The growing concern about the increase in cases of Insulin Resistance: A Comprehensive Review

Dr Sugandha Raghuvanshi, Medical officer
&
Dr Ashok Sharma, MD medicine
Indraprastha Apollo Hospital, New Delhi (India)

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Abstract: Insulin resistance (IR) has emerged as a critical global health issue with significant implications for public health. This metabolic condition is characterized by reduced cellular responsiveness to insulin, leading to hyperglycemia and disruptions in lipid and protein metabolism. IR is closely linked to the rising prevalence of chronic diseases, including type 2 diabetes mellitus (T2DM), cardiovascular diseases, metabolic syndrome, and obesity, which collectively pose immense health and economic burdens worldwide. This comprehensive review provides an in-depth exploration of the multifaceted nature of IR, encompassing molecular mechanisms, genetic predispositions, and modifiable lifestyle factors. The dysfunctions in insulin signaling pathways, including defects in proximal and distal signaling and interorgan metabolic crosstalk, are discussed in detail, along with the contributions of genetic mutations and epigenetic dysregulation. These insights are augmented by an examination of demographic disparities, with a focus on sex- and ethnicity-specific variations, as well as regional prevalence patterns influenced by urbanization and dietary trends. The review highlights the importance of lifestyle interventions, including dietary modifications, regular physical activity, and stress management, as first-line strategies to improve insulin sensitivity. Pharmacological approaches, such as the use of metformin, SGLT2 inhibitors, and newer therapeutic agents targeting specific molecular pathways, are also analyzed. Additionally, emerging therapies, including the potential role of epigenetic modifications and genetic engineering, are presented as promising avenues for addressing IR and its associated complications.

Keywords: Insulin resistance, type 2 diabetes mellitus, metabolic syndrome, cardiovascular diseases, obesity, epigenetic regulation, insulin signaling pathways, public health, lifestyle interventions, pharmacological treatments.

INTRODUCTION

The discovery of insulin in 1921 revolutionized our understanding of glucose regulation, laying the groundwork for research into insulin's broader role in metabolism.[1] Frederick Sanger's sequencing of bovine insulin in 1955 clarified its amino acid structure, earning him the Nobel Prize in 1958.[2] This, along with the later synthesis of bovine insulin in 1965 and the advent of recombinant DNA technology, transformed insulin therapy and underscored insulin's central role in regulating glucose, lipid metabolism, protein synthesis and gene expression.[3,4] Insulin is a hormone produced by the pancreatic β-cells, which regulates glucose homeostasis by promoting glucose uptake into tissues such as the liver, muscle and adipocytes. In healthy individuals, rising blood glucose triggers insulin release, facilitating glucose absorption and inhibiting hepatic glucose production. However, in insulin resistance (IR), this process is impaired.[5] In IR, tissues become less responsive to insulin, resulting in elevated blood glucose levels and disruptions in lipid and protein metabolism. IR is associated with several diseases including obesity, type 2 diabetes (T2DM), metabolic syndrome, cardiovascular disease and some cancers.[6,7]

The global prevalence of IR has become a major public health issue, with studies indicating that approximately one-third of adults in developed countries are affected and the rates continue to rise. The concerning trends, with an annual increase of 1.5-2% in IR cases.[7] The significance of IR extends beyond glucose metabolism, serving as a fundamental cause of chronic diseases such as T2DM and cardiovascular disorders, as noted by Petersen and.[8,9] Given the growing concern over IR, it is crucial to understand its underlying mechanisms and develop effective interventions. Lifestyle changes including dietary modifications and physical activity, are essential first-line strategies to improve insulin sensitivity and reduce insulin resistance.[10,11] Additionally, pharmacological treatments such as metformin, sulfonylureas and SGLT2 inhibitors are commonly used to manage IR and associated conditions.[9]

This review will provide an overview of the mechanisms behind insulin action and resistance, exploring the metabolic pathways involved. We will also examine the diseases linked to IR, the methods for diagnosing it and the current treatment approaches. By highlighting the urgency of addressing IR, we aim to offer insights into how lifestyle changes, medications and emerging therapies can help manage this complex condition and its widespread health impact.

