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Metabolic and non-metabolic mechanisms of hyperinsulinemic cardiovascular damage associated with insulin resistance

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Abstract

Insulin is a hormone secreted by pancreatic β-cells, well known for its role in glucose metabolism. It regulates glucose uptake by cells in insulin-sensitive tissues, enabling its use as an energy source. However, it also performs other equally important functions, such as influencing cell growth, differentiation, and survival, modulating inflammation, and regulating vascular tone. In states of insulin resistance (IR) which are becoming increasingly prevalent worldwide, insulin becomes less efficient at regulating glucose metabolism. Consequently, the pancreas is forced to secrete larger amounts of hormone, particularly following carbohydrate-rich meals, to maintain blood glucose levels within the normal range. In this context, while insulin's action on glucose metabolism is impaired, the resulting hyperinsulinemia overstimulates other insulin signaling pathways that remain largely unaffected. As widely supported by scientific literature, this process leads to significant cardiovascular alterations over time. This narrative review aims to examine the best known metabolic and non-metabolic mechanisms underlying cardiovascular damage associated with hyperinsulinemia in the setting of IR.

Keywords

insulin resistance, hyperinsulinemia, thrombosis, organ damage, cardiovascular damage, mechanisms

Introduction

Insulin is a hormone produced by the β cells of the pancreas, well known for regulating metabolism and blood sugar levels. It enables glucose to enter the cells of responsive tissues to be used for energy. However, insulin also performs numerous other roles in the body that are less well-known but equally important. Among these, it plays a key role in cell growth, differentiation, and survival, modulates inflammation, and regulates vascular tone [1–3]. In states of insulin resistance (IR), chronic hyperinsulinemia occurs since the pancreas attempts to keep blood glucose levels within the normal range. This, over time, leads to the exhaustion of pancreatic β cells, eventually resulting first in prediabetes and then in overt diabetes [3, 4].

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While this response is beneficial for overcoming the IR that has developed in insulin-sensitive tissues, and for keeping circulating glucose levels as close to normal as possible, chronic hyperinsulinemia unfortunately overstimulates other mechanisms and pathways involving insulin, ultimately causing significant damage to our organs over time [3, 4]. This narrative review aims to examine the most known metabolic and non-metabolic mechanisms underlying the dangerous effects of chronic hyperinsulinemia associated with IR on cardiovascular system. Understanding these mechanisms is crucial to grasp why hyperinsulinemia associated with IR should be considered an independent risk factor, which consequently requires prompt attention through general population screening and, where detected, appropriate treatments to slow its adverse progression.

To this end and in order to write this article, the authors examined the relevant papers published from 1990 to 2025 on the topic in English in impacted journals listed in major medical scientific literature databases (PubMed, Scopus, Science Direct, Google Scholar, Research Gate, etc.), by using the following keywords: Insulin resistance, Hyperinsulinemia, Thrombosis, Organ damage, Cardiovascular damage, Mechanisms. The authors used a multi-stage method to filter search results down to final eligible stage (removing duplicates, screening titles and abstracts, and assessing full texts that only deal with the topic of the review). In the end, the authors analyzed all the manuscripts separately and subsequently they met to discuss their conclusions on the subject.

Definition of insulin resistance

IR is a condition, most often caused by unhealthy changes in our lifestyles that have occurred over the centuries, in which a given amount of circulating insulin produces a less effective result than expected regarding glucose metabolism [3, 4]. Its prevalence is progressively increasing worldwide, just as the prevalence of type 2 diabetes of which IR is a primary cause [4, 5]. This phenomenon creates a vicious cycle: to maintain circulating glucose levels within the normal range, the pancreas tends to secrete larger amounts of insulin (hyperinsulinemia), particularly after consuming sugar-rich meals, making hyperinsulinemia a constant feature of IR [4]. As previously mentioned, IR is predominantly caused by an unhealthy lifestyle involving a higher intake of calories (especially carbohydrates) than the ones burned through physical activity; consequently, IR is very often associated with obesity, particularly the visceral type [4–7]. However, genetic and pharmacological causes also exist, albeit less frequently. Insulin regulates not only glucose metabolism which is impaired in IR, but also many other important bodily functions that remain unaffected by IR. As a result, the hyperinsulinemia associated with IR ends up overstimulating these other functions, causing significant functional and structural organ damage over the years. The molecular mechanisms underlying IR are numerous and not all of them are fully understood. They involve the disruption of the biochemical cascade that enables cells to respond correctly to this hormone. Under normal conditions, insulin binds to its receptor, stimulating glucose uptake. In cases of IR, this pathway is blocked at various levels, both receptor and post-receptor, not all of them yet fully known. Among the best known are the defects in the receptor signaling pathway [insulin receptor substrate 1 (IRS-1) and phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)].

