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Physiological Link between Adipose Tissue Hormones and Diabetes Mellitus: A Review

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ABSTRACT

Diabetes is occurred due to a defect in the inequity of the blood's sugar metabolism that results in a remarkably increasing in the concentration of blood glucose for different factors, including genetic, psychological, or biological causes, as well as in consuming high amount of sugar. Several diseases including diabetes have been related to the two kinds of adipose tissue (brown and white). These tissues play a significant role in insulin sensitivity. It has become clear that there are numerous hormones released from adipose tissue. Chemerin has impact in glucose homeostasis, because it involves in both insulin resistance and glucose metabolism, as it enhances insulin-dependent glucose acceptance in adipocytes. Additionally, it is clear that adiponectin prevents the occurrence of diabetes in individuals by moderating glucose tolerance, improving fat metabolism, controlling insulin sensitivity, and altering homeostasis. The type 2 diabetes had relationship with elevated concentrations of the hormone phosphatases in comparison with non-diabetes individuals. Regarding with the hormone resistin, the insulin resistance had great relationship with the hormone concentration in people who had sever insulin resistance

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INTRODUCTION

Blood Glucose

Blood is considered an essential fluid circulating in living body as a key to delivering oxygen and nutrients to cells of living body and removing waste from them, in addition to respiration and regulating the water balance and body temperature [1, 2]. Therefore, it is considered a lifesaver through its control of health and various disorders [3]. The functions of all blood components, such as erythrocytes, leukocytes, platelets, and others, are indispensable [4,5].

Glucose is chief nutrition for humans as most of cells' energy obtained from glucose. Numerous physiological and biochemical pathways occur in the body as a result of glucose activities directly. Glucose is small biochemical substance that produced from the metabolism of carbohydrates, as polysaccharides and oligosaccharides are converted finally into monosaccharides through metabolic processes. The liver is responsible for many metabolism and absorption of glucose in the body. It has a significant relationship with structure of certain amino acids and synthesis of blood groups [6, 7].

The pancreas gland releases several hormones that maintain the normal level of glucose in the blood. The insulin is very significant that decreases the sugar level in the blood, whereas glucagon hormone has contrary function to insulin because the high level of glucose in the blood results under the effect of glucagon. The growth hormone, adrenaline, and the glucocorticoids have role regarding with controlling glucose level in the blood [8]. Currently, the asprosin is termed glycogenic hormone because the major function of this hormone is controlling the glucose level in the blood [9]. The increasing of glucose level continually results the defect in physiology of the cells and the occurrence of illnesses such as diabetes [10].

Diabetes Mellitus

Diabetes is characterized by unusually raising of glucose level in the blood as consequences of disparities in the metabolic pathways of sugar. Diabetes has different causes such as psychological, organic, extreme consumption of sugar, as well as genetic reasons. The abnormal production of insulin from pancreas lead to the incidence of diabetes: two cases, the first is insulin deficiency means the quantity of produced insulin is lower than the normal level, or when there is comprehensive loss of insulin secretion. The second case termed insulin resistance that occurs in many persons suffers from obesity when insulin produces in high quantities, but the cells and tissues do not respond to insulin, hence there is defect in insulin activity [11].

Diabetes is represented one of most important chronic illnesses that distributed among various ages of world people. There are more than 120 million people affected with diabetes in different portions of the world according references. Other references demonstrated that there are several factors such as sex, ethnicity, and geographical zone play role for occurrence of diabetes in the world [12]. Normal individual has about 1 gram/kilogram (90-120 milligram/deciliter) of glucose in the blood. The detection of the disease is made in the laboratory when level of glucose exceeds the normal level; the condition is called hyperglycemia.The sugar is excreted in urine when the level of glucose become above than 180 milligram/100

milliliter of blood, this condition is associated with diminishing the quantities of water, and the patient suffer from thirst due to body dehydration [13].

