaign can serve as a good example. In the last twenty years, it was observed a s significant decrease in the number of smokers from 50% to 25% depicting a reduction to 16% of adult smokers in some population cohorts. In short, obesity is a pandemic health problem that should be fought against as soon as possible in order not to result in any other health problems (Pi-Sunyer, 2003).

Bariatric surgery is declared as the most efficient and durable therapy in treating morbid obese patients. The increase in data shows that bariatric surgery is an efficient and new metabolic treatment to treat uncontrolled obese T2DM patients. The review of current developments in bariatric/metabolic surgery covers 4 major fields. 1) Development of safety: laparoscopic/metabolic surgery has gone under recent

developments and became more safer than minimally invasive surgery. The laparoscopic/metabolic surgery is safer than laparoscopic cholecystectomy. 2) New bariatric/metabolic surgery: the most common bariatric surgery is becoming the laparoscopic sleeve gastrectomy (LSG) because it is simple and effective. Bariatric/metabolic surgery includes treatment modalities such as gastric plication, banded plication, single anastomosis (mini) gastric bypass and Duodeno-jejunal bypass with sleeve gastrectomy. 3) Bariatric/metabolic surgery mechanism: Bariatric surgery has restriction as the most important mechanism. Restriction loss is the reason of weight regain after bariatric surgery. According to the recent studies, changes of gut hormone, microbiota and bile acid after bariatric surgery would be significant for losing weight permanently and for in T2DM remission. Nevertheless, losing weight is the most important element for T2DM remission during the post-metabolic surgery. 4) Patient selection: The insulin resistance patients are found to be the individuals who may benefit most from bariatric surgery. The indication of metabolic surgery of Asian T2DM patients are for people with hardly controlled (HbA1c . 7.5%) disease and with BMI over 27.5 Kg/m2.

1.1.5. Obesity Associated Complications

The rise in the body fatness brings along deep changes in terms of physiological function. The proportion of adipose tissue into different parts mainly causes these changes. Total blood volume and cardiac function alters due to generalized obesity but the restriction of respiratory excursion is caused and respiratory function is changed by the fat distribution around the thoracic cage. The progression of hypertension, increased plasma insulin concentrations and diabetes mellitus, insulin resistance and hyperlipidaemia is mainly because adipose tissue is stored in the intra-abdominal visceral which is closely associated to upper body obesity (Grundy, 2004) (Figure 1.3.).

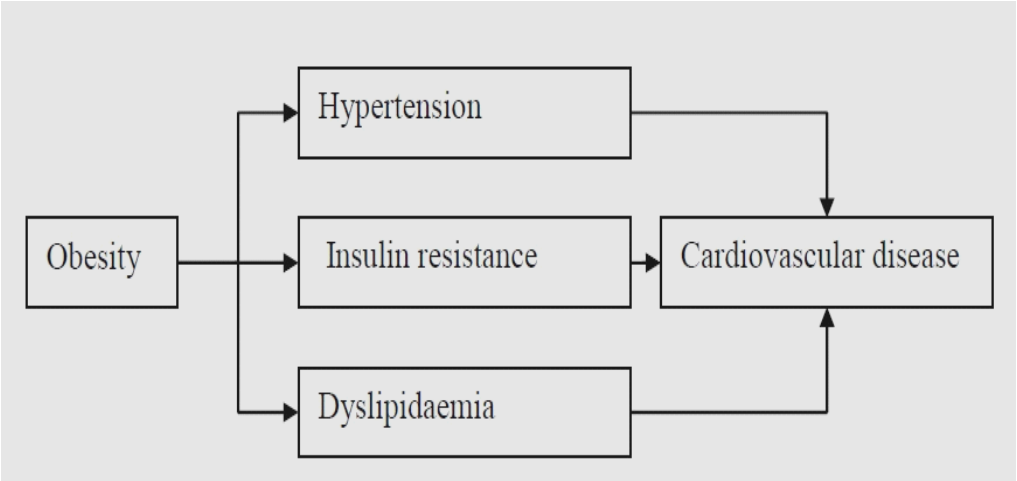

Figure 1.3. Obesity as the underlying risk factor of some disease.

1.1.5.1. Obesity and Type 2 Diabetes Mellitus

High famish plasma insulin and an excessive response against insulin to orally given glucose is associated with obesity. The glucose metabolism is indirectly affected by independent but additive mechanisms due to general body fatness and the distribution of fat in the body. When the glucose level increases and insulin response to orally given glucose happen at the same time, the obesity of the upper body increases together with the insulin resistance measurement. Post-hepatic insulin delivery incrases upto more significant concetrations of peripheral insulin that would result in peripheral insulin resistance in line with the obesity of the upper body.

Obesity is linked to various defects in insulin downstream showing effects on skeletal muscle (Caro et al., 1987) and adipose tissue (Goodyear et al., 1995). However, the location of the defects are persistent in the pathway of insulin signaling. For example, according to Goodyear et al. (1995), the individuals with morbid obesity experience a 35% diminution in terms of insulin-stimulated receptor tyrosine phosphorylation, a 38% decrease in terms of IRS-1 tyrosine phosphorylation and a 3.5-fold reduction in insulin-dependent IRS-1 PI3K activity in comparison with slim people. Goodyear et al. (1995) has also demonstrated that obese patients pertain the density of IR, IRS-1 and the p85 subunit of PI3K; and slim individuals pertain only 55, 54, and 64% of them. In contrast, Vollenweider et al. (2002) states that when any changes in IRS-1-dependent PI3K activation or the expression of proteins IR, IRS-1,

IRS-2, the p85 regulatory subunit of PI3K, Akt, PKC-ζ/λ, GLUT1, or GLUT4 exist, the skeletal muscle of the patients with glucose intolerance and obesity shows an impaired insulin-stimulated glucose uptake. As a matter of fact, when IRS-2 tyrosine phosphorylation which is stimulated by insulin is reduced, IRS-2–dependent PI3K and PKC-ζ/λ activation causes obese patients to lack insulin-stimulated glucose uptake in their skeletal muscle with glucose intolerance (Vollenweider et al., 2002). Moreover, according to recent studies, obesity does not affect and change the activity of PI3K, PDK1 and Akt/PK in slim and obese individuals carry similar levels of PKCλ/ζ (Kim et al., 1999 & Kim et al., 2003). There is a need of more research in order to demonstrate the differences among the previously described findings as the proof is not sufficient. Nevertheless, it is probable that the network of insulin signaling is disturbed depending on the obesity levels or the insulin resistance. The study of Goodyear et al. (1995) included patients whose BMI is 52.9±3.6 kg/m2 whereas the patients of the studies of Vollenweider et al. (2002) and Kim et al. (1999, 2003) had a respective BMI of 32.5±1.6 kg/m2, 31±1.3 kg/m2 and 33.4±1.4 kg/m2. Furthermore, Vollenweider et al. (2002) included patients with glucose intolerance in their study but the glucose tolerance was not tested in the other studies. Obese patients who suffer from type II diabetes that show irregularities in insulin signaling which is related to insulin stimulated skeletal muscle glucose uptake could be used in order to find more data in comparison with the slim individuals or obese non-type II diabetic patients (Kim et al., 1999). It is observed in obese patients with type II diabetes that IRS-1 tyrosine phosphorylation stimulated by insulin and activity of PI3K is 40–50% lower compared to slim or obese individuals (Kim et al., 2003). Therefore, insulin induced IRS-2–dependent PI3K activity is equally lower (Kim et al., 1999). In addition, a decrease of 46% of the expression of PKCλ/ζ has been monitored in obese type II diabetes patients which is observed as a reduced PKCλ/ζ activity in obese type II diabetes patients in comparison with slim and obese individuals (Kim et al., 2003). Considering all these effects, it can be concluded that insulin-stimulated skeletal muscle glucose uptake may be disturbed without being affected by obesity due to insulin resistance and the accompanying compensatory hyperinsulinaemia (Korsheninnikova et al., 2002).

1.1.5.2. Cardiovascular Function in Obesity

It is predictable that the high body fatness would affect the cardiovascular functions. Lean tissue mass expands and adipose tissue which is metabolically active has oxidative demands which increases the total oxygen that body consumes which causes cardiac output to increase more. Nevertheless, when the rates are normal for the body surface area, these values are within the normal range. As the total obesity-related blood volume increases, the body weight increases. The blood volume increases and causes left ventricular preload to rise and cardiac output rests. When the stroke volume increases, the demand for cardiac output also increases whereas no changes take place in the heart rate. When the diastolic filling of the ventricle on the left rises, it results in a rise in terms of obesity in stroke volume. The heart changes structurally depending of the expansion of the volume and rise in the output of the cardiac, and the dimension of the left ventricular cavity grows and the wall stress increases depending on the rise in left ventricular filling. The development of left ventricular goes along with hypertrophy of myocardia by keeping the ratio between the radius of the ventricular cavity and thickness of the wall constant, and eccentric hypertrophy is obtained by the thickening of the wall with the results of development. A directly proportional increase takes place in the left ventricular mass to BMI or level of overweight. Cardiac output and systemic vascular resistance (against which the blood is pumped) functionalizes the blood pressure. In moderate obesity, patients usually suffer from high cardiac output but all obese patients are not necessarily hypertensive. However, the patients with high systemic resistance, hypertension and obesity are likely to suffer from disproportion of increased ventricular wall dimensions to the chamber radius which would gradually cause concentric hypertrophy (Koopelman, 2000).

