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An Overview of the Resistance of Insulin

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ABSTRACT: Obesity and diabetes are becoming widespread in industrialized nations, reaching epidemic proportions. As a result, there is an increasing awareness of the importance of insulin resistance and its related consequences. An in-depth understanding of insulin's role in several physiological processes, its influence on its own synthesis and secretion, and its consequences at both the molecular and systemic levels is highly important for the understanding of several chronic diseases prevalent in Western populations today. This article provides a thorough analysis of insulin, including its historical context, structural makeup, synthesis methods, secretion processes, many functions, and interrelationships. Afterwards. This study also includes evaluations of insulin resistance from both clinical and functional perspectives.

Keywords: Disease; Diabetes mellitus; Insulin; Insulin resistance

1. INTRODUCTION

The initial insulin discovered by 1921, an important event that opened up the potential for methodical investigation into the mechanisms of insulin action. In 1955 [1], Frederick Sanger between the years 1918 to 2013, successfully conducted the sequencing of bovine insulin, therefore determine its precise composition of amino acids. The discovery was the initial one of its kind worldwide. Following this, the production of human insulin was achieved by the use of recombinant DNA techniques and the genetic manipulation of bacteria. The investigation of insulin treatment and the elucidation of its mechanisms of action emerge as significant areas of focus for future study. The small cells in the pancreas produce and release peptide hormone, also known as insulin. It assumed a pivotal function in regulating the uptake of glucose from the circulatory system into the hepatic, adipose, and skeletal muscle cells. Insulin assumes a pivotal part in the regulation of various other physiological functions, besides to its primary function of maintaining glucose homeostasis. These processes contain the production of glycogen, conversion of lipids, DNA synthesis, transcription of genes, transport of amino acids, the production of proteins, and degradation [2].

Since both diabetes and obesity are now epidemics in affluent nations, the importance of developing insulin resistance is becoming more well acknowledged [3]. Its molecular and systemic functions have important ramifications for many types of chronic conditions that are common in modern Westernized community [3]. The exploration of insulin and insulin resistance remains a key area of interest in clinical studies. This research holds significance across various domains, ranging from laboratory settings to patient care and the formulation of public health policies [4].

In typical physiological circumstances, elevated levels of plasma glucose result in heightened production of insulin and elevated levels of circulating insulin. Consequently, this process promotes the transfer of glucose into peripheral tissues while simultaneously limiting hepatic gluconeogenesis. Insulin, a hormone consisting of peptides [5], the β cells situated in the pancreatic islets of Langerhans are responsible for the production of insulin. The fundamental role of this entity is to maintain homeostasis by aiding the cellular uptake of glucose, while also regulating the metabolic processes of carbohydrates, lipids, and proteins. Moreover, insulin facilitates cellular division and proliferation by virtue of its mitogenic properties [6].

Insulin resistance is characterized by a diminished biological reaction when increased insulin level is present. Traditionally, this refers to a reduced sensitivity to the elimination of glucose mediated by insulin. The principal role of this entity is to govern the metabolic processes of carbs, proteins, and lipids through the facilitation of the glucose

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absorption. The phenomenon of compensatory hyperinsulinemia arises when there is an elevation in the production of pancreatic beta cells [7].

All of the human body's many organs, including the liver, muscles, and fat tissue, are on appear. These organs are important for preserving metabolic balance, particularly when fasting and eating occur. Throughout the fasting phase, the brain and other organs receive glucose from the liver's synthesis of glucose, which is determined by the rates of glycogenolysis and gluconeogenesis [8]. The nutritional composition of meals stimulates pancreatic beta cells to release insulin (not shown), which hinders the breakdown of fat cells and the production of glucose in the liver, while facilitating the absorption of glucose into muscle and adipocytes. In the human body, the predominant portion of glucose present in a meal is stored in muscle tissue as glycogen, whereas a very little quantity is absorbed by adipocytes. One of the primary functions of glucose absorption into adipocytes is to produce glycerol-3-phosphate, which is essential for the production of triglycerides, which serve as the primary long-term energy storage form in mammals. The liver absorbs glucose after meals via a mechanism facilitated by insulin and glucose in the bloodstream that circulates through the liver. The primary sources for lipid synthesis (de novo lipogenesis) or the production of extra glycogen via the indirect process of sustained gluconeogenesis are the three-carbon substrates (lactate, amino acids, and glycerol) derived from peripheral glycolysis [9].