Blood Sugar and Insulin Action Mechanism

Beta cells are specialized cells in the pancreas that produce insulin hormone. They are group of cells that distributes in the pancreas as islands; therefore they are called“Langerhans Islet”. The insulin hormone composed of two amino acids chains connected by chemical bonds. The insulin is very beneficial for the body because it prevents the accumulation of glucose and raising it's in the blood in spite of individual consumption of large amounts of sugars and starches. It maintains persistent level of glucose all over [14]. The glucose enters inside the body cells under the action of insulin to burn it and yield energy for completion of physiologic process of different systems of body, as energy production depend upon about 5 grams of glucose sugar found in human blood. The physiology of insulin based on its attachment to "insulin receptors" that they are unusual proteins found on the surface of the cell. Insulin receptors achieve two elementary actions for glucose: the first these receptors represented as key, when they attach to insulin, their openness in the cell wall contributes to introducing the glucose, as these receptors become entrance locks without insulin. Secondly, another protein termed the "glucose transporter" move the glucose inside the cell to burn it and produce the energy when the signals are transported from receptors to the glucose transporter [15].

It is become evident that insulin is very important for introducing the glucose inside the cells and storage it in the liver and muscles that leads to the declining the glucose level in the blood. Diabetes and it's sever consequences affects the human when there is raising in glucose level that exceeds its normal limit as a result of incapability of glucose to across the cell wall that lead to its accumulation in the blood; this condition occurs when there is loss of insulin or presence of troubles in the insulin receptors. On the other hand, this raising in the blood glucose level occurs due to destruction of amino acids and their transformation to glucose sugar in the absence of insulin, this condition is accompanied with increasing in the free fatty acids percentage in the blood due to occurrence of lipolysis, which is likely to be followed by diabetic ketogenic coma as a result of blood acidity, and raising the blood ketone bodies [16]. Therefore, the increasing the blood glucose level controls the production of insulin from pancreas with exciting accuracy and in a planned amount. During fasting, the insulin is produced by one unit every hour, and it's releasing raises to 3-7 units rapidly within a few minutes after consumption of sugars and starches [17]. Therefore, pancreas gland releases several hormones that control level of glucose normally in the blood. The major significant hormone is insulin which makes glucose level below the normal level in the blood, contrary to the activity of insulin, the glucagon hormone increase the blood glucose level, in addition to the impact of numerous hormones represented by glucocorticoids, the growth hormone and adrenaline [18). Controlling the blood glucose by hormones illustrated in (Figure 1).

There are three chief kinds of diabetes according to the World Health Organization instructions [20]:

1- Diabetic Mellitus Type-I

It is defined as insulin-dependent diabetes, the loss of insulin-secreting beta cells from the islets of Langerhans is responsible for suffering the diabetic patient from this kind, and the result is reduction of insulin. The term juvenile diabetes is frequently used to describe this pattern in children and young persons, and occasionally adult individuals may be affected. The whole absence of insulin is the consequence of comprehensive destruction of the beta cells that release insulin, another significant cause is infection of beta cells with viruses. It is related to obesity and may therefore contribute to heart diseases [21].

2- Diabetic Mellitus Type-II

This kind categorized by the treatment of the patient with oral medicine that reduces the sugar level in the blood, so it is known as non-insulin depended diabetes mellitus. It establishes around 90-95% of wholly conditions, hence it represents public pattern of diabetes. In this type, the pancreas produces insulin that has lower sensitivity impact on the cells. Therefore the body cells do not respond to the action of insulin, and there is increasing in the quantity of glucose constantly in the blood. It involves the anti-insulin resistance, as well as the deficiency of insulin production, so it varies from the first pattern. Hence it considered notable diabetes. The cell envelops of different body tissues include insulin receptors that do not affected by insulin in any formula. The prevailing defect in the tissue affection to insulin is the Langerhans Islet in the primary phase, and it is affect by levels of insulin above than the normal level in the blood. A recent investigation concluded a correlation between DMII and *Helicobacter pylori* infection [22,23]. The comparison between DMI and DMII is demonstrated in (Figure 2).

3- Gestational Diabetes

It seen in pregnant due to disparity in glucose tolerance, leading to high rate of mortalities or genetically defects in child, therefore this kind is actual unsafe for the neonatal. It was also documented children were vulnerable to suffering from DMII or children bigger than the normal; the mothers of these children were affected with gestational diabetes [25]. Blood glucose mostly comes back to its normal levels after birth, only to reoccur in the next pregnancy, so 1/3 to 1/2 of women with gestational diabetes may suffer from DMII within 10 years, and there are numerous factors that predispose for evolving gestational diabetes, involving family inheritance of diabetes, fatness, advanced age of the pregnant woman, complications in previous childbirth such as the stillbirth [26].

