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Original Research Article

Effects of Insulin Resistance on Different Organs

Ms. Madonna Nadar[1*], Ms. Mahima Yadav[1], Mr. Ubaidurrahman Khan[1], Ms. Simran Punjabi[1], Ms. Sohani Solanke[1]

[1]Saraswathi Vidya Bhavan's College of Pharmacy, India

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Abstract: ***Background*:** This review will encompass a comprehensive examination of insulin and insulin resistance, spanning its historical background, synthesis, functions, interactions, and related clinical symptoms. Within this section, we will delve into the underlying mechanisms and various scenarios, both physiological and pathological, that contribute to insulin resistance. The prevalence of insulin resistance among adults worldwide ranges from 15.5% to 46.5%. Excessive visceral fat is considered the main cause of insulin resistance. One of the tyrosine kinase receptors belonging to the Class II (Cysteine) family is the insulin receptor (IR). Adipose tissue functions as an endocrine organ, exerting influence over both glucose and lipid metabolism through the release of adipokines, pro-inflammatory factors. The transport of glucose into the interior of adipocytes relies on insulin and is facilitated by GLUT4 transporters. Adipose tissue is estimated to contribute approximately 10% of the overall glucose uptake stimulated by insulin throughout the body. The primary emphasis will be on scrutinizing insulin's functions and how insulin resistance manifests in specific bodily organs and tissues. We will also scrutinize factors like physiological, environmental, and pharmacological influences on insulin activity, along with clinical conditions associated with insulin resistance.

Keywords: Insulin Resistance, Obese, IGF, GLUT4 transporters, IRS.

INTRODUCTION

Within the complex network of metabolic well-being, insulin resistance takes center stage, exerting a significant influence on the intricate equilibrium between energy utilization and storage in the human body. In the face of a growing prevalence of metabolic disorders in our current era, comprehending the nuances of insulin resistance becomes more than just a scientific endeavor—it becomes an essential requirement for shaping public health strategies.

Our exploration commences with a thorough examination of the molecular mechanisms that govern insulin signaling and the factors that contribute to its disruption. We delve into the complex interplay between genetics, epigenetics, and environmental influences, striving to untangle the intricate web that predisposes individuals to insulin resistance. We investigate its effects on lipid metabolism, inflammation, and cardiovascular health, illuminating the expansive repercussions that resonate throughout the body.

Unraveling the complex narrative of insulin resistance reveals an ongoing saga that surpasses the confines of glucose metabolism, imprinting a lasting influence on the coordination of health and disease throughout various organ systems.

MATERIALS AND METHODS

In this article, a detailed review of the effects of insulin resistance in different organs is presented. The information regarding the same was collected from various journals, First a comprehensive search of peer-reviewed journals, PubMed, Google Scholar, and BrowZine Library. Second from around the world through ADA Journals, Wiley online library, British Journal of Diabetes. Tools used for the editing and writing of the literature were Grammarly and Quillbot.

The islets of Langerhans in the pancreas, which create the peptide hormone insulin, are essential for maintaining healthy blood glucose levels. This is accomplished by facilitating the absorption of glucose by cells, controlling the metabolism of carbohydrates, lipids, and proteins, and promoting cell division and development via its mitogenic capabilities [1]. A normal or increased dose of insulin can cause a weakened biological response, which often involves decreased

***Corresponding Author:** Ms. Madonna Nadar
Saraswathi Vidya Bhavan's College of Pharmacy

sensitivity to insulin-driven glucose elimination. This is known as insulin resistance [2].

Synthesis and Release of Insulin

Fig.1. Insulin is encoded on the short arm of chromosome 11 [3], and is synthesized within the β cells of the pancreatic islets of Langerhans as its precursor, known as proinsulin. Proinsulin is produced in the ribosomes located in the rough endoplasmic reticulum (RER) through the translation of mRNA as pre-proinsulin. Pre-proinsulin is formed through a sequential synthesis process that involves the creation of a signal peptide, followed by the B chain, then the connecting (C) peptide, and finally the A chain, which consists of a single chain comprising 100 amino acids.

When mature granules are released into the bloodstream via exocytosis, both insulin and an equimolar amount of C-peptide are discharged. Proinsulin and zinc typically make up no more than 6% of the secretion from the islet cells [4].

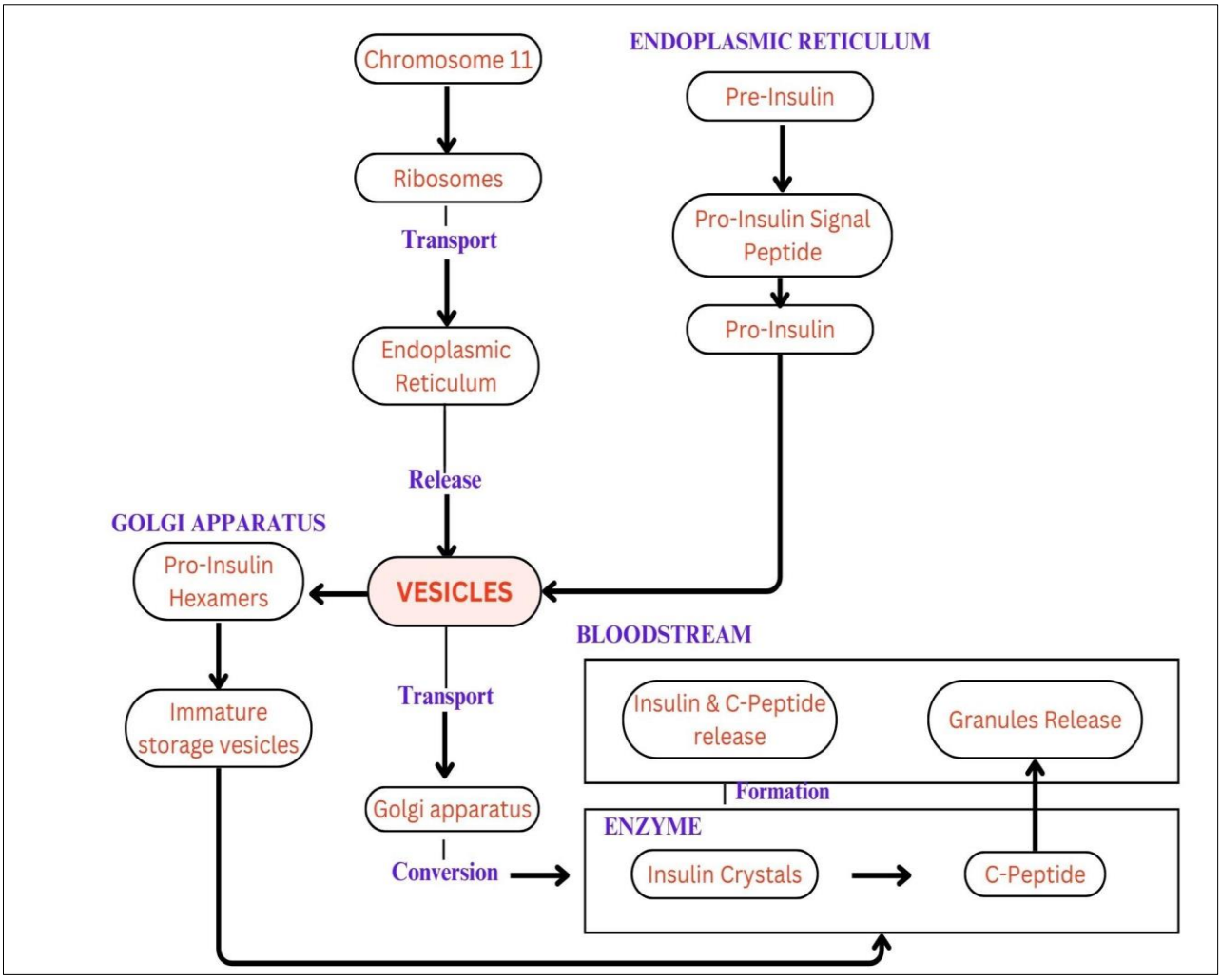

Fig no 1: Synthesis & Release of Insulin

The release of insulin from the islet cells into the portal veins is distinctly pulsatile, representing the combined effect of synchronized secretory bursts originating from numerous islet cells. Moreover, there has been documentation of an ultradian oscillatory pattern in insulin release, along with variations after meals [5].