Under conditions of IR, inflammatory cellular kinases such as c-Jun N-terminal kinase (JNK) and inhibitor of nuclear factor kappa-B kinase subunit β (IKK-β) phosphorylate IRS-1 on serine residues rather than tyrosine. Serine phosphorylation inhibits the activation of the PI3K/Akt pathway, preventing the translocation of glucose transporter type 4 (GLUT4) to the cell membrane and thereby blocking glucose uptake [4, 8, 9]. Naturally, as previously mentioned, there are many others. However, explaining in detail all the mechanisms associated with IR is not the aim of this review, and doing so would lead to excessive length and cause us to lose sight of the article's primary objective which is to review the mechanisms that drive the cardiovascular damage associated with IR.

Hyperinsulinemia and atherothrombosis

This is one of the best-known mechanisms by which cardiovascular damage can occur in individuals with IR. Indeed, IR is a crucial, independent risk factor for the development of atherothrombosis, that is, the

predisposition to atherosclerosis and the formation of thrombi on pre-existing atherosclerotic plaques [10]. This link creates a highly unstable biochemical environment that exposes individuals to an extremely high risk of myocardial infarction and stroke [11].

The molecular and cellular mechanisms linking IR to atherothrombosis fall primarily into three broad categories.

Endothelial dysfunction and inflammation (plaque initiation)

Under normal conditions, insulin stimulates the production of nitric oxide (NO), a molecule that protects blood vessels by keeping them dilated and healthy [12, 13].

In the state of IR:

- The metabolic pathway (PI3K) responsible for NO production is blocked, causing vasoconstriction [4, 14, 15].
- Conversely, the mitogen activated protein (MAP) kinase pathway remains active, promoting inflammation, smooth muscle cell proliferation, and the expression of cell adhesion molecules [such as vascular cell adhesion molecule 1 (VCAM-1)] [3, 4, 14, 15].
- White blood cells adhere to and penetrate the arterial wall more easily, accelerating the formation of atherosclerotic plaque [15].

Plaque vulnerability and instability (progression)

IR does not merely cause plaque to grow; it renders plaque intrinsically dangerous and prone to rupture [16]:

- Increased small, dense low-density lipoprotein (sdLDL): This kind of lipoproteins are a particularly dangerous subclass of LDL cholesterol. They play a key role in the development of atherothrombosis, the pathological process characterized by damage to and progressive occlusion of an artery resulting from the rupture of an atherosclerotic plaque and the subsequent formation of a thrombus. While total LDL cholesterol quantifies the overall mass of transported cholesterol, the predominance of sdLDL (known as phenotype B) indicates a highly unstable and harmful lipid profile quality [17, 18].
- Macrophage death: Macrophages within the plaque become insulin-resistant, undergoing cellular stress and apoptosis (programmed cell death) [19].
- Necrotic core: A defect in the clearance of dead cells (efferocytosis) leads to the formation of an unstable, lipid-rich necrotic core [20].
- Thin fibrous cap: Plaques in insulin-resistant individuals contain less protective connective tissue, making them fragile and highly susceptible to fissuring [21].

Prothrombotic state and platelet hyperactivity (acute thrombosis)

When a plaque ruptures, the bodies of individuals with IR respond in an exaggerated manner, accelerating blood coagulation [22] (Figure 1).

- In the absence of the natural inhibitory effect exerted by insulin, platelets exhibit marked basal hyperreactivity and aggregate much more readily in response to stimuli [12] (Figure 1).
- Inhibition of fibrinolysis [plasminogen activator inhibitor-1(PAI-1)]: There is a marked increase in PAI-1, an enzyme secreted in excess by visceral adipose tissue that prevents the natural dissolution of blood clots [23, 24] (Figure 1).
- Increase in coagulation factors: Circulating levels of fibrinogen and factor VII are significantly elevated [25, 26] (Figure 1).