1.1.5.3. Sleep-Breathing Abnormalities in Obesity

A change of respiratory functions happen during inspiration and expiration due to a high level of fat accumulated in the wall of the chest and abdomen as mechanical properties of the chest and the diaphragm are affected by fat and this reduces the lung volume and amends the ventilation pattern in the lungs. Moreover, as the mass of fat increases, the respiratory system functionning completely decreases. In case that an obese person lies flat, all these effects happen at the peak level. respiratory muscle force should rise in order for fat to obtain the mass loading effect so that it overcomes the

excessive elastic recoil and the elastic breathing work increases. The effects of obesity on respiratory function constitute importance while sleeping (Figure 1.4.) (Koopelman, 1994).

The level of arterial oxygen saturation decreases and the level of carbon dioxide increases along with the decreases in voluntary muscle tone throughout the rapid eye movement (REM) sleep. All people are affected by these changes, however, it is at a considerable rate in obese individuals. Slim individuals experience irregular respiration and occasional apnoeic episodes throughout the REM sleep, but obese subjects whose respiratory mechanics are influenced suffer from this more frequently leading to more severe results such as hypoxia and the following cardiac arrhythmias. According to the research conducted on patients with obesity, the larynx is obstructed and the muscles controlling tongue movement are related. The tongue base drops behind the posterior pharyngeal wall when genioglossus muscle is relaxed and this clogs the pharynx. This event stops the breathing temporarily (apnoea) and decreases the arterial oxygen saturation concentration (hypoxia). In general, some obese men experience low oxygen saturation values during REM sleep but they tend to have normal arterial gases (Koopelman, 2000).

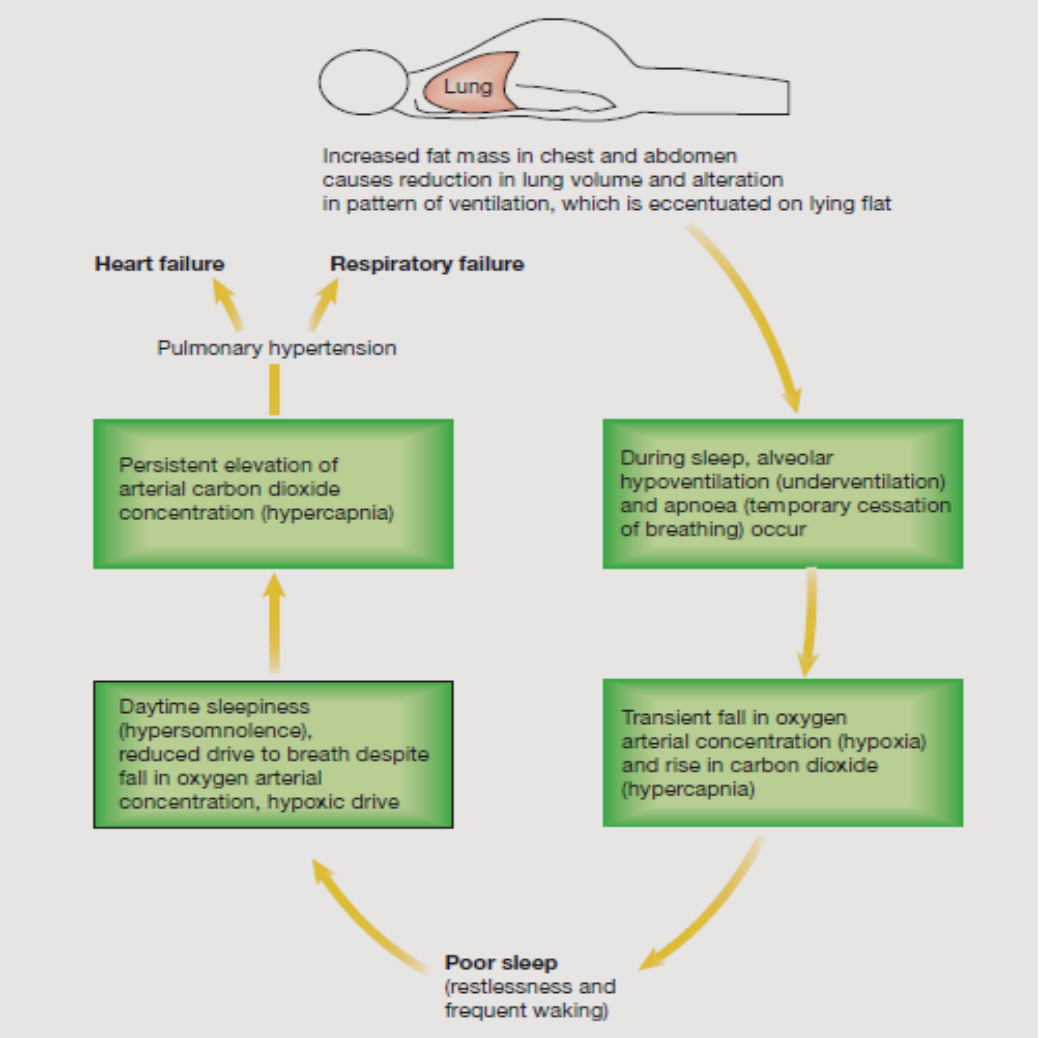

Figure 1.4. Sleep-breathing abnormalities in obesity.

If the body weight increases progressively, respiratory functions are affected during sleeping. Obese individuals are the affected subjects in terms of respiratory functions, particularly lying flat. Alveolar hypoventilation and transient episodes of apnoea may be experienced while sleeping which is followed by a decrease in the saturation of arterial oxygen (hypoxia) and then arterial carbon dioxide (hypercapnia) increases. Certain humanbeings are affected by these circumstances causing them feeling sleepy during the day (hypersomnolence) with persistent hypoxia and hypercapnia, at the same time, pulmonary hypertension develops, heart failure as well as respiratory failure may take place at the end.

1.2. Adipose Tissue

Adipose tissues are the connective tissues that lack a specific anatomy. Nevertheless, different studies suggest that adipose tissues form a large organ with a specific anatomy, supplies of vascular and nerve, complex cytology, and high physiological plasticity (Cinti, 2011). Adipose tissue is categorized as "white" and "brown" adipose tissue depots all over the body as shown in Figure 1.5. White adipose tissue (WAT) mainly contains unilocular lipid-filled adipocytes that are for the storage of lipids while brown adipose tissue (BAT) contains multilocular adipocytes functioning for lipid burning. WAT and BAT are mainly formed of adipocytes but stromal cells such as blood, endothelial, fibroblastic and adipocyte precursor cells that are neceesary for the functioning of adipose tissue are available in both tissue type. The adipose tissue morphology changes throughout the whole development of the adipose tissue (Birsoy et al., 2011), the obesity onset (Sun, Kusminski & Scherer, 2011) and response to cold challenge (Seale et al., 2011), during which the adipose tissue is rendered as powerful in order to comprehend the adipose tissue development, maintenance, growth and remodeling (Berry et al., 2014).

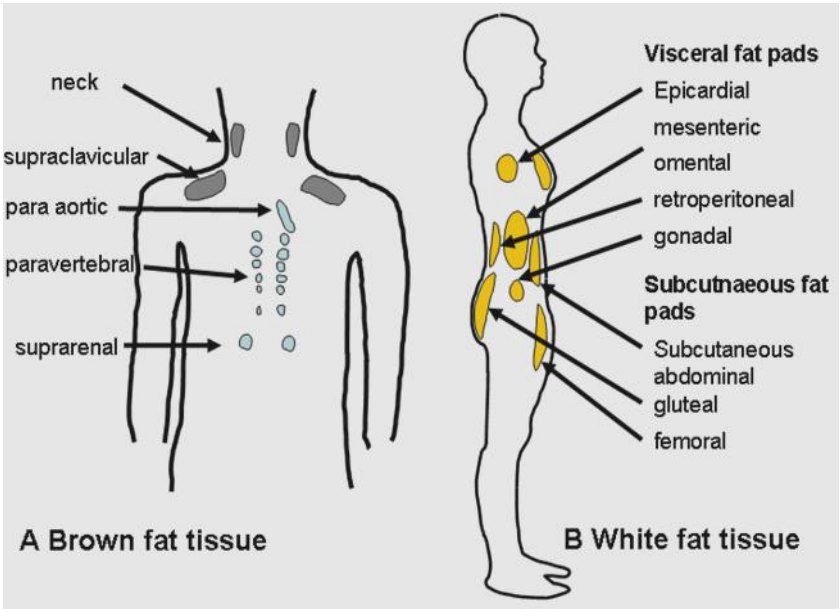

Figure 1.5. Brown fat (A) and white fat (B) tissue distribution in adult.

