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Insulin Resistance: Implications for Nutrition, Oncology, and Diabetes Management-An Updated Review

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Abstract

Background: Insulin resistance—diminished tissue responsiveness to insulin in liver, skeletal muscle, and adipose tissue—drives dysglycemia, dyslipidemia, hypertension, and proinflammatory/prothrombotic states, predisposing to metabolic syndrome, NAFLD/MASLD, and type 2 diabetes (T2D). Clinical diagnosis lacks a single standard; research-grade clamps are impractical, so surrogate indices (HOMA-IR, QUICKI, triglyceride/HDL-C ratio) and metabolic syndrome criteria are used.

Aim: To provide an updated, interdisciplinary synthesis of insulin resistance with practical implications for nutrition counseling, oncology co-management, and diabetes care, spanning etiology, epidemiology, pathophysiology, evaluation, treatment, complications, prognosis, and team-based delivery.

Methods: Narrative integration of current concepts presented in the review, including tissue-specific mechanisms (DAG/PKC signaling defects, de novo lipogenesis, lipotoxicity), population trends (NHANES-based estimates), diagnostic surrogates, and therapeutic modalities (lifestyle, pharmacotherapy, bariatric surgery), framed for interprofessional application.

Results: Acquired drivers—visceral adiposity, caloric excess, physical inactivity, aging, and select medications—predominate, with genetic syndromes and receptor-level defects contributing in a minority. Prevalence has risen substantially in young adults. Practical assessment leverages fasting and dynamic indices and harmonized metabolic syndrome criteria. Lifestyle intervention (dietary energy reduction and lower glycemic load plus structured exercise) is first-line and cost-effective; DPP/DPPOS show substantial diabetes risk reduction. Metformin, GLP-1 and dual GIP/GLP-1 agonists, SGLT2 inhibitors, and selective use of TZDs/DPP-4s complement lifestyle; bariatric/metabolic surgery offers durable benefit in eligible patients. Complications span micro- and macrovascular disease and NAFLD; prognosis is modifiable, with 5–10% weight loss yielding clinically meaningful risk reduction.

Conclusion: A staged, lifestyle-first strategy, augmented by modern pharmacotherapy and surgery when indicated, and delivered by an interprofessional team, can curb progression to T2D and cardiovascular disease while improving quality of life across metabolic and oncology care pathways.

Keywords: Insulin resistance; metabolic syndrome; NAFLD/MASLD; HOMA-IR; QUICKI; DPP/DPPOS; GLP-1; tirzepatide; SGLT2 inhibitors; metformin; bariatric surgery; lipodystrophy; PCOS; NHANES.

Introduction

Insulin resistance is defined as the diminished biological responsiveness of target tissues to insulin signaling. While any tissue expressing insulin receptors can develop resistance, the principal contributors are the liver, skeletal muscle, and adipose tissue. Impaired insulin sensitivity hinders effective glucose uptake, prompting pancreatic beta cells to increase insulin secretion, resulting in hyperinsulinemia. Emerging evidence has explored whether hyperinsulinemia may precede and actively contribute to the development of insulin resistance, a hypothesis that underscores the role of chronic caloric excess in driving metabolic dysfunction. Insulin resistance manifests in multiple metabolic derangements, including hyperglycemia, dyslipidemia, hypertension, hyperuricemia, elevated inflammatory mediators, endothelial dysfunction, and

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a prothrombotic state. Persistent insulin resistance can culminate in metabolic syndrome, nonalcoholic fatty liver disease (NAFLD), and type 2 diabetes (T2D) [1][2][3][4][5]. Although insulin resistance is largely acquired, primarily through excess adiposity, genetic factors have also been implicated. Clinically, insulin resistance lacks a universally accepted diagnostic standard, and its identification typically relies on the constellation of metabolic abnormalities characteristic of metabolic syndrome and insulin resistance syndrome [6][7]. The hyperinsulinemic-euglycemic clamp remains the research gold standard for assessing insulin sensitivity, yet its clinical utility is limited. Surrogate measures, such as HOMA-IR, HOMA2, QUICKI, serum triglyceride levels, and the triglyceride-to-HDL ratio provide practical alternatives. Additional evaluations utilize serum glucose or insulin responses to oral or intravenous glucose challenges to estimate insulin resistance [8][9][10][11].

Insulin resistance is a central pathophysiological mechanism preceding T2D, often by a decade or more. Resistance in skeletal muscle and other peripheral tissues reduces glucose disposal, necessitating higher circulating insulin levels to achieve metabolic homeostasis. This compensatory hyperinsulinemia further perpetuates insulin resistance, establishing a self-reinforcing cycle. Once pancreatic beta-cell function can no longer match insulin demand, hyperglycemia ensues, and the transition to T2D occurs. Weight gain often accompanies hyperinsulinemia; however, this effect is predominantly driven by chronic caloric surplus rather than hyperinsulinemia alone. Progressive tissue resistance diminishes insulin’s anabolic effects, eventually moderating weight gain [12][13][14][15]. Resistance to exogenous insulin has also been described in clinical practice. Patients requiring over 1 unit/kg/day of exogenous insulin to maintain glycemic control are considered insulin-resistant, and those exceeding 200 units per day are categorized as severely insulin-resistant [16]. Beyond T2D, insulin resistance is implicated in obesity, cardiovascular disease, NAFLD, metabolic syndrome, and polycystic ovary syndrome (PCOS), all of which exert a substantial burden on healthcare systems. The microvascular complications of diabetes, including neuropathy, retinopathy, and nephropathy, along with macrovascular sequelae such as coronary artery disease, cerebrovascular disease, and peripheral artery disease, constitute a major proportion of healthcare expenditures as disease severity progresses [17][18][19][20][21][22][23].