In healthy people, high physiological insulin concentrations (1 nM) totally restrict hepatic glycogenolysis, but gluconeogenesis is decreased by only 20% to 30% compared with diabetic-related disease states. Therefore, it may be inferred that the decrease in hepatic glucose production in healthy individuals is mostly attributed to the inhibition of glycogenolysis by insulin. Individuals with insulin resistance (IR) as shown in Figure 1, exhibit a diminished ability of insulin to efficiently control the production of glucose and facilitate the glucose absorption into adipose and muscle cells, as indicated by the lines that are dashed [8].

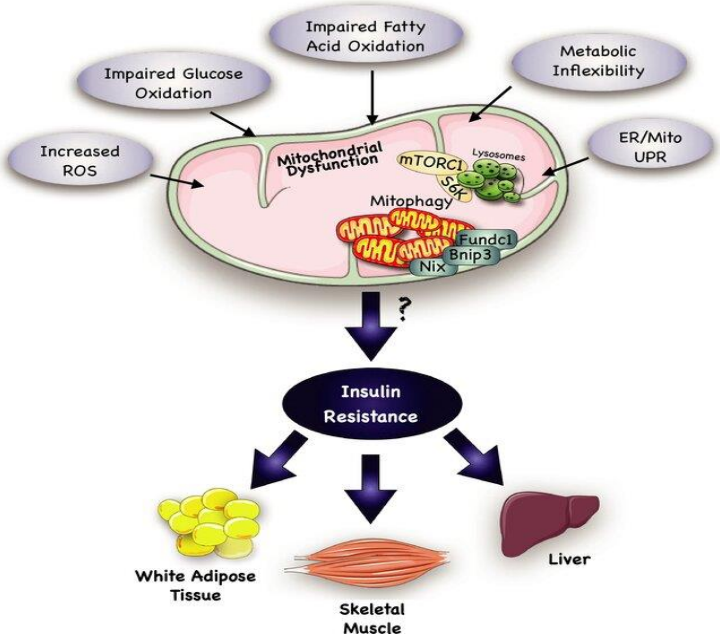

FIGURE 1.- Insulin resistance (IR) exhibits a diminished ability of insulin to efficiently control [8]

2. Insulin's Structure and Chemical Properties

The recognition of insulin as a polypeptide took place in 1928, followed by the subsequent determination of its amino acid sequence in 1952. The chemical under consideration is a dipeptide moiety composed of A and B chains that are interconnected through disulfide bridges. A total of 51 amino acids makes up the amino acid chain, which has a molecular weight of 5802. The substance demonstrates an isoelectric point of 5.5. The A chain has 21 amino acids, while the B chain has 30 amino acids. An N-terminal helix and a C-terminal helix that face different ways are joined to produce the A chain. In contrast, the B chain is characterized by the presence of a center helical segment [9]. The N- and C-terminal helices of the A chain are connected to the central helix of the B chain through two disulfide bonds, so establishing a connection between the two chains. A peptide connects the N-terminus of the A chain in pro-insulin to the C-terminus of the B chain [10]. The pancreatic beta cells are where the 110 amino acids that make up the structure of insulin are first synthesized as a single molecule, known as preproinsulin. Pro-insulin is formed when the 24-amino acid signal peptide is broken enzymatically from one end of the chain during its translocation through the endoplasmic reticulum.

