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Insulin Resistance: Molecular Mechanisms of Signalling, Pathophysiological Impact -A Narrative Review

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Abstract

Background: Insulin resistance is a complicated metabolic state in which the body does not respond to insulin properly and is related to abnormalities in glucose and lipid metabolism and to various metabolic and cardiometabolic disorders. Insulin resistance involves molecular mechanisms that are critical to understanding, improving diagnosis, and identifying potential therapeutic targets.

Methods: We reviewed the molecular and pathophysiological mechanisms of insulin resistance and their implications for metabolic and systemic disorders. We searched PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar for publications from 2000 to 2026. We reviewed the literature for insulin signalling, lipid metabolism, inflammation, oxidative stress, mitochondrial and endoplasmic reticulum dysfunction, insulin resistance in different tissues, insulin resistance and related diseases, and diagnostic and therapeutic potential.

Results: The evidence reviewed here suggests that insulin signalling problems (especially alterations in the IRS/PI3K/Akt pathway) play an important role in inducing insulin resistance through interactions with lipotoxicity, chronic inflammation, oxidative stress, mitochondrial dysfunction, and impaired inter-organ communication. These mechanisms lead to glucose and lipid abnormalities and have been linked to type 2 diabetes and to other cardiometabolic and systemic disorders such as cardiovascular disease, fatty liver disease, hypertension, polycystic ovary syndrome, and chronic kidney disease. Assessment techniques range from simple surrogate measures like HOMA-IR and QUICKI to more dynamic methods like the euglycemic–hyperinsulinemic clamp, depending on the clinical or research context.

Conclusion: Insulin resistance is a disorder that is more complex and tissue-specific than originally thought to be a single linear metabolic defect. Enhanced integration of molecular mechanisms with clinical evidence will help identify clinically relevant biomarkers and targets. New strategies targeting insulin signalling, lipid metabolism, inflammation, and related metabolic pathways are promising and warrant further exploration for clinical efficacy.

1. Introduction

Insulin resistance is a multifaceted condition of decreased insulin sensitivity in target tissues and, therefore, compromised control of glucose, lipid, and protein metabolism [1,2]. Insulin's metabolic effects are mediated mainly by the insulin receptor, a transmembrane receptor tyrosine kinase that activates multiple intracellular signalling pathways, including insulin receptor substrates (IRS) and phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) [3,4]. These pathways normally regulate glucose uptake, glycogen synthesis, lipid metabolism, protein synthesis, and hepatic glucose production. Hyperinsulinaemia may initially help maintain glucose homeostasis in individuals with impaired insulin responsiveness, but as β-cell function progressively diminishes, hyperglycaemia may persist, and T2DM may develop.

Insulin resistance is a clinical phenomenon with implications beyond glucose metabolism. It is linked closely with obesity, metabolic syndrome, cardiovascular diseases, fatty liver diseases, chronic kidney diseases, polycystic ovary syndrome (PCOS) and other systemic diseases [5, 6]. In addition, the latest clinical recommendations prioritise the early detection of metabolic abnormalities in people who are at risk of diabetes and complications associated with this condition [7]. Growing evidence links insulin resistance to abnormalities in lipid metabolism, chronic inflammation, oxidative stress, mitochondrial function, and cellular stress responses [8]. In particular, increased adipocyte tissue and dysfunction can contribute to the production of pro-inflammatory cytokines and other signalling mediators, such as tumour necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β). These mediators can activate intracellular stress pathways that impair insulin signalling, creating a vicious cycle of inflammation and insulin resistance [9,10]. Another possible mechanism of insulin resistance is oxidative stress and mitochondrial dysfunction. Hyperactive mitochondria, in this context, may lead to the overproduction of nutrient molecules and accumulation of reactive oxygen species (ROS), which can lead to mitochondrial dysfunction and disrupt insulin signalling [11, 12].

However, insulin resistance and oxidative stress are related in a reciprocal manner: insulin resistance can lead to further metabolic disturbances which increase cellular stress. Activation of the unfolded protein response (UPR) 1 (PERK pathway), the inositol-requiring enzyme 1 α (IRE1 α) pathway, and the activating transcription factor 6 (ATF6) pathway are other mechanisms that have been found to result in metabolic dysfunction in endoplasmic reticulum (ER) stress. These pathways can be continually activated, leading to inflammation, loss of cell function and poor insulin signalling [13,14]. Together, these observations imply that insulin resistance is a complex phenomenon arising from the interplay of many metabolic and cellular stress pathways, not a single biochemical defect.