Management strategies prioritize lifestyle modifications as the first-line intervention. Nutritional therapy focuses on caloric restriction and reduction of carbohydrate intake to limit excessive insulin demand. Physical activity enhances skeletal muscle insulin sensitivity and promotes energy expenditure. Pharmacological agents may be employed to improve insulin responsiveness and reduce insulin requirements, complementing lifestyle measures to mitigate the metabolic and cardiovascular consequences of insulin resistance [24][25][26]. This synthesis underscores the complexity of insulin resistance, its systemic metabolic implications, and the critical need for multifaceted interventions to prevent progression to overt disease.

Etiology

Insulin resistance arises from a combination of acquired, hereditary, and mixed factors, with the majority of affected individuals exhibiting primarily acquired causes [25]. Acquired insulin resistance is closely associated with increased visceral adiposity, often resulting from ectopic fat deposition and overflow from subcutaneous fat stores. Excess intra-abdominal fat promotes a pro-inflammatory milieu and contributes to lipotoxicity through elevated circulating free fatty acids, impairing insulin signaling in skeletal muscle, liver, and adipose tissue. Aging further exacerbates insulin resistance, as age-related changes in body composition, hormonal profiles, and mitochondrial function reduce insulin sensitivity. Physical inactivity compounds these effects by diminishing skeletal muscle glucose uptake and energy expenditure. Nutritional imbalances, particularly diets high in refined carbohydrates and excessive caloric intake, contribute to hyperinsulinemia and the progressive decline in tissue responsiveness to insulin. Pharmacological agents, including glucocorticoids, anti-adrenergic drugs, protease inhibitors, selective serotonin reuptake inhibitors, atypical antipsychotics, and some exogenous insulin formulations, have also been identified as contributors to acquired insulin resistance. Additional dietary factors, such as high sodium intake, may indirectly exacerbate insulin resistance, while chronic hyperglycemia and persistent elevations of circulating free fatty acids induce glucose and lipotoxicity, reinforcing metabolic dysfunction [25][27].

Genetic determinants play a critical role in insulin resistance, either as primary syndromic disorders or as modifiers of acquired metabolic pathways. Specific inherited conditions, including myotonic dystrophy, ataxia-telangiectasia, Alström syndrome, Rabson-Mendenhall syndrome, Werner syndrome, and lipodystrophies, demonstrate a strong association with impaired insulin action. Polycystic ovary syndrome (PCOS) represents a multifactorial genetic contribution, characterized by insulin resistance linked to ovarian hyperandrogenism, dysregulated glucose metabolism, and altered adiposity. Severe forms of insulin resistance are categorized as type-A and type-B. Type-A insulin resistance results from mutations in the insulin receptor gene, producing marked insulin resistance with clinical manifestations such as abnormal glucose homeostasis, acanthosis nigricans, and ovarian virilization. Type-B insulin resistance, in contrast, is immune-mediated, arising from insulin receptor autoantibodies that disrupt insulin signaling and lead to hyperglycemia, hyperandrogenism, and similar dermatologic manifestations [27].

An alternative approach to classifying insulin resistance focuses on the site of molecular dysfunction relative to the insulin receptor. This framework distinguishes pre-receptor defects, encompassing abnormalities in insulin production or secretion; receptor-level defects, including mutations or autoantibody interference; and post-receptor defects, which impair intracellular signaling pathways downstream of the receptor. Understanding the mechanistic basis of insulin resistance across these categories is essential for targeted interventions, as different etiologies may necessitate tailored pharmacologic, nutritional, and lifestyle strategies to restore insulin sensitivity. Collectively, insulin resistance represents a heterogeneous condition with overlapping metabolic, genetic, and environmental contributors. While acquired etiologies predominate, hereditary syndromes and receptor-specific defects provide insights into fundamental mechanisms of impaired insulin signaling. Recognition of these diverse etiologic pathways informs individualized clinical management and underscores the importance of early intervention to prevent progression to type 2 diabetes, cardiovascular disease, and associated metabolic complications.

Fig. 1: Acanthosis Nigricans.

