The Review Of
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The Role Of Insulin Resistance In Hypertension-The Pathophysiological Mechanisms

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Abstract

Background/Objectives: Considering that insulin resistance has been identified as a potential cause of hypertension and that hypertension remains the primary cause of cardiologic disease, in this study, we aimed to summarize the pathophysiologic mechanisms linking insulin resistance and hypertension.
Methods: A literature search was conducted in the electronic database "PubMed". Studies from the last 15 years were identified. The primary selection was based on abstract contents, whereas the final selection was made after the full texts were read.
Results: We found that insulin resistance contributes to hypertension through numerous mechanisms. Studies have linked compensatory hyperinsulinemia to hypertension through the activation of the sympathetic nervous system and abnormal activation of the renin–angiotensin–aldosterone system, leading to sodium retention. Furthermore, insulin resistance impedes the vasodilatory effect of insulin by blocking its ability to release nitric oxide. Hypertensive patients presented increased levels of asymmetric dimethylarginine, a nitric oxide inhibitor. Early stages of insulin resistance are associated with increased affinity and capacity of endothelin-1 receptors and increased secretion of endothelin-1, a potent vasoconstrictor. Obesity, endothelial dysfunction, insulin resistance in cardiomyocytes and activation of mineralocorticoid receptors are also linked to both insulin resistance and hypertension.
Conclusions: Available evidence suggests that insulin resistance plays an important role in the pathophysiology of hypertension. Its contribution to the development and progression of hypertension should not be overlooked. More studies are needed to elucidate the molecular and cellular mechanisms involved and develop an effective strategy for the prevention and treatment of hypertension in insulin-resistant patients.

Keywords: insulin resistance; hypertension; pathophysiological mechanisms

Introduction

Blood pressure is defined as the force with which circulating blood acts on the wall of the body's arteries [1]. Blood pressure in the clinic is measured as the ratio between the systolic and diastolic pressure values, and when the pressure values exceed 140/90 mmHg, hypertension is considered [2]. There are 4 types of hypertensions:

1. Primary or essential hypertension:
Hypertension that is not related to another medical condition or to a specific cause is thought to be caused by a combination of genetic factors, diet, lifestyle and age [1].

2. Secondary hypertension:
Hypertension, which has an identifiable and potentially reversible cause, is related to another medical condition and is usually caused by various problems with the kidneys, arteries, heart and endocrine system [3].

3. Resistant hypertension:
Hypertension is difficult to correct and requires therapy with many medications. It is classified in this group as hypertension that continues to stay above the predicted values with the administration of optimal therapy [2].

4. Malignant hypertension:
It is defined as a sudden increase in blood pressure, which puts the patient at risk of organ damage. This hypertensive condition represents a medical emergency that requires immediate attention [1].
Hypertension is a major global health issue affecting more than one billion people worldwide, with approximately 60 to 70 million individuals estimated to be affected by insulin resistance in the United States alone [4]. Statistics indicate that more than 40% of individuals older than 50 years may be at risk for insulin resistance; however, insulin resistance can affect anyone at any age [5]. The prevalence of insulin resistance among adults worldwide ranges from 15.5--46.5% [4,5].
Despite various studies, the pathophysiology of hypertension remains incomplete. In recent studies, insulin resistance has been identified as a potential contributor to the development and progression of hypertension [6,7]. Insulin resistance is a metabolic disease characterized by impaired insulin signaling and a reduced response of target tissues to insulin action [6]. It is associated with obesity, physical inactivity and a high-calorie diet, all of which contribute to the development of type 2 diabetes [8].
A recent study published in the Journal of Clinical Endocrinology and Metabolism by researchers at the University of Alabama at Birmingham reported that nearly 40% of nondiabetic youth may have insulin resistance. Although insulin resistance appears more often in obese people, in some studies, it has been proven that even in people with a normal body mass index, insulin resistance can occur, and it can be a hidden cause of later disorders [9]. Insulin resistance can result in hyperglycemia, hypertension, dyslipidemia, visceral fat, hyperuricemia, increased inflammatory markers, endothelial dysfunction, and a prothrombic state [10].
Epidemiological studies have shown a correlation between insulin resistance and hypertension, independent of other risk factors, such as age, sex, body mass index and glucose tolerance [6,7].
The mechanisms that link insulin resistance and hypertension are complex and multifactorial [6]. Insulin resistance affects many physiological systems that influence blood pressure regulation, including the renin–angiotensin–aldosterone system, the sympathetic nervous system, and endothelial function [6,7,11].