White adipose tissue (WAT) is the primary location where the energy is stored in vertebrates. Triglycerides (TG) form the most of the structure of the lipid droplets of the adipocytes. Once the energy expenditure is over the energy intake, free fatty acids (FFA) are released by WAT. Furthermore, WAT is a secretory organ producing a number of adipocytokines that allows self-regulation (autocrine effect), a cross-talk with local (paracrine effect) and distant adipocytes and other brain cells, liver, muscles, pancreas, etc. (endocrine effect) (Kim & Moustaid-Moussa, 2000).

WAT contains different cell types. Adipocytes only constitute one third of the cells and two thirds are formed of stromal vascular fraction which are fibroblasts, macrophages, stromal cells, monocytes and preadipocytes. It is estimated that adipose tissue is produced from an embryonic stem cell precursor (Pittenger et al., 1999). The white adipose tissue develops early during embryogenesis and it continues through the whole life cycle; therefore, on the basis of the energy status and the body storage needs, it increases the size of fat cells (hypertrophy) together with the number of fat cells (hyperplasia) (Kim & Moustaid-Moussa, 2000).

Different locations in the body experience fat development and the fat has different functions at different locations: subcutaneous adipose tissue (SCWAT) serves as an effective insulating layer between the muscles and dermis; visceral adipose tissue serves as a space filler between organs, like gonads (PGWAT), heart, kidneys (PRWAT), or gut as well as protecting the organs against mechanical impacts and keeping them in the right position (Pittenger et al., 1999).

1.2.1. Cytology of Adipose Tissue

Stem cells consist of a capacity of self-renewal, long-term viability and a capacity for multilineage. The potential for multilineage of embryonic stem cells and adult stem cells from the bone marrow possess extensive characters. The potential embryonic stem cell is huge together with political and ethical matters in terms of their use. Thus, stem cells of adults coming from the bone marrow stroma (i.e., mesenchymal stem cells, MSCs) are recommended as an alternative. It is found out that they produce osteoprogenitor cells, MSCs differentiate into chondrocytes, myoblasts, and osteoblasts adipocytes in vitro and undergo differentiation in vivo; these processes render the stem cells as possible recommendations in order to repair mesodermal defects and to manage diseases. Nevertheless, when MSCs have been used clinically, problems such as

morbidity, pain, and low number of cells upon harvest were observed. Therefore, investigators decided to seek other sources for MSCs (Zuk et al., 2002).

Adipose tissue such as bone marrow is created by the mesenchyme and involves an easily segregated stroma that has a supportive (Zuk et al., 2001). Mesenchyme stem cells (MSCs) cannot only differentiate into adipose tissue but also they can turn into many different connective tissue cells such as bone, cartilage, fat, tendon and muscle as shown in Figure (Alderman, 2010). Based on this, it is possible that adipose tissue produces stem cells effective at different locations. A bunch of putative stem cells inside the lipoaspirates of individuals has been classified in advance (Zuk et al., 2001). It is possible to isolate the processed lipoaspirate (PLA) cells within the adipose tissue which are high in amount and they grow continously by exerting the proliferation kinetics in culture. Moreover, similar to the MSCs, PLA cells differentiate in vitro toward the osteogenic, adipogenic, myogenic, and chondrogenic lineages under certain lineage-specific factors. Zuk et al. (2002) studied the capacity of PLA cells to differentiate multilineagely which figured out that the multipotent stem cells which can be compared with MSCs can be differentiated from the adipose tissue of individuals.

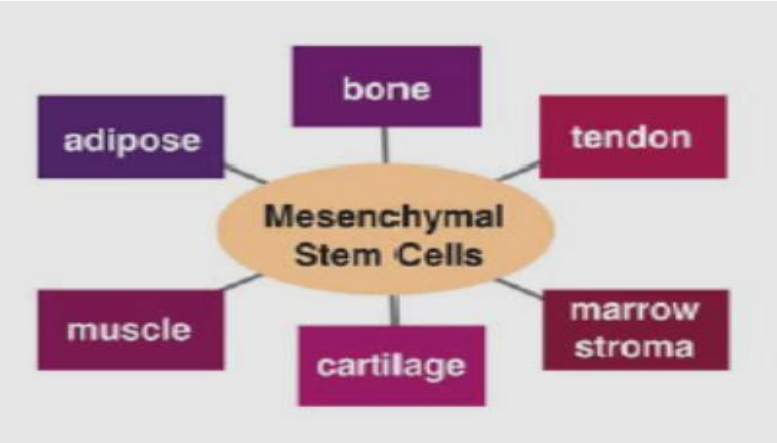

Figure 1.6. Mesenchymal stem cells (MSCs) are multipotent and differentiate into musculoskeletal tissue (Alderman, 2010).

Adipocytes can be defined as the main parenchymal cells that the adipose organ consists of. Adipocytes can be categorised into two and can be easily distinguished in terms of morphology as white adipocytes and brown adipocytes. They are comprised of

leptin- and S100-B-immunoreactive spherical cells, contains a single cytoplasmic lipid droplet and a compressed nucleus form 90% of their volume. Brown adipocytes are polygonal cells that consist of a round shape nucleus and several cytoplasmic lipid droplets. In addition, brown adipocytes are distinguished by containing many mitochondria that are large in dimension surrounded by many cristae. Brown adipocytes contain mitochondria that can be distinguished by the uncoupling protein 1 (UCP1) which is a unique protein that separates oxidative phosphorylation and ATP synthesis followed by heat production (thermogenesis) (Ricquier, 2005 & Frontini et al., 2007). Therefore, both adipocytes are morphologically and physiologically nonsimilar: white adipocytes allow the energy storage to cover the metabolic needs of the organism while brown adipocytes help energy consumption for thermogenesis. The adipose organ stores both cell types in its multiple depots (Murano et al., 2009 & Vitali et al., 2012). White adipocytes differ in size and they are found in subcutaneous depots (mainly large adipocytes) and visceral depots (mainly small adipocytes) (Barbatelli et al., 2010). Brown adipocytes which are found in visceral depots are generally located around the aorta. In addition, paucilocular adipocytes with intermediate morphology that are characterized in between white and brown adipocytes can be found in the adipose organ. In certain cases, it is referred to as 'beige' or 'brite' (brown in white) parts of white adipose tissue which contains brown or brown-like adipocytes at the same time (Cinti, 2012).

1.2.2. Adipose Tissue Depots

The subcutaneous adipose tissue (SAT) deposits are the largest area where the fat can be stored and is distributed throughout the body. Systemic free fatty acids (FFAs) are primarily produced in the abdominal SAT (Jensen, 2008) and it serves as a "metabolic sink" in order for the clearance and storage of excess lipids. Superficial and deep SAT are two different sections form the subcutaneous abdominal fat which are separated by Scarpa's fascia. Both SAT depots are self-distinctive in terms of morphological and metabolic features. The size of superficial SAT adipocytes are bigger in comparison with the deep subcutaneous fat cells (Tordjman et al., 2012). Moreover, the fat lobules are differently organised; superficial SAT are formed of small, tightly packed lobules whereas the deep SAT lobules are larger and randomly distributed. Furthermore, it has been proposed that the deep SAT is more lipolytically

active compared to the superficial SAT (Monzon et al., 2002) as well as being associated to the insulin resistance. Thus, it can be suggested that a strong relationship exists between deep SAT accumulation and insulin resistance more than that of visceral adipose tissue (VAT). However, no relationship exists between the size of the superficial SAT depot and insulin resistance (Kelley et al., 2000 & Smith et al., 2001). Therefore, it is understood that the deep SAT demonstrates the characteristics of VAT rather than superficial SAT. Visceral fat is found intra-abdominally surrounding the organs. In Figure 1.7., acomputed tomography (CT) scan is shown which demonstrates different fat depots in the body. VAT builds up on the basis of various detrimental irregularities in terms of glucose and lipid metabolism as well as disorders such as insulin resistance, dyslipidemia and atherosclerosis. Moreover, insulin demonstrates a weaker anti-lipolytic effect in VAT that may aggravate the degree and effects of visceral obesity. excess VAT may negatively affect the liver as it directly accesses the liver. The portal vein drains the VAT directing the lipids, adipokines, and cytokines coming out of the visceral depot directly to the liver (Wajchenberg, 2000).

