OnLine Journal of Biological Sciences

Literature Review

The Relationship between Obesity, Insulin Resistance and Hypertension: A Review

[1]Masah Mardini, [2]Lana Dardari, [3]Maher Taha, [4]Heba Eyad Shalabi, [5]Grisilda Vidya Bernhardt and [5]Pooja Shivappa

[1]Department of Medicine, RAK College of Medical Sciences, RAK Medical and Health Sciences University, RAK, UAE
[2]Internal Medicine Resident, Cleveland Clinic Fairview Hospital, Cleveland, Ohio, USA
[3]Department of Internal Medicine, Texas Health HEB, Bedford, Texas, USA
[4]Pediatric Resident, Al Qassimi Women's and Children's Hospital, Sharjah, UAE
[5]Department of Biochemistry, RAK College of Medical Sciences, RAK Medical and Health Sciences University, RAK, UAE

Article history
Received: 16-03-2024
Revised: 30-05-2024
Accepted: 03-06-2024

Corresponding Author:
Grisilda Vidya Bernhardt
Department of Biochemistry, RAK College of Medical Sciences, RAK Medical and Health Sciences University, RAK, UAE
Email: grisilda@rakmhsu.ac.ae

Abstract: Obesity is considered a global epidemic with detrimental health effects. It is linked to the development of conditions such as diabetes mellitus, hypertension, hyperlipidemia, coronary heart disease, atherosclerotic cerebrovascular disease, and higher mortality rates, among other conditions. This review elucidates the pathophysiology linking obesity, insulin resistance, type 2 diabetes, and hypertension and includes clinical trials that demonstrate these relationships. Electronic research was conducted using PubMed, Google Scholar, and up to date. The search results included publications written in English from the year 1994-2023. Relevant articles from the reference lists were reviewed to collect pertinent information. Several studies demonstrating the relationships between obesity and insulin resistance, obesity and hypertension, and insulin resistance and hypertension were interpreted and analyzed. The results concluded that there is a significant positive association among these three factors. However, a weak association between insulin resistance and hypertension was found. Many studies have demonstrated the relationships between obesity, type 2 diabetes, insulin resistance, and hypertension. This is important as it increases the opportunity for patient education, the development of drugs that target specific pathways, and the reduction of overall morbidity and mortality.

Keywords: Obesity, Type 2 Diabetes, Hypertension, Insulin Resistance

Introduction

Obesity has been recognized as a global epidemic with detrimental health effects due to its association with an elevated likelihood of diabetes mellitus, hypertension, hyperlipidemia, and cardiovascular disease (Hruby and Hu, 2015). This condition triggers an inflammatory response, characterized by cytokine secretion from visceral adipocytes, leading to chronic systemic inflammation (Bernhardt *et al*., 2022). Such inflammation can alter insulin signaling, accelerating the development of both hepatic and systemic insulin resistance (Hardy *et al*., 2012; Coppack, 2001). This insulin resistance can subsequently contribute to hypertension through various mechanisms, including impaired insulin action on nitric oxide production, increased tissue angiotensin II and aldosterone activity, and oxidative stress (Klabunde, 2011; Mancusi *et al*., 2020; Semlitsch *et al*., 2019; Zhang *et al*., 2014). Understanding the interplay between obesity, insulin resistance, and hypertension is crucial for developing targeted interventions. In this review, we explore the complex relationships among these factors and their implications for pharmaceutical interventions.

Research Question

How does insulin resistance in obese patients contribute to the development of hypertension? This review aims to elucidate the intricate mechanisms linking obesity, insulin resistance, and hypertension, highlighting their clinical significance and implications for therapeutic interventions in combating obesity-related complications and comorbidities.

Methods

We reviewed existing literature to explore the connections between obesity, insulin resistance, and hypertension. The search results included publications written in English from the year 1994 up to the year 2023. We used PubMed, and Google Scholar, up to date to look for studies pertaining to the relationship between obesity,

insulin resistance, and hypertension using the following search terms: "Obesity and type 2 diabetes mellitus", "insulin resistance and hypertension", "insulin resistance and obesity", "obesity and hypertension". Relevant articles from the reference list were reviewed in order to collect relevant information.