Insulin resistance is tissue-specific, and the molecular consequences of impaired insulin signalling are also tissue-specific. Impaired insulin signalling may reduce glucose uptake in skeletal muscle, potentially mediated by impaired GLUT4 transport [15]. The decreased insulin action in the liver causes the normal suppression of gluconeogenesis to be lost, and further lipid production, resulting in hepatic steatosis and systemic metabolic dysfunction [16]. In addition, lipolysis in adipose tissue could raise circulating free fatty acid (FFA) levels, which, in turn, might lead to fat accumulation and impair insulin

sensitivity in the liver and muscle [17]. Insulin signalling is also important in tissues other than the classic metabolic organs. Brain insulin signalling has been linked to neuronal energy metabolism, synapse function, and cognition. In contrast, disturbances in brain insulin signalling have been linked to oxidative stress, mitochondrial dysfunction, and neurodegenerative diseases [18,19]. Likewise, hyperinsulinaemia and altered insulin/IGF related signalling are linked to pathways of cell proliferation and survival that may explain the link between insulin resistance and some cancer types in some contexts [20,21].

Although considerable research has been conducted, important questions remain about how insulin resistance interacts with molecular defects in insulin signalling pathways, lipid accumulation, inflammation, oxidative stress, mitochondrial dysfunction, ER stress, adipose tissue dysfunction, and other regulatory mechanisms in tissue-specific insulin resistance [22,23]. Furthermore, clinically accessible markers like fasting insulin levels and HOMA-IR provide only indirect estimates of insulin resistance and may not capture all insulin-sensitivity differences between tissues. A more holistic understanding of these molecular and tissue-specific mechanisms could help identify clinically relevant biomarkers and therapeutic targets [24].

This review therefore focuses on molecular and tissue-specific changes in insulin signalling pathways and how these pathways interact with metabolic and cellular stress pathways and mechanisms associated with the development and progression of insulin resistance and its associated metabolic and cardiometabolic complications. It also examines the relationships among these mechanisms and their role in disease manifestation across organ systems, as well as available methods to evaluate insulin resistance. The central research question is: What are the interactions between molecular and tissue-specific changes in insulin signalling pathways and metabolic and cellular stress pathways in the development and progression of insulin resistance and associated metabolic and cardiometabolic complications?

2. Methodology

We conducted a structured narrative review to gather the latest research on the biochemical, molecular, cellular, and pathophysiological mechanisms involved in insulin resistance and their relation to key human diseases. The review aimed to integrate molecular data with relevant physiological and clinical information on insulin-signalling pathways, metabolic and cellular stress, inter-organ crosstalk, systemic effects, and novel treatment targets.

2.1. To search the literature. Literature searching technique.

We conducted a literature search in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. We considered publications from January 2000 to September 2026, and highlighted recent studies published in the last five to 10 years. Where applicable, previous landmark research was included. We used Boolean operators (AND/OR) and free-text terms in the search.

The primary search terms used were insulin resistance, insulin signalling, insulin receptor, insulin receptor substrate, PI3K/Akt, GLUT4, oxidative stress, mitochondrial dysfunction, endoplasmic

reticulum stress, chronic inflammation, adipose tissue, skeletal muscle and liver, inter-organ crosstalk, metabolic diseases and therapeutic targets. Search combinations included were “insulin resistance” AND “molecular mechanisms,” “insulin resistance” AND “insulin signalling” AND “PI3K/Akt,” and “insulin resistance” AND “inter-organ crosstalk.”

2.2.Inclusion Criteria

We considered English-language scientific and scholarly literature on insulin resistance-related molecular mechanisms, cellular insulin-signalling pathways, metabolic abnormalities, systemic effects, tissue-specific mechanisms, inter-organ communication, diagnosis, complications, and therapeutic approaches. Original research articles, clinical studies, experimental studies, mechanistic studies, systematic reviews, meta-analyses, narrative reviews, book chapters, doctoral dissertations and other relevant scholarly papers were included if they were eligible for inclusion. In addition, landmark and foundational studies published before the stipulated search period were included when they provided important insight into known mechanisms and concepts of insulin resistance.

