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NEAR EAST UNIVERSITY
INSTITUTE OF HEALTH SCIENCES

A NOVEL LINK BETWEEN OBESITY AND LIPID METABOLISM

EZE CHIDIEBERE EGEONU

BIOCHEMISTRY PROGRAM

MASTER THESIS

NICOSIA-2016

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ASSIST. PROF. DR. EDA BECER

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APPROVAL

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SYMBOLS / ABBREVIATIONS

ACE: Angiotensin Converting Enzyme

A-FABP: Adipocyte Fatty-Acid-Binding Protein

AF: Atrial Fibrillation

AKT: Protein Kinase B

ASCVD: Atherosclerotic Cardiovascular Disease

ATGL: Adipose Triglyceride Lipase

BMI: Body Mass Index

CCL-2: CC Chemokine ligand-2

CCRL2: C-C Chemokine Receptor-like 2

CHD: Coronary Heart Disease

CNS: Central Nervous System

CMKLR1: Chemokine-like Receptor 1

CRP: C-Reactive Protein

CRP: C-Reactive Protein

CVD: Cardiovascular Disease

DCs: Dendritic Cells

DGAT2: Diglyceride acyltransferase 2

EPIC: European Prospective Investigation into Cancer and Nutrition

FPRL1: Formyl Peptide Receptor-like 1

GLUT2: Glucose Transporter type 2

GLUT4: Glucose Transporter type 4

GPR1: G Protein-Coupled Receptor 1

GPCR: G-Protein-Coupled Receptor

GSK: Glycogen Synthase Kinase

HCC: Hepatocellular Carcinoma

HDL: High-Density Lipoprotein

HF: Heart Failure

HIV-1: Human Immunodeficiency Virus 1

HTN: Hypertension

HSL: Hormone Sensitive Lipase

HTR2B: 5-Hydroxytryptamine Receptor 2B

IARC: International Agency for Research on Cancer

ICAM-1: Intercellular Adhesion Molecule-1

IgE: Immunoglobulin E

IGFs: Insulin-like Growth Factors

IL-1: Interleukin-1

IL-1Ra: Interleukin-1 Receptor Antagonist

IL13RA2: Interleukin-13 Receptor Subunit Alpha-2

IP-10: Interferon-gamma Incredicible Protein 10

IRSs: Insulin Receptor Substrates

IRS-1: Insulin Receptor Substrate 1

IRS-2: Insulin Receptor Substrate 2

kDa: Kilodaltons

LA: Left Auricle

LAR: Leukocyte Antigen-related Phosphatase

LPL: Lipoprotein Lipase

LPS: Lipolysaccharide

LVH: Left Ventricular Hypertrophy

LV: Left Ventricle

MCP-1: Monocyte Chemotactic Protein 1

MCP-1: Monocyte Chemoattractant Protein-1

MI: Myocardial infraction

mRNA: Messenger Ribonucleic Acid

NAFLD: Nonalcoholic Fatty Liver Disease

NASH: Nonalcoholic Steatohepatitis

NADPH: Nicotinamide Adenine Dinucleotide Phosphate

NF-kB: Nuclear Factor Kappa B

NK: Natural Killer Cell

OR: Odds ratio

OSA: Obstructive Sleep Apnea

PAI: Plasminogen Activator Protein

PCOS: Poycystic Ovary Syndrome

pDCs: Plasmacytoid Dendritic Cells

P13K: Phosphatidylinositide 3-Kinase

PTPs: Protein Tyrosine Phosphatases

PTP1B: Protein-Tyrosine Phosphatase 1B

RANTES: Regulated upon Activation Normal T-cell Express Sequence

RARRES2: Retinoic Acid Receptor Responder 2

RNA: Ribonucleic Acid

ROS: Reactive Oxygen Species

SFA: Subcutaneous Fat Area

SIV: Simian Immunodeficiency Virus

SNP: Single Nucleotide Polymorphism

TGF-β: Transforming Growth Factor Beta

TIG2: Tazarotine-induced Gene 2

T2DM: Type 2 Diabetes Mellitus

TLR4: Toll-like Receptor 4

TNFα: Tumor Necrosis Factor Alpha

UNOS: United Network of Organ Sharing

VCAM-1: Vascular cell-adhesion Molecule-1

VFA: Visceral Fat Area

WAT: White Adipose Tissue

WC: Waist Circumference

W.H.O: World Health Organization

WHR: Waist-to-Height Ratio

ABSTRACT

Egeonu E.C. A novel link between obesity and lipid metabolism. Near East University, Institute of Health Science, Biochemistry, Master Thesis, Nicosia, 2016.

Obesity is a growing health problem which has reached pandemic proportions. Adipose tissue is a hormonally active organ that produce and releases numerous hormones, called adipokines. Chemerin, a novel adipokine that is highly expressed in adipose tissue and circulating levels are increased in obesity. Chemerin is associated with insulin resistance, diabetes, dyslipidemia, hypertension, and cardiovascular disease. The aim of this study was to investigate the association between chemerin levels in obesity in terms of body mass index (BMI) and lipid parameters. The study included 39 obese and 39 non-obese subjects. Fasting glucose, insulin, HDL cholesterol (HDL-C), triglycerides (TG), total cholesterol (TC), LDL cholesterol (LDL-C) and anthropometric parameters were measured. We determined plasma chemerin levels with an enzyme-linked immunosorbent assay (ELISA). Non-obese subjects had significantly lower chemerin levels compared to obese subjects. The plasma chemerin was significantly correlated with BMI ($p<0.001$), waist circumference ($p=0.02$) and LDL-cholesterol ($p=0.04$) in non-obese subjects. In obese subjects, chemerin was significantly correlated with body mass index (BMI) ($p<0.01$), waist circumference ($p=0.007$) and total cholesterol ($p=0.009$). The results suggest that chemerin may be involved in the regulation of lipid metabolism both in obese and non-obese subjects.

Keywords: Chemerin, obesity, lipid

1. INTRODUCTION

1.1. Obesity

Obesity is characterized as an irregular or extreme fat amassing that includes a danger to wellbeing. The central reason for overweight or obesity is a positive energy balance, in which energy admission surpasses energy consumption over a drawn out time prompting the expanded body mass including the aggregation of subcutaneous and visceral fat (Fair et al. 2009). Nonetheless, obesity is a mind boggling malady brought on by various components, for example, hereditary, eating routine, way of life and natural variables (Moreno-Aliaga et al. 2005).

Obesity speaks to a noteworthy wellbeing trouble influencing more than 20% of Western populaces with relentlessly expanding rate. Obesity outstandingly expands the danger of creating type 2 diabetes, hypertension, coronary heart disease, stroke, fatty liver disease, dementia, obstructive sleep apnea and a few sorts of cancer. However, projections from the World Health Organization (WHO) anticipate for the first time a decrease in the mean life as a result of obesity-related comorbidities, for example, atherosclerosis, diabetes and cancer in 2020. In any case, therapeutic mediation for obesity treatment have given just restricted achievement and there is an unmet requirement for novel pharmacological treatment patterns to advance negative energy balance in backing of nutritional and mental guidance and in addition expanding physical action. A positive energy balance happens when energy admission is more prominent than energy consumption and advances weight pick up/obesity (Olshansky et al., 2005). On the other hand, a negative energy parity or balance advances weight reduction (Figure 1.1).

The predominance of obesity among youngsters, teenagers and grown-ups has been drastically expanding amid the most recent decades (Calle et al. 2004). The World Health Organization (WHO) evaluates that there are presently more than 1.6 billion overweight grown-ups and no less than 400 million of these are obese. Subsequently, obesity is procuring the attributes of a strong pandemia and it has been perceived as one of the major worldwide health issues.

Without a doubt, this health risk is connected to a few sorts of regular infections including cardiovascular disease (Huxley et al. 2010), type 2 diabetes mellitus (Mokdad et al. 2003) and (Crandall et al. 2008), hypertension, dyslipidemia, liver infection furthermore different types of malignancy (Mokdad et al. 2003), (Pischon et al. 2008) and (Farhat et al. 2010). Along these lines, the health penalty of obesity are enormous and shifted, going from an expanded danger of unexpected death to a few non-deadly yet crippling ailments that effectively affect the value of life.

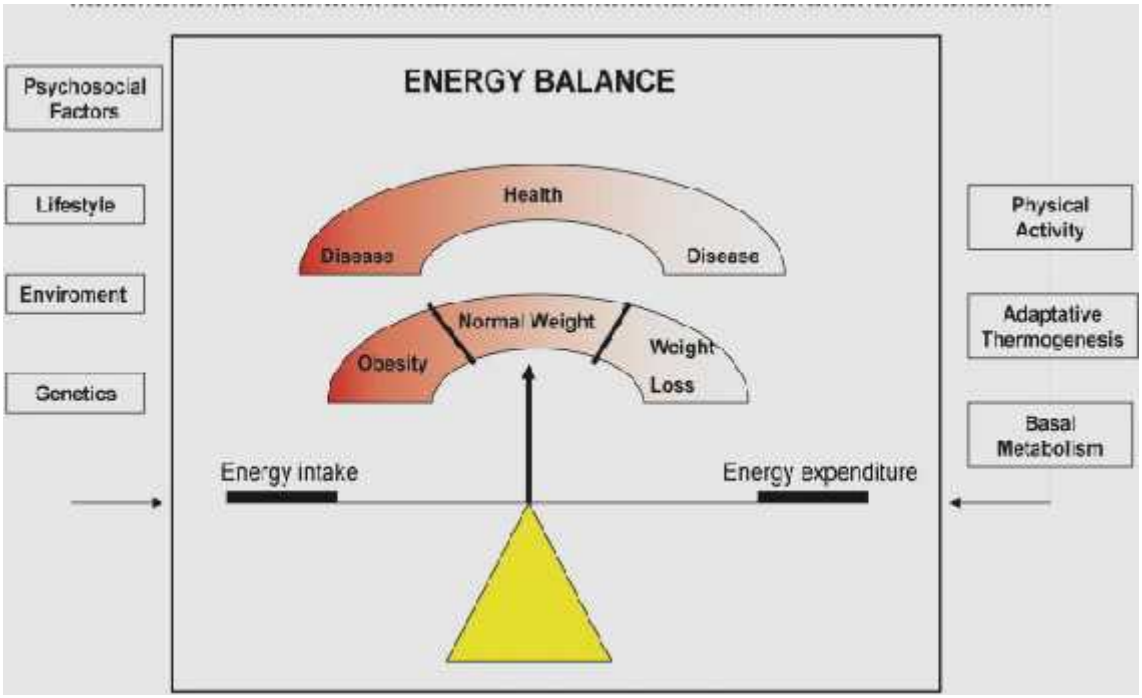

Figure 1.1 Fundamental principles of energy balance.

Obesity is not a single disorder but rather a heterogeneous gathering of conditions with various causes. Body weight is dictated by an association between genetic, ecological and psychosocial components acting through the physiological mediators of energy input and output. Even though genetic contrasts are of undoubted significance, the checked ascent in the commonness of obesity is best clarified by behavioral and ecological changes that have come about because of technological advances.

1.1.1. Classes of Obesity

BMI is a conclusive measure of an individual's height and weight, figured by separating an individual's weight in kilograms by the square of their tallness in metres. Utilizing a measure, for example, BMI takes into account a person's weight to be standardized for their height, consequently giving rise to people of various heights to be compared (Sweeting et al. 2007).

BMI is the most generally utilized measure for observing the predominance of overweight and obesity at population level. It is likewise the most ordinarily utilized method for evaluating whether a distinctive individual is overweight or obese. In spite of the fact that BMI is utilized to group people as obese or overweight, it is just an intermediary measure of indicating issue of accumulated body fat (Table 1.1) (Sweeting et al. 2007).

Table 1.1. Body Mass Index and Weight Status

BMI (kg/m^2)	**Weight Status**
Below 18.5	Underweight
18.5 to 24.9	Healthy weight
25 and above	Overweight
30 and above	Obese

BMI does, in any case, have a few disadvantages. It is just an intermediary pointer of body fatness; variables, for example, fitness (muscle mass), ethnic inception and puberty can modify the relationship amongst BMI and body fatness. Along these line, BMI may not be an exact instrument for evaluating weight status at an individual level, and different methods for measuring body composition might be more valuable and precise (Flegal et al. 2008).

