Role of obesity in development of insulin resistance: A review

Fathi Salim Hudoud
department of Biology/ Faculty of Education Tarhuna/ Azzaytuna University

الملخص :

العلاقة بين السمنة ومقاومة الأنسولين مازالت غير واضحة وغير مفهومة بشكل جيد. و تتمثل هذه العلاقة في المخاطر الصحية للسمنة المرضية و مضاعفاتها مثل مقاومة الأنسولين في جميع أنحاء العالم. كما تعتبر السمنة ومقاومة الأنسولين عاملين رئيسيين لتطور داء السكري من النوع الثاني. إن النشوء المرضي من مقاومة الأنسولين الناجم عن السمنة لا يزال غامض في العديد من الجوانب. إن المقالة الحالية تهدف لوصف العلاقة بين الدهون والسمنة ومقاومة الأنسولين مستندة على الدراسات السابقة والتجارب الطبية، لكي توضح وبشكل دقيق الآليات الجزيئية المعقدة التي لها الدور الرئيسي في تطور هذه العلاقة، وسيتم التركيز على التغييرات الرئيسية التي تحدث في أيض الجلوكوز والدهون المحفزة بفعل الأنسولين. أيضاً، التهاب الأنسجة الدهنية، بالإضافة إلى التغيرات التي تحدث في الأعضاء الأخرى ذات العلاقة مثل (الكبد والعضلات) و التي أخذت تأثيراتها بعين الاعتبار على تطور متلازمة مقاومة الأنسولين. هذه المقالة ستناقش أيضاً الآليات المحتملة التي يعتقد بأنها تربط السمنة ومتلازمة مقاومة الأنسولين بالفسيولوجية المرضية في تطور داء السكري من النوع الثاني.

الكلمات المفتاحية: السمنة ومقاومة الأنسولين والأنسولين والنسيج الدهني وداء السكري.

Abstract:

The relationship between obesity and insulin resistance is widely accepted. This relationship represents several major health hazards including morbid obesity and insulin resistance complications worldwide. The obesity and insulin resistance are two major risk factors for the development of Type 2 diabetes mellitus (T2DM). The pathogenesis of obesity-induced insulin resistance is still obscure in many aspects. The present review is intended to describe the

correlation between lipids, obesity and insulin resistance based on current literature and prospective cohort studies and clinical trials, in order to elucidate involved molecular mechanisms in depth. Specifically, the focus will be on the major changes in glucose and lipid metabolism induced by insulin, also, adipose tissue inflammation as predominantly driven by adipose tissue macrophages, but also related alterations in other organs (liver, muscle) have to be considered and their effect on the insulin resistance development. This review will also discuss some of the potential mechanisms that are thought to link obesity and insulin resistance with the major pathophysiological precursor of T2DM.

Keywords: obesity, insulin resistance, insulin, adipose tissue and diabetes mellitus.

1. Introduction:

Frederick Banting and Charles Best are credited with the discovery of insulin in 1921 while working at the University of Toronto, later receiving a Nobel Prize in 1923. For nearly 100 years, the regulation of insulin secretion and its actions on peripheral tissues has been at the forefront of cell biology and physiological research (Silva Rosa *et. al*., 2020). Insulin secretion and insulin sensitivity are regulated by pancreatic β-cells in a very definite manner to maintain homeostatic concentrations of plasma glucose in healthy individuals (Khalid *et. al*., 2021). Under physiological conditions, insulin stimulates the use of metabolic substrates in multiple tissues including heart, skeletal muscle, liver, and adipose tissue (Ormazabal *et. al*., 2021). Insulin is the main responsible for controlling cell nutrients uptake, usage and storage; it increases blood sugar absorption, mainly in muscular and adipose tissues, where it promotes its conversion into glycogen and triglycerides, respectively, while inhibiting its degradation. In addition, in the liver, it inhibits gluconeogenesis, glycogenolysis and ketogenesis, and promotes protein synthesis, mainly in muscular tissue (Gutiérrez-Rodelo *et. al*., 2017). Insulin stimulates glucose uptake into tissues, and its ability to do so varies greatly among individual persons. In insulin resistance, tissues have a diminished ability to respond to the action of insulin. To compensate for resistance, the pancreas secretes more insulin. Insulin-resistant persons, therefore, have high plasma insulin levels. The syndrome can be defined as a cluster of abnormalities, including obesity, hypertension, dyslipidemia and type 2 diabetes (T2DM), that are associated with insulin resistance and compensatory hyperinsulinemia. However, a cause and-effect

relationship between insulin resistance, these diseases and the mechanisms through which insulin resistance influences their development has yet to be conclusively demonstrated (Rao, 2001). A brief introduction to the concept of insulin resistance is necessary in order to understand these observations. HP Himsworth, working at University College Hospital, London, UK, in the 1930s, was the first clearly to differentiate between the concepts of insulin secretion and insulin sensitivity. He found that some individuals with diabetes (typically lean individuals with an early onset of the disease) responded rapidly to an injection of insulin with a fall in blood glucose concentration. Other individuals, typically more obese and with later onset diabetes, were resistant to the blood glucose-lowering effect of insulin (Frayn, 2001).

Insulin resistance (IR) is a pathological condition in which target tissues (primarily skeletal muscle, liver, and adipose tissue) have an impaired biological response to insulin stimulation (Li *et. al*., 2019). Insulin resistance is significant in public health. Its persistence over time and its tendency to progress clinically are the first stages of the development of Type 2 diabetes (Cordoba‐Rodriguez *et. al*., 2022). Approximately 85-90% of diabetics have T2DM characterized by insulin resistance, meaning circulating insulin cannot bind to receptors thereby limiting downstream biochemical functions, i.e., glycolysis, glycogenesis, lipogenesis, and protein anabolism. Mechanistically, insulin resistance is potentially linked to inflammatory response and oxidative stress (Al-Muzafar *et. al*., 2021). Currently, the fluctuations of IR prevalence in children and adolescents range from 2.2% in those with a healthy weight to 10.8% in those with obesity. Insulin resistance is recognized as a central component of metabolic syndrome (MetS), characterized by central obesity and, at least, two of the following components: high blood pressure (BP), high triglycerides (TG), reduced HDL cholesterol (HDL-C), and elevated fasting plasma glucose (FPG) (Cordoba‐Rodriguez *et. al*., 2022). Insulin resistance is also associated with obesity as well as hypertension, coronary artery disease, and dyslipidemias. Moreover, IR is a feature of a number of syndromes related to abnormal reproductive endocrinology, such as polycystic ovarian syndrome and premature adrenarche. Therefore, it is of great interest to quantify insulin sensitivity and resistance in humans to investigate the pathophysiology and epidemiology of major public health problems and to follow the clinical course of patients on various therapeutic regimens (Baban *et. al*., 2010).

The signal transduction mechanism for glucose-stimulated insulin secretion is unique because it requires the intracellular metabolism of glucose, in opposition to the action of most extracellular stimuli, whose signaling pathway mechanisms normally begin with binding to a plasma membrane receptor, followed by the subsequent trigger of intracellular secondary signals. Glucose is internalized by the pancreatic β-cell through the plasma membrane transporter GLUT2. Once in the β-cell cytosol, glucose undergoes glycolysis to generate ATP, NADH and pyruvate. NADH can be shuttled into the mitochondria to produce ATP at the electron transport chain. Pyruvate is directly transported into the mitochondria, where it is metabolize by the tricarboxylic acid (TCA) cycle to generate NADH and FADH equivalents that produce additional ATP. The increase in cytosolic ATP levels, or better the rise of the ATP/ADP ratio, has been demonstrated to be an essential requirement for the trigger of insulin exocytosis. The increase in the ATP/ADP ratio causes the closure of ATP-sensitive K^+-channel, which depolarizes the β-cell plasma membrane, with a subsequent opening of voltage sensitive L-type Ca^{2+}-channels, and the influx of extracellular Ca^{2+}. The rise in intracellular cytosolic Ca^{2+} concentration acts as a major signal to trigger insulin exocytosis (Alarcón, 2002). Insulin acts through a tyrosine kinase receptor. Insulin binding activates the receptor, which phosphorylates a number of intracellular substrates and initiates the biological response to insulin. The main signalling pathways utilized by the insulin receptor (IR) are the phosphatidyl-inositol (PI) *3*-kinase pathway and the RasIMAP kinase pathway. Insulin receptor substrates (IRSs) play important roles in both processes. Activation of serine/threonine kinases through the PI3-K pathway leads to several of insulin's effects, including the stimulation of glycogen synthesis and glucose transport, and the inhibition of lipolysis and gene expression. The RasIMAP kinase pathway can be activated by insulin through the formation of complexes between the exchange factor SOS and GRB2. Moreover, PI3-kinase-independent pathways have been implicated in some insulin responses, including glucose transport (Nakae *et. al*., 2001).