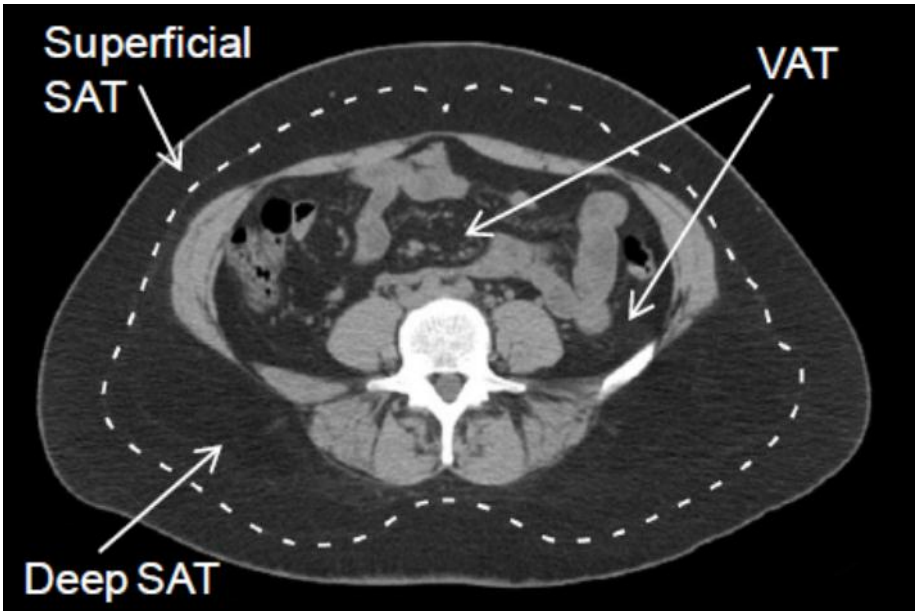

Figure 1.7. A computed tomography scan depicting the superficial and deep subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) depots.

1.2.3. Endocrine Functions of Adipose Tisuue

Adipocytes (adipose cells) mainly serve to store fat (lipids) so that the fat is burnt to be used for the future energy needs of the body. This essential characteristics of adipocytes helped humanity to continue their species (Flier, 2004). Apart from the characteristics of lipid storage and supply of free fatty acids, bioactive molecules (lipids or peptides) are also produced by WAT in large amounts. The hormones such as leptin, adiponectin, resistin and apelin are included in these molecules (Vázquez-Vela, Torres & Tovar, 2008). It has been acknowledged that with the discovery of the hormone produced by these adipose cells called leptin that adipose tissue is an active endocrine gland which can communicate with the brain to participate in the regulation of various body functions. While many significant proteins including proinflammatory cytokines, such as IL-6 (interleukin-6), TNF-α (tumor necrosis factor - α), reninangiotensin system proteins and pro-thrombotic products such as plasminogen activator inhibitor-1 (Flier, 2004) are produced, adiponectin increase insulin-sensitivity, decreases FFA influx, increases β-oxidation in liver and muscle. It also helps to decrease atherogenic risk by depressing the expression of adhesion molecules within the vascular wall. Resistin acts on skeletal muscle, WAT and its high plasma levels are associated with insulin resistance. Apelin contributes to increasing cardiac contractility, decreasing blood pressure and hyperglycemia (Vázquez-Vela, Torres & Tovar, 2008). Obesity may decrease physiological response given by certain adipokines (resistance). Apart from the molecules described above, adipose tissue produces and secretes a variety of other peptides, cytokines and complement factors such as interleukine-6 (IL-6), tumour necrosis factor α (TNF-α), , plasminogen activator inhibitor-1 (PAI-1), angiotensinogen, etc. as well. TNF-α contributes to in the insulin resistance pathophysiology by altering the sensitivity of insulin via the activation of insulin receptor substrate (IRS)-1 abnormal phosphorylation. IL-6 is a component of the stromal vascular fraction which has the control over the hepatic production of inflammatory proteins (Antuna-Puente et al., 2008).

It is suggested that excess intra-abdominal fat would imply the failure of the subcutaneous adipose tissue in a body to act as an “energy sink” when the calorie intake is excess or insufficient due to excess energy intake and/or reduced energy production. This inability may result in a phenomenon such as accumulation of fat at undesired

locations (liver, heart, muscle, etc.) called ectopic fat deposition (Després & Lemieux, 2006). Thus, abundance intra-abdominal fat may be regarded as a warning sign that shows the storage of excess energy in the body at unusual locations which would also increase the risk of CVD and type 2 diabetes (Després & Lemieux, 2006). Adipose tissue is currently considered as a valuable organ formed of a complex network which regulates diverse biological functions (Figure1.8.) (Coelho, Oliveira & Fernandes, 2013).

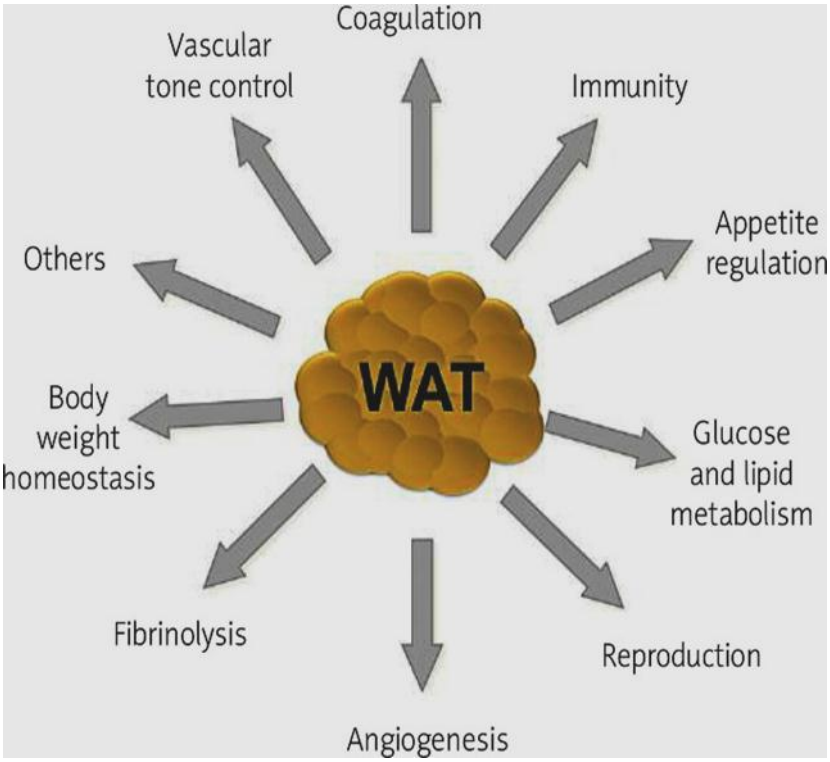

Figure 1.8. Adipose tissue is an important organ of a complex network that takes part in the regulation of a variety of quite diverse biological functions.

1.2.4. The Role of Adipokines

The white adipose tissue (WAT) has been lately recognized as a very active endocrine organ, which secretes various endocrine and paracrine factors termed adipokines (Figure 1.9). Adipokines have a significant role in the inflammation, cardiovascular, metabolism and endocrine system, mediating crosstalk between insulin-sensitive tissues. Some of them participating in the regulation of adipose tissue having a positive or/and negative effects on cardiovascular, inflammatory and metabolic statuses

are the following: Leptin might be both beneficial and harmful. It controls the food intake and energy expenditure (Friedman & Halaas, 1998). Leptin consists of 167 amino acids and its levels are decreased with hunger and increased with overfeeding, thus regulating appetite. Its receptors are found in the central nervous system and other cells such as endothelial cells and adipocytes. Leptin appears that it increases the production of proinflammatory cytokines by regulating different immune cells (Loffreda et al., 1998).

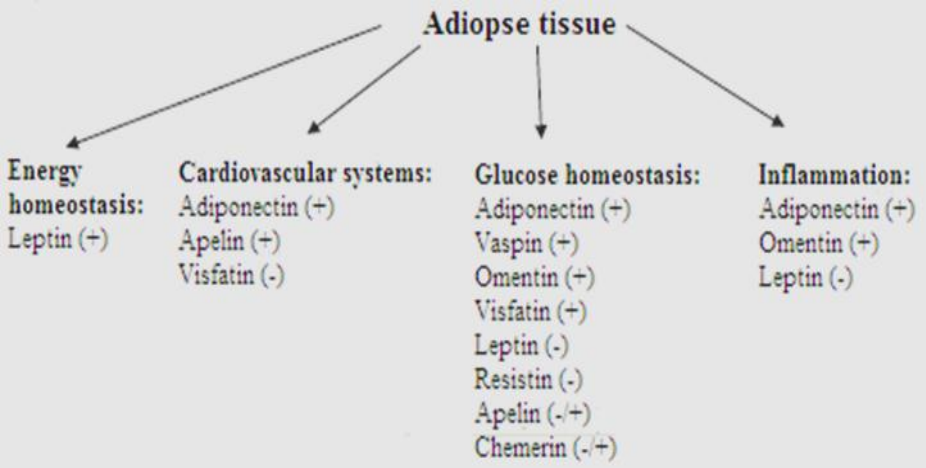

Figure 1.9. Favorable (+) and unfavorable (-) effects of novel adipokines in obesity.

Chemerin's actions differ and show controversial results depending on the cell types. It was found in 2007 and formed of 131-137 aminoacids. Body mass index, blood pressure and triglycerides determine its plasma levels because the metabolic properties of mature adipocytes are different. However, it does not allow the response of vascular inflammation (Katsi et al., 2014).

Resistin is a 12 kDa peptide found in the human adipose tissue produced by macrophages. It is subcategorised into two as a trimer (monomeric form of the peptide hormone) and as a hexamer (dimeric form of the peptide hormone). High plasma levels of resistin increases the risks of CVD (Cardiovascular Disease) and poor prognosis in CAD (Coronary Artery Disease). Resistin levels fall when rosiglitazone treatment is received (Katsi et al., 2014).