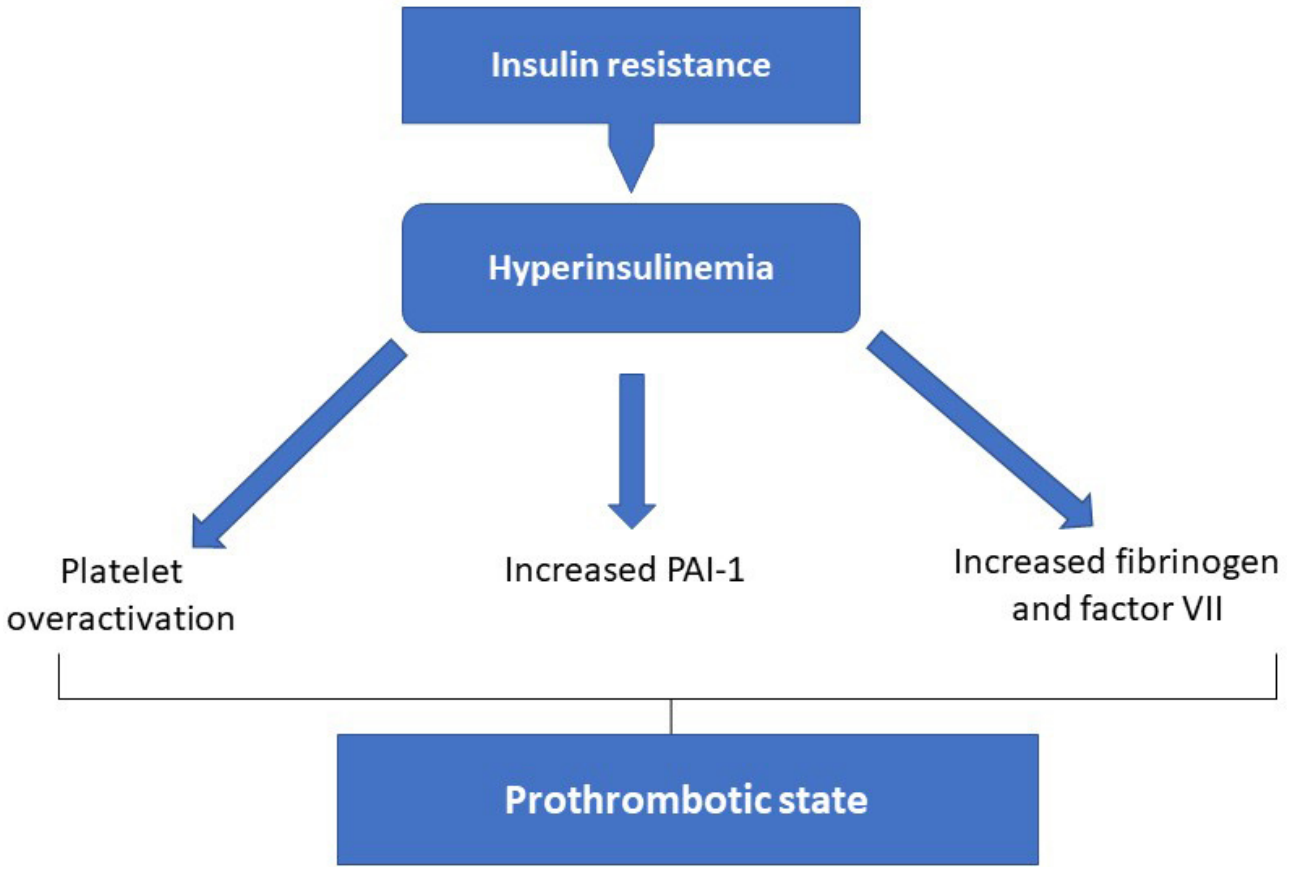

Figure 1. Insulin resistance is a prothrombotic condition. Insulin resistance with associated hyperinsulinemia produces a prothrombotic state due to platelet activation, inhibition of fibrinolysis (increased PAI-1) and an increase in coagulation factors (fibrinogen and factor VII). PAI-1: plasminogen activator inhibitor-1.