METHODOLOGY

The comprehensive literature search covered major databases (MEDLINE/PubMed, Web of Science, Scopus, EMBASE, Cochrane Library, Peer-reviewed). The search strategy employed a combination of Medical Subject Headings (MeSH) terms and free text words, carefully selected to capture all relevant literature. Primary search terms included "Insulin Resistance" and "insulin sensitivity" combined with secondary terms such as "prevalence," "epidemiology" and "incidence" as well as tertiary terms related to risk factors and associated conditions. Included studies were peer-reviewed publications involving human subjects with clear insulin resistance criteria. The review incorporated various study designs from randomized controlled trials to cross-sectional analyses.

EPIDEMIOLOGICAL TRENDS

A. Global Prevalence

Insulin resistance represents a critical global health challenge that has gained significant attention in recent epidemiological research.[12] The complex metabolic condition has emerged as a key predictor of various chronic diseases including type 2 diabetes, cardiovascular disorders and metabolic syndrome. The global prevalence of insulin resistance has shown a dramatic increase over recent decades. A comprehensive meta-analysis by Jiang et al. (2024) demonstrated a substantial rise in metabolic dysfunction across multiple populations.[13] The study highlighted the intricate interplay between genetic predispositions, environmental factors and lifestyle choices in the development of insulin resistance. Regional variations in insulin resistance prevalence are particularly noteworthy. A landmark study in The Lancet by Collaboration NCD Risk Factor (2021) examined global trends across different geographical regions. North American populations consistently show higher rates of metabolic dysfunction, with studies from the Centers for Disease Control and Prevention (CDC) indicating that approximately 35-40% of adults exhibit characteristics of insulin resistance. These regional disparities, emphasizing the role of urbanization, dietary patterns and sedentary lifestyles in driving metabolic changes.[9]

Demographic Considerations

Sex Differences

Studies have shown that premenopausal women have fewer metabolic disorders including lower rates of insulin resistance (IR) compared to men, but this protective effect reduces significantly after menopause.[14] Female sex hormones, particularly estradiol (e.g., 17β-oestradiol), protect proopiomelanocortin (POMC) neurons from IR by enhancing their excitability and linking insulin receptors to transient receptor potential (TRPC) channel activation.[15] Endogenous estrogens primarily exert their protective effects through ER-α activation in tissues such as the brain, liver, skeletal muscle, adipose tissue and pancreatic β cells.[16] Estrogens also influence body adiposity, fat distribution, glucose metabolism and insulin sensitivity, making women more insulin-sensitive than men. Women under the age of 51 show significantly lower fasting glucose and triglyceride levels compared to men.[17] Genetic factors contribute to these differences, such as male homozygotes for polymorphisms in the *PPP1R3A* gene, which affects glycogen synthase activity, being diagnosed with IR or diabetes earlier than women (74). Other factors including differences in visceral and hepatic adiposity, adiponectin levels (an insulin-sensitizing hormone), resting energy expenditure and lipid metabolism, further explain the higher prevalence of IR in men compared to women.[18,19]

Ethnicity Differences

Type 2 diabetes mellitus (T2DM) is projected to affect nearly 600 million people worldwide by 2035.[20] Studies have shown that the prevalence of T2DM varies significantly across different racial and ethnic groups, partly due to

differences in insulin sensitivity, which influence plasma triglyceride levels.[21,22] For example, the Singapore Adults Metabolism Study (SAMS) conducted a subgroup analysis and found that Chinese and Malays exhibit higher insulin sensitivity compared to Asian Indians among lean and young Singaporean males.[23] This finding aligns with reports showing a lower prevalence of T2DM in Chinese (9.7%) and Malays (16.6%) compared to Asian Indians (17.2%). In the United Kingdom, South Asian children demonstrate greater insulin resistance (IR) compared to white European children, with girls being more insulin resistant than boys. These differences are influenced by both ethnicity and body composition.[24] Furthermore, individuals of Aboriginal or South Asian descent, who often have increased levels of body fat and visceral fat deposition, are more prone to developing IR and T2DM compared to other ethnic groups, such as Chinese and Indian populations.[25]

Modifiable Lifestyle Factors

In addition to genetic and physiological factors, modifiable lifestyle elements such as diet, exercise, smoking, sleep and stress significantly contribute to insulin resistance (IR).[26] For instance, irregular eating habits and poor sleep are strongly linked to an elevated risk of obesity and IR. Disruptions to circadian rhythms, caused by factors such as clock gene mutations, disturbed sleep cycles, shift work and jet lag, are also associated with the development of IR.[27] Epidemiological studies suggest that maintaining regular exercise, adhering to a healthy diet (rich in soluble fiber, colorful fruits, vegetables, green tea and low in added sugars, refined carbs and trans fats), moderating alcohol consumption, avoiding smoking and managing stress can enhance insulin sensitivity.[28] While such lifestyle adjustments can naturally improve insulin sensitivity, consulting a healthcare professional is crucial before making significant changes or adding medications.