Adipose tissue is the main energy source in the body, where resident macrophages secrete numerous proteins (Al-Muzafar *et. al*., 2021). Macrophages in fatty tissues are the main cause of inflammatory marker production, i.e., interleukin-6 (IL-6) and tumor necrotic factor (TNFα). During normal homeostasis, these adipokines regulate energy metabolism and maintain both energy expenditure and intake, in addition to insulin sensitivity. However, during

disease pathology, e.g., diabetes and insulin resistance, chronic low-grade inflammation is generated by these molecules. Furthermore, obesity is linked to inflammation in white adipose tissue (WAT), culminating in glucose intolerance, insulin resistance, and diabetes (Al-Muzafar *et. al*., 2021). Macrophage accumulation in adipose tissues in obese patients shares the expression of multiple genes causing adipose tissue inflammation in obesity. Similarly, some genetic modifications such as the glucokinase gene, insulin receptor substrate-I (IRS-I), mitochondrial genes, and so on alter insulin secretion or function, leading to type 2 diabetes (Mukherjee *et. al*., 2013).

During IR, the body's compensatory release of excess insulin to maintain blood sugar stability causes hyperinsulinemia that can progress to type 2 diabetes mellitus (T2D). Prospective studies have highlighted the importance of IR in the pathogenesis of T2D and suggest that IR is the best predictor of future T2D diagnosis. IR and obesity are connected with chronic inflammation in metabolic tissues such as adipose tissue and the liver (Li *et. al*., 2019).

2. Insulin Signaling Pathway and Insulin Resistance

Insulin is a peptide hormone released by islets of pancreatic beta cells. This hormone has significant effects on metabolic pathways, and thereby, it is critical for normal homeostasis of the body metabolism. Insulin acts via complicated sequential steps known as insulin signal transduction (IST) which starts by binding insulin to the α chain of insulin receptor (IR), which is a transmembrane tyrosine kinase composed of two chains as α and β (Yaribeygi *et. al*., 2021). This binding activates receptor autophosphorylation, which triggers a downstream signaling cascade through the phosphorylation of tyrosine residues of the insulin receptor substrates, IRS (IRS-1 or IRS-2), followed by phosphorylation of phosphatidylinositol 3-kinase (PI3K), phosphoinositide dependent kinase-1, Akt (Akt1 and Akt2), protein kinase C (PKC) and mammalian target of rapamycin (mTOR), as well as ribosomal protein S6 kinase beta 1 (S6K1) (Ormazabal *et. al*., 2018). These events provide a suitable binding site for IRS-1 (insulin receptor substrate-1) and activate it, which links to PI3K (phosphoinositide 3-kinase) and catalyzes the conversion of PIP2 (phosphatidylinositol 4,5-bisphosphate) to PIP3 (phosphatidylinositol 3,4,5-trisphosphate). In addition, PIP3 is itself a potent activator for PKB (protein kinase B, also known as Akt), which facilitates glucose entering into the cells by localization of GLUT-4 (glucose transporter type 4). Any defect in these pathways may lead to impaired insulin-dependent glucose entering the cells,

known as insulin resistance in adipocytes and skeletal muscles (Yaribeygi *et. al*., 2021).

Adipose tissue is critically important in influencing both glucose and lipid metabolism by releasing adipokines, proinflammatory cytokines, and free fatty acids (FFAs). Moreover adipose tissue is an insulin-responsive tissue, whereby insulin prompts the storage of triglycerides by such methods as stimulating the differentiation of preadipocytes to adipocytes, inhibiting lipolysis, and increasing the uptake of fatty acids and glucose. Similar to the mechanisms in muscle, insulin exerts its biological effects via the IRS-PI3K-Akt2-GLUT4 signaling pathways. However, both IRS1 and IRS2 are involved in adipocyte insulin signaling, in contrast with hepatocytes, where IRS1 has a more significant role in glucose homeostasis as compared to IRS2. Also, in a similar fashion as the skeletal muscle, Rab GAP TBC1D is expressed in adipocytes, though in lower levels, and contributes to the regulation of insulin signaling through vesicle trafficking and translocation of GLUT4 to the plasma membrane. As mentioned above, a major role of insulin in adipose tissue is to promote the suppression of lipolysis. Lipolysis is a process where lipid triglycerides are hydrolyzed into glycerol and fatty acids and used to provide stored energy during fasting or exercise (Silva Rosa *et. al*., 2020). Insulin signaling enhances lipid storage in adipocytes by two mechanisms, by stimulating triacylglycerol synthesis and by inhibiting lipolysis. Triglycerides are stored in lipid droplets, which contain lipid droplet proteins, including perilipin. The inhibition of lipolysis occurs through the reduction of cAMP levels and the inhibition of protein kinase A (PKA) activity, hence attenuating HSL (hormone-sensitive lipase) phosphorylation and perilipin, causing a decline in the lipolysis rate (Ormazabal *et. al*., 2018). The mechanism that regulates lipolysis is highly dependent on the protein kinase A (PKA) signaling pathway. PKA phosphorylates the hormone-sensitive lipase (HSL) and perilipin (PLIN) to promote lipolysis, where phosphodiesterase 3B (PDE3B) inhibits PKA by degrading cAMP (required for PKA activation). Consequently, PDE3B impedes the action of the pro-lipolytic hormones HSL and PLIN, inhibiting lipolysis. In a fed state, insulin activates Akt2, which activates PDE3 and inhibits PKA, via unknown mechanism, thereby suppressing lipolysis. However, with adipose tissue insulin resistance, there is a decrease in Akt2 phosphorylation, resulting in sustained lipolysis activation. As a result, non-esterified fatty acid (NEFA) production and circulating fatty acids are

increased, which are taken up by the liver and muscle, contributing to ectopic lipid accumulation in both tissues (Silva Rosa *et. al*., 2020).

Insulin rapidly increases glucose transport through the regulated trafficking of the glucose transporter, GLUT4, from intracellular stores to the cell surface in muscle and adipose cells. This is mediated by the phosphorylation of proteins that regulate GLUT4 trafficking, such as TBC1D4/AS160. GLUT4 translocation is thought to be the rate-limiting step for insulin-dependent glucose utilization in these tissues. Once glucose enters muscle and adipose cells, it is rapidly phosphorylated, generating glucose 6-phosphate (G6P). The subsequent metabolism of G6P is coordinated by a series of allosteric and covalent regulatory steps. For example, activation of glycogen synthase and ATP citrate lyase promotes glucose storage into glycogen and lipid, respectively. A recent analysis of the insulin-regulated phosphorylation network in adipocytes identified dozens of metabolic enzymes that undergo insulin-regulated phosphorylation , and these likely play a key role in choreographing the ultimate metabolism of glucose in a manner that is more complex than originally anticipated (Fazakerley *et. al.*, 2019).