The proinsulin undergoes a process of folding and binding, resulting in the acquisition of its ultimate molecular structure. Subsequently, the proinsulin is transported into vesicles that the Golgi apparatus has formed. Subsequently, the enzymatic activity of prohormone convertase 1 and 2 removes the middle part ("the C chain") consisting of 33 amino acids, resulting in the conversion of the structure into its final form with two chains, A and B. An additional two amino acids are cleaved by the enzyme carboxypeptidase E. Biologically active insulin is often monomeric, meaning it occurs as a single molecule. The structure consists of two elongated polypeptide chains composed of amino acids. There are two chains: chain A, which consists of 21 amino acids, and chain B, which consists of 30 amino acids.

The chains are connected by two disulfide bridges, specifically between residues A7 and B7 and between residues A20 and B19. Additionally, chain A contains an internal disulfide bridge between residues A6 and A11. The structure of these joints is conserved throughout all mammalian types of insulin.

Insulin is secreted and forms dimers when two molecules join together, and then it becomes hexamers when six molecules combine. This reaction occurs in the presence of zinc as shown in Figure 2.

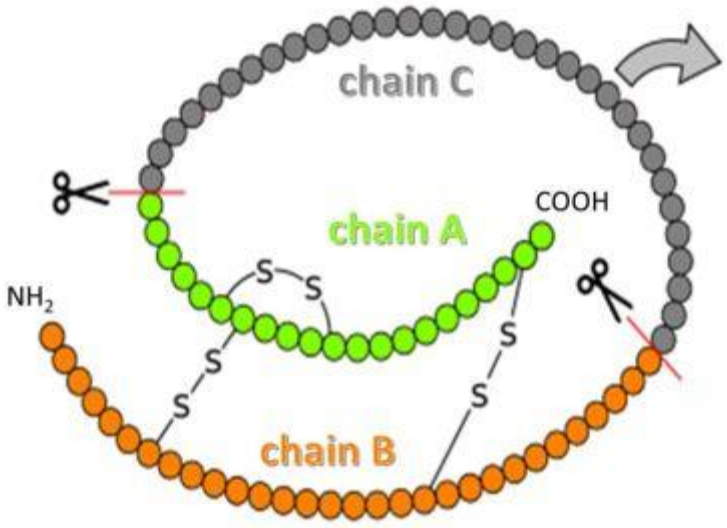

FIGURE 2.- Insulin function in cells

2.1 Insulin Discovery

In 1889, Minkowski and von Mering, German scientists, observed through their experimental investigations involving animals that the surgical removal of the pancreas resulted in the manifestation of severe diabetes [11]. The researchers postulated that a chemical produced by the pancreas played a role in regulating metabolic processes. Subsequent researchers have challenged this notion, observing a correlation between diabetes and the deterioration of the islets of Langerhans. In 1909, Belgian investigator de Meyer introduced the term "insulin" when British scientist Schaefer offered it in 1916 [12].

2.2 Insulin Function

Insulin is produced by the beta cells of the pancreatic islets when blood glucose levels are high. Insulin communicates with cells that the body is in a condition of being nourished, and prompts them to absorb glucose from the bloodstream and initiate other suitable reactions. For instance, in the liver, the process of glycogen synthesis is activated, so ensuring a reserve of glucose for times when blood glucose levels decrease during fasting. Insulin additionally stimulates adipocytes to produce more fat. Diabetes type 1 is characterized by cells in the pancreas ceasing to release insulin, resulting in increased levels of sugar in the blood and heightened fat metabolism. Consequently, glucose is excreted in the urine, and weight loss occurs due to the reduction of stored fat on the body, as seen in Figure 3.