2.3.Exclusion Criteria

Sources were removed from the review if they did not relate to the review objectives, were duplicate publications, lacked sufficient scientific information, did not give enough background information to support the review, or were conference abstracts with insufficient detail. We also excluded publications if the available information was insufficient to interpret the mechanisms, clinical implications, diagnostics, or therapeutic approaches discussed in the review.

3. Insulin Signalling's Molecular Mechanisms and Their Dysregulation in Insulin Resistance

Insulin is a peptide hormone that is secreted from the beta cells of the islets of Langerhans in the pancreas. Insulin, IGF-1 and IGF-2 are structurally similar members of the insulin/IGF peptide family, which are encoded by separate genes in animals. Insulin binds to specific insulin receptors on target cells, resulting in metabolic effects. IGF-1 and IGF-2 stimulate a mitogenic response through cell proliferation and differentiation [25]. Insulin and IGF receptors are highly homologous and share some common features in their downstream signalling pathways but have different affinities for their respective ligands and different physiological roles. [26 -29].

Insulin signalling is a complex, tightly integrated molecular pathway that regulates cellular growth, protein synthesis, lipid metabolism, glucose uptake and energy homeostasis. The biological effects of insulin start when insulin binds to the extracellular α-subunit of the insulin receptor (IR), which is a transmembrane receptor tyrosine kinase [30].

Ligand binding induces a conformational change. This causes autophosphorylation of tyrosine residues in the intracellular β-subunit, which in turn induces conformational changes that create docking sites for other proteins to interact with the receptor and initiate downstream signalling. One key step in this process is the recruitment/ phosphorylation of insulin receptor substrates (IRS-1 and IRS-2). The most important of the downstream signalling cascades activated by the phosphorylated IRS proteins is the phosphatidylinositol 3-kinase/protein kinase B pathway (PI3K/Akt) [31]. When activated, PI3K generates phosphatidylinositol-3,4,5-trisphosphate (PIP3), which recruits and activates Akt. Akt then

regulates metabolic pathways such as glucose transport, glycogen synthesis, lipid metabolism, protein synthesis, and hepatic gluconeogenesis [32].

In skeletal muscle and adipose tissue, Akt stimulates the movement of a glucose transporter (GLUT4) to the plasma membrane. When GLUT4 is more highly expressed at the plasma membrane, glucose uptake increases and blood glucose levels remain normal. Insulin-induced activation of Akt suppresses excessive glucose production from the liver in two ways: by stimulating glycogen synthesis and by suppressing expression of gluconeogenic enzyme genes [33].

Insulin signalling also activates other pathways, and the Ras/Raf/MEK/ERK pathway is more closely related to cellular growth, proliferation, and gene expression. So, through linked signalling networks, insulin signalling co-ordinates metabolic and mitogenic responses. These pathways must be balanced to achieve the metabolic homeostasis required for normal function [34].

But this signalling system slowly deteriorates over time due to insulin resistance. Skeletal muscle and adipose tissue insulin receptor activation, IRS phosphorylation, PI3K/Akt signalling, and GLUT4 translocation may decrease significantly, reducing glucose uptake in these tissues.

However, even when blood insulin levels are high, gluconeogenesis can persist despite poor insulin signalling in the liver. These abnormalities contribute to a progressive metabolic dysfunction and compensatory hyperinsulinemia [35].

Most importantly, insulin resistance is not caused by a single biochemical defect. Insulin signalling may be disturbed by serine phosphorylation of IRS proteins, accumulation of intracellular lipids, oxidative stress, mitochondrial dysfunction and endoplasmic reticulum (ER) stress. IRS–PI3K/Akt activity can also be inhibited by other lipid-derived signalling molecules and inflammatory mediators, like tumour necrosis factor (TNF-α) and interleukin-6 (IL-6). Thus, insulin resistance should be considered a disturbance in the net outcome of multiple cellular processes, including cellular stress responses and inflammatory and metabolic processes [36]. Disrupted insulin signalling affects metabolic organ-to-organ communication. Adipose tissue dysfunction may release excess free fatty acids (FFAs), adipokines, and inflammatory mediators, altering insulin sensitivity in skeletal muscle and the liver. Concurrently, hepatic lipid accumulation can cause systemic insulin resistance, and sustained stress on pancreatic β-cells can cause insulin insufficiency. These interconnected pathways suggest that perturbations in insulin signalling may be linked to systemic metabolic disturbances. Thus, impaired inter-organ communication and impaired insulin responsiveness can create a vicious cycle that leads to metabolic disease [37,38].