1.1.2. Types of Obesity

There are two major types of obesity based on the distribution of excess fat in the body which are, (Figure 1.2)

- Android obesity
- Gynoid obesity

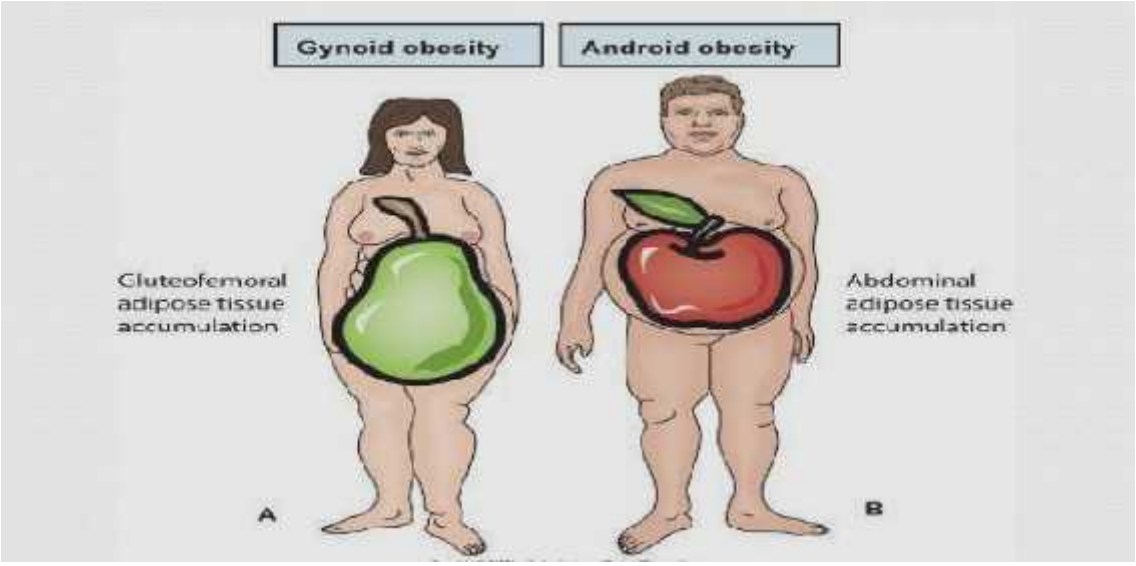

Figure 1.2. Types of obesity according to distribution of excess fat in body. Gynoid type (A) and android type (B).

1.1.2.1. Android Obesity

This includes the gathering or reservation of fat around the stomach area of the body. In that capacity, people with this sort of obesity are seen to have an apple-like body shape. Android obesity is exceedingly related with an adjusted danger element profile adding to high rate of CVD, type 2 diabetes and metabolic disorder.

Android obesity can likewise be experienced in different locations of the upper trunk like the upper chest (front or back) nape region of the neck, and even the shoulders. This sort of obesity is said to happen more as often as possible in male than female (Manigrasso et al. 2005).

1.1.2.2. Gynoid Obesity

This sort of obesity includes the deposition and reservation of too much accumulated fat some place around the hip and thigh region. People with this sort of obesity have rounded hips and their buttocks for the most part look bigger than

ordinary. People with gynoid obesity are called pear obese in light of the fact that they have a body frame that looks strikingly like the state of the pear fruit. Gynoid obese people are said to have much saver circumstance than the android obese people since they have lesser danger of creating unending ailments connected to obesity and overweight (Manigrasso et al. 2005).

1.1.3. Clinical Consequences of Obesity

As indicated by the World Health Organization, the worldwide pervasiveness of obesity has about multiplied somewhere around 1980 and 2008, and more than 10% of the grown-ups age ranged 20 and over is obese in 2008. Projections in light of the ebb and flow obesity patterns evaluate that there will be 65 million more obese grown-ups in the USA and 11 million more obese grown-ups in the UK by 2030, thus, collecting an extra 6–8.5 million instances of diabetes, 5.7–7.3 million instances of heart disease and stroke for USA and UK joined together. The expanded pervasiveness in obesity is additionally connected with expanding commonness of nonalcoholic fatty liver disease (NAFLD). Among the Americas, the predominance of NAFLD is most noteworthy in the USA, Belize and Barbados and Mexico, which have a high commonness of obesity. Obesity, particularly abdominal obesity, is one of the reoccurring notable risk factors for metabolic disorder. Obesity encourages the danger of building up an assortment of pathological conditions, including insulin resistance, type 2 diabetes, dyslipidemia, hypertension and NAFLD (Figure 1.3). Accumulating proof recommends that chronic irritation in adipose tissue may assume a basic part in the advancement of obesity-related metabolic dysfunction (Jung et al., 2014).

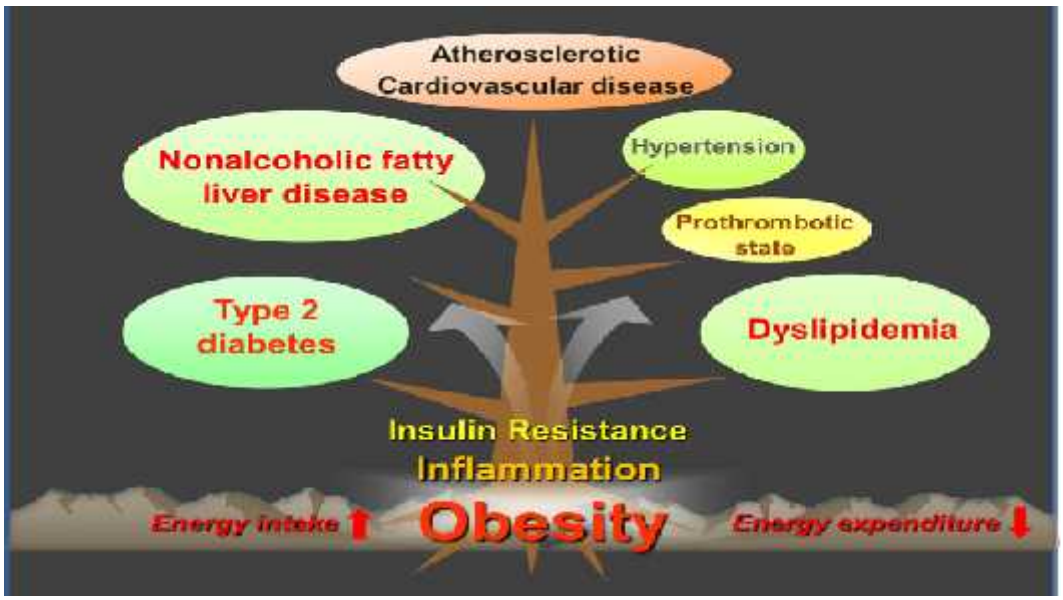

Figure 1.3. Concept of metabolic syndrome.

1.1.3.1. Obesity and Cancer

Energy irregularity is connected with obesity and diverse studies have found a relationship amongst obesity and cancer (Donohoe et al. 2010). The idea of a relationship between dysregulated metabolism and carcinogenesis was initially enunciated by Otto (Warburg et al. 1956). In 2002, the International Agency for Research on Cancer (IARC) expert panel assessed the connection amongst weight and cancer (IARC. 2007) and presumed that some cancers could be averted by maintaining a strategic distance from weight gain. Since the IARC report, numerous observational and epidemiological studies have further researched the relationship amongst adiposity and cancer types including those of colon (Slattery et al. 2010), esophagus, breast, (in postmenopausal ladies) (Maccio et al. 2010), endometrium, kidney, liver, gallbladder and pancreas (Percik et al. 2009). Obesity management is an open door for cancer avoidance (Anderson et al. 2009), and adipose tissue has been proposed as an objective in the treatment of hormone-dependent breast tumor and different sorts of malignancy.

Breast cancer is the second most well-known cancer on the planet and the most well-known neoplasia among ladies. The relationship between markers of body size and danger of breast cancer has been inspected in various studies (Trentham-Dietz et al. 2000). Obesity heightens breast cancer hazard in postmenopausal ladies by around 50%,

presumably by increasing serum concentration of free estradiol (Trentham-Dietz et al. 2000). Interestingly a few studies set up that the relationship between body size and the danger of breast cancer varied by menopausal status (Begum et al. 2009). Actually BMI and body weight have been observed to be positively associated with the danger of breast cancer among postmenopausal ladies, this relationship is more grounded among non-hormone-replacement treatment users than among hormone replacement treatment users (Potischman et al. 1996). However the systems that underlie the relationship amongst obesity and breast cancer danger are not totally caught on. A few hypothesis have been proposed, including adjustments in sex hormones, growth factor and cytokines (Pischon et al. 2008). Another component by which obesity may affect the advancement of breast cancer includes insulin and/or insulin-like growth factor (IGFs) (Frasca et al. 2008).

Colorectal malignancy is the third most basic cancer on the planet. Incidence rates are roughly 10-fold higher in developed than in developing nations (Pischon et al. 2006). A possible relationship between an overabundance of body weight and danger of colon cancer has been inspected in numerous epidemiological and cohort research which have inferred that obesity is connected with a higher danger of colorectal cancer (Bergstrom et al. 2001). Diverse studies have proposed that waist circumference and the waist/hip proportion are likewise emphatically identified with a higher danger of colorectal cancer and large adenomas in men as supported by European Prospective Investigation into Cancer and Nutrition (EPIC), while body weight and BMI are connected with colon cancer hazard in men yet not in ladies (Giovannucci et al. 1995). The purposes behind the sex contrast are theoretical. One hypothesis is that abdominal adiposity, more normal in men than in ladies, is a more grounded indicator of colon malignancy hazard than fringe adiposity (Yamamoto et al. 2010). Be that as it may, the systems required in the relationship between abdominal obesity and increased colon malignancy hazard remains unexplained.

Prostate malignancy is the cancer most often analyzed in men in Europe (Ferlay et al. 2007). More than 40 studies, including forthcoming and case-control studies, looking at the relationship amongst obesity and danger of prostate cancer have given clashing results (Hsing et al. 2007). Be that as it may, a late meta-examination has

proposed a powerless noteworthy positive relationship with an expected increment in prostate cancer hazard (5% excess hazard for every 5 unit increase of BMI) (MacInnis et al. 2006). The relationship between waist circumference or waist hip-proportion and danger of prostate cancer has been analyzed in just a not very many most studies reporting no huge affiliations (MacInnis et al. 2006).

Obesity is connected with a 3-fold increment in risk for adenocarcinoma of the throat (Calle et al. 2004). The connection amongst obesity and danger of esophageal cancer has as of late been affirmed by quantitative meta-examination that included twelve case-control studies (Kubo et al. 2006). High BMI is connected with gastro-esophageal reflux and reoccurring reflux is firmly connected with esophageal adenocarcinoma (Chow et al. 1995). In this way the expanded event in gastro-esophageal reflux itself is thought to be a noteworthy danger element for esophageal malignancy.

Primary liver cancer is a standout amongst the most widely recognized and destructive tumors around the world. The rate is expanding and hepatocellular carcinoma (HCC) has ascended to wind up the fifth most regular cancer and third driving reason for cancer death (El-Serag et al. 2007). Obesity has been set up as a noteworthy danger element for liver ailments. A huge imminent mortality study showed that high BMI was altogether connected with higher rates of liver tumor related death. In comparism with patients with common BMI, the relative danger of mortality from liver malignancy was 1.68 times higher in ladies and 4.52 times higher in men with BMI > 35 kg/m^2 (Gomaa et al. 2008). Correspondingly, information acquired from the United Network of Organ Sharing (UNOS) database on all liver transplantation from 1991 to 2000 completed in the United States demonstrated that the general rate of HCC in patients experiencing liver transplantation was 3.4% with a marginally higher pervasiveness among obese patients at 4.0%. Additionally, in this study obesity was affirmed to be an autonomous danger component for HCC in patients with alcoholic cirrhosis (chances proportion [OR], 3.2) and cryptogenic cirrhosis (OR,11.1) (Nair et al. 2002). Obesity has decisively been set up as a danger component for the promotion of HCC. It is likely that this affiliation represent the progression basic NAFLD to cirrhosis,

but it stays indistinct whether cirrhosis is a fundamental basis for the growth of HCC (Caldwell et al. 2004).