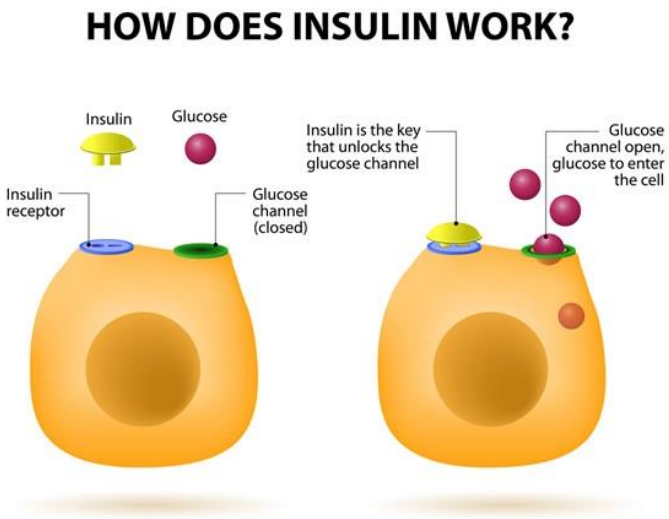

FIGURE 3.- Insulin function in cells [12]

3. Insulin Mechanisms

Elevated glucose levels trigger the first stage of insulin production by stimulating the release of insulin from secretory granules located in the β cell. The enzyme glucokinase is responsible for detecting glucose into beta cells and then converting glucose by phosphorylation, leading to the generation of ATP. The depolarization of the membrane of a cell and the activation of voltage-dependent calcium channels occurs as a result of the closure of K+-ATP-dependent methods. This activation causes an elevation in intracellular calcium levels, which subsequently initiates the secretion of pulsatile insulin [13].

This reaction is enhanced by several glucose action channels such as a Ca2+ dependent pathway that operates independently of the K+-ATP channel. The insulin release is influenced by various variables, including the activation of phospholipases and protein kinase C, which can be triggered by the action of acetylcholine. In addition, the stimulation of adenylyl cyclase function and the growth of β cell protein kinase A contribute to the enhancement of insulin synthesis [14].

The influence of these factors appears to be significant, following the replenishment of secretory granules that have been relocated from reserve reservoirs [15].

4. Insulin Secretion: Regulation and Mechanisms

Cellular-level: The regulation of insulin that synthesis and secretion involve the interaction between nutritional and non-nutrient secretagogues, as well as environmental cues and other hormone. Glucose, among other nutrient secretagogues. Glucose, fructose, mannose, and galactose do not need insulin activity for their entry into the β cell. Non-nutrient secretagogues have the potential to exert their effects via neurological stimulation, namely the cholinergic and adrenergic pathways [16] as shown below: -

1. The Adrenergic Pathway

Catecholamines, via β2-adrenoceptors, often suppress the secretion of insulin in response to stress and physical activity. In addition, the pancreas contains β-adrenoceptors that augment insulin, but this impact seems insignificant. The actions mediated by α2 seem to occur after the impact of nutritional secretagogues [17].

2. Transmission of Cholinergic Signals

The impact of vagus nerve stimulation on pancreatic insulin production has been well acknowledged. This is believed to facilitate the "cephalic phase" of insulin production, which takes place when food is visually seen, scented, or consumed suddenly. The activation of phospholipase C by cholinergic muscarinic receptors [18].

3. Peptide hormones

Several peptide hormones have an impact on the production of insulin. The gut hormones GLP-114 and somatostatin have been shown to augment and impede the action of insulin. The observed mechanisms of action seem to include the production of cyclic adenosine monophosphate and the subsequent activation of a protein kinase that is sensitive to cAMP.8 The mechanisms of action of leptin and adiponectin seem to be comparable [19].

4. Amino acids

The activity of arginine is linked to an elevation in potassium permeability while having no impact on the manufacture of proinsulin. Leucine, a crucial amino acid with a branched chain structure, has a strong ability to

augment the secretion of insulin. It does this by allosterically activating glutamate dehydrogenase and facilitating the formation of α-ketoglutarate, ultimately leading to the production of ATP. Figure (4) provides a schematic representation of the primary routes and factors that impact insulin secretion [20].