Vaspin was distinguished in 2005 and formed of 392-395 amino acids. It belongs to the serine protease inhibitor family. It plays a beneficial role in glucose homeostasis as it increases sensitivity of insulin and limits the food intake via indefinite mechanisms (Hida et al., 2005). Moreover, the expression of proinflammatory adipocytokines is blocked. İt will be available in many types of cells and tissues. It can be found in visceral adipose tissue and is charaterised by insulin like functions which is beneficial for glucose homeostasis. On the other hand, it can upregulate TNF-a and IL-6 in vitro and in vivo which increases metalloproteinase-9 activity that results in a proinflammatory state of monocytes. Figure 1.9. demonstrates different actions of the novel adipokines (Katsi et al., 2014).

Adiponectin was the first 30-kDa protein cloned from fat tissues. Adiponectin is a metabolically active adipokine which is negatively associated with insulin resistance, atherosclerosis and obesity. Fatty acid oxidation is induced by adiponectin promotes via the phosphorylation of 5-AMP-activated protein kinase (AMPK), thereby acetyl- CoA carboxylase is activated. Adiponectin signaling and biological function takes place under the effect of the adiponectin receptors AdipoR1 and AdipoR2. Adiponectin is an anti-inflammatory, antiatherogenic, and antidiabetic metabolically active adipokine which has inverse effects in terms of insulin resistance, atherosclerosis and obesity. Hypoadiponectinemia is considered as an independent risk factor for cardiovascular disease (CVD) and type 2 diabetes.

Most cytokines possess predominant paracrine or autocrine functions. Neverhteless, IL-6 is nonsimilar because most cellular targets of a true endocrine cytokine are far from the site of release and the effects of IL-6 correspond to the serum concentration. Adipocytes and macrophages secrete IL-6 in adipose tissue and it has been illustrated in the research on the measurement of arteriovenous increases of serum IL-6 concentration that net secretion of IL-6 from adipose tissue depots has around 30% of fat accounts in the circulating IL-6 concentrations in humans. Similar to leptin, the increase in the production of IL-6 by adipose tissue is proportional to the increasing adiposity, and circulating IL-6 concentrations correspond to the of body fat and insulin resistance. Nevertheless, similar to leptin, according to in vitro studies, fat produces more IL-6 than visceral fat for a certain amount of adipose tissue which weakens the correspondence between this cytokine and the visceral fat–dependent metabolic

syndrome. Despite the differential regulation of IL-6 secretion from different fat depots and from distinct adipose tissue cell types are resolute, it has been demonstrated that humoral (insulin, glucocorticoids), neural (sympathetic nervous system activity), and paracrine (IL-1, TNF-) signals control the production of IL-6 from fat, and there is room for researh on the factors that increase IL-6 production from visceral fat. On one hand, IL-6 may be a highly pleiotropic cytokine possessing hormonal effects on many tissues, but on the other hand the obesity would metabolically affected by its effects on the endothelium, bone marrow and liver.

1.2.5. Omentin-1

Omentin-1 (intelectin-1, intestinal lactoferin receptor, endothelian lectin HL-1, galactofuranose-binding lectin) (Zhang et al., 2014) is a novel adipose tissue-derived cytokine (adipokine) that is formed of 313 amino acids which originates from omental fat cDNA library. Omentin is mainly found in the visceral rather than subcutaneous adipose tissues (Yamawaki et al., 2010) and it secreted by visceral stromal vascular cells but not adipocytes. Furthermore, according to the data obtained in in vitro experiments, insulin-mediated glucose uptake in human subcutaneous and omental adipocytes is improved by treatment with recombinant omentin-1 enhances and Akt/PKB phosphorylation is also increased. D-glucose and insulin brings down the omentin-1 production in cultured adipocytes. However, studies on humans revealed that the plasma concentration of omentin-1 which is the major circulating isoform in human plasma falls down in type 1 diabetes mellitus patients and glucose ingestion does not affect it (Auguet et al., 2011). Omentin is also known as endothelial lectin HL-1, intelectin-1 found intestinal paneth cells, and intestinal lactoferrin receptor found in small intestine of newborn infants. Despite the fact that biologic function of omentin has not been identified, it has been shown that insulin-mediated glucose transport is improved by omentin in human adipocytes. Overweight and/or obesity are in high correlation with cardiovascular diseases such as hypertension. Thus, it has been recommended that blood pressure can be controlled by the contribution of omentin which would directly show effects on the reactivity of blood vessels. In reality, many reports hypothesized that adipokines like leptin, adiponectin, visfatin and resistin promote the contractility of isolated blood vessels by applying multiple mechanisms (Yamawaki et al., 2010).

Omentin has a function as an intestinal lactoferrin receptor (Suzuki, Shin & Lönnerdal, 2001). Lactoferrin is an 80 kDa protein which has gastrointestinal tract controls like iron absorption, mucosal immunity modulation, and mucosal differentiation stimulation. The multiple lactoferrin biological functions depend on its target cells and the availabilty of certain lactoferrin receptors at their surfaces. Some lactoferrin receptors are said to be controlling some lactoferrin functions such as immune responses modulation and promotion of pro- and anti-inflammatory factors (Suzuki, Shin & Lönnerdal, 2001). Omentin is found in intestines and related to bacterial and parasite infections. The roles that omentin plays instead of lactoferrin have been studied. In this study, omentin-interacting protein(s) or omentin receptors which are identified as omentin interacting protein like lactoferrin were identified (Suzuki & Lönnerdal, 2004).

1.2.5.1. Molecular and Cell Biology of Omentin

Human omentin is located at chromosome 1 and has 8 exons and 7 introns (Schäffler et al., 2005). It is found in fish, frog, mouse, sheep, bovine, and humans. The gene encodes a 313 amino acids (38kDa) secreted protein and can form homotrimers. It is expressed by endothelial cells (Tsuji et al., 2001), epithelial cells (Carolan et al., 2008), goblet cells (Pemberton et al., 2004), Paneth cells (Komiya, Tanigawa & Hirohashi, 1998), small intestinal enterocytes (Wrackmeyer et al., 2008) and mesothelial cells, and it was found as STAT6-dependent (Voehringer et al., 2007). At the same time, it is a GPI-linked protein, and phosphatidylinositol-specific phospholipase C (PI-PLC) can divide the linker (Tsuji et al., 2007).

1.2.5.2. Structure of Omentin-1

Omentin-1 possess the uniprot code Q8WWAO and gene bank expression number AY549722 is another novel adipokine. Omentin was observed in an omental fat cDNA library in 2005 (Yang et al., 2006 & Schäffler et al., 2005) and was initially described to be located in intestinal Paneth cells (Komiya, Tanigawa & Hirohashi, 1998) called intelectin-1 and intestinal lactoferrin receptor (Komiya, Tanigawa & Hirohashi, 1998 & Lee et al., 2001). Additionally, it was observed in endothelial cells and was called endothelial lactin (Lee et al., 2001). It contains 313 amino acids and is mainly found in visceral adipose tissue but not in subcutaneous adipose tissue, particularly in visceral adipose stromal vascular cells (Yang et al., 2006). Omentin-1 is

available in large amount in subcutaneous fat depots and mature adipocytes. It can also be observed in other tissues such as human epicardial fat, endothelial cells, small intestine, thymus, colon, ovary, reticulocytes, placenta and lungs (Yang et al., 2006 & Schäffler et al., 2005). It weighs 35 kDa as a hydrophilic protein. Omentin-1 can be described as a new Ca^{2+}-dependent lectin that possesses affinity for galacto-furanosyl residues (constituents of pathogens and dominant immunogens) (Schäffler et al., 2005). Therefore, the recognition of specific pathogens and bacterial components can prove its inclusion. Omentin-2 is a homolog of omentin-1 characterised by 83% of aminoacid in its structure shared with omentin-1. These two homologs are adjacent to each other in the 1q22-q23 chromosomal region and they are assocaited with type 2 diabetes mellitus (Katsi et al., 2014).

1.2.5.3. Role of Omentin in Energy Metabolism

Energy homeostasis is the process by which the energy levels of the body are kept constant and the balance between the energy intake to expenditure is maintained by storing extra energy for later needs. Energy homeostasis uses insulin as a major regulator. To give an example, glucose and fatty acids are stimulated so that they enter adipocytes for storage and muscle cells for oxidation. In adipocytes, AKT phosphorylation and insulin-mediated glucose transport rise by omentin suggesting its role in glucose metabolism and regulation of insulin sensitivity (Yang et al., 2006). Insulin plays a key function in enhancing the glucose uptake into responsive cells like liver, muscles and fat cells for oxidation or storage purposes. This process takes place via a network of phosphorylation. Insulin is normally secreted after a meal and sticks on the insulin receptor located on the cell surface activating the insulin receptor (IR). The IR binds to its substrate (IRS1/2) activating PI3K at the same time. Then, PI3K activates AKT via phosphorylating AKT at threonine 308 and serine 473. During this activation, AKT transfers the glucose transporter 4 (GLUT4) onto the cell surface in order to transport glucose into cells. The sensitivity of cells to insulin is finely regulated. IRS is considered as one of the most important enzymes in this system that has several potential locations of tyrosine phosphorylation and approximately 50 potential locations of serine/threonine phosphorylation that might be controlled by positive and negative feedback loops in order to maintain the control of the glucose transport (Youngren, 2007). As a good example, serine phosphorylation can occur and

IRS activity increases by activating mTOR-p70S6K pathway by AKT. Besides, mTOR-p70S6K pathway can be blocked by IRS avtivity rised by other cytokines or molecules via a major regulator called AMP-activated protein kinase (AMPK) in energy homeostasis. AMPK is regarded as a metabolic sensor of the cellular energy status (Hardie, 2003).