When prompted by a stimulus like glucose, the secretion of insulin typically follows a biphasic pattern. This entails an initial phase of rapid insulin secretion, succeeded by a less intense yet more prolonged release of the hormone [5].

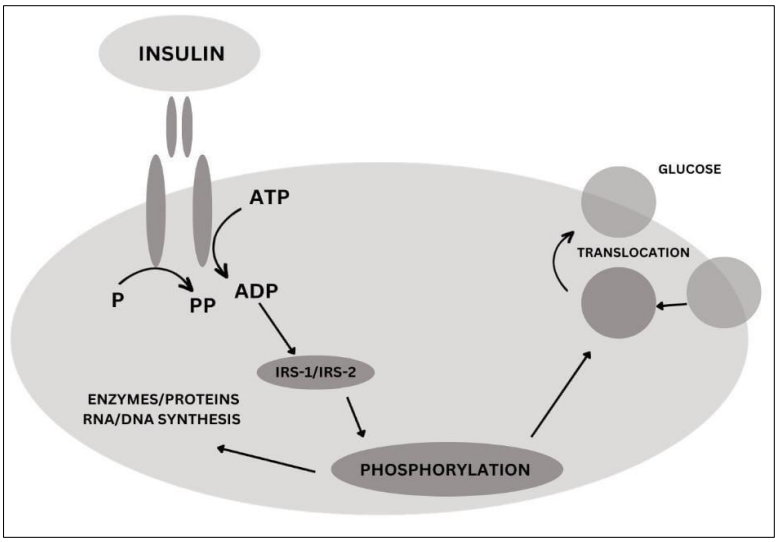

Fig no 2: Pathway of Insulin action

Fig no: 2. Insulin Action Pathways. The extra membrane domain of insulin receptors binds insulin. Both the transmembrane domain and the intracellular domain express tyrosine-dependent kinases (TYR) and are autophosphorylated upon activation from the extramembranous domain. Subsequently, intracellular action is mediated by insulin substrate receptors (IRS) which initiate signal cascades that stimulate enzyme systems, protein synthesis, and gene expression.

Structure of Insulin molecule

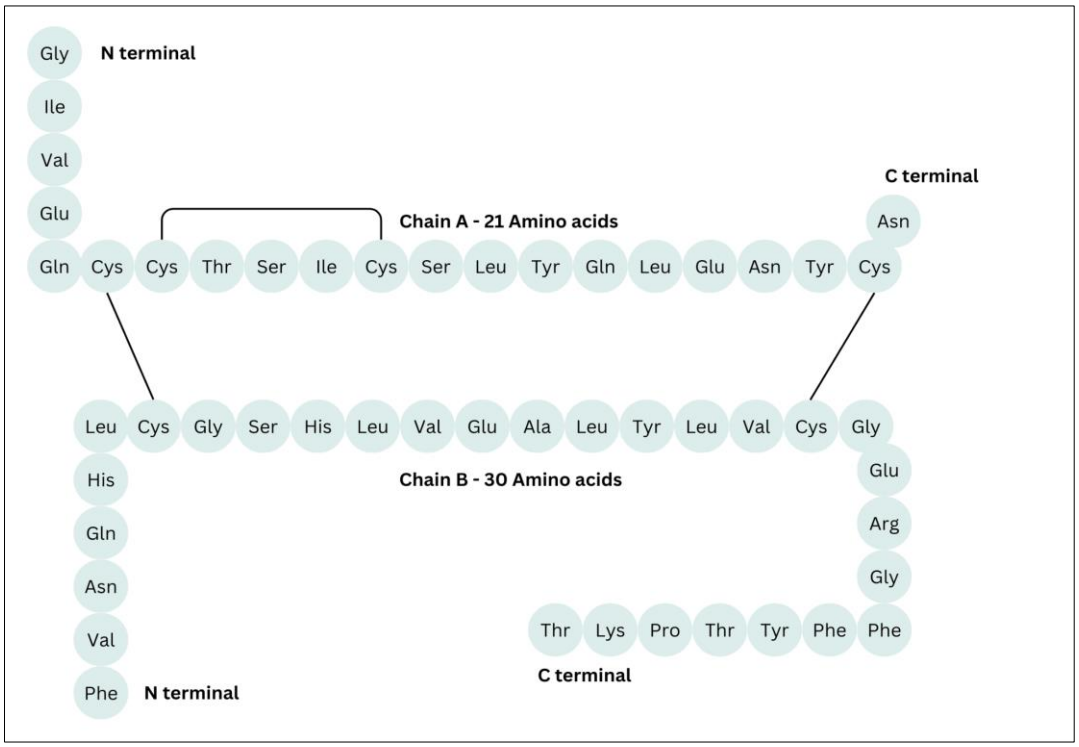

Fig no 3: Primary Structure of Human Insulin

The insulin monomer is composed of a twenty-one amino acid residue "A" chain and a thirty amino acid residue "B" chain bound together by disulfide residues. The insulin monomer has three disulfide residues, two between the "A" and "B" chains (A-B7, "A20" and "B19") and one within the "A" chain (A7 " to"A11 " [4]. The "A" chain has two antiparallel "A" helices between the residues "A2" to "A8" and "A13" to "A19" [1]. The two helices are attached to residues "A9" to "A12" [2]. The conformation of the A chain brings the two end residues of the "A" side by side.

The secondary structure of the B chain includes alpha helices as well as β-sheets. The B chain can exist

in two conformations upon crystallization (T-state) and (R-state) [3]. In T-state, the B chain has a central alpha helices (1→5-helix hydrogen bonding pattern) from B9 through B19. In R-state, continuous alpha helices (B1-B19) from B20 through B23. The glycol-hydrate residues (Gly20 and Gly23) on the B chain allow it to fold into a V-shaped structure [4]. Residues (B24) to (B30) form an elongated β strand structure. The β-turn allows for the chain to be proximal enough for the formation of a β-sheet (PheB24) with the glyco-hydrate residues (TyrB26) in contact with the leucine residues (B11 and B15) to determine insulin receptor affinity [5]. The disulfide bonds (A7-B7) to Cys residues (A20-B19) are responsible for the stability of the original insulin structure. For such small peptide chains, the secondary structure of both A and B chains [5].