Adipose Tissue

Adipose tissue is unique tissues required for physiological process, and storing the energy for the body. It composed from adipocytes that considered peerless kind of cells. The fats are stored and transformed to triglycerides in adipocytes, when the energy is required the free fatty acids and glycerol are released from stored triglycerides in adipocytes after hydrolyzation of triglycerides by lipases, then they moved to the mitochondria of tissues, and oxidized to yield energy [27].

It was noted that adipose tissue has a main relationship with insulin sensitivity. There were several kinds of adipose tissue hormones, representing adipocykines, such as leptin and adiponectin, which may vary in dissimilar conditions, involving metabolic disparities, DMII, or infectious diseases. Therefore, an important function of adipose tissue was detected for keeping

the glucose level constant in the blood as numerous locations in the body stimulated with adipose tissues [28]. Two kinds of adipose tissue were described in the human body, white adipose tissue (WAT) and brown adipose tissue (BAT). Up to 20% and 25% of body weight in men and skin respectively composed from WAT. In immature form, the WAT cell consists of single big thread of fat, after maturation it turns into a tinny film at the margin genetic, and the white area is maintained for transformation of triglycerides to free fatty acids for energy storage [29].

Regarding with BAT, it is an extremely oxidized tissue that composed from various fat cells with mitochondria [30]. Mammals exclusively the species that characterized by a state of hibernation have BAT, in addition to humans mostly the neonates own abundant amount of BAT. Its principal physiology is body warmness in animals or neonates**.** The brown color is attributed to brown fat cells that include huge numbers of mitochondria which comprise iron, it also include numerous slight droplets on the contrary to white adipocytes (fat cells), which include a single fat droplet. The BAT involves more oxygen requirements than utmost tissues, therefor it comprise further blood capillaries than white fat [31]. The kinds of adipose tissue are exhibited in (Figure 3).

Adipokines

They are polypeptide cytokines that are produced from adipose tissue in a controlled system. Although certain of these cytokines are secreted by fat cells, molecules such as tumor necrosis factor (TNF) or interleukin-6 (IL-6) are also released from adipose tissue at higher levels [33]. Leptin was the first adipokine identified in 1994, a novel figure of adipokines was described such as visfatin, adiponectin, apelin, resistin, chemerin, omentin, and other adipokines from that date, and a novel period was marked in the research of WAT. Adipokines are contributed in a numerous of body physiological processes comprising glucose and fat metabolism, the controlling of energy and nutrition, and thermogenesis [34]. They control significant body functions such as insulin releasing and sensitivity, satiety and appetite, energy yielding and consuming, the blood vessels coating physiology, inflammation and blood pressure, and others. It was found that adipokines have relationship with blood sugar and lipid metabolism, obesity, and atherosclerosis [35]. Several of the physiological practices controlled by adipokines are shown in (Figure 4).

Adipokines have adjacent relationship with DM and accompanying consequences, so there is an extent close connection between keeping general energy balance and adipokines. On the other hand, it was noted the association between DM and numerous pathogenic conditions, representing sepsis, obesity, and non-alcoholic fatty liver disease, thus pathologically diffused adipokines may be useful as a biomarker for detecting DM and forecasting diabetes danger [37] as displayed in (Figure 5).

The first adipocaine discovered was leptin in 1994, and from that time a new era was announced in the study of WAT, and a new number of adipocaine was discovered, such as adiponectin, chemerin, visfatin, resistin, omentin, apelin, and other adipokines. Adipokines are involved in a number of bodily functions including energy and nutrition regulation, glucose

and fat metabolism, and thermogenesis [39].