2. Materials and methods

2.1 Purpose and objectives
The purpose and objectives of this research are to evaluate the relationship between insulin resistance and hypertension and to provide a review of the literature on their pathophysiological mechanisms. In particular, this review aims to:
1. Describe insulin resistance and hypertension and give an explanation of their importance in the development of cardiovascular disease.
2. The potential mechanisms of the impact of insulin resistance on the development and progression of hypertension, including endothelial dysfunction, activation of the sympathetic nervous system, and changes in sodium metabolism, are described.
3. The potential therapeutic implications of targeting insulin resistance in the management of hypertension are discussed.

2.2 Research question
P (population): Individuals over 18 years of age diagnosed with hypertension and insulin resistance. Studies involving patients with secondary hypertension will not be considered
I (intervention): Not applicable
C (comparison): Not applicable
O (objective): Impact of insulin resistance on vascular tone, sympathetic nervous system and therapeutic implications in hypertension management.

2.3 Search strategy
This work was carried out according to the protocols of the PRISMA guidelines and the Cochrane Handbook for Systematic Reviews.
The search was performed in English using key words such as “insulin resistance”, “hypertension”, and “pathophysiologic mechanisms”. The search was performed in the PubMed database. Abstracts,

editorial letters and case reports are not included in this literature review. In the case of ambiguities, the authors of the works were contacted.

2.4 Selection of studies

All retrospective, prospective studies or literature reviews based on the
Pathophysiological mechanisms of the influence of insulin resistance on hypertension will be considered for inclusion in this study.

2.5 Data collection and evaluation of studies

Standard data collection forms were used. Tables were designed in MS Excel to collect data such as study characteristics, sample characteristics, number of studies included in the reviews, parameters, and conclusions. Because the studies are heterogeneous, a suitable tool for assessing the quality of these studies has not been identified.

2.6 Data synthesis

A summary of the main results was made in narrative and tabular form. After the results are analyzed, the main conclusions, the applicability of the evidence, the quality of the evidence, and the practical and academic implications of the results are discussed. A PRISMA flow diagram was constructed to illustrate the process of selecting the included studies.

2.7 Data availability

All the data that support the findings of this study are available from the included publications, all of which are cited and accessible via the PubMed database.

2.8 Use of generative AI

No generative artificial intelligence (GenAI) was used to generate any text, data, analysis or interpretation of the study.

3. Results

3.1. Selection of works

From the literature search in the electronic database PubMed, 567 articles were identified, of which 500 were reviewed (56 abstracts and 11 articles that were not in English were removed). After reading the titles and abstracts, we also removed 466 articles that did not aim to study the pathophysiology of the impact of insulin resistance on hypertension, while 34 articles were selected for reading the full text. Finally, 16 publications were selected for inclusion in the data synthesis.
The PRISMA flow diagram that illustrates this process is shown in **Figure 1.**