In the liver, insulin inhibits glucose production and release, by blocking gluconeogenesis and glycogenolysis through the regulation of expression of phosphoenolpyruvate carboxylase (PEPCK). Furthermore, insulin can stimulate glycogen synthesis through Akt2 activation, glycogen synthase kinase 3 (GSK3) inhibition, and glycogen synthase (GS) activation via desphosphorylation of serine residues at both the NH2 and COOH-terminals of these proteins (Ormazabal *et. al*., 2018). In the liver, insulin also promotes lipogenesis, by stimulating the expression of proteins implicated in the de novo lipogenesis like SREBP-1c, FAS or ACC. However, these transcriptional effects require time and can be detected only 8 h after the insulin treatment. Therefore, insulin favors lipogenesis mainly by acting on the enzyme activity, through phosphorylation/ dephosphorylation mechanisms. Mechanistically, the expression and activity of neoglucogenic enzymes (PEPCK and G6Pase) is controlled by FOXO1, even in a hyperglycemic context, as the activity of the transcription factor is not inhibited by AKT. The importance of FOXO1 in hepatic insulin resistance was demonstrated using transgenic animals. In fact, the invalidation of the IR specifically in the liver (LIRKO mice) resulted in hepatic insulin resistance. The concomitant invalidation of FOXO1 was sufficient to suppress this insulin resistance (Beaupere *et. al*., 2021).

3. Molecular Pathophysiology of insulin resistance:

The disturbances in insulin pathway are responsible for the development of insulin resistance. Insulin, by the control of numerous enzymes and kinases during feeding and fasting periods, is a major regulator of energy homeostasis. Thereby, the decline of insulin capability to elevate the uptake of glucose by adipose tissue, liver, and muscle, contributes to the development of insulin resistance. It was found that inhibitory effect of insulin on lipolysis is diminished during decreased insulin sensitivity. As a result, the level of circulating free fatty acids (FFAs) increases. FFAs may be taken up by liver, muscles, and pancreas. Consequently, non-adipose tissue insulin resistance is developed as a result of lipotoxicity. Several molecular pathways have been proposed as playing important roles in this disorder. It was demonstrated that FFAs and related metabolites including ceramides, acyl-CoA, diacyloglycerol via acting on numerous protein kinases, i.e., nuclear factor-κB (NF-κB) kinase-β [IκB kinase-β (IKK-β)], Jun kinase (JNK), PKC ζ/λ, PKC-θ contribute to the phosphorylation of IRS that in turn attenuate insulin signaling (Szymczak-Pajor and ´Sliwi´nska, 2019). Abnormalities of insulin signalling account for insulin resistance. Insulin mediates its action on target organs through phosphorylation of a transmembrane-spanning tyrosine kinase receptor, the insulin receptor (IR). The binding of insulin to the α subunit of its receptor activates the tyrosine kinase of the β subunit of the receptor, leading to autophosphorylation, as well as tyrosine phosphorylation of several IR substrates (IRS), including IRS-1 and IRS-2. These, in turn, interact with phosphatidylinositol 3-kinase (PI3K). Activation of PI3K stimulates the main downstream effector Akt, a serine/theronine kinase, which stimulates the glucose uptake through the translocation of the major glucose transporter GLUT-4 to the plasma membrane. Abnormalities of the IR function that may contribute to insulin resistance include the defects of receptor structure, number, binding affinity, and/or its signalling capacity. It is noteworthy that hyperglycaemia, accounts for the development of insulin resistance through the generation of reactive oxygen species (ROS), which abrogate insulin-induced tyrosine autophosphorylation of IR. In addition, several mechanisms have been described as responsible for the inhibition of insulin-stimulated tyrosine phosphorylation of IR and the IRS proteins, including proteasome-mediated degradation, phosphatase-mediated dephosphorylation, and kinase-mediated serine/threonine phosphorylation. In particular, phosphorylation of IRS-1 on serine Ser612 causes dissociation of the p85

subunit of PI3-K, inhibiting further signalling. In addition, phosphorylation of IRS-1 on Ser307 results in its dissociation from the IR and triggers proteasome-dependent degradation, also impairing insulin signaling (Mancusi *et. al*., 2020).

Beyond anti-insulin receptor antibodies, the genetic causes of severe insulin resistance include primary insulin signaling defects due to mutations and defects in the INSR gene, and impaired adipocyte development, apoptosis, or function. Advances in genetics have driven progress in the field by allowing us to identify several genes responsible for severe insulin resistance and providing an accurate diagnosis of the related syndrome(s). Despite the rarity of severe insulin resistance syndromes, studying these diseases can provide general insights into the pathophysiological mechanisms of insulin resistance (Angelidi *et. al*., 2021). Insulin resistance is believed to have both genetic and environmental factors implicated in its aetiology. The genetic component seems to be polygenic in nature, and several genes have been suggested as potential candidates. However, several other factors can influence insulin sensitivity, such as obesity, ethnicity, gender, perinatal factors, puberty, sedentary lifestyle and diet (Chiarelli and Marcovecchio, 2008). Insulin resistance may be developed through both genetic and acquired factors. The common genetic defects include mutations and polymorphism of insulin receptors, glucose transporters, and signaling proteins involved in insulin signal transduction. The acquired causes of insulin resistance include obesity, physical inactivity, advanced glycation end products (AGE), excess free fatty acids (FFAs), psychological stress, smoking, alcohol intake, or certain medications. All these factors are linked to constant low-grade inflammatory conditions. The sustained elevation of interleukin-1 beta (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), or FFAs impairs the balance of secretion between inflammatory and anti-inflammatory cytokines. This causes accumulation of unfolded protein, leading to activation of unfolded protein response (UPR), induction of endoplasmic reticulum stress (ER stress), and oxidative stress, which further impairs insulin sensitivity (Khalid *et. al*., 2021).

High fat diet (HFD)-induced obesity initiates inflammatory responses and insulin resistance via several mechanisms. Understanding these pathways is vital if novel therapies are to treat diabetes, metabolic syndrome, and its complications (NAFLD and cardiovascular disorders). One such mechanism involves lipid accumulation that potentially leads to adipocyte demise and increased intestinal lipopolysaccharide (LPS) leakage, thereby activating tissue

inflammatory reactions. Similarly, free fatty acids (FFAs) from HFD and LPS stimulation of tolllike receptors increase cytokine production and ultimately lead to immune cell aggregation (Al-Muzafar *et. al*., 2021).

4. The possible relation between obesity and insulin resistance

Insulin resistance is commonly associated with obesity, non-insulin dependent diabetes mellitus, and essential hypertension (Siddiqui *et. al*., 2013). Obesity represents the major risk factor for the development of insulin resistance in children and adolescents, and insulin resistance/ hyperinsulinemia is believed to be an important link between obesity and the associated metabolic abnormalities and cardiovascular risk (Chiarelli and Marcovecchio, 2008). Insulin resistance is significant in public health. Its persistence over time and its tendency to progress clinically are the first stages of the development of Type 2 diabetes. Currently, the fluctuations of IR prevalence in children and adolescents range from 2.2% in those with a healthy weight to 10.8% in those with obesity. Insulin resistance is recognized as a central component of metabolic syndrome (MetS), characterized by central obesity and, at least, two of the following components: high blood pressure (BP), high triglycerides (TG), reduced HDL cholesterol (HDL-C), and elevated fasting plasma glucose (FPG) (Cordoba‐Rodriguez *et. al*., 2022).

Some studies have pointed out that body mass index is positively associated with IR and inflammation in visceral adipose tissue is a main driver of IR. Closely linked to the epidemic of obesity, the number of adults with diabetes increased from 108 million in 1980 to 422 million in 2014, and this figure is projected to rise to 642 million people by 2040 (Li *et. al*., 2019).