Adipose Tissue Hormones Chemerin Hormone

The chemerin hormone is one of the proteins that were newly revealed to be adipokines. It composed from 163 amino acids as a prochemerin that considered an inactive form, and it is changed to active chemerin under the effect of a serine protease, which composed from146 amino acids and has a molecular weight of 16 kDa [40]. It was identified as a gene in 1997, documented in 2007, and described firstly in skin illnesses before psoriasis. Its origin is WAT, and it was detected in elevated levels in the liver, but its reduced level was appeared in the skeleton, heart, lungs, pancreas, kidneys, and ovaries [41]. It has relationship with several illnesses especially cardiovascular diseases. The chemerin receptor transcripts are originated mainly in the lungs, lymph nodes, liver, pituitary gland, spleen, placenta, and also in synovial fluid accumulation was not presented in serum leukocyte accumulations in persons suffer from osteoarthritis [42]. It plays a role in numerous metabolic and non-metabolic physiological processes that may clarify its association with healthiness and illness. However, the liver is an origin of chemerin yielding because its higher level was found in hepatic venous blood samples [43].

Function of Chemerin

Chemerin is characterized by the existence of numerous isomeric formula of its isoform, therefore comprehension of its mechanism of action is very complicated, and it's utilizing falls under tumor detection. It can contribute with the controlling of adipocytes as well as with the controlling of the insulin pathway, and has relationship with metabolism of glycogen [44]. It also has a role in different physiological processes such as cell differentiation, inflammation, and psoriasis skin illnesses. The conditions such as fever, obesity, and exposure to infrared radiation lead to elevated Chemerin's level, also many inflammatory diseases such as chronic pancreatitis, liver illness, ulcerative colitis, and polycystic ovary syndrome cause increasing in the level of chemerin [45]. Several physiologic processes of chemerin determined in (Figure 6).

Chemerin and Diabetes Mellitus

Diabetes is one of the supreme chronic illnesses in nearly all adjacent nations. It happens due to an abnormality in the production of insulin from the beta cells of the pancreas, or in the action of insulin, or both. Glucose metabolism has been associated with complicated group of prominent risk factors that lead to insulin resistance (IR) and what follows the increase in global distribution of DM; the examples of factors are obesity, older age, and lack of physical exercises. The DM is a risk factor for coronary arteries illnesses, and one of the chief outcomes of DM is diabetic nephropathy which often leads to the development of the chronic renal failure condition [46,47].

Chemerin has a significant relationship with IR and glucose metabolism. Taking into consideration that adipose tissue at this period is effective endicrine glands that release several inflammatory adipokines such as leptin, visfatin, chemerin, and others. These adipokines interfere with cellular metabolism of glucose and fats, insulin sensitivity, the inflammatory mechanism, and others [48].

Chemerin contribute to glucose homeostasis because it promotes adipocytes to insulin-dependent absorption of glucose. There is still a question mark about relationship between chemerin and IR as to whether the increasing of chemerin levels leads to IR or an ingredient association with IR. Research works have indicated that IR-associated hyperinsulinemia can control chemerin presentation in obesity, adipose tissue, and defects including diabetic metabolic syndrome. The serum level of chemerin was raised in obese individuals as well as patients suffer from IR and infections [49]. Investigations applied on persons suffer from obesity, particularly in the DMII group, it was found a significant variation in chemerin levels regarding with body mass index among individuals suffer from overweight and obesity. There was a positive relationship between serum's level of chemerin and body mass index, due to great impact of chemerin on obesity. A paper also demonstrated that the diabetic women have prominently high level of chemerin in comparison with women did not suffer from diabetes, additionally the diabetic group characterized by lower level of chemerin in comparison with group that involve women had diabetes and high blood [50]. Research illustrated that elevated level of serum chemerin had relationship with obesity, development of IR and DMII, as chemerin can result IR in persons with obesity and DMII patients and may be employed to evaluate the dangerous of heart disease and atherosclerosis of blood vessels, the serum's level of chemerin was varied prominently between thin and obese persons, as the blood sugar versus serum chemerin significantly and statistically positively correlated [51].

Adiponectin

It is hormone produced by adipose tissue cells (and also from the placenta during pregnancy) into the bloodstream. It is a polypeptide protein composed from 244 amino acids that controls the glucose level in the blood. It has four area sections of adiponectin (the first is a small signal sequence directing releasing of the hormone external the cell; the second is a small section of changeable dimension in diverse species; the third is a 65-amino acid section similar to collagen proteins; and the fourth is the spherical shape). It has been observed that the three-dimensional assembly of the spherical area is identical to the TNF overall, even though the disparate protein sequence [52].