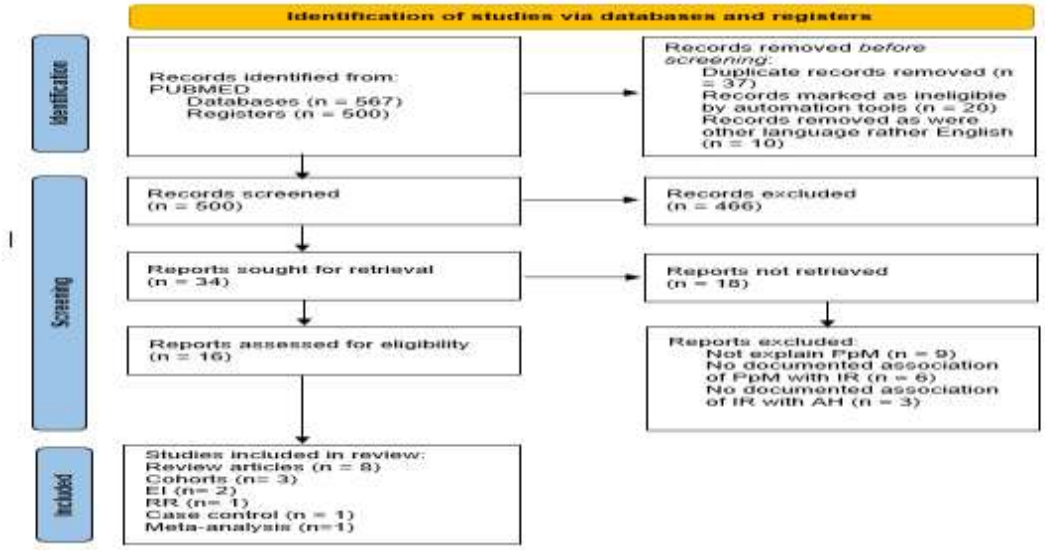

Figure 1. Study protocol and literature selection to collect data for research EI-Experimental investigations; RR-Randomized research; PpM-Pathophysiological mechanism; IR-Insulin resistance; AH-Arterial hypertension.

3.2. Characteristics of selected works

The studies included in this systematic literature review were published from 2007--2021. In terms of methodology, 8 publications were literature reviews, 3 cohort studies, 2 experimental studies, 1 randomized study, 1 case–control study and 1 meta-analysis. The main characteristics of the studies are presented in
Table 1.

Table 1. The characteristics of the selected works.

Articles	Objectives	Methodology	Data on pathophysiology
Sarafidis, P. A.; Bakris, G. L. The ant natriuretic effect of insulin: An unappreciated mechanism for hypertension associated with insulin resistance?	Summary of IR and its AN effect following HTN	Literature review	Insulin stimulates renal sodium absorption mainly in the distal nephron, in individuals with IR effect is enhanced and contributes to HTN.
Shimamoto, K.; Ura, N. Mechanisms of insulin resistance in hypertensive rats.	Evaluation of IR in rats with HTN	Literature review	Almost half of mice with essential hypertension without type 2 diabetes are insulin resistant
Mancusi, C.; Izzo, R.; di Gioia, G.; Losi, M. A.; Barbato, E.; Morisco, C. Insulin resistance: The hinge between hypertension and type 2 diabetes.	Description of the link between IR, HTN and diabetes	Literature review	IR-induced low-grade inflammation causes endothelial dysfunction andmetabolic abnormality
Zhang, H.; Li, J.; Li, R.; Zhang, Q.; Ma, H.; Ji, Q.; Guo, W.; Wang, H.; Lopez, B. L.; Christopher, T. A.; Ma, X.; Gao, F. Reduced cardiotropic response to insulin in spontaneously hypertensive rats: Role of peroxisome proliferator-activated receptor-gamma-initiated signaling.	Validation of the existence of myocardial IR and correlation with HTN	Retrospective research	IR exists in cardiomyocytes and is manifested by reduced insulin-induced glucose uptake and slower response contractile to insulin
Rajagopalan, S.; Alaiti, M. A.; Broadwater, K.; Goud, A.; Gaztanaga, J.; Connelly, K.; Fares, A.; Shirazian, S.; Kreatsoulas, C.; Farkouh, M.; Dobre, M.; Fink, J. C.; Weir, M. R. Design of the Magnetic Resonance Imaging Evaluation of Mineralocorticoid Receptor	Role assessment antagonist of MR in DA	Prospective research	MR activation can affect IR in 5 ways: receptor, transporter, phosphorylation, signaling and oxidative stress of hepatocytes