Obesity today, is a major public health problem across the world. The rapid increase in the incidence of obesity and associated co-morbidities presents a major challenge to health care globally (Siddiqui *et. al.*, 2013). Obesity is a condition in which there is excess storage of fat in the body leading to cardiovascular morbidities, insulin resistance and even the development of type 2 diabetes. In obese patients, adipose tissue releases a high amount of non-esterified fatty acids (NEFA), glycerol, hormones, and proinflammatory cytokines. These elements are involved in the development of insulin resistance. When insulin resistance is accompanied by dysfunction of pancreatic islet β-cells, the cells fail to control blood glucose level due to insulin release impairment. These abnormalities in β-cell function cause development of type 2 diabetes. High lipid level in blood has long been associated with type 2 diabetes.

Patients with non-insulin-dependent diabetes mellitus (NIDDM), also known as type 2 diabetes mellitus, sometimes have abnormal lipid profiles (Mukherjee *et. al*., 2013).

Resistance to insulin has a direct link to the changes in lipid profiles in NIDDM, and usually it is associated with higher concentrations of TG, and lower concentrations of HDL. Insulin resistance develops a number of alterations in lipid metabolism and lipoprotein composition, which renders LDL cholesterol and other lipoproteins more pathogenic in patients with type 2 diabetes. Hypertriglyceridemia results in decreased HDL, which is also a main feature of plasma lipid alterations observed in type 2 diabetic patients. The low level of HDL, which exerts anti-atherogenic and antioxidative effects when present in sufficient amounts, is a key feature of NIDDM. Elevation in plasma TG level is observed when HDL level is reduced. This process is mediated by cholesterol ester transfer protein (CETP). Hypertriglyceridemia may be an increased hepatic secretion of very low-density lipoproteins (VLDL) and a delayed clearance of TG-rich lipoproteins, which may mainly be due to increased levels of substrates for TG production, and enhanced free fatty acids (FFA), and glucose levels. The latter could be secondary to decreased activity of lipoprotein lipase (LPL), a key enzyme for lipoprotein-TG. Thus, there is a strong association between type 2 diabetes and dyslipidemia. The prevalence of obesity worldwide and its increasing association with diabetes demand for a mechanistic understanding of obesity-related insulin resistance as a priority to understand this correlation in a defined way (Mukherjee *et. al*., 2013). Obesity is a chronic and multifactorial disease characterized by an increased body weight with excessive fat accumulation, as well as low grade inflammation. This condition is also associated with insulin resistance, type 2 diabetes mellitus (T2DM) and dyslipidemia, characterized by increased serum triglycerides, decreased high-density cells lipoproteins (HDL) cholesterol and increased small dense low-density lipoprotein (LDL) particles. Despite the alarming prevalence of obesity, defining the pathogenic links between insulin resistance and the associated cardiovascular risk is currently poorly understood (Gómez-Hernández *et. al*., 2021). At the cellular level, obesity is not solely a pathology of adipocytes as there are other cell types within adipose tissue that participate as well. In fact, the presence of infiltrating macrophages in adipose tissue makes obesity comparable to a low-grade chronic inflammation with links between adipose cells and the immune system. At present comprehension of these concepts is

essential for a better understanding of the pathophysiological mechanisms of insulin resistance and type 2 diabetes (Abd-elreheem *et. al.*, 2019). Obesity initially develops pro-inflammation starting from metabolic cells (adipocyte, hepatocyte, or myocyte) and eventually recruits immune cells with the release of inflammatory cytokines such as TNF-α, interleukin (IL)-6, and adiponectin. Secretion of leptin, TNF-α, resistin, adiponectin, inducible nitric oxide synthase (iNOS) and an elevated plasma NEFA level gradually leads to obesity-induced inflammation that may interfere with glucose metabolism and insulin sensitivity and produce type 2 diabetes (Mukherjee *et. al*., 2013).

An elevated amount of adipose tissue draining into the portal vein, chemokines, and IL-6 production can induce liver and systemic insulin resistance (Wondmkun, 2020). Adipose tissue is an organ composed of different depots found in several locations throughout the body and differing in developmental, structural and functional features. The four main functions of the adipose tissue are energy storage in the form of TAG, release of free fatty acids (FFA) and glycerol, and the secretion of adipokines and thermoregulation (Beaupere *et. al*., 2021). Adipose tissue stores excess energy in the form of lipids and are thus able to dramatically change in size in accordance with changing metabolic needs. Moreover, studies have shown that fat tissue exerts important endocrine functions which are mediated by a complex network of various soluble factors derived from adipocytes called adipocytokines including tumor necrosis factor a (TNFα), Interleukin (IL-6), leptin, adiponectin and resistin. Some adipokines play a major role in insulin resistance and cardiovascular complications associated with obesity, especially central or visceral obesity (Abd-elreheem *et. al.*, 2019).

Adipose tissue seems to play a key role in the pathogenesis of insulin resistance through several released metabolites, hormones and adipocytokines that can affect different steps in insulin action (Chiarelli and Marcovecchio, 2008). Adipose tissue is now recognised as an important secretory organ, releasing into the circulation many peptides that affect metabolism, including of course the hormone leptin (Frayn, 2001). The discovery of leptin in 1994 has provided a major new piece in the puzzle of obesity, as it has been found that its level was directly related to the quantity of body fat. Leptin is a 16 kDa non-glycosylated protein secreted in direct proportion to adipose tissue mass as well as nutritional status. Plasma leptin concentrations positively correlate with subcutaneous rather than intra-abdominal fat tissue mass. Leptin exerts an

inhibitory effect on food intake and increases energy expenditure through thermogenesis and physical activity. The idea of leptin as an insulin sensitizing hormone and leptin deficiency or resistance as a potential link between obesity and diabetes has been reviewed recently (Abd-elreheem *et. al.*, 2019). Alterations in the production of, or sensitivity to, leptin cause obesity and diabetes in rodents. In humans, insulin resistance is associated with raised plasma leptin concentrations independent of body fat mass. A causal relationship between leptin and insulin sensitivity has been suggested, and this may help explain the pathogenesis of the insulin resistance syndrome. Ob/ob and db/db mice that lack leptin or are leptin resistant, respectively, are profoundly hyperphagic and hypometabolic, leading to an obese phenotype, and they manifest numerous abnormalities, such as type 2 diabetes with severe insulin resistance, hypothermia and cold intolerance, infertility, and decrease in lean (Siddiqui *et. al*., 2013).

Leptin is an adipocytokine that reduces appetite and IR along with improvement of metabolic disturbances associated with T2DM. Increase in tissue sensitivity of insulin by leptin may be due to its action on oxidation of FFAs, leading to decreased FFAs in the circulation. Unlike other adipocytokines, serum levels of adiponectin are decreased in obesity and T2DM. This cytokine has insulin-sensitizing and antiatherogenic actions. In human obesity and T2DM, this adipocytokine has been shown to stimulate FFAs oxidation, and therefore decrease plasma FFAs oxidation, reduce lipid accumulation and increase insulin sensitivity (Genser *et. al*., 2016). Although leptin is perhaps the most potent anorexic hormone that responds directly to nutritional status, states of obesity in both humans and rodents are commonly associated with leptin resistance and high leptin levels. As such, leptin has not proven to be an effective anti-obesity agent in obese patients. However, when administered to mice or to patients with mutations in the leptin gene or lipodystrophy, the hormone not only reverses obesity, but also has profound antidiabetic effects with dramatically improved insulin resistance. This illustrates well the apparent paradox in which insulin resistance can be overcome by administration of an agent that effectively opposes insulin action. Likewise, metformin and other biguanides mimic part of leptin's indirect action in the liver by activating AMP-activated kinase (AMPK), whereas b3 adrenergic agonists can mimic leptin's indirect actions at the adipocyte by increasing lipolysis and fat oxidation. Both agents improve insulin

resistance, even though they act in a manner that is diametrically opposed to the anabolic effects of the hormone (Saltiel, 2012).