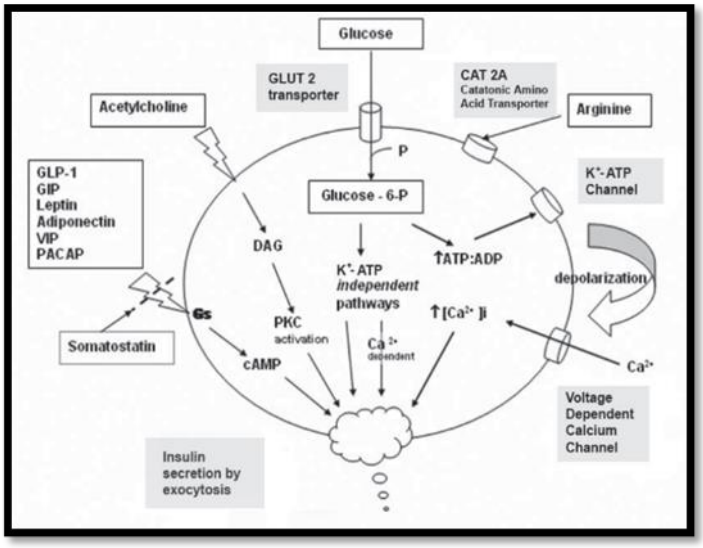

FIGURE 4.- Schematic presentation of insulin secretory pathways [20]

4.1 Influential Factors on Cell Mass

The control of insulin secretion over an extended period of time may be facilitated by the impact on the mass of β cells. In addition to enhancing glucose-stimulated insulin release. To get a thorough examination of this subject, go to Nielsen and Serup [21].

Insulin resistance caused by inflammation

Inflammation is characterized by heightened concentrations of pro-inflammatory cytokines or an augmented quantity of leukocytes inside the bloodstream or bodily tissues. Excessive activation of the inflammatory process often results in a range of abnormalities, including organ malfunction and tissue damage Obesity can cause chronic and moderate inflammatory processes, which is associated with the development of type 2 diabetes mellitus (T2DM). Hepatic and systemic insulin resistance can be caused by an elevated amount of fatty tissue entering the portal vein, which works together with the production of chemokines and IL-6 [22].

4.2 The Role of Toll-Like Receptors in Hyperinsulinemia

Toll-like receptors (TLRs) belong to the class of pattern recognition receptors (PRRs) and serve a crucial role in innate immunity by detecting tissue damage via the recognition of danger-associated chemical patterns. Research has shown that TLR2 and TLR4 have big significant role in insulin resistance development which is linked with obesity. The upregulation of Toll-like receptor 4 (TLR4) expression in adipocytes, hepatocytes, muscles, and the hypothalamus has been shown in both obese mice and individuals with diabetes. This upregulation has been found to have a detrimental impact on insulin sensitivity. Another research has also shown that metabolic endotoxemia during illness induces the onset of inflammation and metabolic problems via the activation of Toll-like receptor 4 (TLR4) in metabolic organs. 17th Furthermore, a range of Toll-like receptor (TLR) inhibitors have been formulated with the aim of controlling excessive inflammation. These inhibitors include small molecule tors, antibodies, and developing nano-inhibitors [23].

Hyperglycemia indicates abnormalities in several organs. Impaired insulin production in the pancreatic islets is attributed to cellular abnormalities. Hepatic gluconeogenesis leads to an increase in glucose synthesis in the liver. Prior to these occurrences, and often predicting them by many decades, there are abnormal changes in the way skeletal muscle reacts to insulin. The focus of our research group has been directed on skeletal muscle in order to get insight into the early phases of the illness. In summary, adiponectin is a plasma protein generated from adipocytes that possesses features such as insulin sensitization, anti-inflammatory effects, and antiatherogenicity. While a complete understanding of its pharmacological and pathophysiological function remains elusive, the presence of low adiponectin levels in individuals with insulin resistance implies that manipulating adiponectin through therapeutic means could potentially offer a new approach to eating insulin resistance.