Mechanism of Insulin Secretion

1. When glucose levels rise it triggers the phase of insulin secretion, in response to glucose. This causes the release of insulin from storage compartments called granules within the β cells. Glucokinase, an enzyme in β cells, detects the presence of glucose. Converts it into a substance called glucose 6 phosphate (G6P). This process generates adenosine triphosphate (ATP) which plays a role in this mechanism [6].
2. The closure of potassium channels leads to the depolarization of the cell membrane followed by the activation of voltage-dependent calcium channels. As a result, intracellular calcium levels initiate a pattern of insulin secretion [7].
3. The enhancement of this reaction involves two pathways; one on calcium but independent of potassium (K+) ATP channels and other pathways affected by glucose that do not rely on either K+ ATP channels or calcium [8].
4. Additional factors contributing to insulin release include activating phospholipases and protein kinase C through substances like acetylcholine. Moreover stimulating adenylyl cyclase activity and activating β cell protein kinase a can potentiate insulin secretion. Hormones such as peptide pituitary adenylate cyclase-activating polypeptide (PACAP), glucagon-like peptide-1 (GLP 1), and Gastric inhibitory polypeptide (GIP) can initiate this mechanism [8].
5. The second phase of glucose-mediated insulin secretion appears to be impacted by these factors. This phase occurs after the storage granules are refilled by moving them from reserve pools [8].

Insulin Receptors and Binding

Insulin exerts its effects by interacting with specific insulin receptors, which form a heterotetramer comprising two α and two β glycoprotein subunits connected by disulfide bonds. These receptors are situated on the cell membrane.

The gene responsible for encoding the insulin receptor is located on the short arm of chromosome 19 [9]. Upon insulin binding to the extracellular α subunit, a conformational change occurs, allowing ATP to attach to the intracellular portion of the β subunit [10]. This ATP binding subsequently initiates the phosphorylation of the β subunit, conferring it with tyrosine kinase activity. This enzymatic activity enables the tyrosine phosphorylation of intracellular substrate proteins referred to as insulin receptor substrates (IRS). The IRS, in turn, can associate with other signaling molecules, facilitating additional cellular responses to insulin [11].

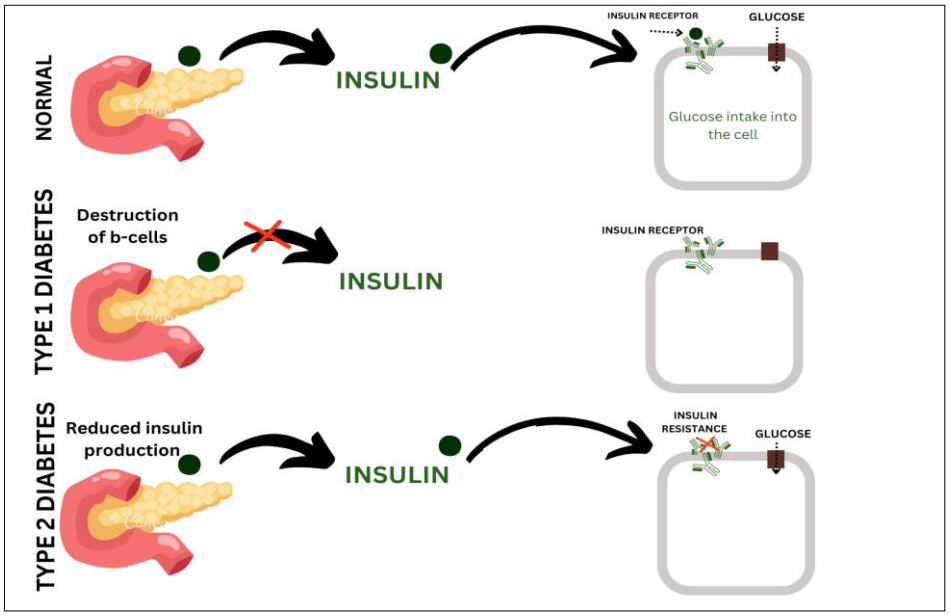

Fig no 4: Binding to Insulin receptors

There Are Four Different Insulin Receptor Substrate (IRS) Proteins with Different Names

- Insulin-like growth factor (IGF) is phosphorylated by the insulin receptor. It mediates insulin mitogenic effects and interferes with glucose sensing and insulin secretion. It is thought that IRS 1 is primarily located in skeletal muscle [12].
- IRS 2 is thought to be primarily located in the liver. It mediates peripheral actions of insulin and contributes to pancreatic β cell growth [11].
- IRS 3 is mainly located in adipose tissue and β cells. It is thought to be mainly located in the liver, thymus, and kidney [13].

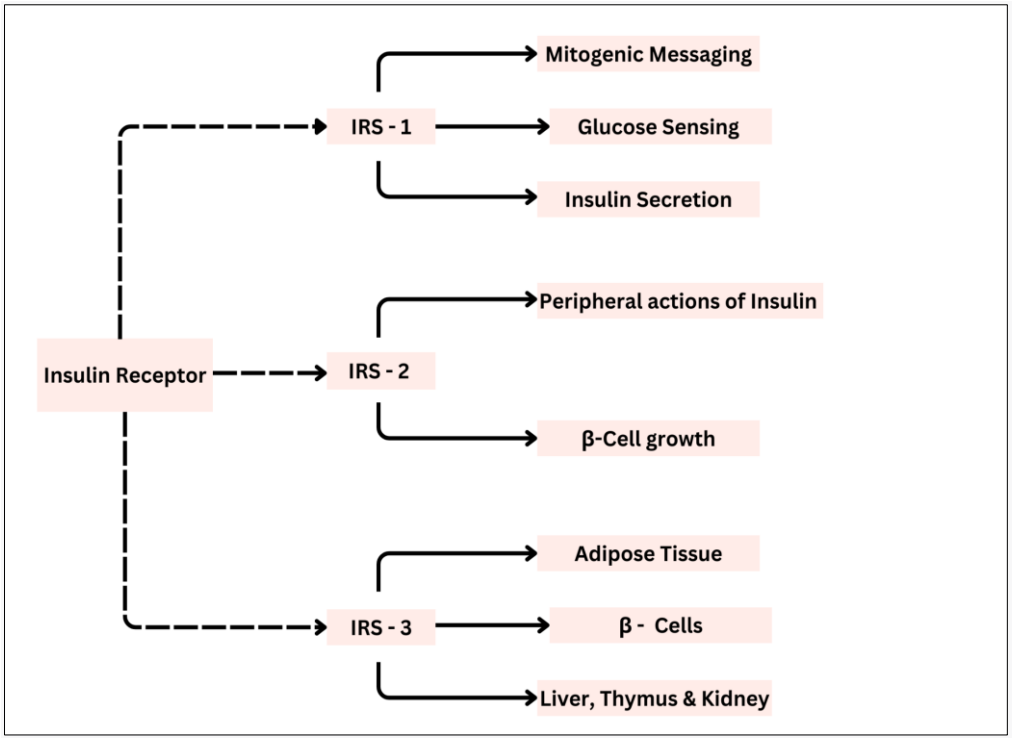

Fig no 5: Insulin Receptors

Mechanism of Insulin Resistance

The physiological effects of insulin are shaped by the intricate interactions with other hormones. While insulin takes the lead in orchestrating metabolic activities during the fed state, it operates in conjunction with growth hormone and insulin-like growth factor 1(IGF-1). Notably, growth hormone is released as a response to various triggers, including insulin, as a safeguard against insulin-induced low blood sugar levels [14].