Globally, the prevalence of obesity has steadily increased during the past 30 years. Izquierdo *et. al*., in his review article, suggested that obese people have elevated serum levels of leptin as explained by leptin resistance in such individuals. This resistance leads to failure of hunger suppression and increased food intake, which ultimately leads to obesity. Obese individuals are also more likely to develop insulin resistance and have high cholesterol levels, which can lead to development of numerous chronic illnesses. Obesity, leptin resistance and insulin resistance are interrelated. Studies have suggested that hyperinsulinemia can be a potential cause of leptin resistance and hence obesity, eventually leading to metabolic syndrome in such individuals (Kumar et. al., 2020).

The exact relationship between leptin and insulin is not clear and is sometimes controversial. Although insulin is secreted from the pancreatic beta cells rather than from adipocytes, the secretion of both hormones is influenced by overall amount of fat stores as well as by short-term changes in energy balance. Also, insulin receptors are located in the same key hypothalamic areas as leptin receptors. Insulin secretion is stimulated acutely in response to meals, whereas leptin secretion is not (Baban *et. al*., 2010). Leptin may act through receptors located in the CNS, but it may also have a direct action on different tissues. There is a direct relationship between leptin and insulin. The presence of leptin receptors in b cells indicates leptin's involvement in endocrine pancreas function. It is assumed that insulin increases leptin production by adipose tissue, whereas leptin inhibits insulin secretion and insulin gene expression. The suppressive action of leptin on insulin production is regulated both by the autonomous nervous system and directly by influence on leptin receptors in b cells. It can inhibit both basal and glucose-stimulated insulin secretion. The mechanisms of the actions are varied: insulin secretion inhibition may be caused by leptin influence on ATP-dependent potassium channels. It is also believed that leptin antagonises cAMP signalling, and diminishes increases of cellular cAMP levels in response to b cells stimulation, for example by GLP-1. It appears that leptin may antagonise insulin secretion from b cells both through cAMP-dependent protein kinase A (PKA), and protein kinase C (PKC). Leptin may play a role in preventing insulin hypersecretion. The mechanism of this regulation is yet to be fully explained (Tucholski and Otto-Buczkowska, 2011).

Leptin secretion and leptin receptors disturbances have been found in diabetes patients. Leptin induces liver gluconeogenesis, inhibits insulin release from pancreatic b cells, and probably also causes break-down of insulin receptors. Finding a link between the presence of active leptin receptors and an increased number of β-cells would appear to be important for the prospects of diabetes treatment. There are many disagreements concerning leptin's concentration in patients with diabetes. This is because the leptin level depends on many factors. An increased leptin level compared to that found in healthy pregnant women has been found in women with gestational diabetes mellitus (GDM) or glucose intolerance freshly diagnosed during pregnancy. An increased leptin cencentration has also been found in newborn babies of mothers with type 1 diabetes (Tucholski and Otto-Buczkowska, 2011). Studies revealed that our brain receives information from insulin and leptin, the transducer of adiposity signals, and integrates this input with signals from nutrients such as FAs. Thereafter, the brain sends signals to regulate the metabolism of macromolecules and feeding behavior to maintain homeostasis of fuel metabolism and energy stores. Peripheral metabolism of glucose is controlled by both leptin and insulin. Peripheral and brain IRs are very crucial for normal insulin function, even though glucose homeostasis in mice with reduced hepatic IRs is altered by the central administration of insulin. Moreover, hypothalamic IRs function inhibition results in impaired hepatic glucose metabolism and insulin resistance. Interestingly, leptin and insulin both enhance the expression of suppressor of cytokine signals-3 (SOCS-3) and sensitivity to both leptin and insulin is increased in mice with reduced SOCS-3 neuronal expression (Wondmkun, 2020).

Increased plasma free fatty acid concentrations are typically associated with many insulin-resistant states, including obesity and type 2 diabetes mellitus (Shulman, 2000). In the adipose tissue, insulin is normally an anti-lipolytic hormone as it decreases the activity of hormone-sensitive lipase (HSL), which is required to release stored fatty acids. With the development of cellular inflammation and insulin resistance in the fat cell, higher levels of free fatty acids (FFA) can leave the fat cell to enter into the circulation and be taken up by other organs, such as the liver and the skeletal muscles that are unable to safely store large amounts of fat. As described later, this leads to developing insulin resistance in these organs. With increased inflammation in the fat cells, there is also a migration of greater numbers of M1 macrophages into the adipose tissue

with a corresponding release of inflammatory cytokines, such as TNFα, which further increases insulin resistance and lipolysis. In the lean individual, only about 10 % of the adipose tissue mass is composed of macrophages, and those macrophages are primarily in the anti-inflammatory M2 state. In the obese individual up to 50 % of the mass of the adipose tissue may contain macrophages but now in the activated pro-inflammatory M1 state. Theoretically, new healthy fat cells could be generated from stem cells within the adipose tissue. However, that process requires the activation of the gene-transcription factor PPARγ. The activity of this gene-transcription factor is inhibited by inflammatory cytokines, such as TNFα (Sears and Perry, 2015).

Fatty acids, in particular saturated fatty acids, activate macrophage like-cells via the lipopolysaccharide (LPS) receptor Toll-like recptor (TLR). FFA concentrations are elevated in obesity and could directly induce inflammatory responses in macrophages and even adipocytes. FFA activate NF-κB and cytokine production in adipocytes and macrophages and induction of inflammatory signaling is blunted in the absence of functional TLR4. Moreover, mice lacking functional TLR4 are substantially protected from high fat diet-induced insulin resistance. These studies suggest TLR4 on adipocytes and macrophages to be a sensor of elevated FFA concentrations, which initiates inflammatory and thus insulin-desensitizing processes (Zeyda and Stulnig, 2009).

Patients with T2DM and insulin resistance often exhibit signs of impaired metabolism, deposition, and concentration of lipids in the skeletal muscle and blood. An abundance of free FAs in the plasma reduces insulin-regulated glucose metabolism, whereas a low level of lipid in the plasma enhances insulin function in the adipocytes, liver and skeletal muscle cells. Increasing plasma FAs in humans and rodents reduce insulin activation of IRS-1- linked PI-3K activity in skeletal muscle (Wondmkun, 2020). Increased FFAs levels are observed in human obesity and T2DM and are strongly correlated with the level of IR. FFAs have anti-insulin action and are produced during the metabolism of lipids. When reaching insulin-sensitive tissues, increased FFAs levels lead to increased liver glucose production and muscular lipid storage, leading to IR state in T2DM patients. In obesity, which is considered a low-grade inflammatory state, increased circulating levels of FFAs appear to be positively correlated with plasma levels of pro-inflammatory cytokines, which are known to be associated with IR and T2DM (Genser *et. al*., 2016).

Adiponectin is one of the most common cytokines produced by adipose tissue, with an important insulin sensitizing effect associated with anti-atherogenetic properties. Whereas obesity is generally associated with an increased release of metabolites by adipose tissue, levels of adiponectin are inversely related to adiposity. Therefore, reduced levels of this adipocytokine has been implicated in the pathogenesis of insulin resistance and metabolic syndrome. Decreased levels of adiponectin have been detected across tertiles of insulin resistance in children and adolescents, where it is a good predictor of insulin sensitivity, independently of adiposity (Chiarelli and Marcovecchio, 2008). Adiponectin reduces endothelial dysfunction by increasing nitric-oxide synthesis and decreasing the expression of adhesion molecules and also prevents atherosclerosis by inhibiting LDL oxidation. Other adipocytokines, such as Apelin, appear to have antiobesity and antidiabetic actions, because of its possible positive role in energy metabolism and insulin sensitivity (Genser *et. al*., 2016).