Findings

Insulin Resistance, Obesity, Inflammation, and Type 2 DM

Obesity, characterized by excessive or abnormal fat accumulation, is commonly quantified using the Body Mass Index (BMI) (Semlitsch *et al*., 2019). However, BMI's inability to distinguish between fat and lean muscle mass limits its accuracy. Waist circumference is recognized as a better predictor of metabolic disorders associated with obesity, including diabetes, hypertension, and dyslipidemia (Zhang *et al*., 2014).

Inflammatory Nature of Obesity

Obesity has emerged as an inflammatory disease, marked by a systemic low-grade inflammatory response influenced by adipocytes (Wondmkun, 2020). These specialized cells secrete adipokines, including pro-inflammatory cytokines like TNF-α, interleukin-6, and leptin (Rosen and Spiegelman, 2006). The imbalance between pro-inflammatory and anti-inflammatory adipokines contributes to chronic inflammation in obese individuals. Furthermore, various cell types within adipose tissue, including macrophages, endothelial cells, and immune cells, participate in the inflammatory process, exacerbating insulin resistance (Cai *et al*., 2022; Bernhardt *et al*., 2021b).

Insulin Resistance and Type 2 DM

Insulin resistance, characterized by impaired insulin signaling, plays a crucial role in the onset of Type 2 Diabetes Mellitus (T2DM). Obesity-induced insulin resistance initially results in compensatory β-cell function to meet the increased insulin demand (Wondmkun, 2020; Biessels and Kappelle, 2005). However, prolonged insulin resistance leads to inadequate glucose disposal and hyperglycemia, culminating in T2DM (Van Greevenbroek *et al*., 2016). The risk of T2DM escalates with increasing BMI across different populations (Van Greevenbroek *et al*., 2016; Bernhardt and D'souza, 2012).

Factors Contributing to Insulin Resistance

1. Adipose tissue expansion: Visceral adipose tissue expansion and adipocyte hypertrophy in obesity contribute to insulin resistance by increasing the secretion of pro-inflammatory cytokines (Coppack, 2001). Adipose tissue hypoxia and adipocyte apoptosis further exacerbate inflammation and insulin resistance (Ginsberg, 2000)
2. Hypoxia and Endoplasmic Reticulum (ER) Stress: Adipose tissue hypoxia induces mitochondrial dysfunction, macrophage infiltration, and ER stress, which all contribute to insulin resistance to insulin resistance (Lionetti *et al*., 2009). ER stress also results in the production of inflammatory signals, impairing insulin signaling (Ginsberg, 2000)
3. Toll-Like Receptors (TLRs): Activation of TLRs, particularly TLR2 and TLR4, by saturated fatty acids and glucose triggers metabolic inflammation and insulin resistance (Vandanmagsar *et al*., 2011; Ye, 2013). Studies have demonstrated the role of TLR4 in negatively affecting insulin sensitivity, while inhibition of TLR4 can alleviate obesity-induced insulin resistance (Vandanmagsar *et al*., 2011; Mogensen, 2009)
4. Mitochondrial dysfunction: Decreased mitochondrial function in obesity leads to excessive lipid buildup in muscle and adipose tissues, exacerbating insulin resistance (Orr *et al*., 2012; Bernhardt *et al*., 2012). This dysfunction impairs insulin-regulated glucose metabolism and GLUT4 translocation, further interrupting insulin signaling (Jeschke and Boehning, 2012)

Tables 1-2 highlight the connection between obesity, inflammation, insulin resistance, and type 2 diabetes mellitus.

The Relationship between Insulin Resistance and Hypertension

Blood pressure, expressed in millimeters of mercury (mmHg), reflects the pressure within the arterial system. Peripheral vascular resistance, also known as Systemic Vascular Resistance (SVR), is the resistance to the flow of blood and contributes to blood pressure regulation by controlling blood flow through vasoconstriction (Daniele *et al*., 2014). Systolic Blood Pressure (SBP) represents the maximum pressure during ventricular contraction, while Diastolic Blood Pressure (DBP) indicates the minimum pressure recorded just before the next contraction. The Mean Arterial Pressure (MAP) represents the average pressure within the arteries throughout a cardiac cycle and can be calculated using the formula: MAP = DBP + ⅓ (SBP- DBP) (Bernhardt *et al*., 2012; Arcidiacono *et al*., 2020). Hypertension is characterized by a SBP above 140 mmHg and a DBP above 90 mmHg (Orr *et al*., 2012).