Research on vitamin D supplementation has shown mixed results. Some studies suggest that vitamin D may reduce IR by increasing insulin receptor gene transcription and exhibiting anti-inflammatory effects[29], whereas others indicate no significant impact[30]. Further research is necessary to clarify the role of vitamin D in managing IR. Both experimental and clinical studies have identified several hormones, such as glucocorticoids, cortisol, growth hormone and human placental lactogen as contributors to IR.[31,32] These hormones may reduce insulin's ability to suppress glucose production and limit insulin-stimulated glucose uptake. Additionally, certain medications including anti-adrenergics (e.g., salbutamol, salmeterol and formoterol)[33,34], HIV protease inhibitors, atypical antipsychotics and some forms of exogenous insulin, can influence insulin signaling and affect IR. The interplay between various risk factors can have synergistic effects on the development of IR. Collaborative efforts between researchers and medical experts are essential to identify effective strategies for reducing the risk of IR and improving metabolic health.

INSULIN SIGNALING AND INSULIN RESISTANCE

Insulin, an endocrine peptide hormone composed of 51 amino acids, is critical for maintaining glucose and lipid homeostasis. It is secreted by pancreatic beta cells and exerts its effects by binding to insulin receptors (INSR) on the plasma membrane of target cells. This binding initiates a cascade of signaling events involving key molecules such as insulin receptor substrate (IRS), phosphatidylinositol 3-kinase (PI3K) and protein kinase B (AKT), which mediate tissue-specific responses to insulin.[35,36] The activation of AKT and its downstream substrates leads to diverse biological effects including glycogen synthesis, inhibition of gluconeogenesis, protein synthesis, adipogenesis, lipid metabolism regulation and suppression of lipolysis.[37,38]

Despite insulin's essential role in metabolic regulation, disruptions in its signaling pathways are central to the pathogenesis of insulin resistance (IR). This condition, characterized by reduced responsiveness of target tissues to insulin, contributes significantly to the global burden of metabolic disorders, particularly type 2 diabetes mellitus (T2DM). As the prevalence of IR continues to rise, understanding its molecular underpinnings has become increasingly critical. This section examines the mechanisms underlying defective insulin signaling and their contributions to IR.

A. DIRECT DEFECTS IN INSULIN SIGNALING

The complex insulin signaling network relies on precise modulation at each step to ensure proper biological responses in various tissues. Defects in the signaling pathway at different levels contribute to the development of IR, disrupting glucose and lipid metabolism.

1. Proximal Insulin Receptor Signaling

Insulin exerts its effects by binding to its receptor (INSR) on target cells, activating IRS proteins (mainly IRS1 and IRS2) and downstream signaling molecules like PI3K and AKT. These processes are critical for maintaining glucose homeostasis.[39] However, defects in INSR expression, ligand binding, phosphorylation and kinase activity are common in IR. Obesity and diabetes are associated with reduced surface INSR content and decreased INSR kinase activity. These defects lead to impaired IRS1 tyrosine phosphorylation, a hallmark of insulin-resistant skeletal muscle.[40] Furthermore, specific knockout of INSR in the liver prevents insulin's suppression of hepatic glucose production, highlighting its role in hepatic IR. IRS proteins are essential for transmitting signals from INSR to downstream effectors like PI3K. Decreased expression or increased serine phosphorylation of IRS proteins reduces their interaction with PI3K, impairing its activation and inducing IR.[41,42] Experimental models further demonstrate that gene deletions in IRS1 or IRS2 result in peripheral IR, impaired glucose transport and diabetes due to defective PI3K/AKT signaling. The importance of PI3K in insulin action is underscored by studies showing that pharmacological inhibitors or genetic knockouts of PI3K abolish insulin-stimulated glucose transport, GLUT4 translocation and DNA synthesis.[43] Similarly, mutations or inhibition of AKT, a critical downstream effector, impair insulin-stimulated GLUT4 translocation and glucose uptake in skeletal muscle and liver.[44] Elevated levels of nonesterified fatty acids (NEFAs) further exacerbate these defects by inhibiting IRS-1-associated PI3K activity, thereby disrupting glucose metabolism. Together, these proximal signaling defects impair the ability of insulin to regulate glucose homeostasis, underscoring their critical role in the pathogenesis of IR.[45]