Epidemiology

Insulin resistance is commonly evaluated in epidemiologic studies through its association with metabolic syndrome or insulin resistance syndrome. National survey data, such as those from the National Cholesterol Education Program Adult Treatment Panel III, indicate that insulin resistance is highly prevalent across adult populations. Historical analyses of the National Health and Nutrition Examination Survey (NHANES) demonstrate the extent of this condition within the United States. Data from 2003 estimated that approximately 22% of adults over the age of 20 exhibited insulin resistance. More recent NHANES assessments in 2021 report that up to 40% of adults aged 18 to 44 demonstrate insulin resistance when assessed using HOMA-IR, reflecting a substantial increase over less than two decades [28][29]. The rise in insulin resistance parallels trends in obesity, but it cannot be solely attributed to excess adiposity. Concomitant increases in hypertension, dyslipidemia, and reduced physical activity contribute to the overall metabolic burden, emphasizing the multifactorial etiology of insulin resistance in modern populations. These lifestyle and metabolic factors interact to exacerbate insulin signaling impairment, increasing the risk for type 2 diabetes, cardiovascular disease, and other related complications. The pediatric population presents additional challenges for epidemiologic assessment. Although rates of childhood obesity and type 2 diabetes have risen sharply, there is no consensus on standardized diagnostic criteria for insulin resistance in children and adolescents. Consequently, prevalence estimates in younger populations are inconsistent, limiting the ability to compare trends across age groups or evaluate long-term outcomes. Demographically, insulin resistance affects individuals across all racial and ethnic groups, though comparative data between populations remain limited. Continued epidemiologic surveillance is essential to understand patterns of insulin resistance, identify high-risk populations, and guide public health interventions aimed at prevention and early management [28][29].

Pathophysiology

Insulin resistance primarily affects skeletal muscle, liver, and adipose tissue, which serve as the principal sites for glucose uptake and energy storage. Skeletal muscle is the largest peripheral reservoir for circulating glucose, responsible for up to 70% of postprandial glucose disposal as determined by hyperinsulinemic-euglycemic clamp studies. When skeletal muscle becomes resistant to insulin signaling, glucose uptake is impaired, resulting in higher circulating glucose levels. This surplus glucose is redirected to the liver, where it fuels de novo lipogenesis (DNL), a process that converts excess glucose into fatty acids and triglycerides [25]. Hepatic insulin resistance develops as a consequence of this substrate overload, further exacerbating systemic metabolic dysfunction. Increased DNL elevates plasma triglyceride levels, promotes the accumulation of ectopic fat in visceral and peri-organ tissues, and contributes to a proinflammatory metabolic environment. Adipose tissue, particularly visceral fat depots, also becomes insulin-resistant, impairing its ability to store lipids safely and promoting lipolysis. The resulting rise in circulating free fatty acids intensifies insulin resistance in the liver and skeletal muscle, creating a self-reinforcing cycle of metabolic dysregulation. Chronic caloric surplus, sedentary behavior, and excess adiposity accelerate these pathophysiologic changes, linking lifestyle factors directly to insulin resistance. The interplay between glucose and lipid metabolism, coupled with ectopic fat deposition, establishes a systemic environment that perpetuates insulin signaling impairment. This dysregulation not only predisposes individuals to hyperglycemia but also contributes to associated metabolic complications, including dyslipidemia, hepatic steatosis, and increased cardiovascular risk, highlighting the central role of multi-organ insulin resistance in the progression of metabolic disease [25].

Skeletal Muscle Tissue, Hepatic Tissue, and Adipose Tissue

Skeletal muscle serves as the primary site for postprandial glucose disposal, accounting for up to 70% of total tissue glucose uptake following caloric intake. In the context of chronic caloric excess, muscle tissue accumulates intramyocellular lipids, including diacylglycerol, which functions as a cellular signal of energy surplus. Diacylglycerol activates protein kinase C theta (PKC-theta), leading to impaired proximal insulin signaling. This impairment reduces the translocation of glucose transporter type 4 (GLUT4) to the muscle cell membrane, thereby decreasing glucose uptake by skeletal muscle. As a result, circulating glucose levels rise, and the excess glucose is redirected to other tissues, primarily the liver, where it contributes to additional metabolic stress [25][30]. The liver plays a central role in energy metabolism, regulating glucose and lipid homeostasis. When skeletal muscle is insulin-resistant, excess glucose is shunted to the liver, increasing substrate availability. Similar to skeletal muscle, hepatic diacylglycerol accumulation activates protein kinase C epsilon (PKC-epsilon), which impairs proximal insulin signaling in hepatocytes. This disruption decreases insulin's ability to suppress gluconeogenesis, leading to continued glucose production despite hyperglycemia. Excess glucose in hepatocytes also drives de novo lipogenesis, producing fatty acids that are stored within the liver or deposited ectopically in visceral tissues. Inflammatory processes associated with adipose tissue dysfunction exacerbate hepatic lipid overload by increasing free fatty acid release, which is re-esterified by the liver. Consequently, hepatic insulin resistance contributes to hyperglycemia, hypertriglyceridemia, and ectopic lipid deposition, forming a key component of systemic metabolic dysregulation [25][30]. Adipose tissue, particularly visceral fat, is highly insulin-sensitive under normal conditions, with insulin suppressing lipolysis to maintain metabolic homeostasis. In insulin-resistant adipose tissue, this suppression is impaired, leading to elevated circulating free fatty acids. These fatty acids exert direct lipotoxic effects on skeletal muscle and liver, further impairing insulin signaling in these tissues. Chronic elevation of free fatty acids also contributes to pancreatic beta-cell dysfunction, linking adipose tissue insulin resistance to impaired insulin secretion. The interdependent dysfunction of skeletal muscle, hepatic, and adipose tissues establishes a vicious cycle, amplifying systemic insulin resistance and promoting the progression of metabolic disorders such as type 2 diabetes, nonalcoholic fatty liver disease, and cardiovascular complications [25][30].