Resistin is a polypeptide released by adipocytes and has been identified as a potential factor. This investigation led to the identification of resistin, a protein associated with resistance to insulin. Resistin belongs to a group of signaling

molecules known as resistin-like compounds, which are particular to certain tissues. The resistinm RNA encodes a polypeptide consisting 114 A. A, which is accompanied by once sequence of 20 amino acids. Resistin is released in the form of a dimer that is connected to disulfide [20].

The induction of resistin gene expression occurs during the process of adipocyte differentiation in 3T3-L1 cells. Additionally, mature adipocytes produce and release the resistin polypeptide. The protein that was secreted was observed to hinder the process of 3T3-LI adipogenesis. The initial findings indicated that resistin may partially account for the relationship between obesity and elevated insulin levels. A recent investigation conducted on mice has indicated that resistin has the ability to specifically hinder the inhibitory effect of insulin on the synthesis of glucose in the liver. Nevertheless, the impact of resistin on insulin resistance linked to obesity has sparked debate due to supplementary evidence [24, 25].

The cytokine TNF-κ has been implicated in the promotion of inflammation and has been associated with the onset of resistance to insulin. The synthesis of TNF-α involves the production of a protein known as transmembrane with a size of 26 kilodaltons, which is situated on the surface of cells. The protein that is produced involves breakdown to generate a soluble version of TNF-α, which has been discovered to have biological applications. Increased production of TNF-κ has been demonstrated with fat cells obtained from animal studies of obesity and resistant to insulin, along with in human individuals. Various pathways were proposed to clarify the influence of TNF-κ on the insulin resistance linked to obesity. The release of adipose tissue TNF-κ into the bloodstream is not observed, as it primarily operates via autocrine and paracrine pathways [26].

Interleukin-6 (IL-6) is a versatile cytokine that circulates in the bloodstream and has a wide range of effects, including inflammation, host defense, and tissue injury. It is among a group of proinflammatory cytokines that have been linked to insulin resistance. Numerous cell types, such as immune cells, fibroblasts, and adipose tissue, release this substance, which circulates in the form of a variable glycosylated protein ranging from 22 to 27 kilodaltons (kDa). Epidemiological and genetic research provide support for the correlation between IL-6 and insulin resistance. There exists a favorable correlation between plasma IL-6 levels and both human obesity and insulin resistance [27].

The significance of adipocytokines in both physiological and pathological processes has only been recognized in recent times as shown Figure 5. Certain adipocytokines, including adiponectin, appear to play a significant role in regulating metabolic homeostasis. However, it is worth noting that certain adipocytokines may also contribute to the onset of insulin resistance in periods of food plenty [28]. The processes via which adipocytokines facilitate insulin resistance are intricate, and our comprehension remains inadequate. Excessive adipose tissue, particularly in inappropriate locations (omental depots), may have negative effects due to the release of certain cytokines: TNF, IL-6, and resistin. On the other hand, the existence of adipose tissue plays a crucial role in the prevention of insulin resistance, primarily through the release of two cytokines: leptin and adiponectin. Certain cytokines are also found in the immune system and perhaps contribute to the connection between the nutritional system and the immunological system. Considering the growing body of research suggesting that insulin resistance could be an inflammatory illness, it is crucial to clarify this connection [29].