Hyperinsulinemia and cardiac damage

Chronic hyperinsulinemia associated with IR is among the most potent hidden risk factors for the development of cardiovascular disease and structural heart abnormalities (Figure 2) [27].

In particular, hyperinsulinemia on the heart acts as a growth factor, also binding to insulin-like growth factor-1 (IGF-1) receptors, resulting in concentric remodeling of the left ventricle and cardiac hypertrophy [28]. This process, also resulting from the development of arterial hypertension and an increase in intra- and peri-myocardial fibrous and adipose tissue, leads to stiffening and diastolic dysfunction. Consequently, filling pressures must rise to ensure adequate filling, a key precursor to the development of heart failure with preserved ejection fraction (HFpEF) [29–35].

Cardiac adipose tissue, specifically epicardial adipose tissue (EAT), loses its protective function in the presence of IR and hyperinsulinemia, transforming into a direct promoter of inflammation and myocardial damage. Under healthy conditions, this fat, located in direct contact with the heart, acts as a thermal buffer and an energy reserve of fatty acids. However, chronic excess insulin and reduced hormonal sensitivity cause its pathological expansion (epicardial steatosis) and a severe biochemical imbalance [36–42]. This interaction creates a vicious cycle that damages the heart through three main mechanisms.

Lipotoxicity and myocardial infiltration

Impaired storage capacity: IR in adipose tissue stimulates uncontrolled lipolysis, releasing massive quantities of free fatty acids (FFAs). No longer managed by epicardial fat, fatty acids penetrate directly into heart muscle cells (cardiomyocytes). Ectopic lipid accumulation generates reactive oxygen species (oxidative stress), leading to mitochondrial dysfunction and the replacement of muscle tissue with fibrous tissue [38, 39, 41, 42]. Mitochondrial dysfunction of the heart is a central pathological feature linking IR to cardiac diseases. When the heart becomes resistant to insulin, there is lower mitochondrial energy production in the myocardium with decreased contraction force [43].