4. Pathophysiological Consequences by Organ System

4.1.Insulin resistance in Type 2 Diabetes Mellitus

Insulin resistance is a fundamental metabolic abnormality that underlies the onset and progression of Type 2 Diabetes Mellitus (T2DM). A blunted biological reaction of target tissues to normal or high levels of insulin, resulting in impaired glucose uptake, disturbed lipid metabolism and ineffective control of hepatic glucose production [39]. Although insulin resistance can also impact the cardiovascular system, pancreatic islets, and other metabolically active organs, skeletal muscle, liver, and adipose tissue are the main tissues affected. Insulin interacts with a transmembrane tyrosine kinase receptor known as the insulin receptor (IR), which activates a series of intracellular signalling pathways [40]. Insulin receptor substrate (IRS) proteins on the receptor, when activated, Phosphorylate and activate phosphoinositide 3-

kinase (PI3K), which in turn activates protein kinase B (AKT). This pathway is responsible for the metabolic effects of insulin such as glucose transport, glycogen synthesis, lipid metabolism, and inhibition of hepatic glucose production [41]. In fat cells and in muscle cells, activation of AKT allows the movement of glucose transporter 4 (GLUT4) to the plasma membrane, allowing glucose to be taken up. This signalling system worsens in insulin-resistant circumstances. Defects in IRS signalling, as well as reduced activity of the insulin receptor, PI3K/AKT and GLUT4 translocation, limit insulin-induced glucose uptake in skeletal muscle and adipose tissue [42]. This results in an excess of glucose in the bloodstream (postprandial hyperglycemia), and finally in fasting hyperglycemia. Insulin resistance also lessens the efficacy of insulin's inhibitory effects on gluconeogenesis and glycogenolysis in the liver, leading to glucose production. These abnormalities, taken together, account for abnormalities of systemic glucose homeostasis. Skeletal muscle insulin resistance is one of the greatest factors in type 2 diabetes and is the major player in insulin-mediated glucose clearance [43].

Possible mechanisms that limit glucose uptake include intracellular accumulation of lipid metabolites, mitochondrial dysfunction, oxidative stress, inflammation, and changes in insulin-signalling proteins in skeletal muscle. The down-regulation of GLUT4 translocation thus reduces glucose utilisation and increases blood glucose. Fat tissue insulin resistance contributes to the metabolic derangements of type 2 diabetes. Normally, the release of free fatty acids (FFAs) is inhibited by insulin, and lipolysis is inhibited. With excess lipolysis, circulating FFAs increase as adipose tissue becomes insulin resistant [44].

When these FFAs accumulate ectopically in the liver, skeletal muscle, and pancreatic β-cells, they can cause lipotoxicity, oxidative stress, mitochondrial dysfunction, and additional defects in insulin signalling. Systemic insulin resistance may also result from dysfunctional adipose tissue’s increased production of pro-inflammatory cytokines and altered levels of adipokines. Another significant factor causing type 2 diabetes is hepatic insulin resistance. In healthy people, insulin inhibits hepatic glucose production after meals [45].

However, when the liver becomes insulin resistant, gluconeogenesis and glycogenolysis remain inappropriately active despite high circulating insulin levels. Thus, increased hepatic glucose production is a key determinant of fasting hyperglycemia in T2DM. Initially, pancreatic β-cells increase insulin output to make up for insulin resistance. This compensatory response causes hyperinsulinemia and keeps glucose concentrations within or near the normal range. However, chronic exposure to hyperglycemia and hyperlipidaemia, oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, and inflammatory signalling progressively impairs β-cell activity. As long as β-cells can correct for insulin resistance, insulin production is adequate to maintain glucose homeostasis in the normal range [46].

Hence, there can be a progression of insulin resistance to type 2 diabetes:

Insulin resistance results in compensatory hyperinsulinemia, which leads to β-cell stress, β-cell dysfunction, decreased glucose tolerance, chronic hyperglycemia, and Type 2 diabetes mellitus [47].