1.1.3.2. Obesity and Diabetes Mellitus

A solid affiliation exists between obesity, glucose intolerance and T2DM. As per the Coronary Artery Risk Development in Young Adult study, an increment in BMI brought about an expanded rate of defected fasting glucose and diabetes in both men and ladies (Lloyd-Jones et al. 2007). Interestingly, both insulin levels and BMI have appeared to be free indicators of cardiovascular ailment (Wing et al. 1989). The danger of developing T2DM appeared to associate with increasing BMI in ladies (Colditz et al. 1995). In this study, a partner of more than 100,000 nurses was followed over a 14 years period. In light of their discoveries, ladies with a BMI of 24.0 to 24.9kg/m^2 had five times the danger of T2DM contrasted with ladies with BMI of not exactly 22 kg/m^2. The risk of T2DM in women with a BMI greater than 31 kg/m^2 and 35kg/m^2 was increased further to 40 times and 93 times, respectively (Colditz et al. 1995).

In reproductive aged women, an elevated BMI at initial pregnancy and at 28-48 year follow-up were both associated with risk of T2DM. The women that developed T2DM had an absolute weight gain of 14 ± 13 kg, with odds of developing T2DM increasing three times with greater than 16 kg weight gain following pregnancy (Dawson et al. 2003). Furthermore, a BMI greater than 30 kg/m^2, or clinically obese by definition, increased the odds of T2DM by 11 times. A similar study in male health professionals, reported 42 times the risk of T2DM in men with BMI greater than 35 kg/m2 compared to men with BMI of less than 23 kg/m^2 (Chan et al. 1994). They also reported both BMI at age 21 and absolute weight gain as independent risk factors for T2DM. Schienkiewitz et al. reported that weight gain in men and women during early adulthood (between ages 25 and 40 years) was associated with increased risk of diabetes than with weight gain in late adulthood (between ages 40 and 55 years) (Schienkiewitz et al. 2006). Furthermore, in those that gained weight in early and late adulthood, the relative risk of T2DM was greater than 14 times compared to those that maintained their BMIs.

The relationship between weight gain and diabetes appears to be relatively consistent among different ethnicities. In cross-sectional study by Cohen et al., the risk of T2DM increased in both obese African American and white adults from the US (Cohen et al. 2009). The relative risk of T2DM increased by 3-4 times with weight gain greater than 40Ibs. Despite the high rate of obesity in African American women, one study found this demographic to have the lowest increase in the risk of diabetes with weight gain. Interestingly, however, Nguyen et al. reported increased prevalence of T2DM in morbidly obese (BMI > 40 kg/m^2) US men and women compared to those of normal weight (BMI < 25 kg/m^2), however African American BMI and diabetes in Korea, however at a much lower BMI than in most western studies. They report that the odds of T2DM are increased three times with BMI > 21.9 kg/m^2 (Moon et al. 2002). The linked between obesity and T2DM is important to delineate to implement interventional strategies.

1.1.3.3. Obesity, Cardiovascular Disease and Hypertension (HTN)

Obese persons have a higher prevalence of elevated blood pressure (hypertension) than lean persons. Moreover, a higher blood pressure is a strong risk factor for CVD (cardiovascular disease), (Chobanian et al. 2004). Well known complication of hypertension are coronary heart disease, stroke, left ventricular hypertrophy (LVH), heart failure, and chronic renal failure. Typically, HTN leads to thickening of ventricular walls without chamber dilation, a process referred to as CR when left ventricle mass is not increased or concentric left ventricular hypertrophy when LV mass is increased, whereas obesity is characterized as increasing chamber dilation without marked increases in wall thickness, a process that leads to eccentric LVH (Lavie et al. 2003).

Despite having a higher prevalence of HTN in obesity, recent data have shown an obesity paradox. Uretsky et al. (Uretsky et al. 2007) investigated the effect of obesity on CV (cardiovascular) outcomes in 22,576 treated hypertensive patients with known congenital heart disease. During 2-year follow up, all-course mortality was 30% lower in overweight and obese patient, despite less effective blood pressure control in these patients compared with the normal weight group. A previous study also showed decreased stroke risk and total mortality among overweight patient compared with lean

patients (Wassertheil-Smoller et al. 2000). Similarly, another major HTN study showed a U-shaped relationship between all-cause, CV and non-CV mortality and BMI, meaning excess mortality at both extremes of BMI (Stamler et al. 1991). In another study of 800 elderly hypertensive patients, total mortality and CV and non-CV major events were highest in those with the leanest BMI quintile (Tuomilehto et al. 1991). The association between BMI and major CV events was U-shaped, whereas non-CV mortality decreased with increasing BMI. In aggregate, these studies suggest that although obesity may be a powerful risk factor for HTN and LVH, obese hypertensive patients may paradoxically have a better prognosis, possibly because of having lower systemic vascular resistance and plasma renin activity compared with more lean hypertensive patients (Lavie et al. 2007).

In a study of 5,881 Framingham Heart Study participants, Kenchaiah et al. (Kenchaiah et al. 2002) shows that during a 14 year follow-up for every 11kg/m^2 increment in BMI, the risk of HF increased 5% in men and 7% in women. In fact, a graded increase in the risk of HF was observed across all categories of BMI. In a study of 47 morbidly obese patients, nearly one-third had clinical evidence of HF and the probability of HF increased dramatically with increasing duration of morbid obesity (Alpert et al. 1997).

Despite the known adverse effects of obesity on both systolic and particularly diastolic CV function and the epidemiologic data showing a strong link between obesity, generally defined by BMI criteria, and HF, many studies have suggested that obese HF patients had a better prognosis (Horwich et al. 2001). It was previously showed in a small study of 209 patients with chronic systolic HF that both higher BMI and percent body fat were independent predictors of better event-free survival (Lavie et al. 2003). Preliminary data in nearly 1,000 patients with systolic HF also showed the prognostic impact of body fat on total survival (Lavie et al. 2003).

In a recent meta-analysis of 9 observational HF studies (n = 28,209) in which patients were followed up for an average of 2.7 years, Oreopoulos et al (Oreopoulos et al. 2008) showed that compared with individual without elevated BMI, overweight and obese HF patients had reductions in CV (- 19% and – 40%, respectively) and all-cause

(- 16% and – 33%, respectively) mortality. Likewise, in an analysis of BMI and in-hospital mortality for 108,927 decompensated HF patients, higher BMI was associated with lower mortality (35). In fact for every 5-unit increase in BMI, the risk of mortality was 10% lower ($p < 0.001$).

Although these investigators raised the possibility that selection bias and baseline characteristics may have affected these results, they also suggested that excess body weight may confer some protective effects on HF mortality (Lavie et al. 2003). Because advanced HF is a catabolic state, obese patients with HF may have more metabolic reserve (Lavie et al. 2003). Cytokines and neuroendocrine profiles of obese patients also may be protective (Oreopoulos et al. 2008). Adipose tissue produces soluble tumor necrosis factor-alpha receptors and could play a protective role in obese patients with acute or chronic HF by neutralizing the adverse biological effects of tumor necrosis factor-alpha (Mohamed-Ali et al. 1999). Additionally, overweight and obese patients with acute and chronic HF have lower levels of circulating atrial natriuretic peptide (Mehra et al. 2004). Obese patients with HF may have attenuated sympathetic nervous system and renin-angiotensin responses (Oreopoulos et al. 2008). Because obese patients typically have high levels of arterial pressure, they may have a better prognosis in advanced HF and may tolerate higher levels of cardio-protective medications (Oreopoulos et al. 2008). Higher circulating lipoproteins in obese patients may bind and detoxify lipopolysaccharides that play a role in stimulating the release of inflammatory cytokines, all of which may serve to protect the obese patient with HF (Lavie et al. 2005). Unfortunately, these studies do not typically adjust BMI for other measures of adiposity.

Obesity plays a major role in adversely affecting major Coronary Heart Disease (CHD) risk factors, including HTN, dyslipidemia, and diabetes mellitus (DM), is the major component of metabolic syndrome, and is probably an independent risk factor for atherosclerosis and CHD events (Lavie et al. 2007). Although recent studies indicate that the various measures to define obesity are not all created equally regarding overall CV disease risk, the consensus is that compared with the traditional BMI assessments, the more refined modalities (e.g., WC, WHR, waist-to-height ratio, and so on) do not add significantly to the BMI assessment from a clinical standpoint (Gelber et al. 2008),

although this has not been assessed risk of CV diseases and CHD. Additionally, excess adiposity has been strongly related to first non-ST-segment myocardial infraction (MI) occurring at a younger age (Madala et al. 2008).

Nevertheless, as with HTN and HF, many studies have also reported an obesity paradox in CHD, including in patients treated with revascularization (Romeo-Corral et al 2006). In a recent systematic review of over 250,000 patients in 40 cohort studies followed up for 3.8 years, Romero-Corral et al. (Romeo-Corral et al 2006) reported that overweight and obese CHD patients have a lower risk for total and CV mortality compared with underweight and normal-weight CHD patients. However, in patients with a BMI $\geq$ 35 kg/m^2, there was an excess risk for CV mortality without any increase in total mortality. These investigators explained the better outcomes for CV and total mortality in overweight and mildly obese CHD groups, which could not be explained by confounding factors, by implicating the lack of discriminatory power of BMI to differentiate between body fat and lean mass. However, data from a recent study have shown the same obesity paradox when comparing patients with high and low percent body fat as with high and low BMI, although did not assess (waist circumference) WC, (waist hip ratio) WHR, and other body composition parameters (Lavie et al. 2009). Importantly, the obesity paradox has also been shown in patients after MI and revascularization, and more recently has been shown in patients referred for exercise stress testing (Romeo-Corral et al 2006). Although the mechanism for this effect is uncertain, in aggregate, these studies suggest that despite the fact that obesity increases the risk for developing CHD, at least overweight and mild obesity do not seem to adversely affect prognosis in patients with established CHD.

1.1.3.4. Obesity and Sleep Apnea

Obesity is a classic cause of alveolar hypoventilation and the obstructive sleep apnea (OSA) syndrome (Trollo et al. 1996). Sleep apnea can be a problem with serious implication for anesthetic management, surgery, effect on pulmonary hypertension, stroke coronary artery disease and cardiac arrhythmias (Candiotti et al. 2009). In fact, OSA may contribute to the pathogenesis of HTN and increased inflammatory and CRP (Shamsuzzaman et al. 2002). Clearly, patients with OSA have increased risk of HTN,

dysrhythmias, pulmonary HTN (present in 15% to 20% with OSA), HF, MI, stroke and overall mortality (Partinen et al. 1988).

1.1.3.5. Obesity in Skin Infection and Cellulitis

Obesity causes change in the skin barrier function, the lymph system, collagen structure and function, and wound healing. Evidence suggests that the vascular supply is impaired in obese persons and obesity affects both macro and microcirculation. Obesity is associated with a wide range of skin diseases (Yosipovitch et al. 2007). Case-control studies indicate an increased risk of cellulitis and skin infections in the overweight (Dupuy et al. 1999) and obese (Karppelin et al. 2010, Bjornsdottir et al, Bjornsdottir et al. 2005). In a prospective case-control study showed obesity to constitute a risk factor for cellulitis in a univariate model, but in a multivariate model the finding no longer persisted after controlling for other factors. However, several studies have indicated that obesity predisposes to erysipelas independently of potential confounders (Karppelin et al. 2010). One prospective cross-sectional study has indicated that obesity is a frequent disease in patients with erysipelas (Pereira de Godoy et al. 2010). Data indicate that obesity predisposes to a significantly increased risk of recurrent soft-tissue infections (Sreeramoju et al. 2011). Data on the association between obesity and the outcome of skin infections are limited. A prospective cohort study has indicated the outcome of cellulitis to be worse in the morbidly obese as compared with non-obese subjects.

1.1.3.6. Obesity and Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) is another consequence of the current obesity epidemic and the hepatic manifestation of the metabolic syndrome. This term encompasses a clinicopathologic spectrum of disease ranging from isolated hepatic steatosis to nonalcoholic steatohepatitis (NASH), the more aggressive form of fatty liver disease and characterized by steatosis, inflammation and progressive fibrosis, ultimately leading to cirrhosis and end-stage liver disease (Ong et al. 2007). The most widely accepted theory that explains the pathogenesis of NASH is titled the “Two Hit Theory” resulting from fatty infiltration of the liver due to obesity and insulin resistance, followed by inflammatory insults, potentially due to oxidative stress (Farrell et al. 2006). Recent studies estimate that NAFLD affects 30% of the general population and as high as 90% of the morbidly obese (Torreset al. 2008). Furthermore, obese patients

are at particularly high risk for NASH in view of the frequent co-existence of other features of the metabolic syndrome; thus, the prevalence of NASH in those patients ranges from 20% - 30% against 5% - 7% in the general population (Anguloet al. 2002).