1.2.5.4. Omentin in Endothelium and Coronary Artery Disease

Omentin's role has been determined in endothelial function (Yamawaki et al., 2010) while vasoconstriction is blocked by the pre-treatment of isolated rat aorta with omentin in either endothelium dependent or independent way. The same condition applied to the isolated rat mesenteric arteries showing the correspondence of this action with the resistance type vessels. The effects of the actions of omentin on endothelium are altered as the ICAM-1 and VCAM-1 expressions are blocked due to the disruption of the NF-Kβ signaling pathway and the elimination of monocyte binding on to TNF-a activated endothelial cells (Zhong et al., 2011). It also promotes activation of the AKT signaling pathway is also activated by altering the function of nitric oxide synthase (NOS) in the endothelium. Consequently, that TNF which is an induced COX-2 expression in human umbilical vein endothelial cells that alters the vascular inflammatory state is blocked (Figure 1.10) (Wang & Nakayama 2010). endothelial function could be identified by the omentin concentration circulating in the body as it is highly relevant to the endothelial dependent vasodilation not only in individuals with insulin glucose tolerance but also with systolic blood pressure and BMI as well as the individuals with normal glucose tolerance (Moreno-Navarrete, 2011).

According to the study conducted on the patients with CAD versus control subjects on the presence and levels of omentin for conventional CAD risk factors, omentin levels are determined as novel biomarkers for CAD when not used with the cardiovascular medication used. The study also shows a negative correlation with HbA1c and a positive correlation with HDL cholesterol (Shibata et al., 2011). Omentin is not only found in visceral adipose tissue, but also found in epicardial adipose tissue, and this describes its potential in coronary artery diseases (Zhong et al., 2011).

Omentin-1 is low in patients with acute coronary syndrome and stable angina versus controls (Zhong et al., 2011). Obesity is considered as a developing cardiovascular risk factor. There is still space in the literature for the study of the role of

omentin-1 in weight loss. Despit the fact that an increase in serum levels was observed in diet induced weight loss in obese subjects by using omentin-1 which was considered as being correlated with enhanced insulin sensitivity, the subjects who underwent weigh loss induced by vertical banded gastroplasty did not experience the same effects on omentin-1 levels in the subcutaneous adipose tissue in another study (Katsi et al., 2014).

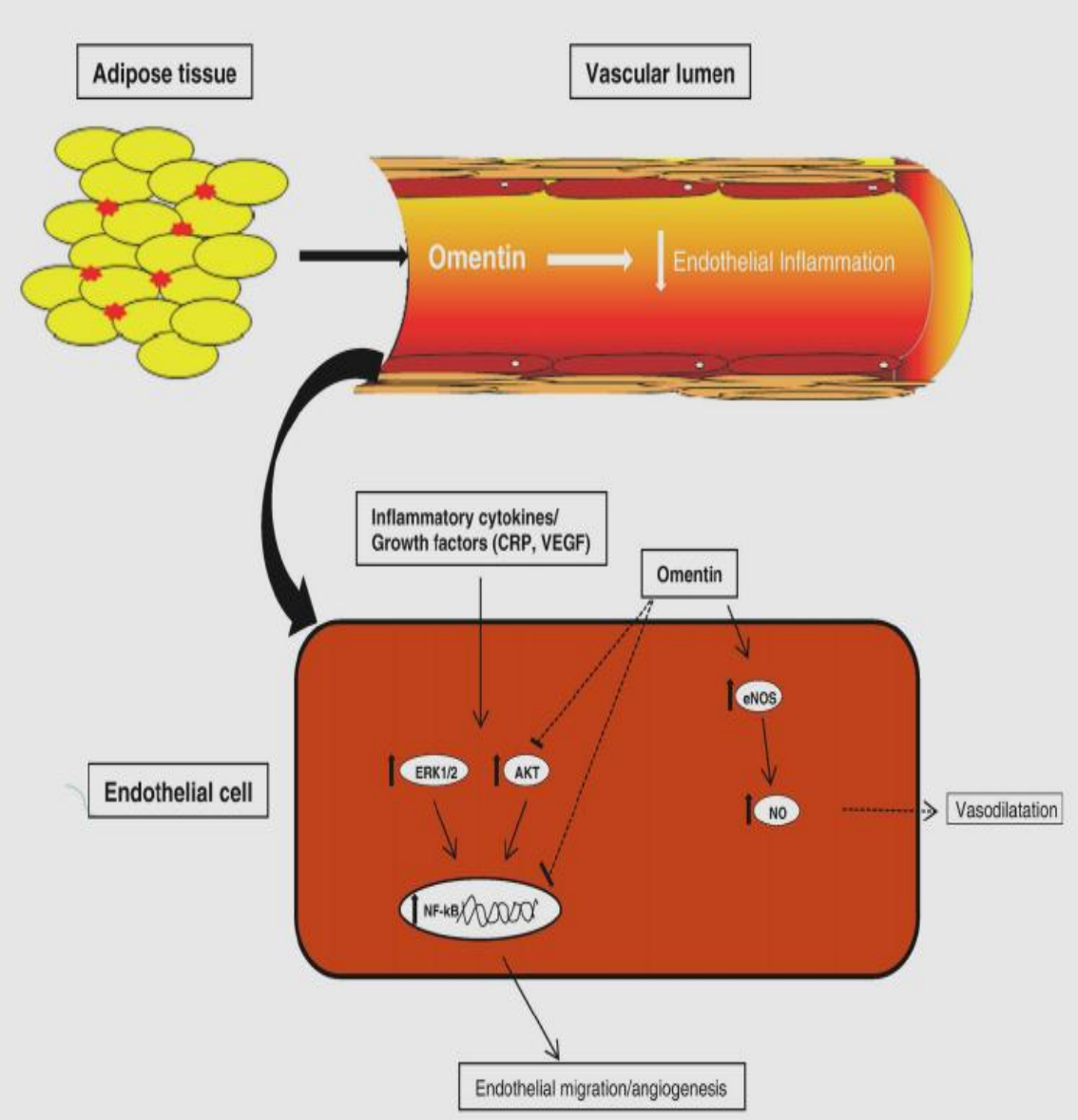

Figure 1.10. Omentin vascular action.

The antiangiogenic effect of omentin by inhibiting Akt and NF-κB pathways, important regulators of inflammation and angiogenesis. Omentin causes vasodilation by increasing nitric oxide production via endothelial nitric oxide synthase.

1.2.5.5. Regulation of Omentin During Infection

The immune system responds to any infection in terms of inflammation at the first place. It is produced by cytokines and other factors like eicosanoids. Eicosanoids contain fever producer prostaglandins which dilates the blood vessels linked to inflammation, and leukotrienes which attract certain white blood cells (leukocytes). Common cytokines include interleukins which carry out communication roles among the white blood cells; chemokines that induce chemotaxis; and interferons with anti-viral effects like stopping the protein synthesis in the host cell. Growth factors and cytotoxic factors may also be released. Immune cells are brought to the infection location by these cytokines and other metabolites and the damaged tissues are healed by removing the pathogens. Proinflammatory cytokines like tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6 give the inflammatory response. The cell death of inflammatory tissues are controlled, vascular endothelial permeability is changed and inflamed tissues are carried into the blood cells and acute-phase proteins are produced by these pleiotropic proteins called cytokines (Takano et al., 2008).

According to some studies omentin is also known as intelectin which rises in amount during parasite infections (Takano et al., 2008), bacterial infections (Chang & Nie, 2007), asthma (Kuperman et al., 2005), and mesothelioma (Wali et al., 2005). Therefore, it is considered to play a key role in innate immunity and inflammation. Omentin is a calcium-dependent lectin and binds to galactofuranose which is found in parasites and bacteria but not generally found in vertebrates in line with its role on the basis of studies (Tsuji et al., 2001). In addition, omentin is bound to Mycobacterium and renders the removal of the bacteria easy by macrophages (Tsuji et al., 2009). Moreover, the risk of Crohn's disease is relevant to the SNP rs2274910 in omentin 1 intron 3 (Barrett et al., 2008). Based on the fact that intestinal inflammation is linked to Crohn's disease, omentin level changes might cause changes immune response to infection which would speed up the transmural inflammation process. Additionally, omentin gene expression was increase in murine species with high levels of IL-13 (Kuperman et al., 2005). According to other studies, an increase in the omentin mRNA levels from human and sheep goblet cell lines was observed in response to IL-13 (French et al., 2007). Nevertheless, the role of cytokine in fighting against obesity and in the regulation of omentin in visceral adipose tissue is not very clear and identified. Omentin involces a

fibrinogen domain similar to the domain that some other proteins contain such as fibrinogen, ficolin, and peroxisome receptor-γ angiopoietin-related (PGAR) (Tsuji et al., 2001). Structure formation in fibrinogen is associated with this domain but it binds carbohydrate in ficolin (Tsuji et al., 2001).