History and Physical

The clinical evaluation of insulin resistance requires a comprehensive assessment, as manifestations vary widely based on the specific type of insulin resistance, its duration, residual beta-cell function, and individual susceptibility to related comorbidities. Patients may present with a spectrum of metabolic and endocrine abnormalities that reflect systemic insulin dysfunction. Commonly observed associated diseases include non-alcoholic fatty liver disease (NAFLD), metabolic syndrome, prediabetes or overt type 2 diabetes, polycystic ovarian syndrome (PCOS), and obesity. In addition, both microvascular and macrovascular complications may be present, including retinopathy, neuropathy, nephropathy, stroke, peripheral artery disease (PAD), and coronary artery disease (CAD). These associated conditions are often interrelated, reflecting the systemic consequences of chronic insulin resistance [25][30]. Clinicians should also assess for associated symptoms indicative of metabolic imbalance. Hypertension and dyslipidemia are frequently encountered, along with increased waist circumference, which may be gender- and ethnicity-specific. In female patients, the stigmata of PCOS, including menstrual irregularities, hirsutism, acne, and alopecia, may be evident. Cutaneous markers of insulin resistance, particularly acanthosis nigricans, serve as visible indicators of chronic hyperinsulinemia and impaired insulin signaling. In cases linked to genetic syndromes, additional phenotypic markers may be present, reflecting syndromic forms of insulin resistance. Type A insulin resistance is typically associated with severe insulin receptor dysfunction, whereas type B insulin resistance is often autoimmune in origin, mediated by insulin receptor autoantibodies. Physical examination, therefore, must be holistic, evaluating both general metabolic signs and disease-specific stigmata to guide diagnosis, inform risk stratification, and tailor subsequent management strategies [25][30].

Evaluation

The evaluation of insulin resistance relies on both direct and surrogate methods, with the hyperinsulinemic-euglycemic glucose clamp recognized as the gold standard. This technique quantifies whole-body insulin sensitivity by administering a continuous high-rate insulin infusion to a fasting, non-diabetic individual while simultaneously monitoring blood glucose levels. A variable-rate 20% dextrose infusion is titrated to maintain euglycemia. The steady-state glucose infusion rate required to offset the hyperinsulinemic stimulus reflects the body's glucose disposal capacity, adjusted for body size. Although highly accurate, the procedure is technically complex, time-intensive, and carries risks associated with prolonged intravenous infusions, limiting its routine clinical use [31]. To circumvent these limitations, several surrogate markers of insulin resistance have been developed. The homeostatic model assessment for insulin resistance (HOMA-IR), which incorporates fasting glucose and insulin concentrations, is widely applied in research. Variants such as HOMA2, the Glucose to Insulin Ratio (GIR), and the Quantitative Insulin Sensitivity Index (QUICKI) offer alternative fasting-based assessments. Indices derived from post-glucose challenge testing, including the Matsuda Index and the Insulin Sensitivity Index (ISI), evaluate dynamic insulin and glucose responses following a standardized oral glucose load. Other markers integrate lipid parameters, such as the McAuley Index, which combines fasting insulin and triglycerides, or the triglyceride/HDL-C ratio. Elevated triglycerides or a high triglyceride/HDL-C ratio, particularly above 3.0, may indicate insulin resistance, though thresholds vary by sex and ethnicity, and correlations are less robust in certain populations [8][9][10][32][33][34][35][36][37].

Despite the availability of these measures, formal assessment of insulin resistance is not integrated into most clinical guidelines. Consequently, diagnosis is often inferred from phenotypic or biochemical manifestations, particularly the presence of metabolic syndrome (MetS) or insulin resistance syndrome (IRS). MetS, as defined by the 2009 harmonized criteria, is diagnosed when three or more of the following are present: elevated waist circumference according to sex and ethnicity, triglycerides ≥150 mg/dL, reduced HDL-C (<40 mg/dL in men, <50 mg/dL in women), hypertension (systolic ≥130 mmHg or diastolic ≥85 mmHg), or elevated fasting glucose ≥100 mg/dL [38]. The American College of Endocrinology further outlines physiologic abnormalities that heighten the risk of IRS, including impaired glucose tolerance, dyslipidemia, proinflammatory markers, endothelial dysfunction, and prothrombotic states [39]. Additional risk factors encompass a body mass index ≥25 kg/m², sedentary lifestyle, non-white ethnicity, age over 40, family history of type 2 diabetes, cardiovascular disease, polycystic ovarian syndrome, nonalcoholic fatty liver disease, and the presence of acanthosis nigricans. Comprehensive evaluation of insulin resistance therefore involves both laboratory assessment and careful clinical appraisal, integrating metabolic, cardiovascular, and anthropometric parameters to identify at-risk individuals and guide interventions.

Treatment / Management

The management of insulin resistance centers on intensive lifestyle intervention, which remains the foundational approach for both prevention and treatment. Dietary modification is critical and should emphasize caloric restriction alongside reduction of high glycemic index carbohydrates, which directly influence postprandial insulin demand. Reducing sodium and saturated fat intake further improves metabolic outcomes. Physical activity complements dietary interventions by increasing energy expenditure and enhancing insulin sensitivity within skeletal muscle, the primary site for glucose disposal [40][41][42]. Exercise promotes translocation of glucose transporter type 4 (GLUT4) to the muscle cell membrane, improving glucose uptake and mitigating hyperglycemia. Structured lifestyle programs incorporating education, individualized counseling, and behavioral support have demonstrated sustained improvements in weight management, glycemic control, and overall cardiometabolic risk. Evidence from large-scale clinical trials, including the Diabetes Prevention Program (DPP) and its follow-up study (DPPOS), underscores the efficacy of lifestyle interventions in preventing type 2 diabetes among high-risk populations. Participants achieving a 7% reduction in body weight through dietary modification and exercise experienced a 58% decrease in progression to diabetes, while metformin therapy alone reduced risk by 31% [24][26]. Lifestyle interventions are therefore both clinically effective and cost-efficient, emphasizing the importance of early and sustained implementation in individuals with insulin resistance.