It was detected in 1995 as extremely displayed in mice adipose cells and in 2007 it was recognized as a transcript greatly displayed in adipose progenitor cells (fat cell precursors). It controls numerous metabolic functions, involving controlling of blood glucose and oxidation of fatty acids [53].

According to the results of investigations, the adiponectin is inversely proportional to body mass index in obese individuals. The level of adiponectin rises during caloric limitation. It represents about 0.01% of blood protein, when it released to the blood. The female's blood has elevated level of adiponectin than males and diabetic patients have lower level in comparison with non-diabetes. An important higher level was reported in the circulatory system of persons suffer from weight loss [54].

Adiponectin promotes synaptic activity and memory in the brain. Decreased cognitive activity has been seen in individuals with slight adiponectin level. Research carried by Abdulsalam Alsamarrai presented that coronary

vascular disease occur more likely in persons have reduced levels of adiponectin as a result of complication of IR and elevated lipid levels [55).

Adiponectin and Diabetes Mellitus

Obesity is commonly caused by ineffectual lifestyle, the number of people suffering from overweight and obesity exceeds 1.4 billion and 500 million respectively according to the World Health Organization. Therefore, obesity is considered a risk factor for diabetes, hence the excess in the mortality rate in people with advanced ages [56]. Diabetes is categorized by increase of glucose in the blood, which is one of the risky conditions that affect other organs, such as the eyes, nerves, blood, and kidneys, and that nearby 90% of diabetic patients represent persons suffer from DMII diabetes [57].

Adipose tissue produces numerous proteins, including adiponectin, which it effective in controlling glucose tolerance, raising fat metabolism, regulating insulin sensitivity, and moderating homeostasis to prevent occurrence of diabetes. The impact of adiponectin on insulin sensitivity was first clarified in mice [58].

It was found that the adiponectin level in plasma have negatively correlated with the evolution of IR and DM, as it was shown that a dose of adiponectin when administrated to diabetic rats result in a prominent diminish in sugar levels of blood [59]. It was improved that adiponectin has insulinogenic features because it represents a key controller of glucose and lipid homeostasis, so it seems that the development of DMII may be related with decreased adiponectin levels, and research works have displayed that increasing of adiponectin levels is preventive feature regarding with lowering the risk of DMII evolution [60], and there was a relationship between DMII and cardiovascular complications as a result of decreased adiponectin levels and risk factors. The investigator of trial exhibited that the obesity and IR are correlated with decreased levels of adiponectin, and that treatment of diabetic patients with adiponectin may diminish IR and maintain normal glucose level in the blood, and adiponectin may be a novel indicator for metabolic regulation in diabetic patients, suggesting the use of adiponectin as therapeutic substance in the future [61].

The level of adiponectin was lower in obese and DMII in comparison with healthy persons. It is recognized that people suffers from obesity and diabetes at the same time, as well as the obesity and an raising in fat cells are the main causes of tissue resistance to insulin. Moreover, fat cells work as an endocrine gland responsible for the production of several hormones that have a main impact on the development of obesity into diabetes in obese peoples. The recently detected hormone adiponectin has a property that when it presents in large quantities the sugar percentage reduces, and in this case, it differs from other hormones of the adipose tissue [62]. Several papers also demonstrated that patients with DMII have lower level of adiponectin, in addition to its feature as an anti-inflammatory, and its association with a trouble of blood lipids. Higher risk of gestational diabetes evolution has relationship with decreased level of adiponectin, and women with gestational diabetes have raised IR than healthy women; (Figure 7) clarifies the association of adipose tissue with pancreatic cell [63].

Resistin

It is produced by adipose tissue and was

detected for the first time in 2001. It is termed resistin because it was primarily believed to be related with the development of IR. Its production is controlled during the differentiation of fat cells and fat deposition. Obese human and mice produce bulky amounts of resistin in comparison with thin individuals. Its levels are linked with the liver illnesses and amount of body mass index. Increase in the level of resistin has relationship with high levels of both glucose and fat; therefore, its level reduces obviously when a person loses weight [64].

Resistin has 12.5 KDa molecular weight. It is a peptide has amino acid cysteine terminal. It is one of the groups of proteins rich in cysteine. It presents in three formulas as a monomer, a trimer, and a hexamer, and the molecule is the lowest in weight. It is the most active and the hormone receptor is termed decorin that situated on the surfaces of cells producing adipose tissue [65].