Insulin resistance is not an isolated condition. It is triggered by genetic susceptibility, excess body fat, lack of physical activity, altered lipid metabolism, oxidative stress, chronic low-grade inflammation and environmental/lifestyle factors. These factors can create a metabolic milieu that increases insulin

resistance and pancreatic dysfunction, reinforcing one another [48]. Insulin resistance should therefore be considered a multisystem metabolic disorder characterised by integrated metabolic disturbances in glucose, lipid, inflammatory, and cellular signalling pathways, not merely a defect in glucose metabolism. Understanding these pathways is crucial for elucidating the shift from metabolic dysfunction to type 2 diabetes and for pinpointing possible treatment targets to stop the progression of the disease and its complications [49].

Insulin resistance has systemic effects on many organ systems, as illustrated in Figure 1. Impaired insulin signalling contributes to a variety of metabolic disorders, hyperinsulinemia, inflammation, oxidative stress, and all of these factors can lead to the development of type 2 diabetes, cardiovascular disease, liver disease, PCOS, obesity and metabolic syndrome, renal disease and hypertension, neurodegenerative disorders, and cancer. The connecting arrows indicate that insulin resistance is a systemic metabolic condition, not simply a problem of glucose metabolism, and that conditions may interact and contribute to insulin resistance.

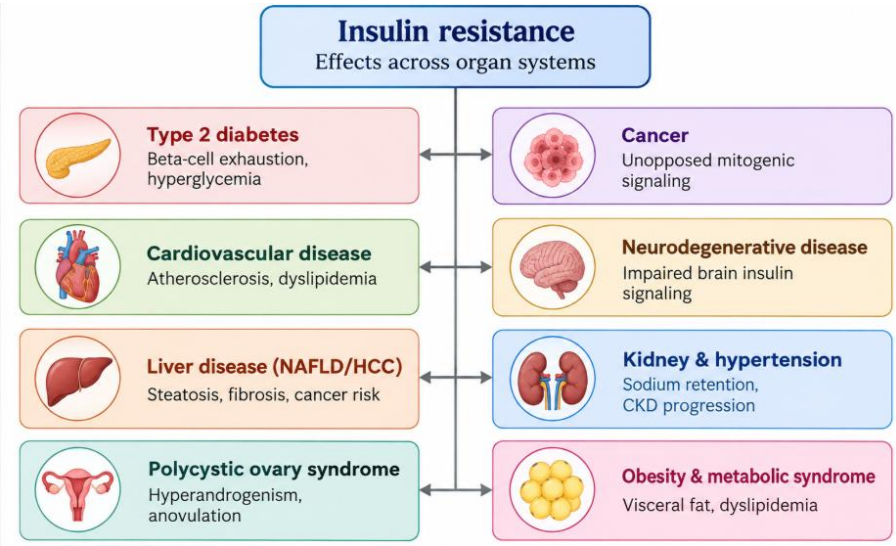

Figure 1: flow diagram of insulin resistance's pathophysiological consequences across the eight organ systems [24].

5. Cardiovascular and Vascular Consequences of Insulin Resistance

Cardiovascular and vascular abnormalities are closely related to insulin resistance, even in those without clinically diagnosed type 2 diabetes mellitus. Several interconnected mechanisms underlie the cardiovascular effects, including endothelial dysfunction, dyslipidaemia, hypertension, chronic inflammation, oxidative stress, abnormal vascular remodelling, and accelerated atherosclerosis [50]. Beyond its metabolic effects, insulin has important vascular effects under physiological conditions. Insulin induces the activation of phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) in endothelial cells, leading to elevated nitric oxide (NO) levels by activation of endothelial nitric oxide synthase (eNOS). NO is involved in vessel relaxation, endothelial function and blood flow [51]. Insulin-insensitive states can selectively impair the insulin-induced PI3K/Akt/eNOS pathway, thereby reducing NO bioavailability,

without affecting the other pathway, the mitogen-activated protein kinase (MAPK) pathway. An imbalance could be related to vasoconstriction, vascular inflammation, and inappropriate smooth muscle responses that may lead to vascular dysfunction and cardiovascular disease [52].