Subjects with Crohn's disease (chronic inflammatory bowel disorder) possess an omental AT with a decreased omentin messenger ribonucleic acid (mRNA) expression; this lack of omentin might be considered significant for transmural intestinal inflammation in these patients (Schäffler et al., 2005). Moreover, patients with rheumatoid arthritis (chronic inflammatory joint disorder) possess synovial fluid with decreased omentin levels (Tan, Adya & Randeva 2010).

Omentin recently decreased C-reactive protein (CRP) and TNF-α–induced nuclear factor κ-light-chain-enhancer of activated B cell (NF-κB) activation in human endothelial cells. Moreover, predictive changes were observed in CRP levels in circulating omentin levels after metformin treatment in overweight women with insulin resistance and a chronic inflammatory disorder called polycystic ovary syndrome (PCOS) (Tan, Adya & Randeva, 2010). Thus, in proinflammatory cases, omentin might play an anti-inflammatory role. In addition, future studies can be conducted in order to find out whether the potential anti-inflammatory role of omentin would lead to changes in the proinflammatory elements in visceral AT, particularly, AT macrophages as it is mainly found in the stromal vascular cells of visceral AT (Tan, Adya & Randeva, 2010).

1.2.5.6. Omentin in Obesity, Diabetes, Insulin-Resistant, and Proinflammatory States

Obese individuals tend to have decreased circulating omentin and omentin gene expressions in their visceral adipose tissue. Additionally, signs of obesity which are body mass index, waist circumference, and circulating leptin are negatively associated with the circulating omentin levels. This means that omentin is controlled by obesity and, thus possibly by leptin (de Souza Batista et al., 2007). Moreover, considering that low level chronic inflammation is related with obesity, omentin levels would also be altered by inflammatory as discussed in the previous section. Furthermore, significantly lower circulating omentin levels and omental AT omentin mRNA expression were observed in subjects with impaired glucose tolerance (IGT) and T2DM subjects

compared to the matched controls subjects (Pan, Guo & Li, 2010). It has been identified that overweight insulin-resistant women with PCOS possess decreased circulating omentin, omental AT omentin mRNA and protein levels (Tan et al., 2008). PCOS which the most common endocrine disorder in 5% to 10% of women that suffer irregular menses and hyperandrogenism in the reproductive age is associated with the metabolic syndrome which would lead to cardiovascular problems (Dunaif, 1997). The associations of omentin with various metabolic parameters are visible in the literature, however the functional studies on the omentin level regulation are still under investigation. The circulating omentin levels were reported as significantly increasing after weight loss an individual under a hypocaloric diet which can be considered as a parallel insulin sensitivity development (Moreno-Navarrete et al., 2010). Moreover, it has been illustrated that insulin and glucose drop the omentin mRNA expression, protein levels, and secretion into conditioned environment in human omental AT explants. In addition, via health individuals underwent an extensive insulin-glucose infusion that carried out a hyperinsulinemic induction brought reduced circulating omentin levels higher (Tan et al., 2008). Nevertheless, according to the data obtained from the study conducted by Wurm et al. (2007), no significant changes were observed in circulating omentin levels before and 2 hours after glucose intake, albeit semiquantified by Western immunoblotting. It has also been proven that insulin possesses anti-inflammatory effects (Dandona et al., 2005); theferore, on the basis of the hypothized anti-inflammatory actions of omentin, insulin-induced suppression of omentin seems paradoxical. Nevertheless, ex vivo (Madonna, Massaro & De Caterina, 2008) and in vivo (Coletta et al., 2008) data are available so as to reveal that insulin could be proinflammatory. For this reason, further studies should be conducted in order to find out the exact relationship between insulin and omentin. A significant increase has also been demonstrated in circulating omentin levels in overweight women with insulin-resistance and PCOS after metformin treatment (6 months treatment; 850 mg twice daily) (Tan, Adya & Randeva, 2010).

Diabetes has rised to the epidemic peak levels in the world and is correlated with serious cardiometabolic disorders. T2DM is another popular name of the disease which is highly associated with obesity, insulin resistance, and inflammation (Eckel et al., 2005). Individuals with T2DM also suffer from cardiovascular morbidity and mortality.

According to the data of a historical cohort study conducted during 22 years, patients with T2DM are under a higher cardiovascular morbidity (risk ratio, 1.76; 95 % confidence interval, 1.34-2.30) and a higher cardiovascular mortality rate (risk ratio, 2.05; 95 % confidence interval, 1.24-3.37) in comparison with nondiabetic controls (Grauw et al., 1995). In addition, it has been recognized that type 1 DM (T1DM) is a proinflammatory state (Devaraj et al., 2008). Moreover, insulin resistance contributes towards progression of T1DM complexities the in obese subjects with T1DM (Bingley, Mahon & Gale, 2008). Recently, we reported decreased circulating omentin and increased adiponectin levels in subjects with T1DM. Adiponectin is an adipokine found at high levels in the blood but it is found at lower levels in individuals with obesity and cardiovascular diseases (Fasshauer, Paschke & Stumvoll, 2004). Furthermore, any significant differences were not observed between nondiabetic control subjects and subjects with T1DM in terms of fasting and postprandial circulating omentin and adiponectin levels (Tan et al., 2008). The previously mentioned patients with Crohn's disease possess decreased levels of omentin (Schäffler et al., 2005). Nevertheless, it was interesting to find out that the patients with Crohn's disease possess higher levels of adiponectin (Yamamoto et al., 2005). According to previously conducted research studies, T1DM is described as a proinflammatory state through an increase in toll-like receptor (TLR) 2 and TLR-4 expression and signaling (Devaraj et al., 2008). It is also impressive to observe that individuals with Crohn's disease are likely to have high TLR-4 expression as they lack TLR-4 signaling. 2 mice with inflammatory bowel disease were used as subjects in order to test the treatment with a TLR-4 antagonist in order to prevent the development of colitis (Gaya et al., 2006). By comparing different studies, it has been shown that apparent indifferent changes exist between fasting and postprandial circulating omentin levels and the reciprocal regulation observed between the insulin-sensitizing adipokines which are adiponectin and omentin in proinflammatory states such as Crohn's disease and T1DM. This would emphasize and prove the role of omentin as an important inflammatory process regulator as discussed in the previous section. In accordance with the study conducted by Yilmaz et al. (2011), it has been demonstrated that patients with nonalcoholic fatty liver disease (NAFLD) had higher circulating omentin levels and it was considered as an independent predictor of hepatocyte ballooning. This is regarded as paradoxical as obesity is positively linked to

NAFLD (Jornayvaz, Samuel & Shulman, 2010) and decreased omentin levels (de Souza Batista et al., 2007).

2. MATERIALS AND METHODS

2.1. Subjects

This prospective study examined patients who attended the outpatient clinic of the Endocrinology Department in Famagusta Goverment Hospital and was performed on two groups. One group was composed of 39 obese patients having a mean age of 44.95 ± 8.84 years and BMI 32.26 ± 4.55 kg/m². The second group was composed of 39 non-obese subjects. The mean age of subjects was 43.8 ± 7.64 years and their mean BMI was 23.68 ± 1.41 kg/m². None of the participants had hypertension, liver, kidney, thyroid, cardiovascular or any active inflammatory diseases and they were also questioned for any medical therapy that might effect the lipid and glucose metabolism. The participants neither received any medications nor participated in any dietary or exercise program. All subjects provided written informed consent before enrollment in the study and the study was approved by the Near East University Research Ethics Committee.

2.2. Anthropometric measurements

All the measurements were performed in the morning with the patients in a fasting state and anthropometric measurements, including weight (kg), height (m), hip circumference (cm) and waist circumference (cm) of each subject were measured barefoot and lightly clothed. Hip circumference was measured by placing a tape measure around the patient's hips at the level of the prominences over the greater trochanters of both femurs. Waist circumference was taken midway between the lowest rip (laterally) and the iliocristale landmark by flexible tape. BMI was calculated as body weight (kg) divided by the square of height (m²) and obesity was defined as BMI ≥30 kg/m² (World Health Organization, 1995).

2.3. Biochemical parameters

Blood samples were obtained after an overnight fasting. The levels of serum glucose, triglyceride (TG), total cholesterol, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels were measured by fully automated clinical chemistry analyzer (Abbott Architect C8000).

2.4. Omentin-1 measurements by ELISA

Plasma omentin-1 levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) human omentin-1 kit (RD191100200R) (BioVendor). Human omentin-1 kit was used according to the protocol of the manufacturer. Results were expressed in ng/ml.