Insulin Resistance and Blood Pressure Regulation

Insulin is essential for regulating numerous physiological processes, including lipid and protein metabolism, ion transport, and Nitric Oxide (NO) synthesis. Insulin indirectly promotes vasodilation through NO production. However, insulin resistance hinders the synthesis of NO and impairs vasodilation, disrupting blood pressure regulation (Mancusi *et al*., 2020).

Table 1: Summary of aspects of the connection between obesity and inflammation in type 2 diabetes mellitus

Aspect	Summary	Cited references.
Obesity definition and measurement	Obesity is characterized by an abnormal or excessive buildup of fat in adipose tissue. It is quantified using Body Mass Index (BMI) and waist circumference. BMI ≥30 kg/m² is defined as obesity	Hruby and Hu (2015); Semlitsch *et al*. (2019)
Obesity and Inflammation in T2DM	Obesity-induced inflammation affects insulin signaling and β cell function, contributing to Type 2 Diabetes Mellitus (T2DM) development. Pro-inflammatory adipokines play a role in this process	Wondmkun (2020); Biessels and Kappelle (2005); Bernhardt and D'souza (2012); Ginsberg (2000)
Role of visceral adipose tissue in inflammation	Visceral adipose tissue secretes pro-inflammatory cytokines, contributing to insulin resistance. Adipocyte hypertrophy and hypoxia plays a role in this process	Ginsberg (2000); Lionetti *et al*. (2009)

Table 2: Summary of aspects of the relationship between insulin resistance and type 2 diabetes mellitus

Aspect	Aspects of relationship	Cited references
Insulin resistance in T2DM	Insulin resistance and β cell dysfunction are key processes leading to T2DM. Increased BMI correlates with a higher risk of T2DM development	Ginsberg (2000); Lionetti *et al*. (2009)
Factors contributing to	Factors include inflammation, oxidative stress, endoplasmic reticulum stress, insulin resistance adipocyte dysfunction, hypoxia, aging, and genetic factors	Ginsberg (2000); Lionetti *et al*. (2009)
Toll-like receptors and inflammation	Toll-Like Receptor (TLR) activation triggers inflammation-associated insulin resistance in obesity. TLR2 and TLR4 are implicated in this process	Vandanmagsar *et al*. (2011); Mogensen (2009)
Mitochondrial dysfunction and insulin resistance	Decreased mitochondrial function leads to increased fat deposition in muscle and adipose tissues, exacerbating insulin resistance	Orr *et al*. (2012); Bernhardt *et al*. (2012)
Lipid metabolism and insulin resistance	Increased free fatty acids impair insulin-regulated glucose metabolism, affects glucose uptake and insulin function in various cells	Orr *et al*. (2012); Bernhardt *et al*. (2012); Jeschke and Boehning (2012)

Mechanisms Linking Insulin Resistance to Hypertension

Insulin resistance leads to elevated blood pressure through multiple mechanisms:

1. Enhanced Angiotensin II (AT II) and aldosterone activity: Insulin resistance promotes increased tissue AT II and aldosterone activity, leading to vasoconstriction and sodium retention, respectively (Arcidiacono *et al*., 2020)
2. Increased sympathetic nervous system activity: Vasoconstriction induced by heightened sympathetic nervous system activity further elevates blood pressure (Arcidiacono *et al*., 2020)
3. Oxidative stress and endothelial dysfunction: Endothelial dysfunction, mediated by increased oxidative stress, precedes peripheral reduction of insulin sensitivity. This phenomenon, known as "endothelial insulin resistance", impairs peripheral tissue blood flow and NO availability, contributing to hypertension (Mancusi *et al*., 2020; Sinha and Haque, 2022). Studies consistently demonstrate a bidirectional relationship between diabetes and hypertension, with diabetic patients often presenting with hypertension and vice versa. The reciprocal relationship underscores the complex interplay between insulin resistance and hypertension.

Table 3 provides a summary of the connection between insulin resistance and hypertension, along with the mechanisms of action involved, offering valuable insights into the pathophysiology of hypertension associated with insulin resistance.