2. Distal Downstream Signaling

The downstream effects of insulin signaling involve diverse targets of AKT activation, which mediate specific responses in different tissues. Among these, GLUT4 is the most well-characterized substrate, playing a pivotal role in glucose uptake in skeletal muscle and adipose tissues.[46] Insulin stimulates the translocation of GLUT4-containing vesicles (GSVs) to the cell surface, facilitating glucose uptake. Impaired translocation of GLUT4 is a hallmark of IR in skeletal muscle and adipose tissues, leading to reduced glucose uptake and metabolic dysregulation. Studies in animal models show that disruptions in GLUT4 translocation result in glucose intolerance and metabolic disease.[47] Further downstream, Tbc1d4, an AKT substrate involved in regulating GLUT4 vesicle activation, is critical for insulin-stimulated glucose uptake. Loss of Tbc1d4 or its phosphorylation impairs GLUT4 translocation and glucose uptake, as observed in experimental models.[48] These findings highlight the importance of downstream signaling molecules in maintaining glucose homeostasis and suggest potential therapeutic targets for improving insulin sensitivity.

B. INTERORGAN METABOLIC CROSSTALK

The growing concern about insulin resistance (IR) is compounded by its complex interorgan metabolic crosstalk. Insulin resistance, a key factor in the development of metabolic disorders like type 2 diabetes (T2DM), involves a series of disruptions in the regulatory pathways that normally maintain glucose and lipid homeostasis. Understanding the interorgan communication involved in IR provides valuable insights into its pathophysiology and the escalating global prevalence of the condition. Insulin signaling plays a central role in calibrating glucose homeostasis by limiting hepatic glucose output through decreased gluconeogenesis and glycogenolysis, while promoting glucose uptake in muscle and adipose tissues. Additionally, insulin regulates lipid metabolism by promoting lipid synthesis in liver and fat cells and inhibiting fatty acid release from triglycerides (TG) in these tissues. These processes work together to maintain a balanced metabolic state.[49] However, in IR, these pathways become dysregulated, leading to impaired glucose uptake and altered lipid metabolism, which in turn contributes to the pathogenesis of T2DM and associated diseases.

1. Insulin's Effect on Hepatic Glucose Metabolism

Insulin plays a pivotal role in regulating hepatic glucose production by activating glycogen synthesis and suppressing glycogenolysis and gluconeogenesis. This action is crucial for reducing hepatic glucose output in response to meals and maintaining glucose homeostasis. In IR, however, the liver becomes less responsive to insulin, impairing its ability to regulate glucose production effectively.[50] The liver's ability to suppress gluconeogenesis is primarily mediated by the inhibition of FOXO1, a transcription factor that promotes the expression of glucose-6-phosphatase (G6pc), a key enzyme involved in gluconeogenesis (109). Mouse models of profound hepatic IR show increased expression of G6pc, suggesting that elevated FOXO1 activity contributes to the persistence of glucose production despite insulin signaling. In addition to gluconeogenesis, insulin regulates glycogen metabolism by modulating enzymes like glycogen synthase (GS) and phosphorylases. Disruptions in these processes can lead to hepatic glycogen accumulation, glucose intolerance and even fasting hypoglycemia.[51,52] Moreover, insulin regulates lipid metabolism in the liver, primarily through the activation of sterol regulatory element-binding protein 1c (SREBP-1c), a key regulator of lipogenesis. Insulin stimulates the cleavage and nuclear translocation of SREBP-1c, which in turn activates genes involved in lipid synthesis. In hepatic IR, this pathway becomes dysregulated, often leading to hepatic steatosis.[53] Overexpression of SREBP-1c is observed in several IR models including IRS2 knockout mice and ob/ob mice, highlighting the central role of this pathway in the development of hepatic IR.[54]