However, patients with isolated steatosis generally have a benign prognosis, some 26-37% of patients with NASH demonstrate progression of fibrosis over time period of up to 5.6 years, with up to 9% progressing to cirrhosis (Adams et al. 2004). BMI and diabetes constitute independent risk factors associated with the progression of fibrosis (Adams et al. 2005). Thus, it has been reported that about 40%-62% of patients with NASH-related cirrhosis develop a complication of cirrhosis after 5-7 years of follow-up (Adams et al. 2005). The increase in the prevalence of childhood obesity results in a rising prevalence of metabolic syndrome and type 2 diabetes mellitus in populations. NASH was first observed in children in 1983 as a pattern of liver injury and it can even develop in obese children under 10 years of age (Patton et al. 2008). The significant relation between fasting insulin, insulin resistance and NAFLD in obese children underlines the clinical dimension of these metabolic disturbances (Denzer et al. 2009).

1.1.3.8. Obesity and Prothrombotic State

Obesity is joined by an expansive number of coagulation and fibrinolytic anomalies (De Pergola et al. 2002). This recommends that obesity stimulates a prothrombotic state. What is not known at present is the manner by which a prothrombotic state will either advance the formation of atherosclerosis or take an interest in the advancement of intense ASCVD occasions. Maybe the most alluring possibility for upgraded atherogenicity connected with coagulation and fibrinolytic variations from the norm is endothelial disfuction. It is accepted by numerous workers that endothelial disfunction is by one means or another required in the atherogenic procedure (Widlansky et al. 2003). A few pathways have been proposed; in this way, however none of these have been substantiated. Maybe more probable, the obesity instigated procoagulant and antifibrinolytic elements adds to an exacerbating of intense coronary disorders. Thrombosis happening with plaque crack or disintegration is a key component in deciding the seriousness of the disorder. On the off chance that typical

coagulation and fibrinolysis are weakened at the period of infection crack or disintegration, then a bigger thrombus ought to form. An alluring theory is that intense plaque interruption is normal, yet just when thrombosis is large there is a noteworthy intense coronary disorder. Assuming this is the case, such could make the nearness of a prothrombotic state critical for deciding the clinical result.

1.2. Adipose Tissue

The first to propose a part past a vault for lipids for adipose tissue was von Gierke, who in 1905 perceived a part for adipose tissue in glycogen stockpiling (Von Gierke et al. 1906). Adipose tissue is causally required in the advancement of these obesity- related syndromes. The fundamental function of white fat tissue (WAT) is triglycerides stockpiling amid energy utilization and fatty acid discharge over times of starvation. White adipose tissue, the dominating structure found in grown-up, involves Adipocytes, pre-adipocytes, macrophages, endothelial cells, fibroblasts, and leukocytes; its diverse component renders white fat an essential middle person of metabolism and inflammation (Juge-Aubry et al. 2005). Since the main adipokine, leptin, was found in 1994, adipose tissue has been conceded numerous essential parts for the host as a rule, making it an endocrine organ in its own particular right (Flier et al. 2004). Essentially, with the advancement of adipose tissue dysfunction, adipokine release is altogether modified toward a proinflammatory, atherogenic and diabetogenic way. These progressions in adipokine discharge are prone to interface hindered adipose tissue capacity to insulin resistance and cardiovascular infection (Figure 1.4).

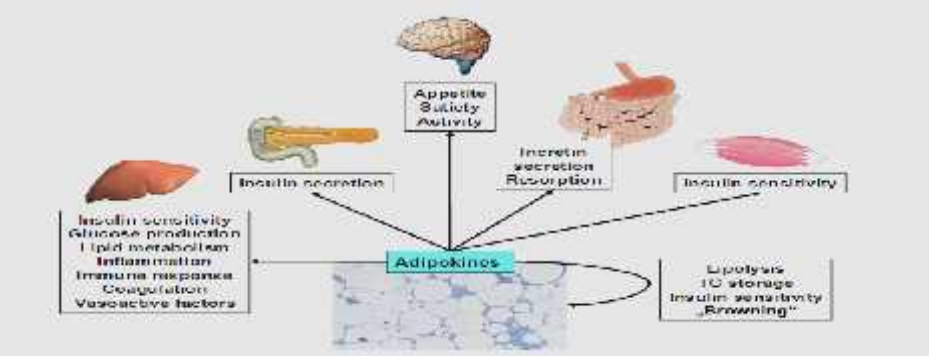

Figure 1.4. White adipose tissue (WAT) secretes various humoral factors called adipokines. Adipokines have important effects on lipid and glucose metabolism, and so on.

Adipose tissue is the main site for storage of abundantly extra energy as triglycerides, and it contains different cell sorts, including for the most part adipocytes, preadipocytes, endothelial cells and immune cells. Amid positive energy parity, fat tissue stores abundance energy as triglycerides in the lipid beads of adipocytes through an expansion in the quantity of adipocyte (hyperplasia) or an extension in the span of adipocytes (hypertrophy) (Hausman et al., 2001). The quantity of adipocytes is for the most part decided in youth and pre-adulthood and stays consistent amid adulthood in both incline and fat subjects, even after checked weight reduction. Thus, an expansion in fat mass in adulthood can essentially be ascribed to hypertrophy. Be that as it may, late study has reported that typical weight grown-ups can extend lower-body subcutaneous fat, however not abdominal area subcutaneous fat, by means of hyperplasia because of overfeeding, recommending hyperplasia of adipocytes can likewise happen in adulthood. Albeit general obesity is connected with metabolic infections, adipose tissue dysfunction brought about by hypertrophy has been proposed to assume a critical part in the improvement of metabolic ailments such as insulin resistance. In contrast to positive energy balance states, when energy is needed between meals or during physical exercise, triglycerides stored in adipocytes can be mobilized through lipolysis to release free fatty acids into circulation and the resulting free fatty acids are transported to other tissues to be used as an energy source. It is generally accepted that free fatty acids, a product of lipolysis, play a critical role in the development of obesity-related metabolic disturbances, especially insulin resistance. In obesity, free fatty acids can directly enter the liver via the portal circulation, and increased levels of hepatic free fatty acids induce increased lipid synthesis and gluconeogenesis as well as insulin resistance in the liver. High levels of circulating free fatty acids can also cause peripheral insulin resistance in both animals and humans. Moreover, free fatty acids serve as ligands for the toll-like receptor 4 (TLR4) complex and stimulate cytokine production of macrophages, thereby modulating inflammation of adipose tissue which contributes to obesity-associated metabolic complications. However, circulating free fatty acid concentrations do not increase in proportion to fat mass and do not predict the development of metabolic syndrome, although many studies suggest a relationship between the release of free fatty acids from adipose tissue and obesity-related metabolic disorders (Kim et al., 2007).

Determinate of adipose tissue mass includes adipocyte volume and cell number (Arner et al. 2010). Adipocyte volume in turn is regulated by storage and removal of triglycerides (Klein et al. 1980). Triglyceride removal rate, is also known as lipid turnover, refers to the removal of lipid of adipose stores through lipolysis (hydrolysis of triglyceride) followed by irreversible process of oxidation. Lipid turnover rate can be estimated by the measurement of lipid age through incorporation of ^{14}C derived from above ground nuclear bomb text into adipocyte triglycerides (Arner et al. 2011). Lipid turnover rate is the inverse of lipid age, so a high lipid age is indicative of low lipid turnover. Lipid age does not appear to be related to adipocyte size, age, or gender (Arner et al. 2011). However lipid age and hence lipid turnover rate is altered by obesity as triglyceride removal rate is decreased in this condition (Arner et al. 2011). Lipid turnover is also inversely related to insulin resistance (Arner et al. 2011).

Three enzymes intercedes fat tissue lipolysis. Adipose triglyceride lipase (ATGL), hormone sensitive lipase (HSL), monoglyceride lipase, (Zimmermann et al. 2002) of these; the initial two intercede the rate restricting step. HSL intercede the cleavage of the second ester bond (Haemmerle et al. 2002). The last enzyme monoglyceride lipase complete lipolysis by separating to the last ester bond from monoglyceride, prompting glycerol discharge (Fredrikson et al. 1986). Basal lipolysis is controlled by ATGL. While HSL intervene catecholamine-invigorated lipolysis and lipolysis stimulated by hormones, for example, insulin and natriuretic peptide. Amid fasting, glucagon and catecholamines invigorate lipolysis in the adipocytes by initiating through PKA a few lipases, bringing about a preparation of FFA from the adipocyte to the dissemination, which are then bound bumin and transported to muscle, liver, heart and different tissues for its oxidation or reesterification. Beta-adrenergic receptors instigate lipolysis, while alfa2-adrenergic receptors intervene lipogenesis. For instance, visceral fat cells are more receptive to beta-adrenergic receptors in contrast with subcutaneous adipocytes. (Figure 1.5) (Langin et al. 2005).

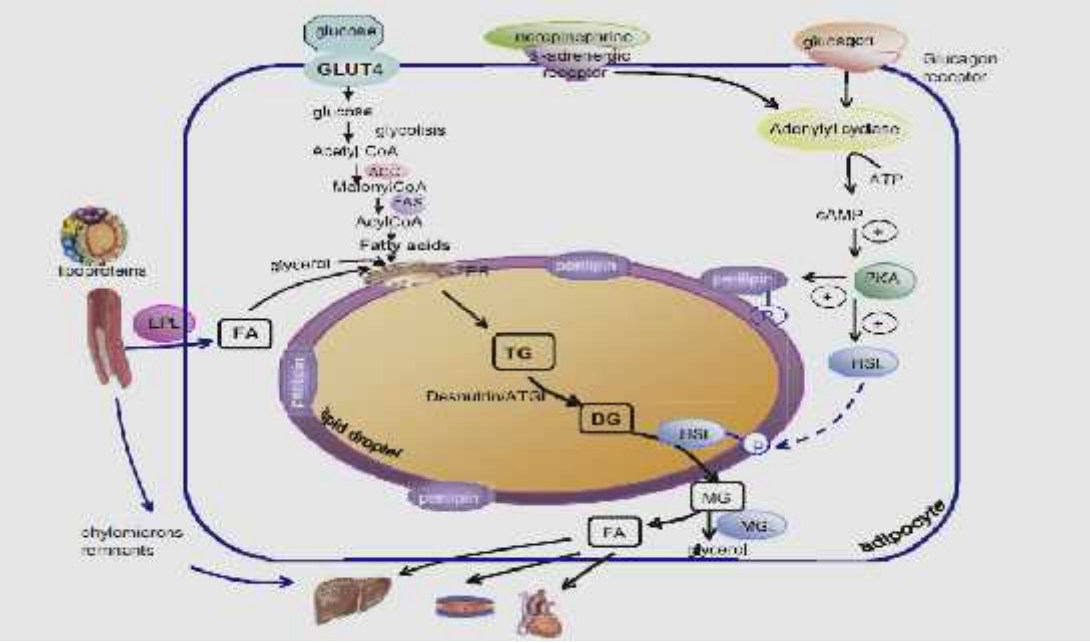

Figure 1.5. Lipogenesis and lipolysis. Excess glucose is oxidized via glycolysis to acetyl-CoA in the adipocyte and then converted into acyl-CoA, which are then esterified in the endoplasmic reticulum (ER) to triglycerides (TG). These are then translocated into the lipid droplet. Fatty acids (FA) obtained from lipoproteins are also esterified into TG and stored. Under fasting conditions, lipolysis is activated by G-protein-coupled receptors resulting in an increase in cAMP that phosphorylates the protein perilipin located in the membrane of the lipid droplet. cAMP also phosphorylates the hormone-sensitive lipase (HSL) that triggers its translocation from the cytoplasm to the lipid droplet and induces with highest specific activity the hydrolysis of diglycerides produced by the adipocyte triglyceride lipase (ATGL) to form monoglycerides (MG). MG is then released to nonadipose tissues, mainly for energy purposes.