Reagent Supplied

Kit Components:

Antibody Coated Microtiter Strips

Biotin Labelled Antibody Conc. (50X)

Streptavidin- HRP Conjugate

Master Standard

Quality Control High

Quality Control Low

Biotin-Ab Diluent

Dilution Buffer

Wash Solution Conc. (10X)

Substrate Solution

Stop Solution

2.4.1. Assay Procedure

1. Pipet 100 µl of diluted Standards, Quality Controls, Dilution Buffer (=Blank) and samples, preferably in duplicates, into the appropriate wells.

2. Incubate the plate at 37°C for 2 hours without shaking.

3. Wash the wells 3-times with Wash Solution (0.35 ml per well). After final wash, invert and tap the plate strongly against paper towel.

4. Add 100 µl of Biotin Labelled Antibody solution into each well.

5. Incubate the plate at 37°C for 30 minutes without shaking.

6. Wash the wells 3-times with Wash Solution (0.35 ml per well). After final wash, invert and tap the plate strongly against paper towel.

7. Add 100 µl of Streptavidin-HRP Conjugate into each well.

8. Incubate the plate at 37°C for 30 minutes without shaking.

9. Wash the wells 3-times with Wash Solution (0.35 ml per well). After final wash, invert and tap the plate strongly against paper towel.

10. Add 100 µl of Substrate Solution into each well.

11. Incubate the plate for 10 minutes at room temperature. The incubation time may be extended [up to 20 minutes] if the reaction temperature is below than 20°C. Do not shake the plate during the incubation.

12. Stop the colour development by adding 100 µl of Stop Solution.

13. Determine the absorbance of each well on a microplate reader set to 450 nm, preferably with the reference wavelength set to 630 nm (acceptable range: 550 - 650 nm). Subtract readings at 630 nm (550 - 650 nm) from the readings at 450 nm. The absorbance should be read within 5 minutes following step 12.

2.5. Statistical Analysis

The distributions of continuous variables in groups were expressed as means ± standard deviation (SD). Differences in baseline characteristics between groups were analysed by Student's t-test. Correlation analysis was performed using Pearson tests. A P value of < 0.05 was considered to indicate statistical significance. All statistical analyses were performed using the SPSS software (ver. 15.0; SPSS Inc., Chicago, IL).

3. RESULTS

Descriptive statistics of anthropometric and metabolic characteristics of the study population are presented in Table 3.1. Obese and non-obese subjects did not differ in age, total cholesterol and LDL cholesterol levels while plasma glucose and triglycerides levels were significantly higher and mean HDL cholesterol levels were significantly lower in obese than non-obese subjects. Non-obese subjects had significantly higher omentin-1 levels compared to obese subjects.

Table 3. 1. Baseline anthropometric and metabolic characteristics

Parameter	Non-obese subjects (n=39)	Obese subjects (n=39)	P
Age	43.18 ± 7.64	44.95 ± 8.84	0.34
BMI (kg/m²)	23.68 ± 1.41	32.26 ± 4.55	<0.001
Waist circumference (cm)	85.57 ± 9.25	102.69 ± 12.64	<0.001
Hip circumference (cm)	98.81 ± 9.73	115.14 ± 13.46	<0.001
Fasting glucose (mg/dL)	93.21 ± 6.74	102.02 ± 11.82	<0.001
Total cholesterol (mg/dL)	207.93 ± 22.26	213.57 ± 21.63	0.26
LDL cholesterol (mg/dL)	124.93 ± 19.90	128.54 ± 15.74	0.37
HDL cholesterol (mg/dL)	59.03 ± 6.90	54.09 ± 12.42	0.03
Triglycerides (mg/dL)	97.91 ± 21.97	119.42 ± 59.92	0.038
Omentin-1 (ng/ml)	432 ± 59.5	377.14 ± 77.49	0.0008

Data are expressed as means ± SD and were compared by t-test.
BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Correlation coefficients between plasma omentin-1 levels with other biochemical parameters in non-obese subjects are presented in Table 3.2. Omentin-1 levels significantly correlated with BMI, waist circumference, and triglycerides while omentin-1 levels did not significantly correlate with hip circumference, fasting glucose, total cholesterol, LDL-cholesterol and HDL-cholesterol.

Table 3. 2. Correlation of plasma omentin-1 levels with baseline parameters in non-obese group.

Variable	Omentin-1	
	r	p
BMI (kg/m²)	- 0.58	<0.001
Waist circumference (cm)	- 0.32	0.04
Hip circumference (cm)	- 0.25	0.12
Fasting glucose (mg/dL)	- 0.22	0.17
Total cholesterol (mg/dL)	- 0.23	0.16
LDL cholesterol (mg/dL)	- 0.26	0.11
HDL cholesterol (mg/dL)	0.21	0.19
Triglycerides (mg/dL)	- 0.34	0.03

BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 3.3 shows correlation coefficients between plasma omentin-1 levels with other biochemical parameters in obese subjects. Omentin-1 levels were significantly correlated with BMI, triglycerides and waist circumferences. On the other hand, omentin-1 levels did not significantly correlate with hip circumference, fasting glucose, total cholesterol, LDL-cholesterol and HDL-cholesterol.

Tablo 3.3. Correlation of plasma omentin-1 levels with baseline parameters in obese group.

Variable	Omentin-1	
	r	p
BMI (kg/m²)	- 0.46	0.003
Waist circumference (cm)	- 0.41	0.009
Hip circumference (cm)	- 0.16	0.33
Fasting glucose (mg/dL)	- 0.21	0.19
Total cholesterol (mg/dL)	- 0.29	0.07
LDL cholesterol (mg/dL)	- 0.25	0.12
HDL cholesterol (mg/dL)	0.20	0.22
Triglycerides (mg/dL)	- 0.35	0.028

BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

4. DISCUSSION

It has been well established that adipose tissues have a role beyond energy regulation and that adipokines have a significant role in the development of obesity and other complications related to obesity. A recently described adipokine, omentin-1, is highly and selectively expressed in visceral adipose tissue and circulating levels are negatively correlated with BMI (Yamawaki et al., 2010). Our results showed that non-obese subjects had significantly higher omentin-1 levels compared to obese subjects. Furthermore, we observed that the omentin-1 was significantly correlated with BMI, waist circumference and triglycerides in both obese and non-obese subjects.

Omentin-1 is a novel fat depot-specific adipokine that was identified from a visceral adipose tissue. In a study performed by de Souza Batista et al. (2007) plasma levels of omentin-1 were measured in lean, overweight, and obese otherwise healthy subjects. The authors found that plasma levels of omentin were highest among the lean subject and these levels were inversely correlated with BMI. Additionally, Stticharron et al. (2014) reported that serum omentin-1 was negatively correlated with BMI in adults. Other study by Catli et al. (2013) demonstrated that serum concentrations of omentin-1 were negatively correlated with BMI in obese children. Consistent with these previous findings, our results showed that omentin-1 levels significantly decreased in obese adults and negatively correlated with BMI in both obese and non-obese subjects.

Waist circumference reflects primarily total abdominal fat, both intra-abdominal (predominantly mesenteric and omental, also referred to as visceral) fat and subcutaneous, while hip circumference gives an estimate of gluteal subcutaneous fat. Previously, an association between blood omentin-1 levels and visceral fat distribution has been reported (Schäffler et al., 2011). De Souza Batista (2007) and Moreno-Navarrete (2010) have also reported that omentin-1 levels were inversely correlated with waist circumference. Considering our results which showed that omentin-1 levels in both obese and non-obese subjects have significantly correlated with waist circumference. These results confirm that high levels of omentin expression in visceral adipose tissue and plasma are related to decreased adiposity.

Omentin-1 seems to enhance insulin-stimulated glucose uptake in cultured human adipocytes. Yang et al. (2006) demonstrated that recombinant omentin-1 enhances insulin stimulated glucose uptake. Several clinical studies shown that decreased level of omentin-1 is promoting insulin resistance in obesity (Tan et al, 2008; de Souza Batista et al, 2007). As a result of the insulin resistance in the adipose tissue and obesity, the free fatty acid (FFA) flux from the adipocytes is increased, which leads to an increased triglycerides synthesis in the hepatocytes. This is responsible for the high triglycerides level in obesity (Kumar et al, 2010). Zhang etal (2014) showed that the level of serum omentin-1 was negatively correlated to triglycerides. Based on the abovementioned studies, we suggest that plasma omentin-1 levels significantly significantly correlated with triglycerides in both obese and non-obese subjects. Thus our results indicate that by the association between omentin-1 levels and triglycerides may establish a positive feedback process in lipid metabolism.

The main limitation of this study were the contricted subject number. The second limitation is that insulin level was not analyzed.

In conclusion, our results suggest that omentin-1 has association with BMIand waist circumference in both obese and non-obese subjects. It does have significant influences on lipid profiles. Based on the literature and our findings, omentin appears to play a role in generating lipid metabolism through unknown feedback mechanism between insulin and hepatocytes functions. . Further detailed studies based on greater populations are needed to confirm these findings and improve our understanding of metabolic changes and functions of omentin-1 in obesity.

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