Assessing Insulin Resistance Using the Homeostasis Model Assessment (HOMA-IR) and the Metabolic Score for Insulin Resistance (METS-IR)

Homeostatic Model Assessment (HOMA-IR)

Homeostatic Model Assessment (HOMA) provides a method for evaluating pancreatic β-cell function and Insulin Resistance (IR) based on fasting glucose and insulin or C-peptide concentrations. This assessment relies on the feedback loop between the liver and pancreatic beta cells, where glucose levels are regulated by insulin-dependent Hepatic Glucose Production (HGP) and insulin secretion is contingent upon pancreatic beta cell response to that glucose level. A deficient beta cell response will result in a diminished response to glucose-stimulated insulin secretion. By comparing a patient's fasting values with the model's predictions, HOMA enables a quantitative assessment of insulin resistance and deficient β-cell function contributions to fasting hyperglycemia (Shah, 2021; Shimoda *et al*., 2015; Abdollahpour Alni and Nikookheslat, 2022).

Metabolic Score for Insulin Resistance (METS-IR)

The metabolic score for insulin resistance is a novel metabolic index designed to quantify peripheral insulin resistance. It serves as a non-insulin-based alternative for evaluating peripheral insulin sensitivity and serves as an alternative to HOMA-IR (Shimoda *et al*., 2015). This index provides a valuable tool for evaluating insulin resistance, offering insights into metabolic health without relying on direct insulin measurements.

Table 3: Mechanisms of action of insulin resistance in hypertension

Mechanism	Aspects of relationship	Cited references
Impaired Nitric Oxide (NO) synthesis	Insulin indirectly induces vasodilation through NO production. Insulin resistance disrupts NO synthesis and impairs vasodilation, leading to altered blood pressure regulation and an increase in blood pressure	Mancusi *et al*. (2020)
Enhanced Angiotensin II (AT II) activity	Insulin resistance contributes to increased blood pressure through enhanced tissue angiotensin II (AT II) activity. AT II promotes vasoconstriction and aldosterone release, leading to increased peripheral resistance and blood volume	Arcidiacono *et al*. (2020)
Enhanced sympathetic nervous system activity	Insulin resistance is linked to enhanced sympathetic nervous system activity, which leads to vasoconstriction, further contributing to hypertension	Arcidiacono *et al*. (2020)
Oxidative stress	Endothelial insulin resistance, driven by elevated oxidative stress, impairs peripheral tissue blood flow and NO availability, linking hypertension to endothelial dysfunction	Mancusi *et al*. (2020); Sinha and Haque (2022)

Studies Demonstrating the Relevance of Obesity to Insulin Resistance

A US-based study was conducted on 23,709 adults aimed to evaluate the correlation between the Visceral Obesity Index (VOI), an "empirical mathematical model used to evaluate the distribution and function of fat" and insulin resistance. The study found a significant increase (60%) in insulin resistance incidence as VOI increased, with participants positive for insulin resistance having a higher BMI compared to those negative for insulin resistance (32.2 vs 25.9, respectively) (Giles *et al*., 2012; Badin *et al*., 2011).

Participants were categorized into three groups and assessed on the role of hypertension in relation to insulin resistance. Group A included 30 participants with type 2 diabetes who were overweight or obese and had hypertension Group B included 30 participants with type 2 diabetes who are overweight/obese without hypertension. Group C included 15 participants with normal weight and normotensive (Lukic *et al*., 2014). Groups A and B had significantly greater plasma insulin levels than Group C, indicating that hypertensive individuals have higher levels of insulin resistance (Badin *et al*., 2011; Lukic *et al*., 2014). Telmisartan was used to treat hypertension in eight trials involving 763 individuals, demonstrating a reduction in HOMA-IR with a dose of 80 mg (Badin *et al*., 2011).