Obesity is connected with expanded triglyceride stockpiling and lessen lipid turnover rate (Arner et al. 2011). The lessen lipid turnover in obesity is for the most part identified with the diminished catecholamine invigorated lipolysis (Arner et al. 2010). Blunted catecholamine invigorated lipolysis in obesity gives off an impression of being free of fat mass as it is even present in first degree non-obese relatives of obese subject (Hellstrom et al. 1996) and after weight reduction in obese insulin-resistant subject (Jocken et al. 2007). Diminished articulation of HSL and ATGL has been see in isolated adipocyte from obese subject (Berndt et al. 2008) and in insulin resistance state free of obesity (Jocken et al. 2007). Diminished articulation of lipolytic B2 adrenoceptors and expanded antilipolytic properties of α-2 adrenoceptors (Mauriege et al. 1991) have likewise been accounted for in obesity and in insulin resistance state and add to the diminishment in catecholamine instigate lipolysis. Also different components, for example, leptin may tweak the outflow of ATGL and HSL in obese subject (Jocken et

al. 2007). In spite of blunted catecholamine actuate lipolysis in obese subject; FAA levels are raised in the obese as a result of higher basal lipolysis identified with higher adipose tissue mass.

Notwithstanding lipid stockpiling, adipocyte number is a determinant of fat tissue mass (Spalding et al. 2008). Indeed, even in adulthood adipocytes are in a consistent condition of flux as preadipocytes convert to lipid-filled full grown adipocytes and older adipocytes experience cell demise (Spalding et al. 2008). It is assessed that 10% of adipocytes are recreated yearly in grown-ups autonomous of BMI (Spalding et al. 2008). In any case, in spite of this steady turnover, adipocyte number is kept consistent free of BMI, (Spalding et al. 2008) and just ascents with great obesity (Arner et al. 2010). Obese grown-ups have higher number of adipocytes contrasted and nonobese grown-ups; in any case, the overabundance adipocytes seem to have collected before adulthood. Indeed, even after noteworthy weight reduction after bariatric surgery, the quantity of adipocytes in the obese grown-ups continues as before (Spalding et al. 2008).). Lipid dividing is another critical controller of body weight. Lipoprotein lipase (LPL) is a multifunctional compound that is delivered by numerous tissues including fat and skeletal muscle and is included in lipid dividing by affecting the accessibility and uptake of FFAs from fat tissue or triglycerides. Varieties in LPL gene have been connected with obesity and DM2 in people (Ehrenborg et al. 1997). Differential articulation of LPL in various tissues can prompt obesity and advance weight recapture after supported weight reduction. As an illustration, fat tissue LPL expression is expanded in obesity yet its responsiveness to insulin is decreased (Sadur et al. 1991). All the more essentially, supported weight decrease is connected with an expansion or no change in basal fat tissue LPL expression yet more prominent responsiveness to insulin. These progressions would support weight recover. Moreover, skeletal muscle articulation of LPL is fundamentally diminished after maintained weight lessening. This diminishing prompts an expansion in respiratory quotient and decreases in fat use favoring weight recover.

1.2.1. Adipose Tissue as an Endocrine Organ

Adipose tissue secretes various peptide hormones and bioactive molecule that demonstration in auto-, para-and endo-crine styles to manage fat tissue and systemic metabolism. As of late, the quantity of adipokines has extended quickly and these additionally incorporate adiponectin, resistin, visfatin, apelin, vaspin, hepcidine, tumor corruption element alpha (TNF-α), chemerin, omentin, MCP-1, and plasminogen activator protein (PAI), numerous initially portrayed as having begun from other tissues than fat tissue (Figure 1.4). Adding to the many-sided quality is heterogeneity as for body site: the contrasting fat warehouses in the body assume particular parts, emitting distinctive arrangements of adipokines (Gesta et al. 2007).

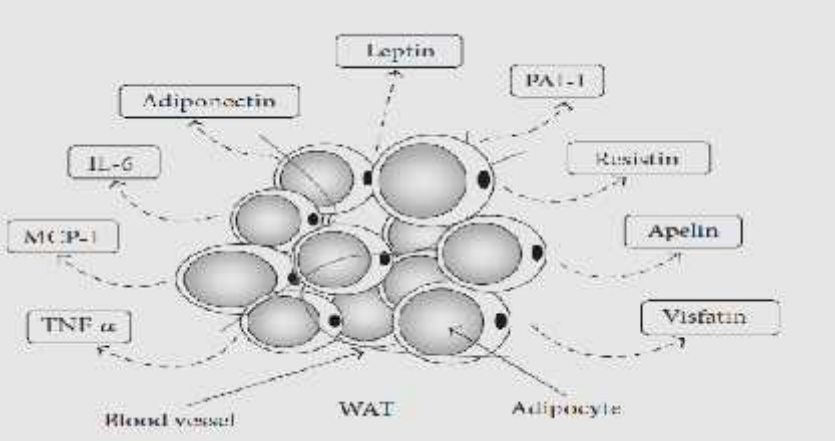

Figure 1.6. Adipokines secreted by white adipose tissue.

1.2.1.1. Leptin

Leptin, a 16-KDa non-glycosylated anorexia peptide, hypothalamically balances body weight, food ingestion, and fat stores (Ge et al. 2002). Leptin, from the Greek-leptos implies incline and is a protein with an molecular weight of 16 kDa, constituted by 167 amino acids. It directs energy metabolism, expanding energy use and diminishing energy utilization. It is now considered that leptin is a metabolic sign for energy adequacy (Zhang et al., 1994). Leptin role was set up by studies utilizing hypothalamic wounds in the brain of corpulent rodents. It was then inferred that leptin controls adipose tissue development through its activity at the central nervous system. Actually, native expression of leptin in hypothalamic locales lessens food intake and body weight in animals. It is at present realized that leptin delicate neurons are situated in the dorsal,

ventral, medial and premammilary nucleus of the hypothalamus. Along these lines, hypothalamus leptin receptors control satiety and energy stability. A few research studies likewise have found that leptin receptors are available in various organs and tissues, for example, liver, skeletal muscle, heart, kidney, pancreas, and among others. These receptors have a place with the class I cytokine receptors and three sorts of leptin receptors have been recognized: long (ObRb), short with 4 isoforms (ObRa, ObRc, ObRd and ObRf) and dissolvable (ObRe) forms. The long isoform (ObRb) is fit for activating complete sign transduction started by leptin connected with energy metabolism. ObRb dimerizes and ties to two molecules of leptin producing a complex that pulls in the Janus kinase 2 (Jak2), which thus phosphorylates itself and the leptin receptor. The phosphorylated receptor ties the transcription component STAT which, after its phosphorylation by Jak 2, dimerizes and translocates into the core to affect articulation of expression of gene, for example, those included in beta-oxidation, uncoupling proteins, and control of food intake. Blockade of leptin flagging is intervened by initiation of phosphatase PTP-1B and SOCS-3 that meddles with Jak2 phosphorylation. These proteins are profoundly communicated in obesity impelled by high fat utilization, diminishing leptin activity and bringing about leptin resistance (Bates et al., 2004).

Leptin levels are relative to insulin levels and conversely corresponding to glucocorticoid concentration (Ge H et al. 2002). Inflammatory cytokines, including TNF, interleukin-1 (IL-1), and leukemia inhibitory element affect leptin creation (Gualillo et al. 2000). Testicular steroids diminish and ovarian steroids increment leptin fixations (Castracane et al. 1998). Leptin manages pancreatic islet cells, growth hormone levels, immunology homeostasis, hematopoiesis, angiogenesis, wound recovery, osteogenesis, and gastrointestinal capacity (Ashwin et al. 2007). In the cerebrum leptin has been appeared to impact the cortex, hippocampus and hypothalamus, applying in the last local control over appetite and levels of sex steroids, thyroxin and growth and development hormone (Irving et al. 2006). Leptin organization can control puberty in grown-ups and youngsters (Strobel et al. 1998). Diminished leptin flagging or receptor capacity expanded energy admission and brings down energy consumption (Friedman et al. 1998), with leptin lack or malfunction itself being a known reason for extreme early-onset obesity, hypogonadism, hyperinsulinemia,

hyperphagia, and impaired T-cell-mediated imminity, treatable with recombinant leptin (Farooqi et al. 2002). Abnormal amounts of leptin in obese patients don't impact hunger concealment as a result of resistance to the hormone, which has been set to be because of leptin receptor flagging defects, downstream blockade in neuronal circuits, and inconsistency in leptin transport over the blood-brain barrier (Flier et al. 2004). Moreover, obesity regularly prompts insulin and leptin resistance and a change to adipose tissue. These conditions cause metabolic dysregulation with increased circulating fatty acid and an expanded discharge of pro-inflammatory adipokines. At the point when left untreated, these conditions cause lipotoxicity, chronic inflammation, hypertension, atherosclerosis and cardiovascular ailment (Gade et al. 2010 and Mathieu et al. 2010). The relationship between hypertension and obesity is very much recorded. Both systolic and diastolic blood pressure increment with BMI (body mass index). Subsequently, fat individuals present higher danger to experience hypertension in examination with non-obese individuals (Kurukulasuriya et al. 2008). Fat people are oftentimes portrayed by an impeded lipid profile, in which plasma triglycerides are raised. This aggravated metabolic profile is all the more frequently seen in obese patients with a high gathering of intra-abdominal fat and has reliably been identified with an expanded danger of cardiovascular maladies (Ohman et al. 2009 and Mathieu et al. 2009). A positive relationship amongst obesity and the danger of creating type 2 diabetes mellitus has been likewise over and again reported in various studies. Intra-abdominal fat amassing has been connected with an expanded danger of prediabetic conditions, for example, impaired glucose resilience and insulin resistance (Ginsberg et al. 2009).

1.2.1.2. Resistin

Resistin is a 12 kDa peptide that for the most part flows as a high-molecular-weight hexamer additionally has an unmistakable, more dynamic low-sub-molecular-weight complex (Patel et al. 2004). The hormone is communicated in most noteworthy concentration in mono-nuclear cells, but on the other hand is found in muscle, pancreatic cells, and adipocytes (Kusminski et al. 2005). Resistin encoding messanger RNA (mRNA) shows an even more extensive territory, having been found in white fat, spleen, hypothalamus, adrenal gland, skeletal muscle, gastrointestinal tract, and pancreas (Kusminski et al. 2005).

Resistin has been agreed a diabetogenic part in mice, however its role in the pathogenesis of human diabetes remains a matter of open deliberation, with no unequivocal part allocated to it as for insulin resistance, its name in any case (Savage et al. 2001). Atherosclerosis aneurysmal vessel wall macrophages discharge resistin (Jung et al. 2005). Chronic kidney illness increments resistin levels (Verma et al. 2003). The hormone amasses in the synovial coating of rheumatoid joint inflammation patients (Kusminski et al. 2005).

1.2.1.3. Adiponectin

The gene for adiponectin, is situated at chromosomal band 3q27, a vulnerability locus for diabetes and cardiovascular ailment (Saito et al. 1999). Adiponectin has both a connector protein, APPL-1, as well as two receptors, AdipoR1 and AdipoR2, each involving seven trans-membrane spaces (Mao et al. 2006). AdipoR1 and AdipoR2 are the fundamental adiponectin receptors regarding glucose and lipid metabolism (Bjursell et al. 2007). Current trials additionally recommend a particle known as T-cadherin to be adiponectin receptor (Hug et al. 2004). The protein, found in both murine and human blood (Menzaghi et al. 2007), represents 0.01% of human plasma protein; its fixation uniquely reduces with morbid obesity (Xu et al. 2007). Adiponectin affects endothelial VCAM-1, ICAM-1, and pentraxin-3 expression (Juge-Aubry et al. 2005). Adiponectin enlarges endothelial nitrous oxide generation, acting to secure the vasodilation (Matsuo et al. 2007).

Adiponectin itself might be hostile to atherosclerotic, as it goes about as an endogenous against thrombotic variable (Ouchi et al. 2003) and hinders macrophage initiation and foam cell amassing, both being basic cytologic components of atheromas (Wang et al. 2005). Stroke, coronary illness, steatohepatitis, insulin resistance, nonalcoholic fatty liver disease, and a wide cluster of malignancy have been connected with diminished adiponectin levels (Trujillo et al. 2005). Hypoadonectinemia has been corresponded with expanded atherosclerosis-related compounds, including adipocyte fatty-acid-binding protein (A-FABP), lipocalin-2, and in addition different markers of oxidative stress (Maturese et al. 2007). The compound has extraordinary potential as a marker for atherosclerotic ailment, its reduction having been appeared to be prescient of

intense coronary disorder, myocardial infarction, coronary artery ailment, and ischemic cerebrovascular illness (Lee et al. 2006).