2. Adipose Tissue and Lipid Metabolism in Insulin Resistance

In adipose tissue, insulin regulates lipid metabolism by stimulating de novo lipogenesis (DNL) and inhibiting lipolysis. These processes are critical for maintaining proper energy storage and metabolic balance. De novo lipogenesis in adipose tissue is regulated similarly to the liver, with the carbohydrate-responsive element-binding protein (ChREBP) playing a significant role in fatty acid production and systemic insulin sensitivity.[55] Genetic ablation of ChREBP impairs insulin sensitivity in adipose tissue, underscoring its importance in maintaining normal metabolic function. In individuals with obesity, larger adipocytes are often associated with decreased insulin sensitivity. These enlarged fat cells show reduced expression of lipogenic genes, which further exacerbates the dysregulation of lipid metabolism in IR. Moreover, insulin suppresses lipolysis in adipose tissue by inhibiting key lipolytic enzymes, such as adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL). In this process, proteins like phosphodiesterase 3B (PDE3B) and ABHD15 play crucial roles in suppressing the cAMP signaling pathway, thereby attenuating lipolysis. Disruptions in this signaling pathway can lead to increased free fatty acid levels in the bloodstream, which further exacerbate IR.[56,57] Interestingly, the suppression of lipolysis in white adipose tissue (WAT) by insulin is linked to the inhibition of hepatic glucose production. As such, impaired lipid metabolism in adipose tissue contributes to the dysregulation of glucose metabolism in the liver, creating a vicious cycle that worsens IR and its associated complications.

3. Protein Synthesis and Insulin Resistance

Insulin also regulates protein synthesis, a key metabolic function in many insulin-sensitive tissues such as the liver, adipose tissue and skeletal muscle. This regulation is mediated by the activation of the Akt and mTOR signaling pathways. Akt phosphorylates the TSC1-TSC2 complex, relieving its inhibition on mTORC1, which promotes protein synthesis in response to insulin.[9] Insulin resistance impairs this pathway leading to decreased protein synthesis in skeletal muscle, which is the largest amino acid reservoir in the body. This reduction in protein synthesis contributes to anabolic resistance in the fed state, particularly in muscle tissue.[58] Further complicating the IR response, Akt/mTOR signaling also involves feedback mechanisms that affect proximal insulin signaling. For instance, PRAS40, an Akt substrate, inhibits mTORC1 by binding to it. However, Akt phosphorylation of PRAS40 relieves this inhibition and promotes protein synthesis. Disruption of these feedback loops in IR can result in reduced insulin signaling and metabolic dysfunction.[59]

C. GENETIC MUTATIONS

The growing concern about insulin resistance (IR) is largely driven by its rising prevalence and its critical role in the development of type 2 diabetes (T2DM), metabolic syndrome and cardiovascular diseases. IR, a condition where the body's cells become less responsive to insulin, has been closely linked to genetic factors, with numerous studies identifying genetic mutations that influence insulin action. Human genetic studies have pointed to various genomic

loci associated with key markers of IR, such as fasting insulin levels, higher triglycerides and lower HDL cholesterol levels, which are all hallmarks of this metabolic disorder. These findings suggest that genetic factors play a significant role in IR, as well as in the broader metabolic syndrome. Epidemiological and family-based genetic studies have provided strong evidence for the genetic basis of IR and its components.[60-63]

With advancements in genome-wide association studies (GWAS) and next-generation sequencing (NGS), researchers have identified several genetic variants linked to insulin resistance. Notable genes involved in metabolic processes have been highlighted including PPARγ, IRS1, IGF1, NAT2, KLF14, GCKR, FTO, TCF7L2, TMEM163, MC4R, SC4MOL, TCERG1L and ARL15, each influencing insulin action through different regulatory mechanisms.[60,64,65] For instance, the PPARγ Pro12Ala variant was one of the first to be associated with a lower risk of developing T2DM and is thought to affect fatty acid and energy metabolism, contributing to insulin sensitivity. Similarly, variations in IGF1 have been shown to reduce insulin sensitivity by lowering plasma levels of insulin-like growth factor 1, which plays a crucial role in growth and metabolic regulation.[66] Another significant genetic contributor is NAT2, a gene recently identified as influencing insulin sensitivity. Furthermore, ARL15, a gene related to adiponectin production, has been associated with lower adiponectin levels, which in turn is linked to reduced insulin sensitivity and higher risk of IR.[67]

Despite these valuable insights, it is important to note that these genetic variants account for only a portion of the heritability of IR, estimated to range from 25% to 44%.195 This indicates that there are still many unknown genetic factors contributing to IR including rare and low-frequency variants. Advances in genomic technologies, such as exosome sequencing, have allowed researchers to identify these rare variants, offering further insights into IR. For example, a low-frequency variant of CD300LG has been associated with elevated levels of HDL cholesterol, a marker linked to IR, while a variant in TBC1D4 has been connected to higher fasting glucose levels and reduced insulin sensitivity.[68,69] These findings underscore the complexity of IR and suggest that further research into rare genetic variants is needed to fully understand its genetic underpinnings.