Obesity and T2DM are associated with the overproduction of proinflammatory cytokines such as Tumor necrosis factor-α (TNF-α) Interleukin-6 (IL-6). These cytokines are produced by the adipocytes among many other cell types and inhibit insuling signaling which in turn promote IR (Genser *et. al*., 2016). Elevated production of tumour necrosis factor (TNF)-α by adipose tissue decreases sensitivity to insulin and has been detected in several experimental obesity models and obese humans (Hirosumi *et. al*., 2002). TNFα was the first cytokine to be implicated in the pathogenesis of obesity and insulin resistance. Adipose tissue expression of TNFα is increased in obese rodents and humans and positively correlated with adiposity and insulin resistance. Recent studies suggest that macrophages are the major source of TNFα in adipose tissue. Chronic exposure to TNFα induces insulin resistance both in vitro and in vivo. Treatment with neutralizing soluble TNFα receptors improves insulin sensitivity in rodent obesity. Targeted gene deletion of TNFα or its receptors significantly improves insulin sensitivity and circulating FAs in rodent obesity. Several potential mechanisms for TNFα's metabolic effects have been described, including the activation of serine kinases such as JNK and p38 mitogen-activated protein kinase (MAPK) that increase serine phosphorylation of IRS-1 and IRS-2, making them poor substrates for insulin receptor-activating kinases and increasing their degradation. In humans, circulating TNFα levels are increased in obese nondiabetic and T2DM individuals, but the correlation between insulin

resistance and plasma TNFα levels is relatively weak (Qatanani and Lazar, 2007).

Interleukin-6 (IL-6) is another inflammatory cytokine released by adipose tissue and its levels are increased in obesity. IL-6 stimulates the hepatic production of C-reactive protein and this can explain the state of inflammation associated with obesity, and could mediate, at least partially, obesity-related insulin resistance (Chiarelli and Marcovecchio, 2008). Adipose tissue IL-6 expression accounts for 30% of systemic IL-6, and circulating IL-6 concentrations are positively correlated with obesity, impaired glucose tolerance, and insulin resistance. Plasma IL-6 concentrations predict the development of T2DM, and peripheral administration of IL-6 induces hyperlipidemia, hyperglycemia, and insulin resistance in rodents and humans. IL-6 impairs insulin signaling in part by downregulation of IRS and up-regulation of SOCS-3 (Qatanani and Lazar, 2007).

Data based mainly on animal studies also suggest that increased levels of resistin, another molecule produced by adipose tissue, could impair insulin sensitivity (Chiarelli and Marcovecchio, 2008). Several studies support the positive relationship between insulin resistance and elevated plasma resistin levels in obese and type 2 diabetic individuals, whereas other studies have shown contradictory findings. Beside its role in obesity and insulin resistance, resistin is greatly implicated in proinflammatory processes which are causally involved in the development of insulin resistance in both rodents and humans. Resistin regulates the production of key pro-inflammatory cytokines, such as TNF-α and IL6, through the activation of NF-κB signaling pathways in macrophages contributing to profound alterations of peripheral insulin signaling pathways resulting in an insulin-resistant state (Abd-elreheem *et. al*., 2019). The enzyme iNOS is a key inflammatory mediator in obesity and causes insulin resistance in the skeletal muscles. It inhibits secretion of adiponectin from adipocytes and impairs insulin secretion in the liver. Elevated iNOS in blood vessels causes vascular dysfunction in obesity (Mukherjee *et. al*., 2013).

Other cytokines such as IL-1 beta, Resistin, Retinol binding Protein-4, Visfatin, Plasminogen Activator-1 (PAI-1), Monocyte Chemoattractant Protein-1, fibrinogen and angiotensin are increasingly produced by the adipose tissue in obesity and T2DM. These cytokines contribute to inflammation, lipid accumulation and participate to the develoment of endothelial dysfunctions and

therefore myocardial infarction, stroke and cardiomyopathy (Genser *et. al*., 2016).

Studies showed that, in obese animals, hypoxia response in adipose tissue is common. The results of most studies on adipose tissue hypoxia have revealed the presence of a strong association between adipose tissue hypoxia (ATH) and major chronic disorders like obesity pathogenesis. ATH may stimulate cellular mechanisms for leptin elevation, mitochondrial dysfunction, macrophage infiltration, chronic inflammation, adiponectin reduction, ER stress, and adipocyte death in obese individuals. In addition, inhibition of adipogenesis and triglyceride synthesis by hypoxia may be a new mechanism for elevated FAs in the blood during obesity (Wondmkun, 2020).

Ectopic fat deposition, when adipose tissue storage space is insufficient (e.g., metabolically unhealthy obesity), and/or, conversely, extreme lipoatrophy, in which adipose tissue stores are nonexistent, leads to hypoleptinemia, abnormal adiponectin levels, and insulin resistance Adiponectin, an adipokine abundantly expressed in white and brown adipose tissue, is inversely proportional to adipose tissue, especially centrally deposited adipose tissue. Adiponectin exerts a potent insulin sensitizing action through its receptors, AdipoR1 and AdipoR2, which activate AMP-activated protein kinase (AMPK) and peroxisome proliferator activated receptor-α (PPARα) signaling pathways . Decreased adiponectin levels associate with conditions closely linked to insulin resistance, such as type 2 diabetes, hypertension, and cardiovascular disease. The adipokine leptin regulates appetite, body fat mass, metabolism, glucose homeostasis, insulin sensitivity, fatty acid oxidation, and neuroendocrine and reproductive function. Leptin mediates its actions through several signal transduction pathways, including the Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) pathway, involved with energy homeostasis and possibly neuroendocrine function. Several leptin-deficient syndromes or leptin resistance states associate with insulin resistance and diabetes, including severe insulin resistance in lipoatrophic subjects. Since leptin receptor and insulin receptor pathways overlap, e.g., the JAK/STAT3, AMPK, and PI3K pathways, leptin therapy may contribute to the leptin-mediated attenuation of insulin resistance directly, as well as indirectly through CNS or peripheral actions. Systemic inflammation caused by proinflammatory cytokines such as TNF-α and IL-6 is directly correlated to the amount of adipose tissue. In these phenotypically severe insulin resistant syndromes, there is chronic exposure to proinflammatory

mediators, which may interrupt insulin signaling in the β cells of pancreatic islets and also induce insulin resistance in both liver and adipocytes (Angelidi *et. al*., 2021).

White adipocytes store fat, if intake exceeds the needed amount. However, this prolonged state causes hyperplasia and hypertrophy of adipocytes as well as adipose tissue hypoxia. The result of these undesired disturbances is low grade chronic inflammation (sub-inflammation) that accompanies insulin resistance. In this condition, insulin is not able to further stimulate energy stored in adipocytes. The pancreatic β-cells undergo adaptive changes leading to the production and secretion of large amount of insulin creating state of hyperinsulinemia. Hyperinsulinemia triggers the pancreatic β-cells exhaustion resulting in decline of their mass. Finally, when the reduction of the pancreatic β-cells mass up to 60%, T2DM is diagnosed. Overstimulation of pancreatic β-cells in insulin resistant state contributes to the elevated level of Ca^{2+} and overstimulation of insulin secretion. Thus, the excessive Ca^{2+} signaling is involved in death of the pancreatic β-cells (Szymczak-Pajor and ´Sliwi´nska, 2019).

Growing evidence revealed that insulin resistance is also closely related to obesity and coexisting oxidative stress as well as low grade inflammation. Reactive oxygen species (ROS) act as a signaling molecules that activate numerous cellular stress-sensitive pathways, i.e., NF- κB, JNK/SAPK, p38MAPK, and hexosamine, involved in cellular damage and inflammation, both of which are associated with pancreatic β-cells dysfunction, insulin resistance, and diabetices complications (Szymczak-Pajor and ´Sliwi´nska, 2019).