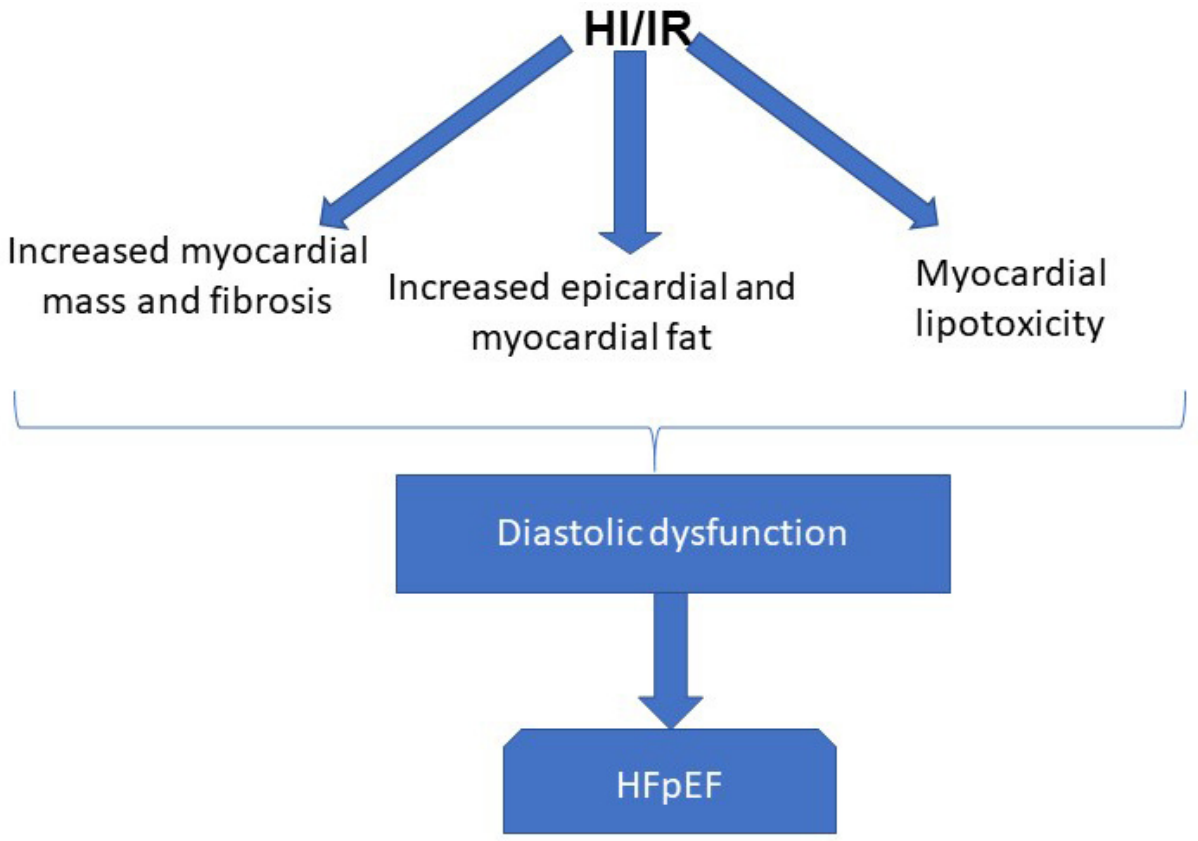

Figure 2. Insulin resistance and cardiac abnormalities. Hyperinsulinemia (HI) associated with insulin resistance (IR) produces increased fibrosis and concentric remodeling of left ventricle, increase of epicardial and intramyocardial adipose tissue and lipotoxicity, which in turn produce diastolic dysfunction of left ventricle and finally heart failure with preserved ejection fraction (HFpEF).

Paracrine secretion of inflammatory cytokines

Inversion of the adipokine profile: Expanded cardiac adipose tissue drastically reduces the production of adiponectin (a protective, anti-inflammatory hormone). The fat releases highly inflammatory molecules directly into the myocardium and coronary arteries, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and resistin. Due to the absence of a fascial barrier between epicardial fat and the coronary arteries, this inflammation directly promotes plaque development in the blood vessels, accelerating atherosclerosis [25, 44, 45].

Structural remodeling and arrhythmias

Stiffness and thickness: The increased volume of fat surrounding the heart exerts physical constriction, contributing to diastolic dysfunction (impaired heart relaxation). The infiltration of fat cells and inflammatory factors secreted by the tissue alter the electrical properties of the atrium, significantly increasing the risk of cardiac arrhythmias [29, 31, 32].

Hyperinsulinemia and arterial hypertension

Hyperinsulinemia may produce arterial hypertension through more associated relevant mechanisms [45] (Figure 3).

Alteration of vascular homeostasis

In healthy individuals, insulin stimulates the production of NO, a potent vasodilator. In the presence of IR, this metabolic pathway is blocked. Conversely, hyperinsulinemia stimulates the secretion of endothelin-1 (ET-1), a strong vasoconstrictor, shifting the balance of blood vessels toward persistent constriction. Furthermore, insulin stimulates the proliferation of vascular smooth muscle cells and promotes the formation of advanced glycation end products (AGEs), making arteries stiff and less elastic [46, 47].