Pharmacologic strategies are considered adjunctive, particularly for individuals with elevated glucose or coexisting metabolic disorders. Metformin is the most widely used agent, improving insulin sensitivity primarily in the liver and skeletal muscle. Its use extends to polycystic ovary syndrome (PCOS) and is endorsed in mild to moderate renal impairment if the estimated glomerular filtration rate exceeds 30 mL/min/1.73 m² [24][26][43][44][45]. Glucagon-like peptide-1 (GLP-1) receptor agonists, including liraglutide and semaglutide, enhance pancreatic insulin secretion, inhibit glucagon release, and promote weight loss, thereby indirectly improving insulin sensitivity. The dual GLP-1 and gastric inhibitory polypeptide (GIP) agonist tirzepatide demonstrates similar metabolic benefits and is FDA-approved for type 2 diabetes management [46][47][48]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors facilitate urinary glucose excretion, lower circulating glucose levels, reduce insulin demand, and are associated with modest weight loss [49][50]. Thiazolidinediones enhance insulin-mediated glucose uptake in skeletal muscle and adipose tissue and suppress hepatic gluconeogenesis, though adverse effects such as weight gain and fluid retention limit their widespread use [51][52]. Dipeptidyl peptidase-4 (DPP-4) inhibitors prolong endogenous GLP-1 and GIP activity, contributing to improved postprandial glucose regulation [4]. Surgical interventions, particularly bariatric procedures including sleeve gastrectomy, gastric banding, and Roux-en-Y gastric bypass, are indicated for individuals with obesity and severe metabolic dysfunction. Bariatric surgery achieves substantial and sustained weight loss, which significantly improves insulin sensitivity and glycemic control. The STAMPEDE trial demonstrated the superiority of surgical intervention over medical therapy in achieving durable diabetes remission and reducing insulin resistance, highlighting surgery as a critical option for selected high-risk patients [53][54][55]. Overall, the management of insulin resistance requires a multimodal approach integrating lifestyle modification, pharmacologic therapy, and surgical options when indicated. Early identification and intervention are essential to prevent progression to type 2 diabetes and to reduce associated cardiovascular and metabolic complications.

Differential Diagnosis

A comprehensive differential diagnosis is essential when evaluating insulin resistance because many metabolic and endocrine conditions can mimic or exacerbate its biochemical and clinical manifestations. Lipodystrophy—in acquired, localized, or generalized forms—should be considered when there is disproportionate loss of subcutaneous fat with paradoxical ectopic lipid deposition in hepatic or skeletal muscle compartments, often accompanied by severe dyslipidemia and insulin-requiring diabetes at relatively low body mass index (BMI). The redistribution pattern, physical stigmata (eg, acanthosis nigricans may be present but is not specific), and advanced hepatic steatosis out of proportion to adiposity help differentiate lipodystrophy from obesity-related insulin resistance [56]. Polycystic ovarian syndrome (PCOS) is a common, sex-specific differential in reproductive-age individuals. Hyperandrogenic signs (hirsutism, acne), menstrual irregularities, polycystic ovarian morphology, and ovulatory dysfunction point toward PCOS, which is frequently undergirded by insulin resistance but requires a distinct workup and management pathway focused on reproductive and metabolic endpoints. Obesity is both a risk factor and a phenotypic confounder. Stratification by BMI—overweight (25.0–29.9 kg/m²), class I (30.0–34.9 kg/m²), class II (35.0–39.9 kg/m²), and class III (≥40 kg/m²) obesity—helps estimate cardiometabolic risk and guides intensity of intervention, but BMI alone does not establish insulin resistance because lean individuals may be insulin resistant and some people with obesity may remain insulin sensitive [57]. Hypertension, defined by ACC/AHA as systolic blood pressure ≥130 mm Hg or diastolic ≥80 mm Hg, commonly coexists with insulin resistance in the metabolic syndrome; however, essential hypertension can occur independently and warrants exclusion of secondary causes (renal parenchymal disease, renovascular hypertension, primary aldosteronism) before attributing elevated blood pressure solely to insulin resistance [58]. Hypertriglyceridemia (≥150 mg/dL) often accompanies insulin resistance; the lipid triad of elevated triglycerides, low HDL-C, and small dense LDL suggests insulin resistance physiology, but primary or familial dyslipidemias must be considered when triglyceride elevations are extreme or present early in life.