1.2.1.4. Apelin

Apelin, delivered by adipocytes, vascular stromal cells, and the heart, increment with expanded insulin levels furthermore with obesity (Lee et al. 2006). Cardiovascular apelin levels are down-regulated by angiotensin II and reestablished with angiotensin type I receptor blocker in animal models with heart failure 48. Ischemic cardiomyopathy (Atluri P. et al. 2007) and hypoxia (Ronkainen et al. 2007) increment in apelin levels, Atrial filbrillation and severe heart failure have been connected with diminished apelin levels (Chong et al.2006). Apelin has positive hemodynamic impact, having been appeared to be an inotrope in healthy and failing rat hearts and in disconnected cardiomyocytes (Grisk et al. 2007). Apelin may control insulin resistance by encouraging articulation of brown fat tissue uncoupling proteins and modifying adiponectin levels (Higuchi et al. 2007).

1.2.1.5. Visfatin, Hepcidine, Omentin, Vaspin, Adipsin and Angiopoietin

Less very much depicted, yet likely similarly imperative, different compounds have been found to be results of white fat. Visfatin, additionally delivered by lymphocytes, diminishes insulin resistance (Fukuhara et al. 2005). Visfatin hinders apoptosis of enacted neutrophils (Jia et al. 2004), ensnaring it both as a reason for harm in such conditions as intense lung damage (Ye et al. 2005) and as a potential helpful agent in sepsis (Jia et al. 2004). Visfatin organization to mice diminishes blood glucose levels, mice having one allele have expanded plasma glucose (Fukuhara et al. 2005). Levels of hepcidine, which was initially portrayed as a urinary antimicrobial peptide, increment with obesity and connect with levels of C reactive protein and IL-6 (Jia et al. 2004). Vaspsin, a serine protease inhibitor, lessens levels of leptin, resistin, and TNF, it enhances insulin affectability and shows diminished concentration in the physically fit and expanded concentration in obese patients, particularly those with weakened glucose resilience (Youn et al. 2008). Hepcidine directs iron ingestion by enterocytes, and iron transport over the placenta. Omentin levels diminish with obesity and insulin resistance

and expansion as high-density lipoprotein and adiponectin build up (De Souza C.M et al. 2007).

Adipsin, otherwise called complement factor D, is predominantly delivered by monocytes rate-restricting step in the complement initiation elective pathway and, some way creates an acylation stimulating protein that expands adipocyte triglyceride generation (White et al. 1992). Angiopoietin-like peptide-4, prompted by peroxisome proliferator-activated receptor PPAR-α in liver and PPAR-γ in fat tissue, demonstrates levels that relate with lipoprotein (Mandard et al. 2006) on the grounds that other comparative proteins are inhabitant in the liver and the gut, the protein may well be a piece of a flagging pathway that directs lipid metabolism and reservation (Mandard et al. 2006).

1.2.1.5. Chemokines

Chemokines, customarily seen as controllers of chemotaxis of inflammatory cells, are presently known to be vital mediators betweens a wide array of phenomena, including lymphoid organ advancement, rheumatoid arthritis, and atherosclerosis, chemokines act locally, implying that one can see chemokine movement in perivascular fat in cardiovascular ailment, subcutaneous fat in inflammatory skin infections, and perirenal fat in glomerulonephritis (Momtani et al. 2004). Chemokines created by fat, including IL-8, MCP-1, interferon-gamma increducible protein 10 (IP-10), and managed upon enactment typical T-cell express arrangement (RANTES) are regularly controlled by hormone-like adipokines, including leptin, obesity, and insulin-resistance-affecting hormones (Kralisch et al. 2007). Epicardial fat creates more MCP-1 than does subcutaneous fat (Mazurek T. et al. 2003); there exists a MCP-1 polymorphism connected with high coronary atherosclerosis hazard (Kim et al. 2007).

1.2.2. Chemerin

The chemerin gene was initially distinguished as a novel retinoid-responsive gene in psoriatic skin sores. It is otherwise called tazarotine-induced gene 2 (TIG2) or retinoic acid receptor responder 2 (RARRES2) (Nagpal et al. 1997). The main confirmation for the natural capacity for the chemerin protein came later, with a report

which showed chemerin as a discharged ligand of the vagrant G protein-coupled receptor chemokine-like receptor1 (CMKLR1) (Wittamer et al. 2003).

Late studies and revelations have exhibited that chemerin likewise serves as a ligand for no less than two extra receptors including; chemokine (C-C motif) receptor-like (CCRL2) and G protein-coupled receptor (GPR1). In spite of the fact that the capacity of GPR1 and CCRL2 in mammals stay unclear, yet diverse cell sorts required in inborn and adaptive immunity express CMKLR1, and chemerin is currently referred to work as a chemoattractant that advances the enlistment of these cells to lymphoid organs and locales of injury (Vermi et al. 2005). It has been appeared in a parallel line of examination that chemerin expression and release has been appeared to increment significantly with adipocyte differentiation (Bozaoglu et al. 2007). Besides, loss of chemerin or CMKLR1 expression totally annuls adipogenesis in cell-based models, and changes the outflow of gene imperative in glucose and lipid metabolism, including GLUT4, DGAT2, leptin and adiponectin (Goralski et al. 2007).

1.2.2.1. Structure of Chemerin

Human prochemerin is synthesized as a 163-aa protein with a 20-aa hydrophobic signal peptide which is expelled by obscure proteases. The discharged full grown prochemerin contains 143-aa (chem 21-163) with insignificant chemotactic action. Chemerin share little homology in essential amino acid arrangement with other known proteins. Rather, it has a collapsed structure like cystatins and cathelicidins (Zabel et al. 2006). The anticipated structure of chemerin taking into account cystatins uncovered an opposite orientation of chemokines, having a cluttered C-end, a β-pleated sheet, and a N-terminal α-helix. Inside the cystatin-fold space of chemerin, there are three intra-chain disulfide bonds, though cystatin is balanced out by just two disulfide bridges. Essential structure of chemerin is exceedingly monitored among various species, particularly in the C-terminal locale. Human chemerin offers a general 84%, 76%, 66%, and 63% amino acid grouping relate to pig, steers, rat, and mouse chemerin, individually. Inside the exceedingly labile C-terminal area is the arrangement "AGEDxxxxxxPGQFAFxK(R)ALxxx" Wittamer et al, found that the 9-mer peptide YFPGQFAFS got from human chemerin is most dynamic in chemotaxis of CMKLR1-positive cells. As of late, Cash et al. showed that the 15-mer peptide

AGEDPHGYFLPGQFA got from mouse chemerin has strong anti-inflammatory properties. (Cash et al. 2008).

Chemerin is interpreted as a 163 amino acid pre-proprotein that is emitted as a 143 amino acid proprotein, with a molecular weight of 18kDa, after proteolytic cleavage of a signal peptide (Meder et al. 2003) (Figure 1.7). This proprotein has low biological function, and along these lines requires further extracellular C-terminal handling by plasmin, carboxypeptidases or serine proteases of the coagulation, fibrinolytic and inflammatory cascade (Zabel et al. 2006).

The degree of C-terminal cleavage is needy of the area from which chemerin is detached. For instance, chemerin from human ovarian ascites liquid, serum and hemofiltrate need six, eight and nine C-terminal amino acids, individually (Zabel et al. 2006). These are predictable discoveries taking into account the perceptions that few proteins are fit for preparing chemerin to a dynamic structure. As indicated by in vitro research, it has been demonstrated that cathepsin G cleaves seven C-terminal amino acids from prochemerin, elastase can bind to six, eight, or eleven, plasmin cleaves five, and tryptase cleaves five or eight (Zabel et al. 2005) (Figure 1.7.).

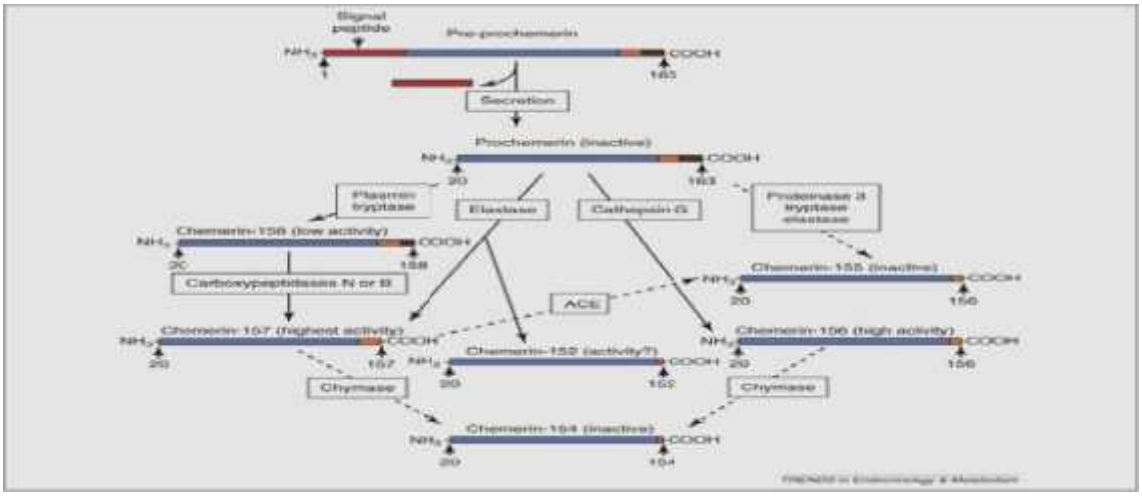

Figure 1.7. Proteolytic processing of chemerin. Chemerin is produced as a pre-proprotein, pre-prochemerin (1–163), which requires N-terminal cleavage of a secretion signalpeptide before it is secreted as an inactive precursor protein, prochemerin (20–163). Extracellular proteolytic processing of the carboxyterminus of prochemerin exposes the bioactive region. Cathepsin G cleaves seven C-terminal amino acids from prochemerin (chemerin-156), elastase is able to cleave six (chemerin-157), eight (chemerin-155) or eleven (chemerin-152), plasmin cleaves five

(chemerin-158), and tryptase cleaves five (chemerin-158) or eight (chemerin-155). Multiple cleavages might be required to fully activate chemerin, with an initial tryptase cleavage resulting in chemerin with low activity (chemerin-158), and a second cleavage by carboxypeptidase N or B producing highly active chemerin (chemerin-157). Chemerin-156 and -157 activities are terminated by chymase cleavage to produce inactive chemerin-154. Chemerin-157 activity might also be terminated by ACE cleavage to produce inactive chemerin-155. The number (e.g. -157) refers to the terminal amino acid position of the processed protein. Solid arrows represent activation pathways; broken arrows represent inactivation pathways.

Various cleavages are required to completely initiate chemerin sometimes. For instance, an underlying tryptase cleavage at amino acid 158 results in chemerin with low action. Be that as it may, this chemerin with low action serves as a substrate for a brief moment cleavage via carboxypeptidase N or B, creating completely initiated bioactive chemerin (Du et al. 2009) (Figure 1.7). Proteolytic handling is additionally accepted to be included in the inactivation of chemerin. Especially, neutrophil-inferred serine protease prtienase, mast cell chymase and angiotensin converting enzyme (ACE) have been appeared to change over bioactive types of chemerin to inert subsidiaries (John et al. 2007) (Figure 1.7). Accordingly proteolytic preparing of chemerin is a key administrative component that may decide both systemic and local concentration of bio-active chemerin.

1.2.2.2. G-Protein Coupled Receptors of Chemerin

CMKLR1, additionally named as chemR23, is a G-protein-coupled receptor (GPCR) communicated mostly by macrophages, natural killer cells, plasmacytoid dendritic cells (pDCs), and myeloid dendritic cells (Vermi et al. 2005). CMKLR1 offers phylogenetic homology with some chemo-attractant receptors including C5a-R, C3a-R, and formyl peptide receptor-like 1 (FPRL1) (Zabel et al. 2006). It is accounted for that eicosapentenoic acid determined lipid known as determining E1 is a ligand for CMKLR1. Determining E1 is thought to apply inflammatory impacts through the actuation of CMKLR1 (Arita et al. 2005). CMKLR1 is likewise utilized as a co-receptor for immunodeficiency virus SIV and some essential HIV-1 strains (Martensson et al. 2006). Autonomous studies from a few research centers all exhibit that CMKLR1 is a leukocyte chemoattractant receptor for chemerin. CMKLR1 is in charge of guiding the relocation of dendritic cells to lymphoid organs and inflammed skin (Vermi et al. 2005).