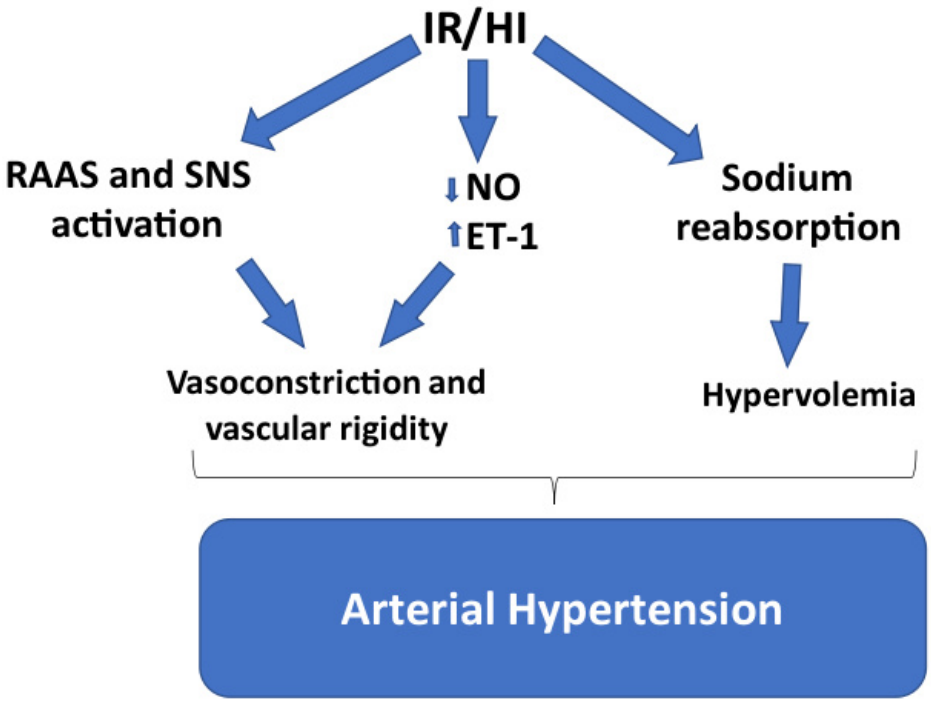

Figure 3. Insulin resistance and arterial hypertension. Hyperinsulinemia (HI) associated with insulin resistance (IR) can lead to arterial hypertension by stimulating vasoconstriction and vascular stiffness, as well as by increasing blood volume. This occurs primarily through reduced nitric oxide (NO) secretion and increased endothelin-1 (ET-1) secretion, activation of the sympathetic nervous system (SNS), renal tubular sodium reabsorption, and stimulation of the renin-angiotensin-aldosterone system (RAAS).

Activation of the sympathetic nervous system (SNS) and adrenergic stimulation

Excess insulin stimulates the central nervous system, which responds by increasing the release of norepinephrine. Norepinephrine causes peripheral blood vessels to constrict and increases heart rate, leading to an immediate rise in blood pressure [48, 49].

Sodium reabsorption

Insulin directly stimulates the renal tubules to retain more sodium and consequently more water. This fluid accumulation expands the total circulating blood volume, exerting greater physical pressure on the arterial walls [50, 51].

Stimulation of the renin-angiotensin-aldosterone system—hormonal cascade effect

Hyperinsulinemia directly activates components of the renin-angiotensin-aldosterone system (RAAS), which regulates blood pressure. The body becomes much more sensitive to the effects of angiotensin II and aldosterone which further potentiate vasoconstriction and fluid retention [35, 52, 53] and in turn worsen IR.

Potential treatments

Although this review does not aim to detail the specific mechanisms of available medications, the following is a brief overview of therapeutic intervention that can be implemented once IR is identified. First and foremost, lifestyle modifications are necessary where required [54, 55]. Dietary adjustments are essential; the diet should be normocaloric, varied, and low in carbohydrates (to prevent insulin spikes) [56]. In obese individuals, all available measures, both pharmacological and non-pharmacological, should be employed to achieve weight loss [57, 58]. Recent scientific literature has further highlighted the importance of consistent and appropriate physical activity [59]. Specifically, it has been shown that contracting muscles produce and release small protein (myokines) that interact with the muscles themselves, as well as the heart, brain, liver, adipose tissue, and bones, thereby positively influencing overall health [60]. Notably, these proteins also play a beneficial role in counteracting IR [61]. Consequently, skeletal muscle should be regarded as a true endocrine organ.

Apart from this, where indicated, medications and natural substances known to counteract IR may be used. Among medications, the best-known are glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors, supported by extensive scientific literature and proven to improve cardiovascular outcomes in at-risk individuals [62, 63]. Another long-established drug used to combat IR in type 2 diabetes is metformin [64]. Furthermore, there are many natural substances supported by scientific literature regarding their ability to counteract IR. I will mention just a few of the ones I am most familiar with: berberine, quercetin, silymarin, and L-arginine. For the mechanisms by which these drugs and natural compounds counteract IR, the specific literature is referred to for the sake of brevity [65, 66].

Discussion

IR accompanied by hyperinsulinemia is a pathological condition whose pathophysiological aspects and adverse effects on human health have been known for years. IR is not overlooked by the scientific community; on the contrary, it is considered one of the central pillars of modern metabolic medicine and the subject of thousands of clinical studies each year. However, it yet remains overlooked too often from a practical clinical perspective. A vast body of scientific literature clearly supports the view that it should be considered a major, independent cardiovascular (but not only) risk factor, requiring prompt action [11, 13, 27, 32, 34, 67–71]. However, for a variety of reasons, this has not yet happened.