Glycemic disorders must be parsed carefully. Type 1 diabetes is typically characterized by autoimmune β-cell destruction with absolute insulin deficiency, positivity for pancreatic autoantibodies (eg, GAD65, IA-2, ZnT8), and lower C-peptide. Type 2 diabetes presents with insulin resistance and progressive β-cell dysfunction, often in the context of overweight/obesity and familial clustering. Other forms of glucose intolerance, including impaired fasting glucose, impaired glucose tolerance, and gestational diabetes, mark earlier points on the dysglycemia continuum; they signal elevated risk without meeting diagnostic thresholds for diabetes and necessitate targeted lifestyle or pharmacologic prevention. Clinicians should also consider endocrine and iatrogenic mimics—Cushing syndrome, acromegaly, hypothyroidism, and glucocorticoid or antipsychotic exposure—each of which can precipitate or amplify insulin resistance and dyslipidemia. Finally, ethnocultural risk, sleep-disordered breathing, and NAFLD-related metabolic dysfunction may provide additional diagnostic clues to the underlying pathophysiology rather than discrete alternative diagnoses.

Prognosis

The prognosis of insulin resistance spans a wide continuum, reflecting the interplay among disease subset (eg, metabolic syndrome versus lipodystrophic states), severity and chronicity of insulin resistance, residual pancreatic β-cell reserve, heritable predisposition to vascular and endocrine complications, and adherence and response to evidence-based therapy. At one end of the spectrum, mildly insulin-resistant individuals—often identified through screening—may remain asymptomatic for years if they adopt and sustain lifestyle modification. At the other, long-standing, severe insulin resistance is strongly associated with adverse macrovascular and microvascular outcomes, including accelerated atherosclerosis, ischemic heart disease, cerebrovascular events, and chronic kidney disease, which collectively drive morbidity and mortality. From a population standpoint, coronary artery disease remains the leading cause of death in the United States, and diabetes ranks among the top causes of mortality; insulin resistance provides the shared pathophysiologic substrate for both, through dyslipidemia, endothelial dysfunction, inflammation, and prothrombotic tendencies. The presence of insulin resistance in PCOS is associated with an adverse reproductive phenotype—anovulation, subfertility, gestational complications—and a higher lifetime risk of type 2 diabetes and cardiovascular disease, emphasizing that prognostic assessment must incorporate reproductive and cardiometabolic horizons. In rare genetic syndromes or severe fatty deposition diseases, mortality may be driven by profound dyslipidemia, pancreatitis, or advanced liver disease.

Importantly, prognosis is modifiable. Early recognition through risk-based screening enables timely intervention, particularly in individuals with family history, gestational diabetes, or features of metabolic syndrome. Weight loss of even modest magnitude (5%–10%) improves insulin sensitivity, lowers blood pressure, and corrects dyslipidemia, thereby reducing long-term vascular risk. Structured programs that combine dietary quality, caloric moderation, and progressive physical activity deliver additive benefits. Pharmacotherapies—metformin, GLP-1 receptor agonists, dual GIP/GLP-1 agonists, SGLT2 inhibitors—further reduce glycemia and improve weight and cardiometabolic risk profiles when indicated. Broader public health measures that improve access to healthy food, safe spaces for activity, sleep health, and obesity care can shift population risk curves. Collectively, heightened clinical awareness, multifaceted therapy, and sustained lifestyle change offer a realistic path to attenuating the epidemic trajectory of obesity and downstream insulin resistance, with the potential to lower incident diabetes and cardiovascular events across the lifespan [59].

Complications

Insulin resistance is a fundamental driver of both microvascular and macrovascular disease. On the microvascular side, chronic hyperglycemia and associated metabolic perturbations promote retinopathy, nephropathy, and peripheral neuropathy. Retinal microangiopathy manifests as microaneurysms, hemorrhages, exudates, and neovascularization that can progress to vision-threatening complications if unrecognized. Diabetic nephropathy begins with hyperfiltration and microalbuminuria, advancing to proteinuria, declining glomerular filtration rate, and eventual end-stage kidney disease in a subset of patients. Distal symmetric polyneuropathy produces paresthesias, pain, and loss of protective sensation, predisposing to foot ulceration and infection. In the central nervous system, insulin resistance correlates with increased risks of stroke, cognitive decline, mood disorders, and gait instability, reflecting widespread microvascular and neurodegenerative effects. Cardiac and systemic macrovascular complications include coronary artery disease (CAD), peripheral artery disease (PAD), and cerebrovascular accidents (CVA). Beyond epicardial atherosclerosis, cardiac microvascular dysfunction may present as angina, coronary spasm, and even cardiomyopathy despite unobstructed large vessels, underscoring the multifaceted nature of ischemic symptoms in insulin resistance. Vascular remodeling, endothelial dysfunction, dyslipidemia (elevated triglycerides, low HDL-C), and pro-inflammatory/prothrombotic states all converge to accelerate plaque formation and destabilization.

Metabolic liver disease is a critical extra-vascular complication. Non-alcoholic fatty liver disease (NAFLD)—recently reframed as metabolic dysfunction–associated steatotic liver disease (MASLD)—is tightly linked to insulin resistance and type 2 diabetes. Individuals with T2D have roughly a twofold higher risk of NAFLD, and a clinically meaningful subset progresses to steatohepatitis and fibrosis, which increase liver-related and cardiovascular mortality. Rising global prevalence, including in children and adolescents, elevates NAFLD to a frontline concern for clinicians managing insulin resistance [19][20]. Additional complications include obstructive sleep apnea, hypertension, and gout, which synergize to amplify cardiometabolic risk. In reproductive-age individuals with PCOS, insulin resistance contributes to infertility, pregnancy complications (gestational diabetes, hypertensive disorders), and adverse offspring metabolic programming. The cumulative burden of these complications is not inevitable. Multimodal risk factor control—glycemia, blood pressure, lipids, weight, and smoking cessation—markedly reduces event rates. Early treatment of albuminuria, retinal surveillance with timely laser or anti-VEGF therapy, and neuropathy prevention through foot care and glucose optimization avert disability. Finally, targeted NAFLD strategies, centered on weight reduction and cardiometabolic control, can reverse steatosis and stabilize or regress fibrosis in early stages, highlighting the reversibility of many complications when insulin resistance is addressed decisively and early.