Antagonism in Diabetic Atherosclerosis (MAGMA)			
Jia, G.; Sowers, J. R. Hypertension in diabetes: An update of basic mechanisms and clinical disease.	Update on the mechanisms of HTN in diabetes	Literature review	Patients with type II diabetes often encountered with coexisting hypertension as a consequence of IR as opposed to type I diabetes (diabetic nephropathy)
Cooper, S. A.; Whaley-Connell, A.; Habibi, J.; Wei, Y.; Lastra, G.; Manrique, C.; Stas, S.; Sowers, J. R. Renin-angiotensin-aldosterone system and oxidative stress in cardiovascular insulin resistance.	Review of the role of the RAA system and oxidative stress in cardiovascular IR	Literature review	Activation of the RAA system changes the signaling pathways of insulin and IGF-1 which leads to the formation of free radicals, dysfunction endothelial growth and pathological remodeling
Rao, A.; Pandya, V.; Whaley-Connell, A. Obesity and insulin resistance in resistant hypertension: Implications for the kidney.	Review of the contribution of obesity to IR and the action of IR in HTN	Literature review	Obesity causes IR which contributes to dysfunction endothelial, reduced NO release, abnormal activation of the RAA system and sodium retention - contributing to HTN
Gamboa, A.; Okamoto, L. E.; Arnold, A. C.; Figueroa, R. A.; Diedrich, A.; Raj, S. R.; Paranjape, S. Y.; Farley, G.; Abumrad, N.; Biaggioni, I. Autonomic blockade improves insulin sensitivity in obese subjects.	Evaluation of the role of increased sympathetic nerve activity in IR and HTN	Experimental study	Autonomic blockade improves HNA in IR patients but has no effect in IS patients. The enhancement of SA contributes to IR.
Lin, Y.-J.; Juan, C.-C.; Kwok, C.-F.; Hsu, Y.-P.; Shih, K.-C.; Chen, C.-C.; Ho, L.-T. Endothelin-1 exacerbates development of hypertension and atherosclerosis in modest insulin resistant syndrome.	The association of Endothelin-1 (ET-1) with IR and HTN	Experimental study	The capacity of ET-1 receptors increases in the early stages of IR. ET-1 and insulin are stimulators of proliferation and migration of VSMC. All these contribute to the increase of HTN.
Perticone, F.; Sciacqua, A.; Maio, R.; Perticone, M.; Maas, R.; Böger, R. H.; Tripepi, G.; Sesti, G.; Zoccali, C. Endothelial dysfunction, ADMA and	It evaluates the correlation between ADMA and IR without excluding their effect on HTN	Case–control research	Hypertensive patients in sober state have higher values of ADMA and insulin as well as higher prevalence of IR compared to normotensive ones.

insulin resistance in essential hypertension.			Modifications in ADMA values significantly affect IR.
Da Silva, A. A.; do Carmo, J. M.; Li, X.; Wang, Z.; Mouton, A. J.; Hall, J. E. Role of Hyperinsulinemia and Insulin Resistance in Hypertension: Metabolic Syndrome Revisited.	Examines the relationship between hyperinsulinemia and IR in patients with MS and HTN	Literature review	Hyperinsulinemia induces sodium reabsorption mechanisms and increases SA resulting in HTN. Hyperinsulinemia in patients without IR does not significantly affect HTA.
Tran, L. T.; Yuen, V. G.; McNeill, J. H. The fructose-fed rat: A review on the mechanisms of fructose-induced insulin resistance and hypertension.	Review of the interlinking mechanisms between IR and HTN	Literature review	Insulin increases SA, secretion of ET-1 and its receptors, response of coronary vessels to TxA2 and decreases amount of NO contributing to HTN. Estrogen plays a protective role against IR and HTN while testosterone serves as a bridge between them.
Teunissen-Beekman, K. F. M.; Dopheide, J.; Geleijnse, J. M.; Bakker, S. J. L.; Brink, E. J.; de Leeuw, P. W.; Serroyen, J.; van Baak, M. A. Differential effects of proteins and carbohydrates on postprandial blood pressure-related responses.	Differences in blood pressure values after carbohydrate consumption in contrast to those after protein consumption	double-blind, six-arm randomized crossover trial	After maltodextrin consumption BP is lower than after protein consumption, the opposite happens with insulin concentration.
da Silva, A. A.; do Carmo, J. M.; Li, X.; Wang, Z.; Mouton, A. J.; Hall, J. E. Role of Hyperinsulinemia and Insulin Resistance in Hypertension: Metabolic Syndrome Revisited.	To find the connection between hyperinsulinemia and insulin resistance in hypertension as a cause–effect of obesity and metabolic syndrome.	Cohort study	Hyperinsulinemia can cause increased sympathetic nervous system activity and renal sodium retention, which can increase blood pressure.
Takatori, S.; Zamami, Y.; Hashikawa-Hobara, N.; Kawasaki, H. Insulin Resistance-Induced Hypertension and a Role of Perivascular CGRPergic Nerves.	To determine how hypertension is affected by perivascular nerves and those	Meta-analysis	Hypertension caused by insulin resistance can result from increased density and function of sympathetic nerves, and

	containing genes for peptide-calcitonin.	decreased density and function of these nerves.