5.1. Endothelial Dysfunction

Insulin resistance is associated with cardiovascular disease, and endothelial dysfunction is an important link between these two. Under normal physiological conditions, insulin enhances endothelial NO production through the PI3K/Akt/eNOS pathway. NO causes vasodilation inhibits platelet aggregation and smooth-muscle proliferation and vascular inflammation [53]. Insulin resistance diminishes insulin signalling through the PI3K/Akt/eNOS pathway, reducing endothelium-dependent vasodilation and NO availability [53].

Concurrently, the relative preservation of MAPK signalling could contribute to the production of endothelin-1 and other vasoconstrictive and pro-inflammatory mediators. As a result, the vasodilatory and vasoconstrictive signalling changes contribute to endothelial dysfunction [54]. Endothelial injury may become worse due to the ongoing low-grade inflammatory status, hyperglycaemia, high free fatty acid levels, dyslipidaemia and increased release of reactive oxygen species (ROS). ROS can quickly deplete NO bioavailability and impair eNOS function, both of which decrease vascular function [54]. Insulin resistance may also lead to endothelial dysfunction, and endothelial dysfunction may lead to insulin resistance. Increased NO may lead to decreased skeletal-muscle blood flow and microvascular recruitment, which will decrease insulin and glucose delivery to peripheral tissue. This also further decreases glucose uptake and can play an additional role in insulin resistance [55]. This could be a vicious cycle of sub-optimal insulin signalling, reduced bioavailability of NO, endothelial dysfunction and reduced microvascular perfusion, all of which can progress to CMVD [55].

5.2. Dyslipidaemia and Atherosclerosis

Insulin resistance is closely linked with atherogenic dyslipidaemia and the development of atherosclerosis. There are increased triglycerides, enhanced production of very low-density lipoprotein (VLDL), decreased high-density lipoprotein cholesterol (HDL-C), and an increase in the number of small, dense low-density lipoprotein (LDL) particles that are insulin resistant [56]. This lipid pattern makes circulating lipoproteins more atherogenic and may promote oxidative modification and retention in the arterial wall [56].

Impaired insulin action in adipose tissue leads to lipolysis and the release of free fatty acids (FFAs) into the bloodstream. Increased FFA delivery to the liver may increase hepatic triglyceride and VLDL production. Further changes in lipid exchange between circulating lipoproteins lead to the creation of small, dense LDL particles and decreased HDL-C levels [57]. Small, dense LDL particles are likely to accumulate in the arterial intima, are more likely to be oxidized, and may play a significant role in atherogenesis [57].

Compensatory pancreatic insulin secretion may also impact vascular and inflammatory pathways via hyperinsulinemia. These abnormalities, along with hyperglycemia, elevated FFAs, oxidative stress, and

chronic low-grade inflammation, can contribute to endothelial injury, vascular inflammation, plaque formation and progression of atherosclerosis [58]. This is a mutual effect, as vascular dysfunction and atherosclerosis can reduce tissue perfusion and insulin delivery, especially in skeletal muscle, which can further exacerbate peripheral insulin resistance [59].

This means that insulin resistance, adipose lipolysis, hepatic VLDL/triglyceride production, atherogenic lipid abnormalities, endothelial dysfunction, and vascular inflammation may be part of an integrated metabolic–vascular pathway [59].

5.3. Vascular Remodelling and Hypertension

Insulin resistance is often accompanied by hypertension, especially in people who are obese, have excess stomach fat, have metabolic syndrome, and have type 2 diabetes mellitus. The connection between these and obesity is multifaceted, including endothelial dysfunction, sympathetic nervous system activation, renal sodium retention, renin–angiotensin–aldosterone system (RAAS) activity, chronic inflammation, and oxidative stress [59].

Insulin defects in the vascular endothelium could impair the endothelium's ability to synthesise nitric oxide (NO) through the PI3K/Akt/eNOS pathway and to mediate endothelium-dependent vasodilation. The latter, on the other hand, might induce vasoconstrictive mechanisms such as endothelin-1 via a relatively intact MAPK-dependent signalling pathway. This imbalance can result in elevated blood pressures (hypertension) [61]. Hyperinsulinaemia, also linked to insulin resistance, can lead to renal sodium retention, increasing extracellular fluid volume and cardiac output. RAAS can be activated, increasing aldosterone activity and promoting sodium retention, and increasing angiotensin II activity and promoting vasoconstriction [62]. Additionally, hypertension is associated with insulin resistance, which is also linked to endothelial dysfunction, oxidative stress, inflammation, and vascular remodelling, mediated by angiotensin II and aldosterone [62].