Patient Education

Prevention of insulin resistance and its sequelae should proceed on primary, secondary, and tertiary levels, each requiring tailored messaging and resources. Primary prevention emphasizes public education, regular health monitoring, and adoption of sustainable lifestyle behaviors. Patients benefit from concrete, achievable goals: a nutrient-dense dietary pattern that limits added sugars and refined grains, emphasizes non-starchy vegetables, lean proteins, legumes, whole grains, nuts, and unsweetened dairy;

portion awareness supported by plate models or meal planning; and progressive physical activity that accumulates at least 150 minutes per week of moderate-intensity aerobic exercise, augmented by resistance training for muscle insulin sensitivity. Addressing sleep duration and quality, stress management, and minimizing sedentary time further supports glycemic control. Behavioral strategies—self-monitoring, motivational interviewing, and social support—increase adherence and long-term weight management success. Secondary prevention targets early detection and timely intervention. Risk-based laboratory screening (fasting plasma glucose, HbA1c, lipid profile, liver enzymes in suspected NAFLD), oral glucose tolerance testing in select cases, and screening for PCOS features in reproductive-age individuals enable earlier lifestyle or pharmacologic treatment. The Diabetes Prevention Program (DPP) and its long-term follow-up, DPP Outcomes Study (DPPOS), demonstrate that intensive lifestyle intervention reduces progression from prediabetes to type 2 diabetes by ~58%, while metformin confers significant benefit in younger, heavier individuals and those with prior gestational diabetes, validating both modalities as evidence-based prevention tools [24][26]. Embedding these programs within primary care and community settings, and culturally adapting them, enhances reach and durability.

Tertiary prevention addresses established complications to reduce morbidity and mortality. Public acceptance of more intensive measures—including bariatric/metabolic surgery in eligible individuals—can produce substantial and durable improvements in weight, glycemic control, and cardiovascular risk, while also ameliorating NAFLD and obstructive sleep apnea. Patient education should normalize the chronic, relapsing nature of obesity and insulin resistance, reduce stigma, and clarify that pharmacotherapy or surgery complements—not replaces—lifestyle measures. Clinicians should teach patients how to interpret biometrics (weight trends, blood pressure, lipids, HbA1c), recognize symptoms that merit urgent evaluation (chest pain, focal neurologic deficits, foot ulcers), and engage in shared decision-making about medications that improve insulin sensitivity and confer cardio-renal protection. By aligning expectations, enhancing health literacy, and fostering self-efficacy, deterrence and education translate into earlier engagement, better adherence, and, ultimately, fewer complications.

Pearls and Other Issues

A central pearl is that intensive lifestyle intervention remains the first-line therapy for metabolic syndrome and insulin resistance. Exercise is a "medicine" with dose–response benefits: moderate-intensity aerobic activities such as brisk walking, cycling, or swimming improve skeletal muscle glucose uptake via insulin-dependent and insulin-independent (AMPK-mediated) pathways, while resistance training increases muscle mass and basal metabolic rate, further enhancing insulin sensitivity. Addressing barriers—time constraints, joint pain, safety concerns, low motivation—through tailored plans (interval walking, low-impact options, supervised programs) and behavioral supports (habit stacking, prompts, social accountability) is crucial. Dietary modification should prioritize quality over short-term restriction: reduce sugars and high glycemic index carbohydrates, limit ultra-processed foods, and emphasize whole, minimally processed options with adequate protein to support satiety and lean mass preservation. For pharmacotherapy, clinicians should consider agents that improve insulin sensitivity or facilitate weight loss in appropriate patients. Metformin remains a foundational therapy due to its hepatic glucose output suppression, modest weight neutrality or loss, and favorable safety profile. GLP-1 receptor agonists and dual GLP-1/GIP receptor agonists offer potent weight reduction, improved glycemic control, and documented cardiovascular benefits in high-risk populations. SGLT2 inhibitors provide cardio-renal protection and modest weight loss with low hypoglycemia risk, making them valuable in patients with heart failure or chronic kidney disease in addition to type 2 diabetes [60][61][62]. Medication selection should be individualized, considering comorbidities, patient preferences, cost/access, and potential adverse effects. Other practical issues include careful evaluation for secondary contributors (Cushing syndrome, hypothyroidism, medications such as glucocorticoids or atypical antipsychotics), routine assessment of sleep-disordered breathing, and incorporation of vaccination strategies (eg, influenza, pneumococcal, hepatitis B) given elevated cardiometabolic risks. Clinicians should not overlook psychosocial determinants—food insecurity, stress, depression—which can derail adherence if unaddressed. Finally, periodic reassessment of goals, medication tapering or escalation based on response, and transition planning (eg, pregnancy intentions in PCOS) ensure that management remains responsive over time, consolidating early gains into durable risk reduction.