3.3. The identified pathophysiological mechanisms

Sarafidis and Bakris (2007), in their article regarding the effect of AN IR, reported that hyperinsulinemia can cause a 50% decrease in urinary sodium excretion and a 30% increase in free water excretion without a change in rate. of glomerular filtration, plasma aldosterone levels and the amount of filtered glucose. This insulin-mediated sodium retention is followed by water retention and increases in extracellular and intravascular fluid volumes and stroke volume. This, in turn, results in an increase in blood pressure (in healthy individuals, this mechanism is compensated for by the excretion of sodium and water via the suppression-natriuresis mechanism) [12].

Shimamoto and Ura (2006), in their article on the assessment of the RI in rats with HTN, noted that, in their work with two groups of normotensive rats, one group had a family history of hypertension, whereas the other group did not, where glucose clamp testing for insulin sensitivity revealed that those with a family history of hypertension genetically had lower insulin sensitivity than did the group that had no family history of hypertension. They also revealed the mechanisms that in rats with HTN may have led to IR, such as insulin resistance in adipocytes (based on the levels of adiponectin, the levels of which are lower in IR), skeletal muscles, the phosphorylation of tyrosine (an amino acid component of insulin), the suppression of GLUT transporters, and abnormalities in CD36 [13].

Mancusi et al. (2020) reviewed the documented high incidence of diabetes in hypertensive patients and examined the effects of insulin, a pleiotropic hormone with a wide range of action on lipid and protein metabolism, ion transport, amino acid activity, the cell cycle and nitric oxide (NO) synthesis. These authors emphasized that IR contributes to an increase in blood pressure via many mechanisms, including increasing the activity of angiotensin II and aldosterone in tissues and increasing sympathetic activity and oxidative stress. Oxidative stress causes disordered endothelial function, which disrupts endothelial insulin signaling, leading to hypertension [14].

Zhang et al. (2008), through clinical experiments, reported correlations between hypertension, insulin resistance and hyperinsulinemia and reported that patients with type II diabetes had 1.5- to 2-fold greater morbidity from hypertension than did the general population; therefore, they hypothesized that improving insulin signaling in these patients may reduce cardiovascular complications and decrease the morbidity rate. They also investigated the roles of insulin in the inflammatory response and NO production but demonstrated how insulin plays a positive role in myocardial contraction by increasing transient Ca2+ levels via the PI-3 (phosphatidylinositol 3) kinase pathway. In this study, they reported that insulin resistance in the heart not only plays a role in the appearance of HTA but also may play a role in heart attack [15].

Alaiti et al. (2017) selected a group of female and male patients over the age of 45, and by means of diagnostic methods (MRI- before and after treatment) and certain treatments (placebo, with herbs), they also revealed how MR activation affects IR in 5 ways: weak expression of insulin receptors and GLUT transporters, aberrant phosphorylation resulting in the activation of a number of cascade kinases, reducing insulin signaling from the heart and skeletal muscle, and finally promoting oxidative stress in hepatocytes and promoting gluconeogenesis. These data suggest that MR antagonists can be used as a therapeutic modality for the treatment of type II diabetes mellitus [16].

Jia and Sowers (2021) reviewed new data and updated the results and reported that approximately 60–76% of obese patients in primary health care also suffer from hypertension. They reported that approximately 26% of cases of hypertension in men and 28% of cases of hypertension in women were overweight and that obese children were 3 times more at risk of developing hypertension than nonobese children were. They emphasized that in type I diabetes, the main cause of hypertension was diabetic nephropathy, whereas in type II diabetes, they emphasized that there could be causes of improper activation of the RAA system, such as the sympathetic nervous system, mitochondrial function disorder, oxidative stress, and inflammation, which correlate with, and with the preliminary works for more self-raised hypertension, the response of the sympathetic nervous system to insulin, where β-

adrenergic receptors are stimulated, where through the activation of serine and threonine kinases, insulin signaling is engaged and, as a result, IR increases [17].
Lastra et al. (2007), with a review of the literature, emphasized precisely the role of the RAA system and oxidative stress in insulin resistance and concluded that the RAA system contributes to the involvement of the signaling pathways of insulin and IGF-1, which results in insulin resistance and the formation of free radicals, consequently disrupting the endothelial function of blood vessels and pathological growth and remodeling, leading to the development of hypertension [18].