Conversely, hormones such as glucagon, glucocorticoids, and catecholamines take charge of metabolic processes during the fasting state [15].

- Glucagon is involved in the process of glycogen synthesis, gluconeogenesis, and ketogenesis
- Catecholamines are involved in lipolysis as well as glycogen synthesis.
- Finally, glucocorticoids are involved in muscle breakdown as well as gluconeogenesis and lipolysis

In some circumstances, an excess of these hormones may contribute to insulin resistance, although this does not generally account for the root cause of the condition.

The bulk of the time, changes in insulin signaling after the receptor has been engaged are considered to cause insulin resistance to show up at the cellular level. Despite several study findings, it is unclear if they directly relate to insulin resistance in humans.

The insulin receptor, IRS proteins, or PIP-3 kinase's tyrosine phosphorylation may be reduced, deficient, or subject to genetic variants as potential methods. Alternatively, it could be caused by anomalies in how GLUT 4 transporters work [16].

Site of Insulin Action and Manifestations of Insulin Resistance

The effects of insulin, insulin insufficiency, and insulin resistance vary depending on the unique metabolic requirements of the tissues and organs involved. Insulin-dependent tissues, such as adipose tissue and muscle, rely on insulin for intracellular glucose transfer. However, due to the diverse actions of insulin in different tissues, the signs of insulin resistance and the subsequent increase in insulin levels, which are a result of compensatory mechanisms, are widespread and diverse [17].

Insulin Resistance - Heart

Insulin resistance and diabetes can cause many types of heart-related conditions. Heart disease happens when blocked arteries create problems with blood flow. High blood sugar levels can cause inflammation and damage to the lining of the blood vessels, leading to the formation of plaques or fatty deposits that can narrow the arteries and restrict blood flow to the heart. This can lead to a range of cardiovascular problems, including heart attacks, strokes, and heart failure [18].

Mechanism of Insulin Resistance Effects on Heart

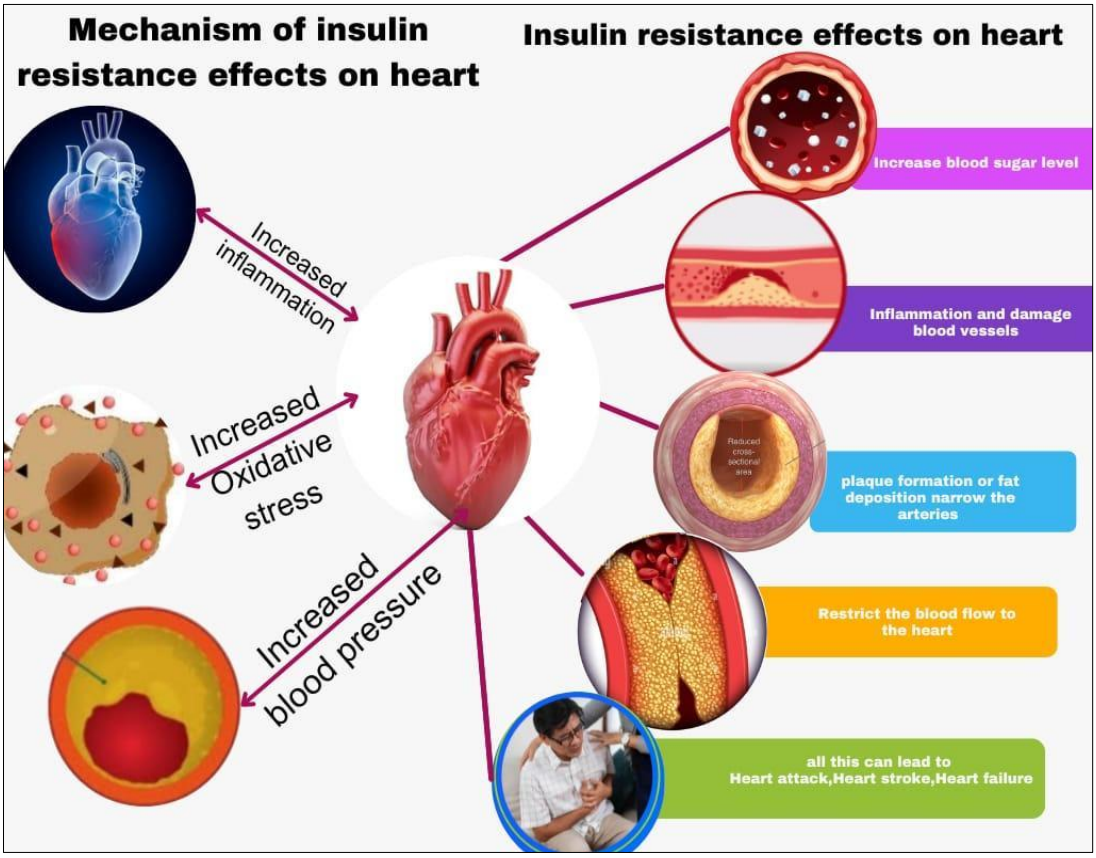

Fig no 6: Mechanism of Insulin Resistance in Heart

Increased Oxidative Stress

β cells and endothelium become dysfunctional due to oxidative stress caused by glucose and FFA excess in these cells. Endothelial dysfunction may lead to the development of cardiovascular disease, β cell dysfunction is characterized by an alteration of insulin secretion [19].

Increased Inflammation

Increased information contributes to insulin resistance by interfering with insulin signaling pathways. Insulin resistance and an excess lipid pool also trigger inflammatory signaling pathways like c-Jun N-terminal kinase (JNK), IκBα kinase β and nuclear factor KB (NF-kB), resulting in the production of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), plasminogen activator inhibitor-1 (PAI-1), monocyte chemoattractant protein-1 (MCP-1), leptin and resistin. JNK pathway phosphorylation IRS then can not bind to insulin receptors properly and leads formation of FFAs which leads to various cardiovascular diseases [20].

Increased Blood Pressure

Increased blood pressure can cause insulin resistance by altering the delivery of insulin and glucose to skeletal muscle cells, resulting in impaired glucose uptake. Insulin resistance also decreases nitric oxide production, which helps dilate blood vessels and improve blood. Due to all this, it will lead to cardiovascular disease including heart attack, heart stroke, and heart failure [21].

Treatment

When pioglitazone was introduced to routine preventive treatment, the researchers saw that it decreased the absolute risk of recurrent stroke and heart attack by 2.8% and the relative risk by 24% [22]. Empagliflozin, a recently developed diabetes medication, demonstrates promising effectiveness in both the treatment and reversal of heart failure [23].

Insulin Resistance – Kidney

Inside the kidney, insulin acts at various sites in the nephron from glomerulus [28-32], to renal tubules [30, 31], to modulate different functions of the kidney

such as glomerular filtration [33], renal gluconeogenesis [34], renal sodium handling [35], and among others by binding to insulin receptors [37]. D. Butlen *et al*., first studied the localisation of insulin receptors in the kidney. It is now known that insulin receptors are located throughout the nephron [36]. Insulin shows its activity by binding to insulin receptors and activates it [37]. The activated insulin receptor triggers signaling cascades. Insulin receptors have many substrates but insulin receptor substrate families are best described. IRS has six isoforms but IRS1 and IRS2 are involved in most metabolic effects of insulin receptor activating [38]. Through IRS the signal is transmitted to phosphoinositide-3-kinase (PI3K) and phosphoinositide-dependent-kinase1 (PIDK1) and leads to phosphorylation of Akt [38], which mediates numerous cellular functions including angiogenesis, metabolism, growth, proliferation, survival, protein synthesis, glycogen synthesis, transcription [39-41]. Other pathways like the Mitogen-activated protein kinase pathway (MAPK) an essential secondary branch of the insulin signaling pathway, regulates cell growth and cell proliferation [39-41].