Another connection between insulin resistance and high blood pressure is through activation of the sympathetic nervous system. Insulin resistance, obesity and hyperinsulinaemia may also stimulate sympathetic activity, leading to elevated heart rate, vasoconstriction, and renal sodium retention. Sympathetic stimulation is therefore continuously required to sustain high blood pressure and further worsens vascular dysfunction [62].

Visceral adiposity is especially relevant because excess fat is associated with higher production of FFAs, inflammatory cytokines, and adipokines, which can profoundly affect insulin resistance and hypertension. In addition, ROS can decrease NO bioavailability, and endothelial dysfunction and inflammatory mediators from dysfunctional adipose and vascular tissue may induce vascular remodeling and arterial stiffness [63]. In addition, chronic hypertension may lead to structural changes which result in damage to microcirculation, tissue hypoperfusion, and oxidative stress that can further contribute to insulin resistance by impairing insulin delivery and peripheral insulin uptake [64]. Changes in insulin and growth factor signalling can also affect the vascular smooth-muscle cells and cause insulin resistance. The activation of these proliferation pathways may contribute to migration and proliferation of vascular smooth-muscle cells, thus resulting in arterial stiffening and vascular remodelling. Such changes may happen in parallel,

along with endothelial dysfunction, inflammation and lipid deposition, and impact the structure and function of the blood vessels as well [60]. The relationship between insulin resistance and hypertension can be considered a reinforcing metabolic-vascular cycle of hyperinsulinism, endothelial dysfunction, sympathetic activation, activation of the renin-angiotensin-aldosterone system (RAAS), renal sodium retention, increased vascular resistance, oxidative stress, inflammation and vascular remodelling [64]. These interactions might explain this link between insulin signalling, vascular function, renal sodium handling and neurohormonal control. They may offer a therapeutic approach to favour insulin sensitivity in the presence of a well-controlled cardiovascular risk profile [65].

6. Diagnostic and Assessment Approaches

Several approaches measure insulin resistance, ranging from simple surrogate markers to more complex physiological methods. HOMA-IR and QUICKI are favoured because they rely on fasting glucose and insulin, are inexpensive and easy to use, and suit large studies. However, both are indirect measures and are affected by variability in insulin assays, population characteristics, and the lack of universally accepted cut-off values.

The euglycemic/hyperinsulinemic clamp is regarded as the standard technique for measuring insulin sensitivity because it directly measures insulin-mediated glucose disposal. However, its technical complexity, invasiveness, cost and time make it mainly applicable for specialized research applications [66].

Measuring insulin along with the oral glucose tolerance test (OGTT) provides dynamic information about glucose handling and insulin secretion. Gastric emptying, insulin release and peripheral glucose uptake, however, can influence the results. Simple, useful surrogate markers are available for assessing insulin resistance; these are not direct measurements of insulin resistance but markers of metabolic risk, such as the triglyceride-to-HDL ratio and waist circumference. In general, the method should match the assessment purpose: for clinical and epidemiological studies, use simple surrogate indices; for precise physiological studies, use dynamic methods (e.g., clamp). Shown in Figure 2.