GPR1 with obscure organic capacity is a vagrant GPCR. As of late, chemerin is recognized as an endogenous ligand for GPR1. GPR1-transfected cells react to chemerin incitement with a hoisted intracellular calcium discharge to a level 30% of that seen in cells releasing CMKLR1 (Barnea et al. 2008). An iodinated chemerin C-terminal section chem149-157 is utilized for radio-ligand–binding research and affirms that chem149-157 ties to GPR1. The coupling constant (Kd) of chem149-157 with GPR1-communicating cells is 5.3 nM, equivalent to 4.9 nM for CMKLR1-transferred cells. With the identification of GPR1 as chemerin receptor, the new part of GPR1 other than as a co-receptor of HIV and SIV infection ought to be investigated.

The third vagrant GPCR distinguished as chemerin receptor is CCRL2. Zabel et al. characterized mouse mast cell-expressed CCLR2 as a silent chemokine receptor-like GPCR which has a pro-inflammatory capacity by introducing bound attractants for flagging receptor communicated on neighboring cells. (Zabel et al.2008). CCRL2 itself does not trigger chemerin disguise or backing chemerin-driven signal transduction. CCRL2 may encourage CMKLR1 capacity by expanding local chemerin fixation, which is more available to cell-flagging receptor CMKLR1. Mast cell-communicated CCLR2 can improve tissue swelling and leukocyte penetration in an IgE-interceded mast cell-subordinate mouse passive cutaneous hypersensitivity model, particularly when low measures of antigen-specific IgE are utilized (Yoshimura et al. 2008).

1.2.2.3. Chemerin in Metabolism and Obesity

Notwithstanding having a vital energy stockpiling capacity, white adipose tissue serves as a dynamic endocrine organ that secretes various hormone-like compounds called adipokines (Goralski. et al. 2007). These adipokines incorporate proinflammatory cytokines and related proteins, compliment related proteins, proteins of the fibrinolytic cascade, vaso-active proteins, and other naturally dynamic peptides with hormone-like activities.

Adipokine influence adiposity, adipocyte metabolism and inflammatory reaction of adipose tissue, and have a noteworthy part in systemic lipid and glucose metabolism. It was initially reported in 2007 that both chemerin and CMKLRI were emphatically

communicated in white adipose tissue from mouse, rodent and human examples, which distinguish chemerin as a novel adipokine with potential autocrine and paracrine capacities (Bozaoglu. et al. 2007). In expansion to this abnormal state of expression, white adipose tissue perhaps at the same time has a considerable capacity to bioactivate chemerin. For example, cathepsin G (Karlsson et al. 1998), and tryptase(Lopez et al. 2008) are communicated in fat tissue which propose that chemerin - 155,- 156 and - 158 all bioactive proinflammatory types of chemerin, can be delivered in this tissue. Catheptin S, which is accepted to create a anti-inflammatory chemerin derivaties, is likewise communicated in adipose tissue (Taleb et al. 2005).

In conclusion the declaration of chymase and ACE in fat tissue (Galvez-Prieto et al. 2008), proposes that bioactive types of chemerin can be inactivated in the fat tissue. Chemerin expression and discharge increment significantly with adipogenesis and loss of chemerin or CMKLR1 expression in preadipocytes extremely debilitates separation into mature adipocytes (Muruganandan et al. 2010).

Aside from this autocrine capacity in adipocyte, chemerin and CMKLR1 flagging may have paracrine capacities inside adipose tissue as proposed in the past segment, chemerin serves as a chemoattractant for different sorts of inmmune cells and may along these lines add to white fat tissue inflammation with obesity. What's more, fat tissue is a very vascularized tissue and hindering angiogenesis has been appeared to anticipate fat tissue development and the improvement of obesity, diabetes and cardiovascular infection (Rupnick et al. 2002).

CMKLR1 is communicated in human endothelial cells and is upregulated by the proinflammatory cytokines TNFα, IL-6, and IL-1β. Late studies have additionally demonstrated that chemerin enacts key angiogenic pathways and actuates angiogenesis in vitro (Kaur et al. 2010). In this way, the hoisted expression and discharge of chemerin amid adipogenesis could likewise bolster fat tissue development by inciting angiogenesis and expanding fat tissue vascularization. The main part of human information bolsters a linkage between chemerin, obesity and metabolic disorder, a bunch of metabolic issue that expand the danger for diabetes and cardiovascular malady. For instance, an investigation of a Mexican-American populace reported

fundamentally higher serum chemerin levels in patients with type 2 diabetes mellitus contrasted and normglycemic controls, and in obese and overweight subjects compound with incline control (Bozaoglu et al. 2010). Plasma chemerin levels -corresponded emphatically with body mass index, fasting glucose, fasting serum insulin, plasma triglycerides and total serum cholesterol and adversely connected with high density lipoprotein (HDL) cholesterol (Bozaoglu et al. 2009).

A different investigation of a Mauritan populace of blended ethnicity exhibited that subsequent to modifying for sex and age, serum chemerin levels were essentially lifted in overweight as well as obese subjects and that they were emphatically corresponded with waist circumference, waist to hip proportion, Homeostasis Model Assessment of Insulin Resistance result and triglycerides, and contrarily related with HDL (Bozaoglu et al. 2007). Also, different studies have reported higher chemerin levels in patient T2DM and obesity, and additionally a positive relationship between's serum chemerin levels and leptin, resistin and C reactive protein, TNFα and IL-6 (Lehrke et al. 2009).

Another study on a Causcasian populace found that people with metabolic disorder had altogether higher serum chemerin levels in comparison with health subjects and constructive connections were seen between serum chemerin and glucose, triglyceride, systolic blood pressure and diastolic blood pressure (Stejskal et al. 2008). Moreover, selecting a serum chemerin focus limit of 240 ug/L permitted the scientists to determine metabolic disorder to have an affectability of 75% and specificity of 67% (Stejskal et al. 2008). Independent of the extensive proof interfacing coursing chemerin levels with adiposity and different parts of the metabolic disorder, it is still uninformed of any genome-worldwide investigations recognizing the gene encoding chemerin or any related receptors as applicant susceptibility loci for human infection. Despite the fact that a late extensive affiliation study (Bozaoglu et al. 2009), reported that serum chemerin levels are firmly heritable and found that solitary nucleotide polymorphism (SNP) demonstrating the most grounded proof of relationship with plasma chemerin levels was situated in the EIDL3 gene, which has a known part in angiogenesis. At present, focused on hereditary investigations of chemerin and CMKLR1 are exceptionally restricted. The main case in the current logical writing reported that

despite the fact that SNPs of the chemerin quality were not connected with aggregate adiposity, there was a relationship with expanded visceral fat mass in incline subjects (Mussig et al. 2009).

This crude data proposes an impact of chemerin on local fat conveyance and specifically, instinctive adiposity, which is most unequivocally connected with the metabolic disturbances that can happen with obesity (Hamdy et al. 2006). These previously stated studies exhaustively recognize a relationship between serum chemerin levels and obesity. However the wellspring of raised chemerin levels which are communicated in anatomical locales notwithstanding fat, for the most part eminently the liver, stays to be absolutely settled.

A late examination of portal, hepatic and systemic venous blood chemerin levels in people showed comparable chemerin levels in the portal and systemic vein, proposing that visceral fat tissue is not a noteworthy giver to serum chemerin levels (Weigert et al. 2010). Despite the fact that, chemerin levels were higher in hepatic vein blood tests, showing that chemerin is incorporated and emitted by the liver (Weigert et al. 2010). In a different study, serum chemrin levels in patients who had experienced bariatric surgery with the end goal of weight reduction were fundamentally lessened after surgery, and connected with BMI and fat mass (Sell et al. 2010). Likewise examination of chemerin in ladies with polycystic ovary syndrome (PCOS), a typical endocrinopathy connected with insulin resistance, pancreatic β-cell dysfunction, disabled glucose resilience, T2DM, dyslipidemia and visceral obesity, uncovered that both chemerin mRNA and protein levels are raised in subcutaneous and omental fat tissue from patients with PCOS (Tan et al. 2009). Also, chemerin emission from female fat tissue explants uncovered an essentially higher arrival of chemerin from obese versus incline subjects (Sell et al. 2009). Despite the fact that proof exists for a linkage between flowing chemerin levels and parts of metabolic disorder, different studies recommend that local concentration may be a more vital determinant of pathologic outcomes, for example, cardiovascular sickness. For instance, serum chemerin levels were accounted for to be just feebly associated with coronary plaque burden and the quantity of non-calcified plaques in people (Lehrke et al. 2009). In addition, after alteration for built up cardiovascular sickness hazard factors, these relationships were

no more present. Be that as it may, another study exhibited that aortic and coronary atherosclerosis was emphatically associated with chemerin expression in psoriatic and pericoronary fat tissue, individually (Spiroglou et al. 2010) which recommends that privately delivered chemerin influences the improvement of atherosclerosis in paracrine way (Spiroglou et al. 2010). Despite the fact that serum chemerin levels don't foresee coronary atherosclerosis, local chemerin fixations may impact plaque advancement. Atherosclerosis is a dynamic inflammatory ailment and the gathering of macrophages in atherosclerotic plaques decidedly connect with disease progression. A potential clarification is that expanded local chemerin fixations in coronary vessels advance macrophage enlistment and impact inflammatory reaction in atherosclerotic plaques. Despite the fact that plainly serum chemerin levels are raised in obesity, the systems managing chemerin expression remain ineffectively caught on. It has been demonstrated that insulin increments chemerin emission from fat tissue both dosage and time conditionally in vitro and in tissue explants (Tan et al. 2009). IL-1β, a proinflammatory cytokine connected with insulin resistance, actuates chemerin mRNA expression and emission measurements conditionally from 3T3-L1 determined adipocytes (Kralisch et al. 2009). TNF-α, another proinflammatory cytokine connected with insulin resistance, additionally expands serum chemerin levels in vitro and increases chemerin synthesis and discharge from 3T3-L1 adipocytes (Parlee, et al. 2010). An impelling in expression brought about by proinflammatory cytokines propose nuclear element kB may regulate chemerin mRNA expression (Kralisch et al. 2009). These discoveries are upheld by the way that hyperinsulinemia and hoisted proinflammatory cytokine levels are regularly connected with obesity.

1.2.2.4. Chemerin and Inflammation

The initially recognized capacity of chemerin, acting through CMKLR1, was to advance chemotaxis of immature dendritic cells (DCs) and macrophages (Wittamer et al. 2003). CMKLR1 is currently surely understood to be communicated in a number invulnerable cells, including juvenile plasmacytoid DCs, myeloid DCs, macrophages and natural killer cell (NK) (Prolini et al. 2007), and that serum chemerin levels relate with levels of the pro-inflammatory cytokines tumor necrosis factor (TNF)- α, interleukin (IL-6) and C receptive protein (CRP) (Lehrke et al. 2009). Pathologically, chemerin is communicated in psoriatic sores (Nagpal et al. 1997) and a few effector

cells of the innate inmmune framework that are affected by chemerin, including DCs, monocytes, macrophages and NK cells have been embroiled in the pathogenesis of psoriasis (Ottaviani et al. 2006). Chemerin expression is accepted to be a marker for the early period of newly developing lesion, furthermore is thought to advance the enrollment and enactment of plasmaacytoid DCs (Skrzeczynska-Moncznik et al. 2009). This proposes chemerin and CMKLR1 are included in the enrollment of different immune cells into the lesion and might impact the cross-talk between various cell type in charge of controlling the progression of psoriatic aggravation (Grosa et al. 2005).