The glomerulus is the filtering unit of the kidney [42]. Podocytes are specialized cells only found in the kidney glomerulus, wrapped around capillaries and cells of Bowman's capsules [43]. Podocytes together with the endothelial cells of the glomerular capillary loop and the glomerular basement membrane form a filtration harrier [44]. Insulin helps to maintain the integrity of this barrier and helps regulate size-selective permeability of the barrier by controlling podocyte contractility [46], thus preventing excessive passage of proteins from the blood into urine thereby avoiding proteinuria [49]. Physical alteration in the structure of the podocyte due to injury, loss, or mutation (known as podocyte foot process effacement) may degrade filtration barrier integrity, and proteinuria and glomerulosclerosis may occur [49], and are major causes of diabetic nephropathy [45]. Welsh *et al*., generated a podocyte-specific insulin receptor knockout mice (podIRKO) model and found that insulin signaling through Akt and MAPK is abrogated and results in podocyte foot process effacement, thickening of glomerular basement membrane and cell malfunction or death leading to proteinuria [29].

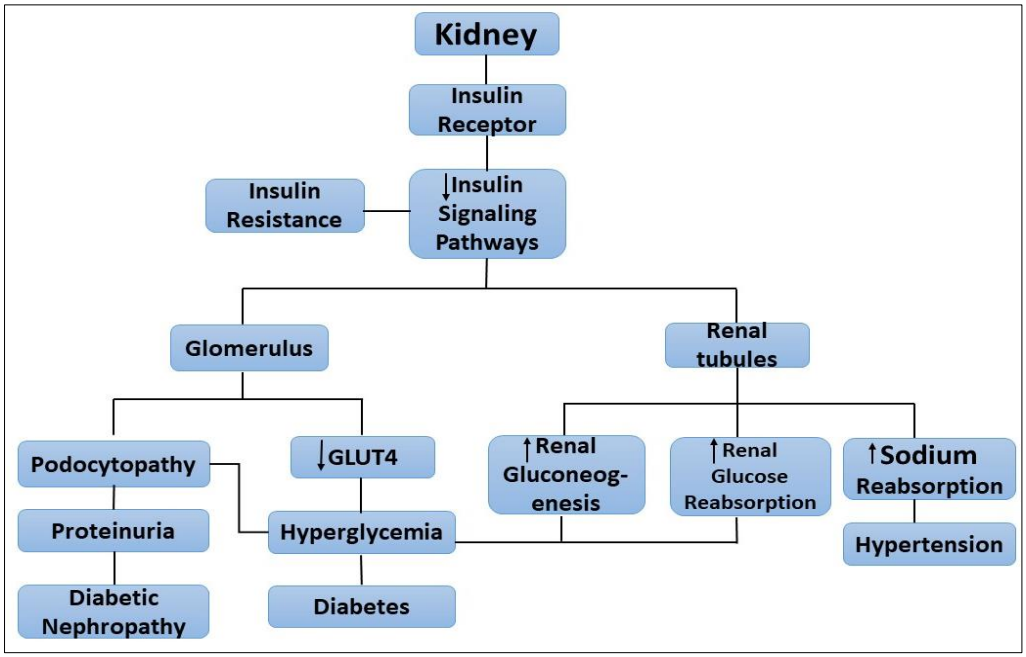

Fig no 7: Insulin Resistance in Kidney

Insulin also stimulates glucose absorption in podocytes via glucose transporters viz. GLUT4 and GLUT1 [47]. Generally, they are located in cytoplasmic vesicular structures, but in the presence of insulin, they are translocated from the cytoplasm to the plasma membrane [57]. Beatriz Santamaria *et al.*, found that IRS2 expression is more in podocytes than IRS1, so they studied the impact of IRS2 deletion in mice and found that in the absence of IRS2, there was a decrease in basal glucose uptake, completely abrogated insulin-mediated glucose uptake, and GLUT4 translocation was also decreased due to impaired Akt pathways [47]. This condition can result in elevated blood sugar levels, known as hyperglycemia [58, 59], which will further lead to podocyte injury [60]. These studies suggest that insulin signaling pathways are disrupted in insulin resistance states.

Insulin after glomerulus enters into renal tubules [50], consisting of the proximal tubule, loop of Henle, distal tubule, and collecting ducts [48]. The renal proximal tubules are responsible for reabsorbing glucose from the glomerular filtrate and releasing it back into the circulation [51]. Insulin has been found to have a direct impact on the handling of glucose by these proximal tubules [52]. Renal glucose reabsorption occurs via

glucose transporter proteins, particularly sodium-dependent glucose cotransporters (SGLTs). SGLT2, situated in the S1 segment of the proximal tubules, is responsible for reabsorbing a significant portion of filtered glucose [54]. This contributes to the maintenance of blood glucose levels within a normal range. Acute exogenous insulin infusion can stimulate renal glucose excretion, indicating that insulin enhances the removal of glucose by the kidneys, possibly mediated by SGLTs [45]. Insulin resistance can disrupt insulin's normal regulatory effects on glucose handling possibly via SGLTs. This can lead to increased glucose reabsorption in the kidneys, contributing to hyperglycemia [50].

Insulin also has a regulatory impact on renal gluconeogenesis of the proximal tubule. Insulin inhibits this process thereby reducing glucose production and release into the bloodstream. In insulin resistance and diabetes mellitus, the interplay between insulin and renal gluconeogenesis can become disrupted. This leads to elevated blood glucose levels and the development of hyperglycemia, a hallmark of diabetes [53-56].

Insulin influences the reabsorption of sodium in the proximal tubules of the nephron. It activates luminal sodium-hydrogen exchangers (NHE3) in these tubules, leading to increased sodium reabsorption. This effect contributes to sodium homeostasis and the regulation of extracellular fluid volume [57]. Unlike other actions of insulin, sodium reabsorption is preserved in insulin resistance and may eventually lead to sodium retention, edema, and hypertension -57-46].

Insulin Resistance - ADIPOSE TISSUE

In the post-meal (postprandial) state, the transport of glucose into the interior of adipocytes relies on insulin and is facilitated by GLUT4 transporters. Adipose tissue is estimated to contribute approximately 10% of the overall glucose uptake stimulated by insulin throughout the body [61]. Insulin plays a multifaceted role: it enhances the uptake of glucose, encourages the formation of fats (lipogenesis), and inhibits the breakdown of stored fats (lipolysis), consequently limiting the release of FFAs into the bloodstream.

In a resting (basal) state, adipocytes do not rely on glucose for their energy needs. Instead, they have the capacity to generate energy intracellularly by oxidizing fatty acids when there is an absence of sufficient insulin activity. Simultaneously, this process results in the liberation of FFAs into the circulation. These FFAs can be directly utilized by other organs like the heart. Alternatively, they may undergo conversion in the liver, where they are transformed into ketone bodies. These ketone bodies offer an alternative energy source for the brain, particularly during extended periods of fasting or starvation [62].