D. EPIGENETIC DYSREGULATION

Recent research highlights the significant role of epigenetic modifications, such as DNA methylation and histone modifications, in the development of insulin resistance (IR), particularly in conditions like obesity and type 2 diabetes (T2DM). These modifications influence gene expression and contribute to the onset of metabolic disorders like IR.[70]

DNA Methylation

DNA methylation, which involves adding a methyl group to the cytosine of CpG dinucleotides in gene promoters, is a crucial regulator of gene expression. It is controlled by DNA methyltransferases (DNMTs). This modification affects genes involved in insulin signaling, such as insulin (INS), insulin receptor substrate 1 (IRS1), insulin-like growth factors (IGF-1/2) and glucagon-like peptide-1 receptor (GLP-1R).[71,72] In IR, altered methylation patterns in these genes have been observed. For example, elevated methylation of the INS promoter suppresses insulin mRNA expression in obese individuals with T2DM. Similarly, increased methylation of IGF-1 is linked to reduced IGF-I serum levels in T2DM patients. Genes like IGFBP-1 and IGFBP-2, which are involved in insulin regulation, also show altered DNA methylation in T2DM, affecting their expression and contributing to insulin resistance.[73] Methylation of genes involved in lipid metabolism and inflammation is also relevant. For instance, the genes encoding peroxisome proliferator-activated receptors (PPAR-α and PPAR-γ), key regulators of lipid metabolism, show increased methylation in obesity, leading to reduced protein expression and dyslipidemia.[74] Additionally, inflammatory genes like CCL2 and TNF-α are dysregulated in obese individuals due to altered DNA methylation, exacerbating IR.[75] Epigenetic modifications also affect stress-related genes. For example, hypoxia-inducible factor 3α (HIF3A), involved in adipose tissue dysfunction, shows reduced methylation in obesity, resulting in its upregulation and contributing to IR. Similarly, genes related to endoplasmic reticulum (ER) stress, such as ERO1LB and NFE2L2, exhibit altered methylation patterns in obesity, linking these changes to IR.[76,77]

Histone Modifications

Histone modifications including methylation and acetylation, are essential for regulating gene expression. Methylation of histones can either activate (e.g., H3K4, H3K36) or repress (e.g., H3K9, H3K27) gene transcription, depending on the modification site.[78] Altered histone modifications have been observed in IR, particularly in genes related to insulin signaling. For example, decreased histone acetylation and methylation of the PPARG gene are linked to reduced PPARG expression, contributing to IR.[74] Similarly, changes in histone modifications in genes like CDKN1A and PDE7B impair glucose-stimulated insulin release in T2DM.[79] Histone acetylation plays a key role in making chromatin more accessible to transcription factors, enhancing gene expression. In contrast, histone deacetylation typically inhibits gene expression by promoting chromatin condensation. In IR, genes such as IGFR, InsR, IRS1 and GLUT4 show increased deacetylation, while genes like IRS2 and AMPK are acetylated.[80,81] These findings indicate that histone acetylation and deacetylation play critical roles in insulin signaling. Studies also reveal that histone modifications are associated with obesity and IR. For example, the histone mark H3K4me3 in human adipose tissue is positively correlated with BMI and HOMA-IR, suggesting its involvement in metabolic dysregulation. Additionally, differential histone modifications have been identified in liver tissues in IR, further supporting the role of epigenetic regulation in insulin dysfunction.[82]

COMMON DISEASES ASSOCIATED WITH INSULIN RESISTANCE

Insulin resistance (IR) characterized by the body's reduced response to insulin is a key factor in various metabolic and systemic diseases. While it is most commonly linked to type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS), recent research highlights its association with a broader range of conditions including cardiovascular disease (CVD), obesity, polycystic ovary syndrome (PCOS) and even disorders like Parkinson's disease and gout. Studies including those from the UK Biobank presented at the European Association for the Study of Diabetes (EASD) reveal that IR contributes to 31 distinct diseases emphasizing its wide-reaching impact on health. Factors such as sedentary lifestyles, poor dietary habits, and obesity are driving the increasing prevalence of IR, making it a critical public health concern.[83] The growing concern about the increase in cases of insulin resistance is largely driven by its association with these widespread and potentially life-threatening conditions.