Visfatin Hormone

It is a recently described hormone that is created and produced principally in WAT. It is a polypeptide of 491 amino acids and is produced solely from visceral adipose tissue. It has significant role in diabetes, obesity, and lipid defects because it has currently been confused in occurrence of IR and naked insulin-mimetic impact through attachment to the insulin-1 receptor [66]. It has been established that glucose metabolism disturbance occur in the total body when there is a deficiency of the hormone phosphasate that may damage the chief adipose tissue activities and metabolic pathways. Therefore, visfatin may attach non-competitively to the insulin receptor at a location dissimilar from insulin and it causes hypoglycemia than insulin by decreasing glucose releasing from liver cells and encouraging glucose employment in fat and muscle cells [67].

The hormone phosphatases were formerly defined as being secreted especially by visceral adipose tissue and entering into macrophages. They were also detected in white blood cells, chiefly in granulocytes, and in numerous other cells including lungs, skeletal muscles, heart muscle cells, spleen, liver, brain cells, testes, kidneys, and pancreatic cells [68].

Relationship of Visfatin and Resistin with Diabetes Mellitus

Several investigations have studied the correlation between phosphatases levels and persons suffer from DMI and DMII. Pathophysiology of DMII has significant relationship with IR and obesity. High levels of phosphatases are IR character in obese diabetics [69].

The result of numerous research works revealed that the levels of the hormone visfatin was increased in individuals with DMII in comparison with non-affected persons, as clarified in a Chinese work when the visfatin levels was higher than the normal level in diabetic patients. Another research performed in Tikrit reported that obese and diabetic people have elevated visfatin levels [70]. While a paper illustrated that females with gestational diabetes have declined levels of visfatin, and this may demonstrate that the hormone has correlation with occurrence of gestational diabetes [71].

Regarding with hormone resistin, its levels were positively linked with IR especially with extreme IR. Researches demonstrated that there is a statistical manifested relation between serum levels of resistin, IR and obesity, as the results of Al-Shamma showed that resistin level was

above than the normal in individuals have obesity and diabetes in comparison with healthy persons [72]. Based on the information mentioned in this review, it has been shown that diabetes has a close correlation with an increase in the level of some adipose tissue hormones and also with a decrease in the levels of other hormones of the same tissue.

CONFLICT OF INTEREST

No conflict of interest to be declared by the authors.

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FIGURES

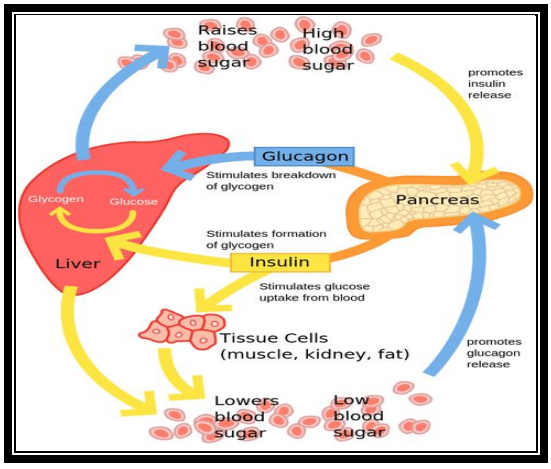

Figure 1: The role of hormones to regulate the glucose level [19]

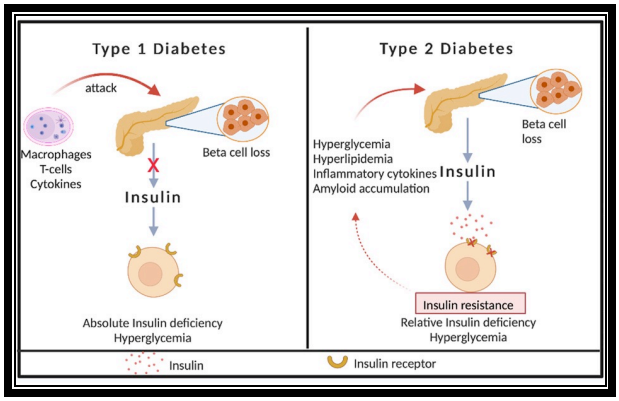

Figure 2: The difference among type 1 and type 2 diabetes [24]