Rao A et al. (2015) presented data on the mechanisms by which obesity contributes to RI and how the latter contributes to HTN. Increased adiposity initiates a series of oxidative and proinflammatory reactions that result in the development of IR. IR inhibits the use of glucose by muscles through constrictive and remodeling changes in the endothelium of blood vessels and causes HTN by acting similarly to the microvascular bed of the kidneys, where it causes retention and reabsorption of sodium and changes the vasodilator effect of insulin [19]. Under normal conditions, the binding of insulin to the corresponding receptors signals the release of NO, a vasodilator, a pathway that is impaired in cases of IR, thus resulting in impaired endothelial vasodilator function and thereby contributing to HTN. Damage to insulin signaling also contributes to HTN by increasing sodium reabsorption in the kidneys. IR increases the activity of the proximal tubule NHE3 exchanger, resulting in sodium retention. IR also causes inadequate activation of the RAA system, which also contributes to the development of endothelial dysfunction and HTN [19].

Gamboa A et al. (2014) evaluated the role of increased sympathetic nerve activity in the RI using a ganglionic blocker, trimethaphan [20]. Obesity is one of the most frequent causes of HTA and RI, but not all obese patients are insulin resistant. In this study, the HTA of obese patients was normalized with autonomic blockade, confirming the hypothesis that sympathetic nerve activation contributes to HTA. However, a previous study revealed that this occurred only in patients with RIs, whereas insulin sensitivity had no effect on those with RIs [20]. Additionally, the study concluded that the autonomic block improved insulin sensitivity, suggesting that the increase in sympathetic nervous activity contributes to IR, which causes a compensatory increase in insulin in the blood, followed by a further increase in SA [20].

Lin Y-J et al. (2015), in their experimental work in mice, reported the correlation of endothelin-1 (ET-1) with IR and HTN [21]. This study revealed that the affinity and capacity of ET-1 receptors are increased in the early IR phase. ET-1 is among the most potent vasoconstrictors of blood vessels, and in addition, this study concludes that ET-1 is a stimulator of the proliferation and migration of vascular smooth muscle cells (VSMCs), thereby reducing the lumen of blood vessels; therefore, it is worth mentioning as a contributing factor in HTN. As ET-1 and insulin seem to have the same effects on VSMCs, in patients with IR in which there is also hyperinsulinemia, their contributions and actions only increase in the context of HTN [21].

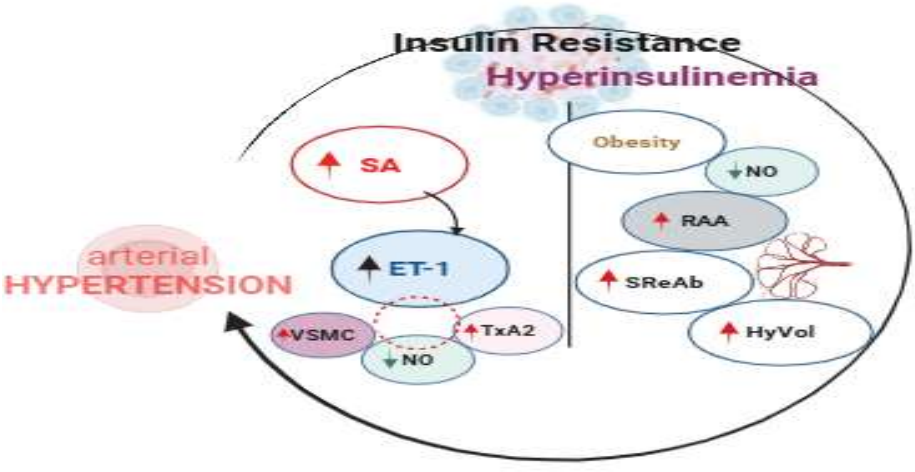

Figure 2. **Pathophysiological mechanism of AHT due to insulin resistance and hyperinsulinemia.**

SA- sympathetic activity; ET-1-endothelin-1; VSMC-vascular smooth muscle cells; NO-Nitric oxide; TxA2-thromboxane A2; RAA-renin angiotensin aldosterone; SReAb-Sodium reabsorption; HyVol-Hypervolemia