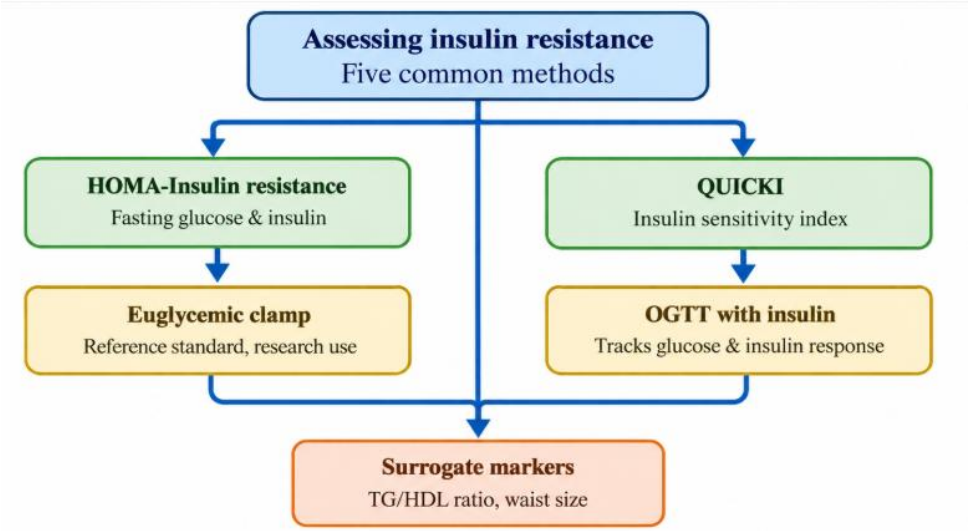

Figure 2. Overview of Common Methods for the Assessment of Insulin Resistance

7. Discussion

Insulin resistance is a multiple tissue-dependent process characterised by defects in insulin signalling, lipid accumulation, inflammation, oxidative stress, mitochondrial dysfunction, endoplasmic reticulum dysfunction, and inter-organ communication. The evidence reviewed here suggests that defects in the IRS/PI3K/Akt pathway may lead to failure of glucose uptake in skeletal muscle and adipose tissue and failure to suppress hepatic glucose production. These mechanisms are linked to metabolic and cellular stress and are linked to cardiometabolic diseases such as type 2 diabetes.

Insulin resistance is also linked to cardiovascular disease complications such as endothelial dysfunction, dyslipidaemia, inflammation, oxidative stress, vascular remodelling, and disordered renal and neurohormonal regulation. Thus, insulin resistance must be viewed as a complex metabolic process, and not just a linear defect. Surrogate assessments (like HOMA-IR versus QUICKI) should also be considered when using surrogate methods versus dynamic methods (like the euglycemic–hyperinsulinemic clamp).

8. Limitations

This review has several limitations. This was a structured narrative review, not a systematic review or meta-analysis; as such, we did not undertake quantitative synthesis or a formal risk-of-bias assessment. The evidence comprised various study types and populations, making direct comparisons difficult. Insulin resistance is also tissue-specific, and results from experiments in other species may not directly apply to people. Another problem is that surrogate measurements, like HOMA-IR and QUICKI, have methodological drawbacks and cannot directly assess tissue-specific insulin sensitivity.

9. Conclusion

Insulin resistance is a polygenic metabolic disorder, with multiple interacting molecular and cellular mechanisms that go beyond impaired glucose regulation. A spectrum of alterations in insulin receptor signalling, specifically the IRS/PI3K/Akt pathway, lipid accumulation and lipotoxicity, chronic inflammation, oxidative stress, mitochondrial dysfunction, endoplasmic reticulum (ER) stress, and disturbed communication among the cells and inter organ communication, can impair insulin action and disrupt metabolic homeostasis. These abnormalities can involve multiple tissues and play a role in the development and progression of type 2 diabetes and other insulin-resistance-related disorders such as atherosclerosis, fatty liver disease, polycystic ovary syndrome, chronic kidney disease, and other disorders.

Choose an insulin resistance assessment based on the clinical or research objective. HOMA-IR and QUICKI are practical surrogate measures useful in clinical and epidemiological studies; meanwhile, the euglycemic–hyperinsulinemic clamp is a more direct measure of insulin sensitivity, is technically more demanding, and is used mainly for specialised research purposes. Other parameters, such as indices derived from the OGTT, triglyceride-to-HDL ratio, and waist circumference, can provide additional information on glucose metabolism and metabolic risk but are not equivalent measures of insulin resistance.

Insulin resistance is best viewed as a tissue-specific, multifactorial pathway rather than a linear one. Preserved or altered signalling across pathways may contribute to the wide spectrum of clinical syndromes associated with insulin resistance. Still, interactions between these pathways and disease depend on tissue and disease context. Better understanding of these interactions might help identify clinically important therapeutic targets and risk predictors. Future studies should combine molecular, experimental and human clinical data to decipher the mechanisms involved and assess the potential of targeted interventions that can enhance insulin sensitivity and alleviate the burden of insulin resistance-related diseases in different tissues**.**

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