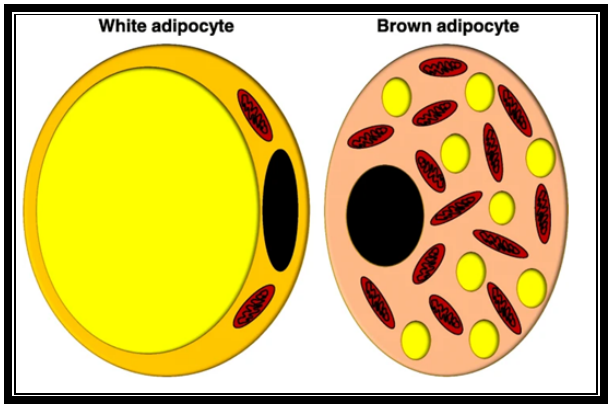

Figure 3: The types of adipose tissue [32]

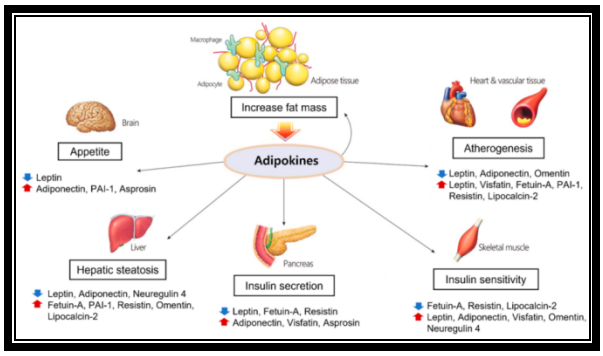

Figure 4: Some physiological processes regulated by adipokines [36]

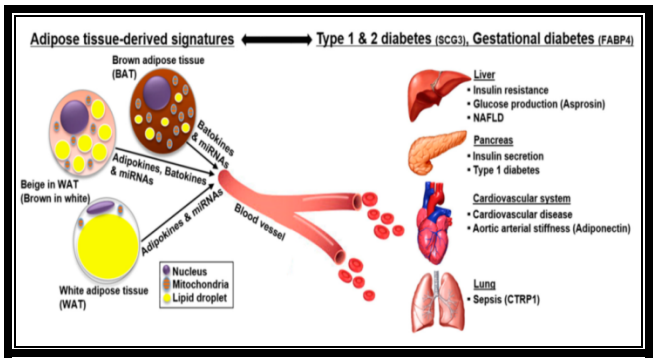

Figure 5: The role of adipokines in diabetes and its related pathogenic phenomena [38]

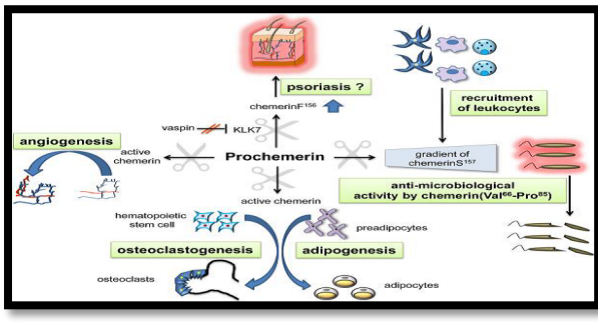

Figure 6: Chemerin's entry into a variety of functions [42]

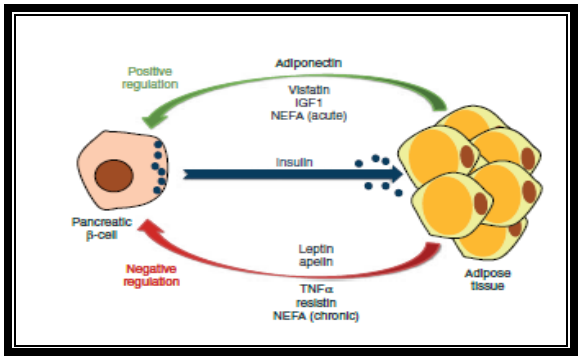

Figure 7: Relationship between adipose tissue and pancreatic cell [58]