Role

The accumulation of adipose tissue, as seen in obesity, is linked to the development of insulin resistance. Conversely, a deficiency of adipose tissue, as observed in lipodystrophy, is also associated with insulin resistance [63]. Obesity-related insulin resistance is not an isolated issue; it is often accompanied by unfavorable changes in various physiological systems. This interplay is now recognized as the primary reason why individuals with obesity face a significantly heightened risk of cardiovascular disease. Therefore, it becomes essential to delve into the mechanisms by which increased fat storage in adipose tissue can trigger widespread alterations in glucose and lipid metabolism, as well as other bodily functions such as coagulation and blood pressure regulation [64].

However, the situation is further complicated by the presence of lipodystrophy, a condition characterized by a deficiency of adipose tissue. In lipodystrophy, which can manifest as either total or partial loss of adipose tissue, typically affecting the extremities, insulin resistance is also prevalent, and there is a high incidence of type 2 diabetes mellitus(T2DM) [65].

Physiological Influence on Insulin Resistance
Obese

Insulin resistance becomes more pronounced as the body mass index, waist circumference, and particularly the waist-hip ratio increase [66]. These parameters are indicative of higher adiposity, especially elevated levels of visceral adipose tissue, which refers to fat located within the abdomen, and around the intestines, and is often associated with liver fat accumulation. Visceral adipose tissue exhibits metabolic characteristics that differ from those of subcutaneous fat. It is more metabolically active, leading to increased turnover of FFAs. This heightened flow of FFAs contributes to cellular insulin resistance and boosts the production of very low-density lipoproteins (VLDL) in the liver [67].

In obesity-related insulin resistance, the primary affected tissues are believed to be muscle and liver, with the excess FFAs released by adipocytes promoting the accumulation of triglycerides in these tissues. This phenomenon is more likely to occur when adipocytes themselves are insulin-resistant [68].

Moreover, the flux of FFAs is more substantial from visceral adipose tissue and is particularly prevalent in individuals who have genetically mediated insulin resistance within their adipocytes [69, 70]. Although variations exist in how increasing adiposity affects individuals, it is generally observed that weight gain exacerbates insulin resistance in those predisposed to it, while weight loss tends to improve insulin sensitivity [71].

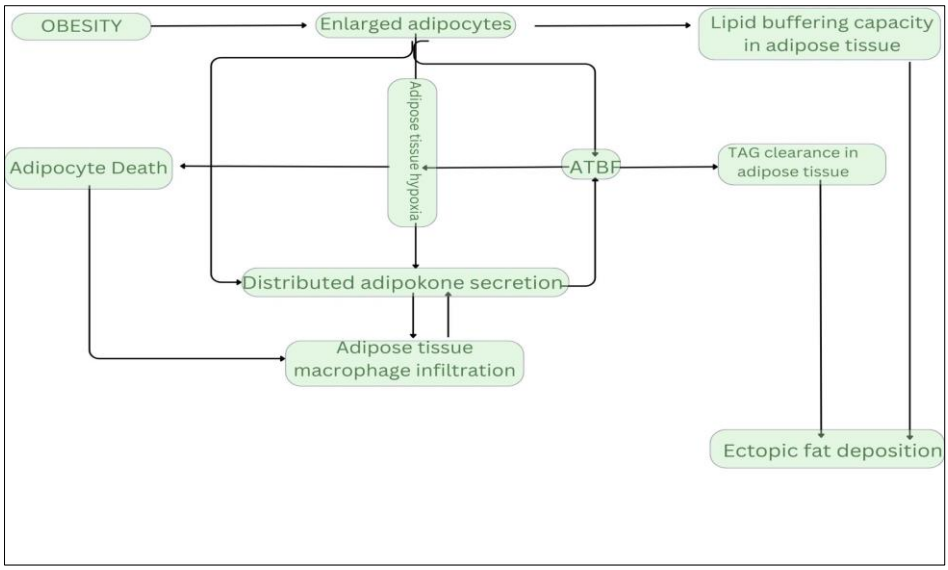

Fig no 8: Mechanism of Insulin Resistance in Obese condition

This explains the role of currently identified adipocytokines and hormones released by adipose tissue in the development of insulin resistance and the frequently accompanying chronic inflammatory state seen in visceral obesity [72].

The adipose tissue has its own network of nerves and blood vessels and consists of two distinct cellular subtypes, each with its own morphology and function. White adipocytes are primarily dedicated to storing energy, while brown adipocytes are primarily responsible for dissipating energy rather than storing it [73]. White adipose tissue efficiently stores triglycerides and fatty acids thanks to insulin's ability to significantly boost both glucose uptake and lipogenesis.

It is well-established that when there are defects in the process of channeling fuels into adipocytes, either due to increased adipose tissue mass or elevated levels of circulating FFAs, it can lead to conditions such as dyslipidemia, obesity, insulin resistance, and ultimately, T2DM [74]. Obesity is a pathological condition that is strongly linked to metabolic disorders, including insulin resistance and T2DM.

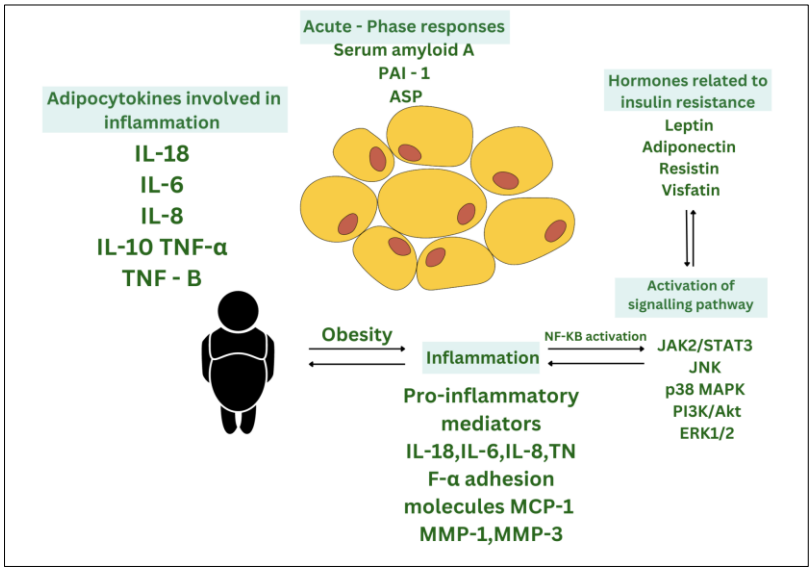

Fig no 9: Insulin Resistance in Obese condition

Fat tissue fills in as an endocrine organ, affecting glucose and lipid digestion by discharging adipokines, favorable to fiery factors, and free unsaturated fats (FFAs). These substances antagonistically influence glucose digestion and ATP union in muscles, bringing about the age of destructive lipid metabolites and disturbances in insulin flagging. Insulin's impacts on fat tissue include two vital components [75, 76].

1. Stimulation of glucose uptake and triglyceride synthesis: Insulin encourages the uptake of

glucose and the synthesis of triglycerides within adipose tissue.

2. Suppression of triglyceride hydrolysis and release of FFA and glycerol: Insulin also stops triglycerides from breaking down, which stops FFAs and glycerol from being released into the bloodstream.

Fat tissue insulin resistance is a condition in which adipose tissue shows resistance to insulin-mediated lipolysis, even when insulin levels are high.