While researchers study the complex links between IR and the cardiovascular system [11, 13, 27, 32, 34, 67–71], the brain [72, 73], the longevity [74–76], and the autoimmune diseases [77, 78], certain structural limitations are evident within the standard healthcare system. In fact, primary care tends to monitor only fasting blood glucose levels. This value remains normal for years because the pancreas produces more hormone to compensate. Furthermore, no pain is felt in the early stages. The few existing symptoms are often mistaken for stress or general fatigue: intense drowsiness and brain fog after meals (especially those high in carbohydrates), persistent difficulty in losing weight (particularly around the midsection), and sudden hunger pangs accompanied by uncontrollable cravings for sweets.

Consequently, metabolic resistance is detected belatedly, only when it progresses to prediabetes or type 2 diabetes. In addition, in major diagnostic manuals, IR is not classified as a distinct disease, but rather as a dysfunction or risk factor within the framework of metabolic syndrome. Treating IR requires significant interventions regarding diet, stress management, and physical activity. Standard medical consultations within public health services often lack the time and resources to guide patients through this behavioral therapeutic process.

Although the euglycemic-hyperinsulinemic clamp is the gold standard for diagnosing IR, using this type of test for population screening is not feasible [79]. However, there are numerous surrogate indices for indirectly assessing the presence of IR, such as the homeostatic model assessment for insulin resistance (HOMA-IR) and the triglyceride-glucose (TyG) index, correlating sufficiently with the clamp and identifying individuals at risk of adverse cardiovascular events [80–82]. While these indices may not detect 100% of patients, they are nonetheless capable of identifying the vast majority of them and can be used until other equally simple but more sensitive and specific indices will be identified. These indices have existed for many years but, unfortunately, little has been done to standardize their values and establish definitive cut-off points for IR. In our own small clinical experience, given the existence of a fairly well-established IR cut-off for HOMA-IR (> 2.5), we calculated the TyG value in 500 adult patients of both sexes, in the 18–65 years age range, with a HOMA-IR > 2.5, and consistently found it to be ≥ 8.5. TyG might be simpler, more reliable, and less expensive than HOMA-IR, because it is derived from parameters whose values have been standardized for many years, such as glucose and triglycerides. In contrast, HOMA-IR requires insulin measurement which is more costly and not yet perfectly standardized across different laboratories despite the passage of time.

Conclusions

Along with numerous other publications on the subject, this brief review of the mechanisms underlying damage caused by hyperinsulinemia associated with IR clearly highlights that there are ample grounds to consider it an independent risk factor for the development of cardiovascular abnormalities and disease that requires prompt clinical intervention. Such an approach could be implemented through mass screening of the general population using simple surrogate markers for IR, followed by treatment of identified individuals, in the hope of slowing the condition's progression toward diabetes and cardiovascular disease. In the near future, this could lead to greater healthy longevity with a lower burden of chronic disease and a significant reduction in healthcare costs. Furthermore, national health authorities need to launch public awareness campaigns regarding the existence of this condition, the complications associated with neglecting it, and the potential benefits of adopting healthier lifestyles. Obviously, randomized controlled trials on large sample of population and with adequate follow-up are needed to verify with certainty whether this kind of intervention can improve cardiovascular outcomes.

Abbreviations

Akt: protein kinase B

ET-1: endothelin-1

HFpEF: heart failure with preserved ejection fraction

HOMA-IR: homeostatic model assessment for insulin resistance

IR: insulin resistance

IRS-1: insulin receptor substrate 1

NO: nitric oxide

PAI-1: plasminogen activator inhibitor-1

PI3K: phosphoinositide 3-kinase

RAAS: renin-angiotensin-aldosterone system

sdLDL: small, dense low-density lipoprotein

SNS: sympathetic nervous system

TyG: triglyceride-glucose

Declarations

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During the preparation of this work, authors used the Google Gemini for help in creating figures. After using the tool/service, authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Author contributions

SF: Conceptualization, Writing—original draft, Writing—review & editing. FA and VF: Methodology, Formal analysis, Writing—original draft, Writing—review & editing. All authors read and approved the published version.

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The authors declare they have no conflicts of interest.

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Consent to participate

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Consent to publication

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