Chemerin and CMKLR1 seem to assume critical parts in other immune system states, for example, trial immune system encephalomyelitis, a murine model of numerous sclerosis. In this model, CMKLR1 invalid mice grew less extreme clinical what's more, histologic sickness and had lower CNS irritation with respect to control mice (Graham et al. 2009). Since macrophages assume a critical part in proliferating the inflammatory cascade, lost CMKLR1-subordinate enrollment of these cells by chemerin could represent the watched inflammatory cascade. Despite the fact that much test proof backings a pro-inflammatory role for chemerin/CMKLR1, different studies propose that this flagging pathway may have an anti-inflammatory capacity. For example, a study by Luangsay et al, utilizing a lipolysaccharide (LPS)-induced mouse model of intense lung aggravation exhibited that chemerin treatment at the same time expanded the assembly of airway macrophages and diminished neutrophil recruitment and enactment, recommending both a pro-inflammatory and anti-inflammatory function of chemerin and CMKLR1. (Luangsay et al. 2009). These chemerin-prompted impacts were not seen in CMKLR1 invalid mice (Luangsay et al. 2009). Curiously, CMKLR1 invalid mice treated with LPS alone showed unmistakably more noteworthy neutrophil and macrophage enrollment in lung tissue contrasted and that of wild type mice, demonstrating the significance of CMKLR1 as an anti-inflammatory middle person. As of late, it is presently clear that obesity is ordinarily connected with endless poor quality systemic inflammation.

Notwithstanding adipocytes, fat tissue contains various lymphocytes situated in the stromal vascular portion, including macrophage, NK cells and T-cells (Anderson, E.K. et al. 2010). As people get to be obese coming about to the extension of their

adipocytes, fat tissue experiences molecular and cell adjustments influencing systemic metabolism and inflammation. Serum levels of the inflammatory markers TNF-α, IL-6 and CRP are lifted in obesity (Cottam et al. 2004) and fat tissue seems, by all accounts, to be a significant wellspring of these cytokines (Trayhurn et al. 5005).

1.2.2.5. Role of Chemerin in Glucose Homeostasis

Obesity is a built up danger component for insulin resistance and T2DM and modifications in adipokine emission in obesity are accepted to assume a noteworthy part in the improvement of these metabolic disorder (Muoio et al. 2006). The hoisted serum chemerin levels seen in human and mice propose that chemerin may likewise impact the dysregulation of glucose metabolism that regularly happens with obese. Nonetheless, it is noteworthy to note that hyperinsulinemia, which regularly found in patients who are obesed and have T2DM, has been accounted for to build serum chemerin levels (Tan et al. 2009). In vitro studies utilizing 3T3-L1 adipocytes have given clashing results, with one study reporting diminished insulin-empowered glucose uptake (Takahashi et al. 2008) and another demonstrating expanded insulin-fortified glucose uptake and insulin receptor substrate 1 (IRS1) tyrosine phosphorylation after chemerin treatment (Kralisch et al. 2009). Despite the fact that the approach of these studies contrasted in a few regards. For instance, the study reporting expanded glucose uptake treated 3T3-L1 adipocytes with around 6 nM chemerin for 12 hours in media with serum before measuring insulin-invigorated glucose uptake (Takahashi et al. 2008).

The study that experienced a diminishing glucose uptake treated the adipocytes with 10 uM chemerin for 49 hours without serum media before measuring glucose uptake (Kralisch et al. 2009). In this manner, the distinctive focuses, treatment terms and conditions may have added to the discrepant results, so that the shorter, lower dosage treatment may have created an intense increment in glucose uptake, while the more drawn out, higher measurement treatment may have brought about a negative input reaction, or conceivably the foundation of a safe express that delivered a net lessening in glucose uptake.

In another study, treatment of essential human skeletal muscle cells with 60 nM chemerin for 24 hours brought about an expansion in phosphorylation of an IRS1 serine

buildup known for adversely adjusting the activity of insulin incidental with a diminishing in insulin-stimulated glucose uptake (Sell et al. 2010). A corresponding lessening of AKT, glycogen synthase kinase (GSK) 3α and GSK3βphosphorylation was additionally watched. In mice, chemerin treatment intensifies glucose intolerance in obese/diabetes (db/db), however not normoglycemic models by diminishing serum insulin levels, lessening fat tissue glucose uptake and bringing about a huge abatement in liver and aggregate tissue glucose uptake (Ernst et al. 2010).chemerin-induced dysregulation of glucose uptake in adipocyte and myocyte societies recommends an insulin-subordinate GLUT4 mechanism, though a decline in serum insulin levels and liver glucose in obese/diabetic (db/db) mice recommend an insulin-subordinate GLUT-2 component. In this manner, the instrument by which chemerin adjusts glucose homeostasis stays obscure and these clashing discoveries show a need to clear up the part of chemerin in glucose metabolism.

1.2.2.6. Role of Chemerin and Diabetes

Chemerin is a recently depicted adipokine with consequences for adipocyte separation and metabolic in vitro (Bozaoglu et al. 2007). Studies have demonstrated that chemerin expression is expanded amid the separation of 3T3-L1 cells murine pre-adipocytes into adipocytes. Hereditary thump down of chemerin or its receptor, CMKLR1, impedes separation of 3T3-L1. Articulation of chemerin and CMKLR1 in full grown adipocytes recommends an autocrine/paracrine system. These information show that chemerin is a novel adipokine managing adipocyte capacity. Hatching of 3T3-L1 cells with recombinant chemerin protein advanced insulin-fortified glucose uptake with upgraded insulin flagging. This recommend chemerin may assume a part in insulin sensitivity and therefore a potential restorative focus for diabetes. Chemerin affects ERK1/2 phosphorylation in 3T3-L1 cells. ERK1/2 flagging is typically required in adipogenesis and lipolysis. Quality articulation of chemerin and CMKLR1 is fundamentally higher in adipose tissue of obese diabetes inclined Psammomys obesus. In human, plasma chemerin levels in healthy contributors are not fundamentally not quite the same as type 2 diabetes patients. Be that as it may, plasma chemerin levels in mass index, coursing triglycerides, and circulatory triglyceride, proposing a solid relationship of this protein with weight related entanglements (Bozaoglu et al. 2007).

1.2.2.7. Role of Chemerin in Psoriasis

Psoriasis is a sort 1 interferon-driven T cell-intervened infection. It is described by the enlistment of pDCs into the skin. Immunohistochemistry examination uncovers that chemerin is distinguished in prepsoriatic skin adjacent to active sores and early sores, yet not from ceaseless plaques. Neutrophils and CMKLR1-positive pDCs are likewise decidedly stained. Fibroblast refined from the skin of psoriatic injuries express more elevated amounts of chemerin mRNA and protein than fibroblasts from unaffected psoriatic skin or healthy donor and advance pDC movement in vitro in a chemerin-subordinate way (Albanesi et al. 2009). Skrzeczynska-Moneznik et al (Skrzeczynska-Moneznik et al. 2009). Reported that chemotactically dynamic chemerin is available in lesional skin of psoriasis patient, which involves the determined power of pDC amassing in psoriatic skin. In this way, chemerin/CMKLR1 axis assumes an essential part in psoriasis and may give a restorative focus to this ailment.

1.2.2.8. Role of Chemerin as a Potential Biomarker of Tumors

Adrenocortical tumor (benevolent) is a typical illness with a rate of 4% in the US populace. Utilizing microarray investigation, chemerin is among the main five qualities that have a positive relationship with tumor size. The other four qualities are IL13RA2, HTR2B, CCNB2, and SLC16A (Fernansez-Ranvier et al. 2008). Chemerin protein and transcript are additionally identified in skin squamous cell carcinoma (SSC). They are rich in typical epidermis and contiguous skin to SSC lessions, yet scarcely noticeable around the keratin pearls of SCC (Zheng et al. 2008). Interestingly, chemerin mRNA expression in mesothelioma is up-directed contrasted and non-harmful mesothelial cells (Mohr et al. 2004). Taken together, chemerin might be a valuable biomarker for tumor diagnostics.

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. Chemerin measurements by ELISA

Plasma chemerin levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) human chemerin kit (Cat. No.: RD191136200R) (BioVendor). Human chemerin 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 room temperature (25°C) for 1 hour, shaking at 300 rpm on an orbital microplate shaker.

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 room temperature (25°C) for 1 hour, shaking at 300 rpm on an orbital microplate shaker.

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 room temperature (25°C) for 1 hour, shaking at 300 rpm on an orbital microplate shaker.

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 15 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. Obese subjects had significantly higher chemerin 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
Chemerin (ng/ml)	90 ± 36.5	122 ± 28.9	<0.001

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 chemerin levels with other biochemical parameters in non-obese subjects are presented in Table 3.2. Chemerin levels significantly correlated with BMI, waist circumference, and triglycerides while chemerin levels did not significantly correlate with hip circumference, fasting glucose, total cholesterol, LDL-cholesterol and HDL-cholesterol.

Table 3.2. Correlation of plasma chemerin levels with baseline parameters in non-obese group.

Variable	Chemerin	
	r	**P**
BMI (kg/m²)	0.61	<0.001
Waist circumference (cm)	0.36	0.02
Hip circumference (cm)	0.25	0.12
Fasting glucose (mg/dL)	0.28	0.08
Total cholesterol (mg/dL)	0.23	0.16
LDL cholesterol (mg/dL)	0.33	0.04
HDL cholesterol (mg/dL)	- 0.22	0.17
Triglycerides (mg/dL)	0.38	0.017

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

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

Table 3.3. Correlation of plasma chemerin levels with baseline parameters in obese group.

Variable	Chemerin	
	r	**P**
BMI (kg/m²)	0. 57	<0.001
Waist circumference (cm)	0.42	0.007
Hip circumference (cm)	0.22	0.17
Fasting glucose (mg/dL)	0.25	0.12
Total cholesterol (mg/dL)	0.41	0.009
LDL cholesterol (mg/dL)	0.21	0.19
HDL cholesterol (mg/dL)	- 0.20	0.22
Triglycerides (mg/dL)	0.29	0.07

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

4. DISCUSSION

Obesity is characterized by an excess accumulation of white adipose tissue which is an active endocrine organ, secretes a number of peptides with diverse biological an physiological functions including regulation of satiety, carbohydrate, lipid metabolism and insulin sensivity. The signaling molecules secreted from adipose tissue are collectively called adipocytokines. Chemerin is an adipocytokine that plays a role in obesity (Kershaw et al., 2004). In the present study, we observed that the chemerin was significantly correlated with BMI and waist circumference in both obese and non-obese subjects. Additionally, chemerin levels were correlated with total cholesterol in obese subjects. In non-obese subjects, chemerin was positively correlated with LDL-cholesterol levels.

The scientific literature describes chemerin level elevation as increasing the human body mass index (BMI) above 25 kg/m^2, compared to people with a BMI below 25 kg/m^2. Chemerin levels correlate positively with body mass index; body fat mass is the most important factor determining chemerin concentration. The positive correlation of chemerin levels with BMI has been corroborated widely. Maghsoudi et al. (2015) reported an association between the chemerin concentration and BMI in a population of Iran. It has also been reported that chemerin levels correlated with obesity and high BMI (Shin et al., 2012). In accordance, we also found a significant correlation between BMI and chemerin concentration in both obese and non-obese subjects.

Waist circumference reflects primarily total abdominal fat, both visceral and subcutaneous fat. Obese subjects with metabolic syndrome had elevated levels of circulating and gluteal subcutaneous adipose tissue (SAT) secreted chemerin. In addition, circulating chemerin levels were positively associated with deposition of visceral adipose tissue (VAT) (Jialal et al. 2013, Maghsoudi et al. 2015 and Shin et al. 2012) showed that waist circumference was positive relation with chemerin levels. Similar to the previous findings, we saw positive association between chemerin levels and waist circumference in both obese and non-obese subjects. These results confirm that high levels of chemerin expression in visceral adipose tissue and plasma are related to increased adiposity.

Recent studies have demonstrated that chemerin induces insulin resistance in adipocytes and skeletal muscle cells in vitro and that chemerin levels in humans are associated with multiple components of the metabolic syndrome including body mass index (BMI), triglycerides, total cholesterol, LDL- cholesterol and high-density lipoprotein (HDL)- cholesterol and hypertension. These findings suggest that chemerin may play a role in the pathophysiology of obesity (Becker et al., 2010). Lörincz et al. (2014) has also reported that chemerin was positively correlated with LDL-cholesterol levels in nondiabetic obese and nonobese subjects. Based on the abovementioned studies, we suggest that plasma chemerin levels significantly correlated with LDL-cholesterol in non-obese subjects. Thus our results indicate that by disturbing the lipid metabolism, chemerin may lead to metabolic syndrome and consequent obesity.

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 chemerin has association with BMI and waist circumference in both obese and non-obese subjects. It does have significant influences on lipid profiles. Based on the literature and our findings, chemerin 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 chemerin in obesity.

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