The role of obesity in the pathophysiology of type 2 diabetes and insulin resistance has been attested to in several studies (Mukherjee *et. al*., 2013). Study by Yoshioka *et. al*., (2017) conducted to investigate the therapeutic of *Sasa veitchi* leaf extract (SE) on features of obesity induced by a high-fat diet (HFD), such as hyperglycemia, insulin resistance, and inflammatory response. Four-week-old male ddY mice were freely fed HFD or control normal diet for 12 weeks; half was given SE in addition twice per day in weeks 8-12. Treatment with SE significantly decreased body weight, adipose tissue weight, plasma glucose, insulin, leptin, and tumor necrosis factor α compared with HFD groups, and markedly reduced the impairment of glucose and insulin tolerance in obese mice. The findings of study demonstrated that SE may reduce obesity-induced glucose and insulin tolerance, not only by suppressing inflammatory responses

but also by improving insulin signaling (Yoshioka *et. al*., 2017). Also, study by Clausen *et. al*., (1995) investigated the two aminoacid polymorphisms in codons 513 and 972 of the protein insulin receptor substrate-1 (IRS-1), which is important in cellular insulin action, and associated with changes in insulin sensitivity in a random sample of young healthy adults. Insulin sensitivity and secretion were measured during a combined intravenous glucose and tolbutamide tolerance test in 380 unrelated white subjects aged 18-32. IRS-1 polymorphisms were examined by single-strand conformation polymorphism and verified by restrictionenzyme digestion. Where the results suggest that the codon-972 IRS-1 gene variant may interact with obesity in the pathogenesis of common insulin-resistant disorders (Clausen *et. al*., 1995).

In another study by Weiss *et. al*., (2002) examined the effect of varying degrees of obesity on the prevalence of the metabolic syndrome and its relation to insulin resistance and to C-reactive protein and adiponectin levels in a large, multiethnic, multiracial cohort of children and adolescents. This study administered a standard glucose-tolerance test to 439 obese, 31 overweight, and 20 nonobese children and adolescents. Baseline measurements included blood pressure and plasma lipid, C-reactive protein, and adiponectin levels. Levels of triglycerides, high-density lipoprotein cholesterol, and blood pressure were adjusted for age and sex. The results demonstrated that the prevalence of the metabolic syndrome increased with the severity of obesity and reached 50 percent in severely obese youngsters. Each half-unit increase in the body mass index, converted to a z score, was associated with an increase in the risk of the metabolic syndrome among overweight and obese subjects (odds ratio, 1.55; 95 percent confidence interval, 1.16 to 2.08), as was each unit of increase in insulin resistance as assessed with the homeostatic model (odds ratio, 1.12; 95 percent confidence interval, 1.07 to 1.18 for each additional unit of insulin resistance). The prevalence of the metabolic syndrome increased significantly with increasing insulin resistance (*P* for trend, <0.001) after adjustment for race or ethnic group and the degree of obesity. C-reactive protein levels increased and adiponectin levels decreased with increasing obesity (Weiss *et. al*., 2002).

In addition, study by Sinha *et. al*., (2002) determined the prevalence of impaired glucose tolerance in a multiethnic cohort of 167 obese children and adolescents. All subjects underwent a two-hour oral glucose-tolerance test (1.75 mg of glucose per kilogram of body weight), and glucose, insulin, and C-peptide levels were measured. Fasting levels of proinsulin were obtained, and the ratio of

proinsulin to insulin was calculated. Insulin resistance was estimated by homeostatic model assessment, and beta-cell function was estimated by calculating the ratio between the changes in the insulin level and the glucose level during the first 30 minutes after the ingestion of glucose. Results showed that the impaired glucose tolerance was detected in 25 percent of the 55 obese children (4 to 10 years of age) and 21 percent of the 112 obese adolescents (11 to 18 years of age); silent type 2 diabetes was identified in 4 percent of the obese adolescents. Insulin and C-peptide levels were markedly elevated after the glucose tolerance test in subjects with impaired glucose tolerance. After the body-mass index had been controlled for, insulin resistance was greater in the affected cohort and was the best predictor of impaired glucose tolerance. This study concluded that impaired glucose tolerance is highly prevalent among children and adolescents with severe obesity, irrespective of ethnic group. Impaired oral glucose tolerance was associated with insulin resistance while beta-cell function was still relatively preserved (Sinha *et. al*., 2002).

Additionally, study by Abd-elreheem *et. al*., (2019) aimed to discover the role of leptin, adiponectin and resistin as a link between obesity and insulin resistance type 2 diabetes assessment of their levels in normal weight, obese before and after weight reduction as well as obese diabetic subjects. Forty-five female subjects divided into four groups, 15 subjects with normal weight-as control group (group I), 15 obese subjects (group II), 10 subjects from group II followed a weight reduction regimen for 2 months (group III) and 15 obese diabetic subjects (group VI). Serum insulin, leptin, adiponectin and resistin were measured by ELISA. Lipid profile was measured by a spectrophotometric method. Results of the study showed that the obese and obese diabetic subjects have got higher serum leptin and resistin levels when compared with controls. In contrast, serum adiponectin concentration was significantly lower in obese before diet and obese diabetic subjects when compared to the control group. After weight loss, significant improvement has been observed in all parameters. The findings from bivariate correlation analysis were further explored using multiple linear regression analysis which confirmed that resistin rather than adiponectin and leptin was an important determinant of insulin resistance (Abd-elreheem *et. al*., 2019).

In conclusion, obesity is an epidemic widely, and the rates of insulin resistance in individuals are rising. The correlation of obesity and insulin resistance may lead to Type 2 diabetes development. However, The treatment of

obesity, insulin resistance and related metabolic abnormalities in patients include a comprehensive lifestyle modification plan and careful consideration of medical and/or therapeutical interventions. The prevalence of obesity and insulin resistance are an area of intense scientific interest, accept for further investigation.

References

1. Abd-elreheem, Mohamed T.; Soliman, Ayman S.; Rasheed, Wafaa I.; Jawad, Amira M., and Abd-elreheem, Noha T., The Association between Resistin, Leptin and Adiponectin with Obesity and Type 2 Diabetes Mellitus. *Med. J. Cairo Univ*., 2019, 87(7): 4227-4237.

2. Alarcón, C.; Wicksteed, B.; and Rhodes, C.J. Regulation of the production and secretion of insulin. *AV Diabetol*, 2002, 18: 168-174.

3. Al-Muzafar, H.M.; Alshehri, F.S., and Amin, K.A., The role of pioglitazone in antioxidant, anti-inflammatory, and insulin sensitivity in a high fat-carbohydrate diet-induced rat model of insulin resistance. *Brazilian Journal of Medical and Biological Research*, 2021, 54(8): e10782.

4. Angelidi, Angeliki M.; Filippaios, Andreas; and Mantzoros, Christos S., Severe insulin resistance syndromes. *J Clin Invest*., 2021, 131(4):e142245.

5. Baban, Rayah S.; Kasar, Khawla A.K. and Al-Karawi, Isam N., Fasting glucose to Leptin ratio as a new diagnostic marker in patients with Diabetes mellitus, *Oman Medical Journal*, 2010, 25(4): 269-275.

6. Beaupere, Carine; Liboz, Alexandrine; Fève, Bruno; Blondeau, Bertrand; and Guillemain, Ghislaine, (2021): Molecular mechanisms of Glucocorticoid-induced insulin resistance, *Int. J. Mol. Sci*., 2021, 22, 623.

7. Clausen, Jesper O; Hansen, Torben; Bjorbaek, Christia; Echwald, Soren M; Urhammer, Soren A; Rasmussen, Susanne; Andersen, Carsten B; Hansen, Lars; Almind, Katrine; Winther, Kaj; Haraldsdottir, Johanna; Borch-Johnsen, Knut; and Pedersen, Oluf, Insulin resistance: interactions between obesity and a common variant of insulin receptor substrate-1. *Lancet*, 1995, 346: 397-402.

8. Chiarelli, Francesco; and Marcovecchio, Maria Loredana, Insulin resistance and obesity in childhood, *European Journal of Endocrinology*, 2008, 159, S67-S74.