Metabolic Syndrome

Metabolic Syndrome (MetS) is a significant concern due to its association with insulin resistance (IR) and its contribution to a variety of metabolic disorders. MetS is defined by a cluster of conditions that include hypertension, obesity, dyslipidemia, and IR, all of which increase the risk of cardiovascular diseases and type 2 diabetes mellitus (T2DM).[84] According to a 2009 scientific statement by the World Health Organization, MetS is characterized by elevated blood pressure, high triglycerides, abnormal LDL/HDL cholesterol ratios, and abdominal obesity.[60] The prevalence of MetS is alarming, affecting approximately 25% of the global young adult population. Regional statistics are equally concerning, with prevalence rates of 24% in India, 28% in the United States, 30.1% in Tehran, 33.4% in Turkey, and 39.3% in Saudi Arabia.[85] In a recent study presented at the Annual Meeting of the European Association for the Study of Diabetes (EASD), insulin resistance was identified as a contributing factor to over 31 diseases, emphasizing its far-reaching impact on health[83]. Among these conditions, the relationship between IR and MetS-related disorders, such as sleep disorders and bacterial infections, was particularly notable. The study reinforced the central role of lifestyle factors, including physical inactivity and obesity, in exacerbating IR and driving MetS prevalence[83]. Hyperlipidemia, a hallmark of MetS, further underscores the metabolic complexities associated with IR, making the management of modifiable factors such as diet and exercise essential.[85,86]

Obesity

Obesity, a global epidemic, has become a critical driver of insulin resistance and related diseases. Since the 1970s, the prevalence of obesity has nearly tripled, affecting over 1.9 billion people worldwide in 2016, with more than 650 million classified as obese.[87] Obesity significantly contributes to numerous health complications, including hypertension, dyslipidemia, cardiovascular diseases, T2DM, and even certain cancers. As a largely preventable condition, obesity represents one of the most pressing global health challenges.[88] The findings presented at the EASD further highlight the strong correlation between obesity and IR. Individuals with higher TyG index scores—a measure of IR—were often obese and less physically active, underscoring the importance of lifestyle

interventions.[83] The study also documented a 7% increase in obesity risk for every one-unit increase in IR, emphasizing the reciprocal relationship between these conditions. While not all individuals with obesity develop IR, the most insulin-resistant individuals are at the highest risk for T2DM and cardiovascular complications making targeted interventions essential.[83,87,89]

Diabetes Mellitus

Diabetes mellitus (DM) is a metabolic disorder marked by impaired glucose regulation, and its prevalence continues to rise globally. Insulin resistance plays a pivotal role in the pathogenesis of type 2 diabetes mellitus (T2DM), which accounts for 90-95% of diabetes cases.[90,91] Currently, 425 million people worldwide are affected by diabetes, a figure expected to rise by 50% by 2045. The disease also contributes to substantial mortality, claiming 1.6 million lives in 2016 alone. Chronic complications of diabetes, including retinopathy, nephropathy, neuropathy, and cardiovascular diseases, further exacerbate its burden.[92] In the EASD study, IR emerged as a defining feature of diabetes, with a 166% increased risk of T2DM for every one-unit rise in IR.[83] This underscores the critical role of IR in the progression from impaired glucose tolerance to overt diabetes. Hyperinsulinemia, an early compensatory mechanism in IR, accelerates β-cell dysfunction and is closely linked to cardiovascular risks.[86] As 80% of T2DM patients are overweight or obese, lifestyle and pharmacological interventions targeting IR remain vital.[93,94]