Perticone F et al. (2010) evaluated the association of nonsymmetrical dimethylarginine (ADMA) with IR and its action when it was present together without excluding its association with HTN. ADMA is an inhibitor of NO synthesis, whereas NO is the most potent vascular vasodilator, in the absence of which signs of IR and HTN are expected to be observed; therefore, the correlation of ADMA with both IR and HTN is worth studying [22]. The study is of the case–control type where the differences between hypertensive and normotensive patients were analyzed. In hypertensive patients, higher fasting insulin values, higher ADMA values and a greater prevalence of IR were observed than in normotensive patients. The higher values of ADMA and their linear correlation with the RI in hypertensive patients found in the present study support the hypothesis that modifications in ADMA values significantly affect the RI in these patients. Since both ADMA and RI contribute to the pathogenesis of cardiovascular diseases, it is plausible that their joint presence has a multiplier effect on increasing the risk of HTA [22]. Da Silva et al. (2020) described the mechanisms through which IR and hyperinsulinemia in patients with metabolic syndrome (MS) influence HTN. Until 30 years ago, the RI and hyperinsulinemia were considered strong contributors to HTN and MS [23]. The paper shows that in MS patients with severe IR, the increase in blood insulin values triggers different mechanisms that increase sodium reabsorption and activate the sympathetic nervous system directly or indirectly, causing HTN over time. However, many other studies have shown that hyperinsulinemia without IR does not play a major role in increasing arterial pressure [23]. However, although hyperinsulinemia may not initiate HTN associated with MS, hyperglycemia and dyslipidemia, which are associated with IR, contribute to ongoing vascular and renal damage that, over time, may worsen HTN and cause tissue damage [23]. Tran L-T et al. described the relationship between the RI/compensatory insulinemia and the development of HTN. This paper also describes the role of the sympathetic nervous system and the increased production of vasoconstrictors such as ET-1, angiotensin II and prostaglandin in the development of HTN. The studies included in their paper investigated these mechanisms in mice fed fructose [24]. Another mechanism that links HTN and IR is the stimulation of the sympathetic nervous system by insulin. It is thought that the increase in SA through vasoconstriction and the reduction in IS tissue perfusion contribute to IR development, the result of which is compensatory hyperinsulinemia that acts as a continuous stimulator of the sympathetic nervous system. In this study, doubts are expressed as to which is the initiating process, but it is thought that the primary process is the SA [24]. With hyperinsulinemia, an increase in the secretion of ET-1 (a powerful vasoconstrictor) and the expression of its receptors has also been observed, which contributes to changes in blood circulation and eventually the development of HTN [24]. An important mediator of HTN that leads to IR is the excessive activation of the RAA system, which results in an increase in the value of angiotensin II. The latter contributes to the development of RIs through vasoconstrictor activity by reducing blood flow in IS tissues [24]. Prostaglandin H2 (PGH2) can be converted to TxA2, a vasoconstrictor, through thromboxane synthase. Insulin has been reported to increase the responsiveness of coronary vessels to TxA2, confirming the possibility of a correlation between hyperinsulinemia and HTN [24]. IR and compensatory hyperinsulinemia are related to a reduction in NO synthase activity, which results in a low level of NO, a vasodilator, and consequently, increased vasoconstriction of the vessels, which eventually results in HTN [24]. This study also describes the role of sex and hormones in IR and HTN. Studies have shown that male rats with chronic insulin treatment have a greater prevalence of IR than females do and that, in contrast with females, only hyperinsulinemic males develop HTN. Since the development of IR and HTN in ovariectomized women after chronic fructose feeding was prevented by estrogen treatment, the study concluded that estrogen has a protective effect against IR and HTN. On the other hand, all men who underwent gonadectomy after chronic fructose feeding had IR, but none of them developed HTN (because testosterone is missing), leading to the conclusion that testosterone may be a link between IR and HTN [24]. Teunissen - Beekman et al. (2014) described the difference in HTN after carbohydrate and protein consumption. In this study, after the consumption of

maltodextrin, the arterial pressure (BP) and concentrations of NO, GLP-1 and glucagon were lower than those after the consumption of proteins, whereas the concentration of insulin was higher after the consumption of maltodextrin than after protein consumption. However, low BP is not necessarily associated with low concentrations of NO, GLP-1 and glucagon [25].