9. Cordoba‐Rodriguez, Diana Paola; Iglesia, Iris; Gomez‐Bruton, Alejandro; Rodriguez, Gerardo; Casajus, Jose Antonio; Morales‐Devia, Hernan; and Moreno, Luis A., Fat-free/lean body mass in children with insulin resistance or metabolic syndrome: a systematic review and meta-analysis. *BMC Pediatrics*., 2022, 22:58.

10. Fazakerley, Daniel J.; Krycer, James R.; Kearney, Alison L.; Hocking, Samantha L. and James, David E., Muscle and adipose tissue insulin resistance: malady without mechanism?, *Journal of Lipid Research*, 2019, 60:1720-1732.

11. Frayn, Keith N., Adipose tissue and the insulin resistance syndrome. *Proceedings of the Nutrition Society*, 2001, 60, 375.380.

12. Genser, Laurent; Mariolo, James Rossario Casella; Gissey, Lidia Castagneto; Panagiotopoulos, Spyros; and Rubino, Francesco. Obesity, Type 2 Diabetes, and the metabolic syndrome pathophysiologic relationships and guidelines for surgical intervention. *Surg Clin N Am*, 2016, 96, 681-701.

13. Gómez-Hernández, Almudena; de las Heras, Natalia; López-Pastor, Andrea R.; García-Gómez, Gema; Infante-Menéndez, Jorge; González-López, Paula; González-Illanes, Tamara; Lahera, Vicente; Benito, Manuel; and Escribano, Óscar. Severe hepatic insulin resistance induces vascular dysfunction: Improvement by liver-Specific insulin receptor Isoform A Gene therapy in a Murine Diabetic model. *Cells*, 2021, 10, 2035.

14. Gutiérrez-Rodelo, Citlaly; Roura-Guiberna, Adriana; and Olivares-Reyes, Jesús Alberto, Molecular mechanisms of Insulin resistance: An Update. *Gac Med Mex*, 2017, 153:197-209.

15. Hirosumi, Jiro; Tuncman, Gurol; Chang, Lufen; Gorgun, Cem Z.; Uysal, K. Teoman; Maeda, Kazuhisa; Karin, Michael; and Hotamisligil, Gokhan S. A central role for JNK in obesity and insulin resistance, *Nature*, 2002, Vol.420, 353-356.

16. Izquierdo, Andrea G.; Crujeiras, Ana B.; Casanueva, Felipe F. and Carreira, Marcos C. Leptin, Obesity, and Leptin Resistance: Where are we 25 years later?. *Nutrients*, 2019, 8:2704.

17. Khalid, Mariyam; Alkaabi, Juma; Khan, Moien A. B. and Adem, Abdu. Insulin signal transduction perturbations in insulin resistance. *Int. J. Mol*. Sci., 2021, 22, 8590.

18. Kumar, Ratan; Mal, Kheraj; Razaq, Muhammad Khalid; Magsi, Mansoor; Memon, Muhammad Khizar; Memon, Sidra; Afroz, Maham Noor; Siddiqui, Humza F. and

Rizwan, Amber. Association of Leptin With obesity and insulin resistance. *Cureus*, 2020, 12(12): e12178.

19. Li, Jun; Bai, Litao; Wei, Fan; Zhao, Jing; Wang, Danwei; Xiao, Yao; Yan, Weitian; and Wei, Junping. Therapeutic mechanisms of herbal medicines against insulin resistance: A review, *Front. Pharmacol*., 2019, 10:661.

20. Mancusi, Costantino; Izzo, Raffaele; di Gioia, Giuseppe; Losi, Maria Angela; Barbato, Emanuele; and Morisco, Carmine. Insulin resistance the hinge between Hypertension and Type 2 Diabetes. *High Blood Pressure and Cardiovascular Prevention*, 2020, 27:515–526.

21. Mukherjee, Biswajit; Hossain, Chowdhury M.; Mondal, Laboni; Paul, Paramita; and Ghosh, Miltu K. Obesity and insulin resistance: An Abridged molecular correlation. *Lipid Insights*, 2013:6, 1-11.

22. Nakae, Jun; Kido, Yoshiaki; and Accili, Domenico. Tissue-specific insulin resistance in type 2 diabetes: lessons from gene-targeted mice. *Annals of Medicine*, 2001, 33:1, 22-27.

23. Ormazabal, Valeska; Nair, Soumya lekshmi; Elfeky, Omar; Aguayo, Claudio; Salomon, Carlos; and Zuniga, Felipe A. Association between insulin resistance and the development of cardiovascular disease. *Cardiovasc Diabetol*, 2018, 17:122.

24. Qatanani, Mohammed; and Lazar, Mitchell A. Mechanisms of obesity-associated insulin resistance: many choices on the menu, *Genes and development*, 2007, 21:1443-1455.

25. Rao, Goutham, (2001): Insulin Resistance Syndrome. *American Family Physician*, 2001, 63(6): 1159-1163.

26. Saltiel, Alan R. Insulin Resistance in the Defense against Obesity. *Cell Metabolism*, 2012, 15, 798-804.

27. Sears, Barry; and Perry, Mary. The role of fatty acids in insulin resistance. *Lipids in Health and Disease*, 2015, 14:121.

28. Shulman, Gerald I. Cellular mechanisms of insulin resistance, *J Clin Invest.*, 2000, 106(2):171-176.

29. Siddiqui, Muhammad; Ashraff, Suhel; Siddiqui, Muhammad A.; and Carline, Thomas E. Obesity and Insulin Resistance: Management in Diabetes. *Turk Jem*. 2013, 17: 57-62.

30. Silva Rosa, Simone C. da; Nayak, Nichole; Caymo, Andrei Miguel; and Gordon, Joseph W. Mechanisms of muscle insulin resistance and the cross-talk with liver and adipose tissue. *Physiological Reports*., 2020; 8:e14607.

31. Sinha, Ranjana; Fisch, Gene; Teague, Barbara; Tamborlane, William V.; Banyas, Bruna; Allen, Karin; Savoya, Mary; Rieger, Vera; Taksali, Sara; Barbetta, Gina; Sherwin, Robert S.; and Caprio, Sonia. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med*, 2002, 346(11): 802-810.

32. Szymczak-Pajor, Izabela; and ´Sliwi´nska, Agnieszka. Analysis of association between Vitamin D deficiency and insulin resistance. *Nutrients*, 2019, 11, 794.

33. Tucholski, Krzysztof; and Otto-Buczkowska, Ewa. The role of leptin in the regulation of carbohydrate metabolism. *Polish Journal of Endocrinology*, 2011, 62(3), 258-261.

34. Weiss, Ram; Dziura, James; Burgert, Tania S.; Tamborlane, William V.; Taksali, Sara E.; Yeckel, Catherine W.; Allen, Karin; Lopes, Melinda; Savoye, Mary; Morrison, John; Sherwin, Robert S.; and Caprio, Sonia. Obesity and the Metabolic Syndrome in Children and Adolescents, *n engl j med*, 2002, 350;23, 2362-2374.

35. Wondmkun, Yohannes Tsegyie. Obesity, Insulin resistance, and Type 2 Diabetes: Associations and therapeutic implications, *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*. 2020:13, 3611-3616.

36. Yaribeygi, Habib; Maleki, Mina; Sathyapalan, Thozhukat; Jamialahmadi, Tannaz; and Sahebkar, Amirhossein. Pathophysiology of physical inactivity-dependent insulin resistance: A Theoretical mechanistic review emphasizing clinical evidence. *Journal of Diabetes Research*, 2021, Vol.2021.

37. Yoshioka, Hiroki; Mori, Mihoko; Fujii, Hirohisa; and Nonogaki, Tsunemasa. *Sasa veitchii* extract reduces obesity-induced insulin resistance and hepatic steatosis in obese mice fed a high-fat diet. *Nagoya J. Med. Sci*. 2017, 79, 279 - 290.

38. Zeyda, Maximilian; and Stulnig, Thomas M. Obesity, Inflammation, and Insulin resistance - A Mini-Review. *Gerontology*, 2009, 55:379-386.