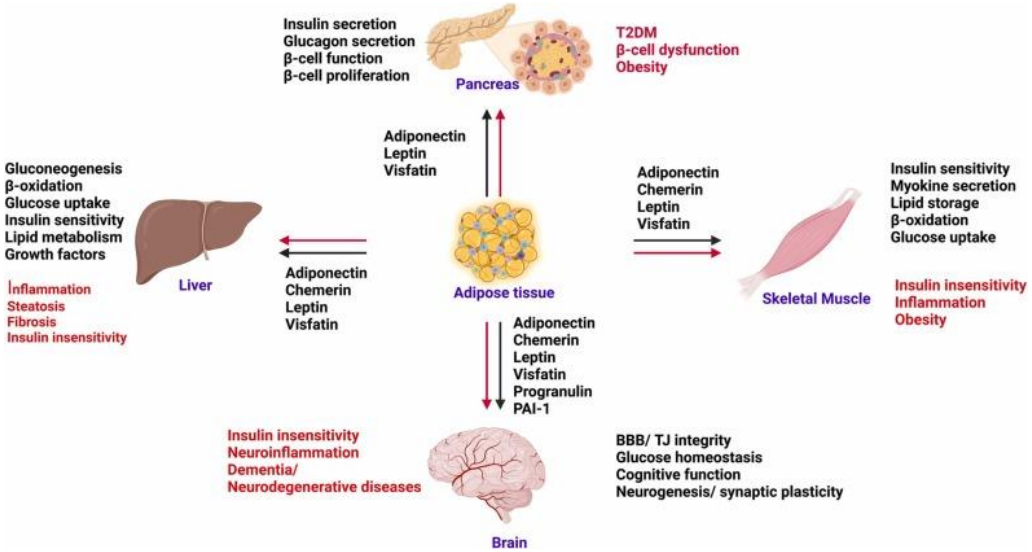

FIGURE 5.- adipocytokines in both physiological and pathological processes

4.3 Role of Insulin on T2D

Type 2 diabetes mellitus (T2D) is a significant medical problem in the 21st century. The excessive consumption of affordable, high-calorie, unsatisfying, and extremely appetizing food in developed countries has resulted in an extraordinary rise in obesity rates. The country of America has a rate of prevalence over 50% for both diabetes and obesity. Although not all persons who are obese acquire type 2 diabetes (T2D), obesity has a substantial role in the initial stages of T2D. Moreover, the incidence of T2D has closely mirrored the rates of obesity. T2D is primarily characterized by fasting hyperglycemia, which is mostly caused by insufficient functioning of insulin, the primary hormone responsible for reducing glucose levels. Therefore, it is crucial to comprehend the processes by which insulin functions in order to advance the development of successful therapeutic approaches for combating type 2 diabetes (T2D) [30].

Insulin is a polypeptide hormone secreted by the system of endocrine glands. It binds to receptors on the plasma membrane of certain cells to regulate a complete anabolic response depending on the presence of nutrients. Insulin or insulin-like peptides (ILPs) are present in all species. In invertebrates, ILPs mainly have a role in promoting cell division signalling, whereas their effects on metabolic processes and fuel selection are less significant. Mammals have employed gene duplication activities during evolution to create distinct roles for the hormones known as insulin, insulin-like growth factor (IGF)-1, and IGF-2. IGF-1 and IGF-2 promote cellular proliferation and differentiation in animals, whereas insulin mostly governs metabolic functions. However, the absence of precise borders between these functional differences is highlighted by the substantial resemblance between the insulin and IGF-1 receptors. These kinds of receptors frequently form hybrid heterodimers in several kinds of cells and have multiple common downstream effectors. The similar signalling properties of insulin and IGF-1 are thought to have a role in the well-documented link between elevated levels of insulin in the bloodstream (hyperinsulinemia) and many forms of cancer. This work investigates the physiological consequences of mammalian insulin attaching to the receptor for insulin and the molecular processes that cause a decrease in insulin's actions in the insulin-resistant state linked to the development and advancement of type 2 diabetes (T2D) [30, 31].

These receptors are found in several types of somatic cells, however insulin mainly influences the regulation of glucose levels by directly influencing skeletal muscle, liver, and white adipocytes. These tissues possess distinct tasks in preserving a consistent metabolic state, necessitating tissue-specific insulin signal transduction pathways. Insulin increases the use and storage of glucose in skeletal muscle by increasing the transit of glucose and stimulating the synthesis of glycogen. Insulin promotes the synthesis of glycogen, increases the expression of genes involved in the formation of fats, and decreases the expression of genes involved in the generation of glucose in the liver. Insulin suppresses the degradation of lipids and promotes the absorption of glucose and the synthesis of fats in white adipose tissue (WAT). While the specific outcomes may differ, the immediate elements that carry the insulin message are very same in all cells that react to insulin. The diversity in physiological insulin responses among various cell types is mostly attributed to distinct distal effectors that work Section II will examine the direct effects of insulin on skeletal muscle, liver, and white adipose tissue (WAT). The primary focus will be on the signal transduction processes that are connected with the control of metabolic fluxes, as illustrated in Figure 6.