The study hypothesizes that low BP is associated with a high level of NO, which, through vasodilation, reduces peripheral resistance [25]. Da Silva AA described how other mechanisms, such as physical compression of the kidneys, activation of the renin–angiotensin–aldosterone system, hyperleptinemia, stimulation of the brain melanocortin system, and activation of the SNS, play critical roles in the onset of hypertension in obese subjects with metabolic syndrome. However, the metabolic effects of insulin resistance, including hyperglycemia and dyslipidemia, appear to interact synergistically with elevated blood pressure to cause vascular and renal damage that may exacerbate hypertension [26]. To elucidate the mechanisms of hypertension caused by insulin resistance, Takatori S et al. investigated the effects of hyperinsulinemia or hyperglycemia on vascular responses mediated by perivascular nerves, including adrenergic sympathetic nerves and calcitonin-related peptide-containing nerves [27]. Hypertension caused by insulin resistance can result from increased density and function of sympathetic nerves and decreased density and function of these nerves [27].

4. Discussion

From the literature search in the PubMed electronic database, we identified 16 articles that aimed to study the relationship between insulin resistance and arterial hypertension. Much of the related research has involved experiments conducted in mice, suggesting that the same mechanisms occur in humans. These studies demonstrated that obesity also contributes to endothelial dysfunction, reduced NO release and abnormal activation of the renin–angiotensin system. Insulin resistance exists in cardiac cells and not only plays a role in the occurrence of arterial hypertension but also may play a role in heart attack. The renin–angiotensin system contributes to the involvement of insulin signaling pathways and IGF-1, resulting in insulin resistance and free radical formation. The increase in insulin levels in the blood stimulates various mechanisms that increase the reabsorption of insulin sodium and activate the sympathetic nervous system directly or indirectly by also causing arterial hypertension in time. Stimulation of the sympathetic nervous system by insulin is the mechanism that links hypertension arterial and insulin resistance. The increase in insulin resistance in isolated adipose cells after hypertension was quantified spontaneously in mice.

These results are consistent with the conclusion that fructose-induced hypertension in mice is associated with volume overload. The results of these studies revealed that the perfused livers of trained rats secreted significantly less VLDL-TG, whereas the LPL activity in the adipose tissue of the other groups was similar.

As summary the main mechanisms related to the impact of IR on HTN are:

- Insulin stimulates sodium absorption, sympathetic nervous system activity, and myocardial contractility.
- In IR, these effects are intensified, contributing to HTN, endothelial dysfunction, and increased risk of heart attack.
- IR induces inflammation, reduces nitric oxide, increases ET-1 activity, and promotes vascular smooth muscle proliferation, narrowing vessels and raising BP.
- Obesity-related IR worsens endothelial function, RAA activation, and sodium retention
- Sympathetic nervous system activation and mineralocorticoid receptor MR signaling aggravate IR.
- RAA system and ADMA alterations impair insulin/IGF-1 signaling, leading to oxidative stress and vascular dysfunction.
- IR is found in hypertensive mice and salt-sensitive humans, with genetic links.
- Dietary factors (fructose, maltodextrin, protein) and magnesium shifts affect insulin response, while exercise or somatostatin can prevent IR-related HTN.

These findings confirm that insulin resistance is not only a metabolic problem but also a factor that contributes to a plethora of other problems, including vascular dysfunction and hypertension. This multifactorial mechanism involves a number of different systems, including SNS activation, hormonal dysregulation, genetic predisposition, endothelial dysfunction, and vasoconstrictor and vasodilator

activity. This emphasizes the importance of considering insulin resistance during the evaluation and management of hypertensive patients.

This review highlights the need to direct future research toward the following:

- More specific in vitro and in vivo studies on the molecular and cellular pathophysiology
- Clinical trials on the impact of antidiabetic drugs and their effects on hypertension management

5. Patents

This research did not result in any patents.

Supplementary Materials: Not applicable

Author Contributions

BN, NJN, RM: Conceptualization, Study Design, Methodology, Drafting the Manuscript,
FB, DS: Validation of data, Formal Analysis, Data Curation
NJN, RM: Literature Review, Data Verification, Manuscript Editing
BN: Final Manuscript Editing
All authors have read and agreed to the published version of the manuscript.

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Abbreviations

The following abbreviations are used in this manuscript:

IR	Insulin resistance
IGF	Insulin like growth factor
HTN	Hypertension
MR	Mineralocorticoid receptor
DA	Diabetic atherosclerosis
IS	Insulin resistant
RAA	Renin angiotensin aldosterone
AN	Anti-natriuretic
SA	Sympathetic activity
VSMC	Vascular smooth muscle cells
BP	Blood pressure
MS	Metabolic syndrome
ADMA	Asymmetric Dimethylarginine
ED	Endothelial disfunction
CGRP	Calcitonin Gene-Related Peptide

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