When insulin levels are high, it can interfere with muscle insulin signaling, cause liver gluconeogenesis to kick in, and interfere with the body's insulin response to glucose.

In people who are overweight but not diabetic, as well as T2DM patients, insulin plays a role in the development of T2DM. Insulin is an adipogenic hormone that helps the body absorb circulating fatty acids and increases triglyceride synthesis. This leads to the build-up of adipose tissue and ectopic fat throughout the body, including in the liver, muscle, and pancreas. The exact role of adipose tissue in T2DM has yet to be fully understood [78].

A Role of Adipokines Insulin Resistance

In patients with T2DM, lipid metabolism, deposition and concentration in skeletal muscle, and blood are often impaired [101]. A high level of FFAs in plasma reduces insulin-mediated glucose metabolism, while a low level of lipids in plasma increases insulin function in adipocytes, liver, and skeletal muscle cells; increasing plasma FFAs in both humans and rodents also reduce insulin activation in IRS-1-linked PI3K in skeletal muscle. Lipid-related insulin resistance has also been associated with defects in translocation (GLUT4) of glucose transporter 4 [102]. Various adipokines (e.g., adiponectin; TNF-α; resistin; IL) play a role in this disease state [103], an increase in adiponectin increases insulin sensitivity, while resistin exerts insulin-antagonist effects. For example, resistin induces insulin resistance by inhibiting glucose transport in vitro, and increases in vivo hepatic glucose production, as well as fasting blood glucose concentration [102]. Trelagliptin succinate reduces the content of resistance (i.e., insulin resistance) in fat cells [104].

A Role for Adipose Tissue P53 in the Regulation of Insulin Resistance

Various triggers, including factors such as telomere dysfunction and oxidative stress, have the capability to initiate a state termed "cellular senescence," which entails irreversible growth arrest in cells. The management of this response is intricately overseen by tumor suppressor proteins like p53 and pRb. There is mounting evidence suggesting that senescent cells contribute to alterations associated with the aging process and age-related diseases [79].

In our study, we demonstrate that the expression of p53 within adipose tissue plays a pivotal role in the development of insulin resistance, a primary factor in age-related cardiovascular and metabolic disorders [80]. We observed that an excess intake of calories resulted in the accumulation of oxidative stress within the adipose tissue of mice with a condition resembling T2DM. This excess calorie consumption also promoted changes reminiscent of senescence, such as heightened activity of senescence-associated β-galactosidase, increased levels of p53 expression, and the enhanced production of pro-inflammatory cuti kinds [81].

When we inhibited the activity of p53 within the adipose tissue, we observed a significant improvement in these senescence-related alterations. Additionally, the expression of pro-inflammatory cytokines decreased, and insulin resistance in the mice with T2DM-like symptoms improved notably [82]. Conversely, elevating p53 levels in adipose tissue triggered an inflammatory response that led to insulin resistance. Notably, adipose tissue from individuals with diabetes also exhibited features resembling sene science [83].

Our findings shed light on an aspect that was previously not fully recognized: the role of p53 expression in adipose tissue in regulating insulin resistance. This suggests that signals related to cellular aging within adipose tissue could represent a novel target for the treatment of diabetes.

Tumor Necrosis Factor-*α*

TNF-α, initially associated with the onset of insulin resistance in animals, has been linked to obesity as it is prominently overexpressed in adipose tissue and decreases with weight loss, contributing to improved insulin sensitivity [84]. In both laboratory and real-world settings, TNF-α has been shown to potentially disrupt insulin signaling. It also reduces adiponectin expression within adipose tissue and lowers circulating levels in obese individuals. The use of anti-TNF-α antibodies has been shown to enhance insulin sensitivity in obese rodents, further validating its role in the development of insulin resistance [85].

When researchers increased the availability of FFAs by infusing a mixture of soybean oil (known as Intralipid) along with heparin, they observed elevated TNF-α mRNA levels in both adipose tissue and skeletal muscle in both rats and humans [86]. Additionally, studies with TNF-α knockout mice have shown that these mice do not develop insulin resistance when exposed to a high-fat diet, highlighting the cytokine's role in mediating insulin resistance induced by FFAs [87].

Furthermore, thiazolidinediones (TZDs), a class of drugs used to treat diabetes, have been found to reduce TNF-α expression in adipocytes and counteract TNF-α-induced insulin resistance in rodent models. However, there is ongoing debate about whether TNF-α

exerts its effects systemically or locally, with some researchers suggesting a more localized impact rather than a broad, whole-body effect [88].

Brain Insulin Resistance

Insulin has been considered insensitive to the brain for many years after its discovery. Unlike liver and fats insulin does not stimulate glucose uptake in the brain, rather GLUT-1 and GLUT-4 are responsible for glucose transport in the brain which are insulin independent [89, 90]. However recent findings have shown the presence of insulin and expression of insulin receptors in the brain [89-91]. Insulin enters into the brain from the bloodstream across the blood-brain barrier through a saturable transport system [89- 93]. Some studies suggest that insulin is also synthesized in the brain and insulin mRNA expression is also detected [89-94], from cultured cells of rats and mice. However, insulin was only found in neurons but not in glial cells [93, 94].

Insulin performs several actions in the brain by binding to insulin receptors. These receptors are found throughout the brain with the highest density in the hypothalamus, hippocampus, olfactory bulb, striatum, cerebral cortex, and cerebellum. Specific actions of insulin in the brain are dependent on the widespread distribution of insulin receptors, suggesting that insulin has crucial and diverse roles in the brain [89-94]. In neurons, insulin is involved in numerous neurosynaptic functions. It enhances neurite outgrowth, modulates catecholamine release, regulates the expression and localization of Gamma-aminobutyric acid (GABA), N-methyl-D-aspartate (NMDA), and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, and modulates synaptic plasticity through AKT pathway and NMDA receptor signaling [92-94]. Insulin inhibits apoptosis and thus promotes neuronal survival by regulating the expression of FOXOs [94, 95].

FOXO belongs to the forkhead box transcription family that acts as a nuclear transcriptional factor. It regulates cell survival, growth, differentiation, proliferation, reactive oxygen species (ROS) suppression, cell cycle, metabolism, and autophagy in mammals. Insulin via the AKT/PKB signaling pathway is involved in the regulation of cell survival and proliferation by phosphorylating FOXOs [96-98]. This phosphorylation results in nuclear exclusion and leads to the degradation of FOXOs by ubiquitin-proteasome pathway [96-97]. The nuclear exclusion of FOXOs by the insulin signaling pathway results in the inhibition of target gene expression and regulating FOXO activity in cells [97, 98]. This causes the accumulation of FOXOs in cytoplasm [96]. FOXOs also mediate cell cycle arrest, DNA repair, and apoptosis, thus signaling through the AKT pathway lowers the expression of negative cell cycle regulators [96]. The inability of insulin to phosphorylate FOXO results in permanent localization, causing unchecked expression of target genes associated with defective insulin signaling pathway i.e. insulin resistance [97]. This causes apoptosis which contributes to the development of neurodegenerative diseases like Alzheimer's (AD), Parkinson's (PD), and Huntington's (HD) diseases [98, 99]. These neurodegenerative diseases may develop cognitive symptoms and even dementia [100].