Furthermore, insulin exerts significant indirect effects on target tissues in addition to its direct actions. Studying the secondary effects of insulin in cells in culture is challenging due to their coupled and context-specific character. As a result, these effects are less well understood compared to the direct, cell-autonomous actions of insulin. Indirect insulin action may be shown in how insulin inhibits lipolysis in white adipose tissue (WAT), resulting in a decrease in hepatic acetyl-CoA levels. Consequently, this decrease in acetyl-CoA content has an allosteric impact, resulting in a decrease in pyruvate carboxylase activity. This mechanism, in addition to inhibiting the turnover of glycerol, allows insulin to inhibit lipolysis in white adipose tissue, thereby suppressing hepatic gluconeogenesis. Insulin inhibits the production of glucagon in the islet cells of the pancreas by paracrine signalling, which means it indirectly impacts glucagon secretion. besides that, insulin also functions in the central nervous system (CNS) to produce the effects it does. These routes are significant in understanding the indirect actions of insulin. The examination of these physiological processes will occur in section III [32].

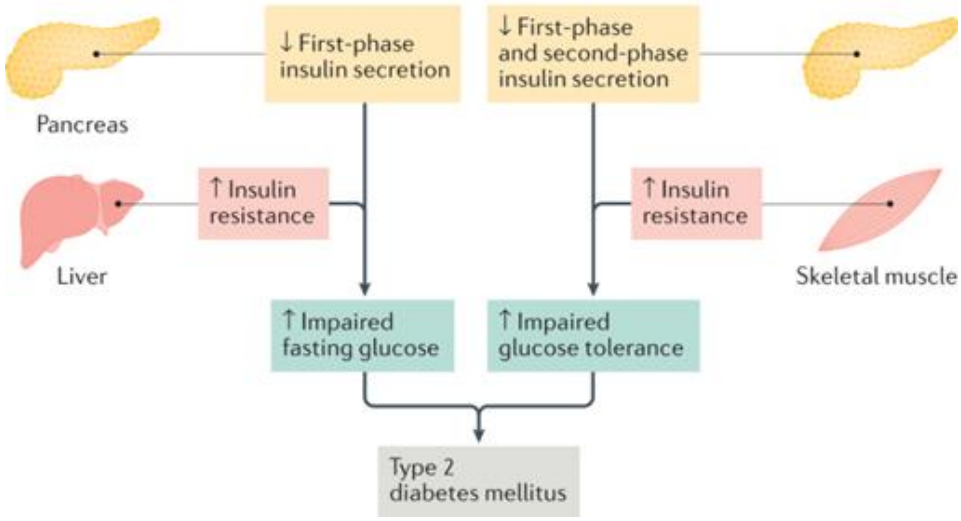

FIGURE 6.- Role of insulin in T2D

5. Conclusions

The bulk of mammalian cells primarily rely on glucose as their substrate. Proper insulin signaling is crucial in insulin-dependent cells, as a decrease in insulin sensitivity leads to insulin resistance (IR). In metabolic syndrome and type 2 diabetes (T2D), insulin resistance (IR) is a prevalent characteristic of metabolic disruption. The presence of insulin resistance (IR) leads to altered insulin signaling, resulting in hindered glucose entry into adipocytes and skeletal muscle cells. While the exact etiology of insulin resistance (IR) remains uncertain, it is widely believed that many factors such as oxidative stress, inflammation, insulin receptor mutation, endoplasmic reticulum (ER) stress, and mitochondrial dysfunction play a role in its development. According to the literature review, it has been observed that deficiencies in the manufacture and release of insulin, as well as impairments in insulin signaling, have a detrimental effect on the sensitivity of insulin-dependent cells.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest

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