Enhancing Healthcare Team Outcomes

Given the multisystem nature of insulin resistance, an interprofessional team delivers superior outcomes by coordinating prevention, treatment, and complication surveillance. An obesity medicine specialist can guide comprehensive medical management for weight reduction, while a bariatric surgeon evaluates candidacy for metabolic surgery when criteria are met. Endocrinology provides disease-modifying therapy for type 2 diabetes, complex dyslipidemia, and PCOS, optimizing pharmacologic regimens to balance glycemic control, weight, and cardio-renal protection. Cardiology and cardiac surgery address ischemic heart disease, heart failure, arrhythmias, and indications for revascularization, whereas vascular surgery manages PAD and carotid disease to prevent limb loss and stroke. Gastroenterology focuses on NAFLD detection and fibrosis staging, and neurology manages cerebrovascular disease and peripheral neuropathy, integrating secondary prevention strategies. Frontline education and behavior change are amplified by a nurse diabetes educator, dietitian, and physical therapist, who translate clinical recommendations into actionable daily routines, meal plans, and safe exercise prescriptions. The pharmacist reinforces medication adherence, identifies drug–drug interactions, and troubleshoots adverse effects, enhancing persistence and safety. Social workers mitigate access barriers—transportation, coverage, caregiving burdens—while a psychologist provides cognitive-behavioral therapy or motivational interventions to sustain lifestyle changes. Technology can augment this model: while evidence for continuous glucose monitoring (CGM) in non-diabetic insulin resistance is limited, remote monitoring and telehealth have improved outcomes in type 2 diabetes and can facilitate frequent touchpoints and timely therapy adjustments. Ultimately, the lynchpin of success remains lifestyle change, wherein dietary intervention (calorie moderation plus lower glycemic load) and structured physical activity synergistically improve insulin sensitivity at the tissue level and reduce cardiometabolic risk [63][64]. By integrating clinical expertise with patient-centered coaching and social support, the interprofessional team transforms episodic care into sustained risk modification, decreasing hospitalizations and long-term complications.

Outcomes

When insulin resistance is identified early and managed with sustained lifestyle measures and, when indicated, modern pharmacotherapy, outcomes are generally favorable. Patients who adhere to a structured plan—combining weight reduction, regular aerobic and resistance exercise, high-quality nutrition, adequate sleep, and stress management—often realize improvements in fasting glucose, HbA1c, triglycerides, HDL-C, blood pressure, and inflammatory markers. These biomarker shifts translate into lower rates of incident type 2 diabetes, fewer cardiovascular events, and slower progression of microvascular complications. Weight-loss–induced remission of prediabetes is common, and even partial weight loss confers meaningful benefit. In NAFLD, 7%–10% weight reduction is associated with histologic improvement, offering a path to disease modification alongside cardiometabolic risk reduction. Despite these encouraging trends, adherence remains the critical determinant of long-term success. Many patients struggle with sustainability because of environmental barriers, time constraints, medication costs, and competing life demands. In such contexts, the addition of pharmacologic agents—metformin, GLP-1RA, dual GIP/GLP-1, SGLT2i—can bolster weight and glycemic outcomes, improve patient momentum, and reduce cardio-renal risk. For selected individuals with severe obesity or refractory metabolic disease, bariatric/metabolic surgery yields durable weight loss, high rates of diabetes remission or improvement, and reductions in all-cause and cardiovascular mortality, especially when paired with lifelong nutritional support and follow-up care. Conversely, undertreated insulin resistance often progresses to type 2 diabetes, amplifying risks of myocardial infarction, stroke, heart failure, kidney failure, vision loss, and neuropathic complications that erode quality of life and increase healthcare utilization. Therefore, systems-level strategies—care pathways, quality metrics, proactive recalls, and population health analytics—should support consistent screening, timely therapy intensification, and patient engagement. Above all, the interprofessional team approach is pivotal: coordinated care that aligns clinical targets with patient values increases adherence and persistence, producing superior long-term outcomes and narrowing the gap between potential and realized benefit in everyday practice [62][65].

Conclusion:

Insulin resistance is a systemic, tissue-level disorder with far-reaching cardiometabolic consequences but a highly modifiable trajectory. The cornerstone of management is intensive lifestyle intervention—nutritional quality and caloric moderation alongside structured aerobic and resistance training—which improves insulin sensitivity in muscle and liver and attenuates de novo lipogenesis. Contemporary pharmacotherapy (metformin; GLP-1 and dual GIP/GLP-1 agonists; SGLT2 inhibitors) adds durable weight loss, glycemic control, and cardio-renal protection, while bariatric/metabolic surgery offers the greatest magnitude and durability of benefit in carefully selected individuals. Practical evaluation relies on surrogate indices and harmonizes metabolic syndrome criteria, with risk stratification that accounts for NAFLD/MASLD, PCOS, and vascular comorbidities. For oncology settings, proactive metabolic optimization can enhance overall resilience during cancer care. Ultimately, a coordinated, interprofessional model—linking endocrinology, nutrition, primary care, cardiology, hepatology, and behavioral health—translates evidence into sustained risk reduction, fewer complications, and better patient-reported outcomes across the lifespan.

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