Polycystic Ovary Syndrome

Polycystic Ovary Syndrome (PCOS), a multifactorial disorder predominantly affecting women of reproductive age, is closely associated with insulin resistance.[95] Approximately 60-70% of women with PCOS exhibit IR, making it a critical factor in the syndrome's development and progression.[96] PCOS is often linked to obesity, which exacerbates IR. However, even lean women with PCOS may display significant IR highlighting its independent role.[97] The EASD study linked higher IR to increased mortality risk in women, further emphasizing the importance of managing metabolic dysfunctions like PCOS[83]. Hyperinsulinemia, a central feature of IR, stimulates excessive androgen production, leading to hallmark PCOS symptoms such as hyperandrogenism and anovulation.[95] This connection underlines the need for comprehensive management strategies targeting both metabolic and reproductive complications.[98]

Cardiovascular Disease

Cardiovascular disease (CVD) remains the leading cause of mortality globally and is closely linked to insulin resistance and metabolic syndrome.[99] IR contributes to a range of metabolic disturbances that elevate cardiovascular risk, including dyslipidemia, hypertension, and obesity [14]. Individuals with T2DM, who often exhibit profound IR, face a 2-8 times higher risk of CVD compared to non-diabetics. This increased risk shortens life expectancy by 5-15 years.[99,100] The EASD findings reinforced these associations, documenting a 24% increased risk of ischemic heart disease with each one-unit rise in IR[83]. The metabolic inflexibility caused by IR forces reliance on fatty acid oxidation in cardiac tissues, promoting lipotoxicity and cardiac remodeling.[99] Additionally, chronic inflammation and hyperglycemia associated with IR exacerbate vascular dysfunction, making early interventions vital in reducing cardiovascular risks.[83,100]

Atherosclerosis

Atherosclerosis, a major contributor to cardiovascular morbidity, is strongly associated with insulin resistance. IR disrupts endothelial function by impairing nitric oxide production and promoting procoagulant pathways, accelerating plaque formation and vascular inflammation.[101] Hyperinsulinemia, a consequence of IR further exacerbates endothelial dysfunction and promotes atherosclerotic processes.[99] The EASD study expanded on this understanding, linking IR to various conditions, including a 31% increased risk of pancreatitis, which often coexists with atherosclerotic risk factors.[83] These findings emphasize the interconnected nature of IR, inflammation and vascular dysfunction in the pathophysiology of atherosclerosis.[83,102]

Hypertension

Hypertension, a major contributor to cardiovascular morbidity and mortality, is intricately linked to insulin resistance.[100] IR increases plasma volume and promotes sodium reabsorption in the kidneys, leading to chronic elevations in blood pressure. Additionally, hyperinsulinemia activates the sympathetic nervous system, compounding the hypertensive effects of IR.[103] The EASD study highlighted a 21% increased risk of hypertension for every one-unit rise in IR, further solidifying its role as a critical factor in blood pressure regulation.[83] The interplay between IR, adipose tissue distribution and chronic inflammation highlights the importance of comprehensive strategies targeting lifestyle and metabolic risk factors to mitigate hypertension and its complications.[83,100]

CONCLUSION

Insulin resistance (IR) represents a growing global health challenge with profound implications for metabolic, cardiovascular, and systemic health. As a critical driver of chronic conditions such as type 2 diabetes mellitus (T2DM), cardiovascular diseases, metabolic syndrome, and obesity, IR underscores the need for urgent and comprehensive public health strategies. The multifactorial etiology of IR, encompassing genetic predispositions, epigenetic dysregulation, and modifiable lifestyle factors, highlights the complexity of this metabolic condition. Advancements in understanding the molecular mechanisms underlying insulin signaling defects and interorgan crosstalk have provided valuable insights into the pathogenesis of IR. These findings, combined with emerging evidence on genetic and epigenetic contributors, pave the way for targeted therapeutic interventions. Lifestyle modifications, including dietary changes, physical activity, and stress management, remain foundational in improving insulin sensitivity. Pharmacological treatments, such as metformin, SGLT2 inhibitors, and newer molecularly targeted therapies, offer additional avenues for managing IR and its complications. Addressing the IR epidemic requires a coordinated, multidisciplinary approach involving researchers, healthcare providers, policymakers, and public health professionals. By integrating personalized medicine with community-level interventions, it is possible to reduce the prevalence of IR and mitigate its far-reaching health impacts. Future research should focus on refining diagnostic tools, exploring innovative therapies, and addressing demographic and regional disparities to create equitable health solutions. Through such concerted efforts, the burden of IR and its associated diseases can be significantly alleviated, improving quality of life and global health outcomes.

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