INSULIN RESISTANCE ON LIVER

INTRODUCTION

The main role of insulin in the liver is to inhibit the production of glucose when blood glucose levels rise. However, this function is compromised in hepatic insulin resistance, leading to increased postprandial blood sugar levels. The occurrence of hepatic insulin resistance is strongly associated with non-alcoholic fatty liver disease (NAFLD) and plays a significant role in the development of T2DM [101].

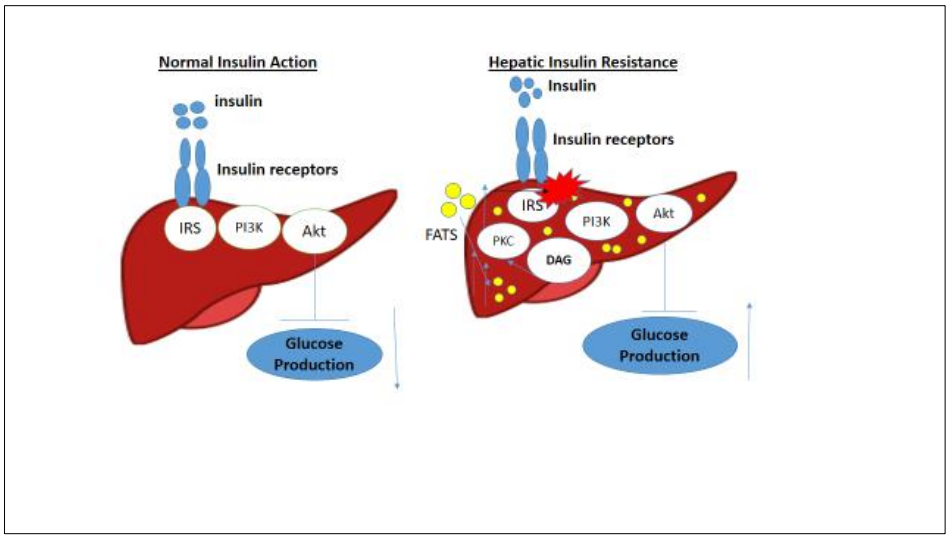

Fig no 10: Hepatic Insulin Resistance

- **Too Much Fat in the Liver**

When there's too much fat being delivered to the liver, or the body isn't burning fat properly, it can lead to the buildup of specific fat molecules called diacylglycerols (DAGs) inside liver cells [101].

- **Activation of PKCε**

This excess of DAGs triggers a process that activates a protein called PKCε. PKCε, once activated, interferes with the normal functioning of insulin. It does this by inhibiting the ability of insulin to activate its receptor and promote the necessary signals in the cell [101, 102].

- **Saturated Fatty Acids and Inflammation**

Saturated fatty acids, which are found in certain types of fats, can also contribute to insulin resistance. They do this by triggering inflammation through a signaling pathway involving a protein called TLR-4 and an adaptor protein called MyD88 [103].

- **Ceramide Synthesis**

In response to this inflammation, there's an increased production of a type of fat molecule called ceramides. These ceramides start to accumulate in the cells [104].

- **Inhibition of Insulin Signaling**

The buildup of ceramides then interferes with the normal signaling of insulin, particularly by inhibiting a key step involving a protein called Akt. This inhibition hampers the cell's ability to respond properly to insulin [105].

In simpler terms, too much fat in the liver can lead to the production of certain molecules that interfere with the normal action of insulin, making the body less responsive to its effects. This process is also influenced by specific types of fatty acids and inflammation, which further contribute to insulin resistance [106].

The first proposes that excess lipid delivery to the liver and/or reductions in fatty acid oxidation result in the accumulation of intracellular DAGs. This increase in hepatic DAG content leads to activation of PKCε which, in turn, inhibits insulin-stimulated insulin receptor kinase phosphorylation of IRS proteins and impairs activation of downstream signaling [106]. Also, saturated fatty acids induce insulin resistance by activating inflammatory TLR-4 signaling through the adaptor protein MyD88 leading to increased de novo ceramide synthesis, accumulation of ceramides and, ceramide-mediated inhibition of insulin signaling through inhibition of Akt phosphorylation [107].

Insulin binds to and activates the insulin receptor kinase during normal insulin action (left panel), which phosphorylates IRS proteins, recruits and activates PI3K, activates Akt, and ultimately suppresses the production of glucose while stimulating its uptake and storage as glycogen. According to recent research, this signaling system is malfunctioning in hepatic insulin resistance (right panel) [107]. Hepatic accumulation of DAGs due to:

1. Elevated supply of FFAs to the liver,
2. Enhanced de novo lipogenesis, and/or
3. Reduced hepatic fat oxidation initiates PKC activation, subsequently inhibiting insulin receptor kinase activity. This inhibition disrupts downstream insulin signaling, ultimately impairing insulin's ability to suppress hepatic glucose production and promote glucose uptake and glycogen storage [105-107].

CONCLUSION

Reviewing different studies, it has been observed the IR mechanism can be explored to reverse the T2DM and other health disorders caused due to it. Some medications that can reduce insulin resistance include metformin and thiazolidinediones along with exercise and a no-carb diet. Suitable in vivo and in vitro studies are required to extensively study the mechanism and possible therapeutics in it.

Aim: To study the effects and mechanisms of insulin resistance in different vital organs.

Objectives

- To find causes of insulin resistance including adipose tissue relationship.
- To find the effect of IR on the heart, kidney, liver, and brain.

GLOSSARY

- Pro-inflammatory factors - Proinflammatory cytokines these macrophages are mainly activated and play a role in increasing the severity of inflammatory responses.
- GLUT4 transporters - Glucose transporter type 4 is a human protein that is encoded in human beings by the human insulin-releasing factor (IL-1) subfamily (IL-2A4) gene.
- GLUT4 is an insulin-dependent glucose transporter that is mainly found in adipose tissue and skeletal and cardiac muscle.
- ultradian oscillatory pattern - Rhythms with periods ranging from fractions of hours to several hours. Ultradian oscillations are often less regular and less reproducible than circadian rhythms.
- Transmembrane - taking place or existing across a membrane.
- Glucokinase - catalyzes the first reaction of the glycolytic pathway and acts as the primary glucose sensor in the body.
- PACAP - Pituitary adenylate cyclase-activating peptide (PACAP) is a neuropeptide implicated in a wide range of functions, such as nociception and in primary headaches.
- Heterotetramer - a protein complex made up of

four identical subunits which are associated but not covalently bound
- Mitogenic Messaging - activation of Ras, a GTPase, that then activates the rest of the MAPK pathway, ultimately expressing proteins that stimulate cell cycle progression
- Lipodystrophy - Abnormal distribution of adipose tissue (fat tissue) in the body
- Pulsatile - Beating rhythmically
- Adipocytokines - They are cell-signaling molecules (cytokines) produced by the adipose tissue that play functional roles in energy or metabolic status of the body, inflammation, obesity.
- Lipogenesis - Synthesis of fatty acids from nonlipid precursors
- Senescence - Cellular response characterized by a stable growth arrest and other phenotypic alterations that include a proinflammatory secretome
- Postprandial state - The period following a meal
- Resistin - Cysteine-rich hormone secreted from white adipocytes.
- Homeostasis - Self-regulating process by which a living organism can maintain internal stability while adjusting to changing external conditions.
- Metformin - a member of the biguanide class of drugs, which is widely used in the treatment of type-II diabetes. It is also being explored as an antineoplastic.
- Trelagliptin succinate - Drug used for the treatment of T2DM

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