Another study sought to assess the correlation between weight and insulin resistance in 538 Mexican women with PCOS. Participants in the overweight (BMI 25-29.9 kg/m²) and obese groups (BMI >30 kg/m²) showed significantly elevated fasting glucose and insulin levels compared to those in the normal weight group (BMI 18.5-24.9 kg/m²). The prevalence of insulin resistance was 56.7% and 78.2% in the overweight and obese groups, respectively, and 19.3% in the normal weight group (Badin *et al*., 2011; Reyes-Muñoz *et al*., 2016). To further assess the correlation between obesity and insulin resistance, recognizing any improvement in insulin resistance with weight reduction is useful. This was demonstrated in 24 overweight individuals who were each prescribed Orlistat 120 mg and had their weight, insulin resistance, and HOMA scores measured over three months. Significant improvements in HOMA score (decreased by 1.7) and weight reduction (mean of 8 kg) were observed (Badin *et al*., 2011). Similarly, 80 obese individuals with a history of T2DM underwent 12 weeks of aerobic exercise and diet restrictions, resulting in a significant reduction in BMI (10.12%) and HOMA-IR (24.04%) (Badin *et al*., 2011; Scherrer *et al*., 1994).

Furthermore, a study comparing insulin resistance levels, plasma insulin, and pro-inflammatory cytokines in overweight individuals with T2DM with and without hypertension concluded that there is a significant positive correlation between plasma insulin levels, increased body weight, and T2DM (Scherrer *et al*., 1994; Suárez-Sánchez *et al*., 2017).

These studies collectively demonstrate the strong correlation between obesity and insulin resistance, highlighting the importance of weight management interventions in improving insulin sensitivity and mitigating the risk of metabolic disorders. Table 4 provides a concise summary of the main findings, highlighted relationships, and cited references for each study demonstrating the relevance of obesity to insulin resistance.

Obesity and Hypertension

One of the primary risk factors for essential hypertension is obesity, as evidenced by numerous clinical studies. In a study evaluating the relationship between IR and MAP in 162 participants, just over 50% of individuals with altered BP were found to be overweight or obese (Wallace *et al*., 2004).

A US-based study examining the correlation between obesity and increased MAP revealed a 3.5-fold higher risk of hypertension in individuals suffering from obesity, attributed to inflammatory markers associated with increased adipose tissue. Similarly, a study in Eritrea involving 2,352 respondents aged 15-64 found a correlation between a BMI of >30 kg/m^2 and elevated systolic, diastolic, and mean arterial pressures (Bello-Chavolla *et al*., 2018).

Research has also shown the beneficial effect of weight reduction on blood pressure. A study evaluating the impact of laparoscopic sleeve gastrectomy on hypertension in 3,997 participants showed significant resolution or improvement in hypertension in 75% of participants at 48 months follow-up, with 58% achieving complete resolution at 1-year follow-up (Abd El-Kader and Al-Jiffri, 2018). Similarly, a study involving 263 hypertensive patients undergoing

bariatric surgery found 65% achieved complete remission at 1-year follow-up (Moriconi *et al*., 2023).

Furthermore, lifestyle interventions have demonstrated efficacy in lowering blood pressure among individuals with obesity. A study involving 24 obese older men undertaking combined resistance and aerobic exercise regimens for 12 weeks demonstrated significant decreases in BMI, SBP, MAP, and PP. Similarly, a 12-week lifestyle intervention program focused on family involvement resulted in statistically significant improvements in BMI, SBP, lipid profile, postprandial glucose, and leptin levels in 43 participants, with 36% showing left ventricular hypertrophy, a common consequence of chronic hypertension (Wallace *et al*., 2004; Moriconi *et al*., 2023; Morais *et al*., 2016).

In a study involving 891 overweight and obese adults, participants in the obese group exhibited higher blood pressure measures, including SBP, DBP & MAP, compared to those in the normal weight group, with a 1.97-fold increased risk for HTN in the obese group (Mufunda *et al*., 2006; Owen *et al*., 2018).

Table 5 provides a concise summary of the main findings, cause for the relationship, highlighted relationship, and cited references for each aspect of the relationship between obesity and hypertension.

Insulin Resistance and Hypertension

In a study involving 10,810 Hispanics, excluding those with diabetes or on anti-hypertensive medications, the relationship between IR and BP (systolic and diastolic BP) was evaluated. A positive linear correlation between SBP and HOMA-IR was observed in males, a non-linear correlation in females, and a positive linear trend with DBP regardless of gender (Mufunda *et al*., 2006).

Table 4: Studies demonstrating the relevance of obesity to insulin resistance

Study title	Main findings	Highlighted Relationship	References
US study	Evaluation of 23,709 adults revealed a correlation between Visceral Obesity Index (VOI) and insulin resistance	Positive correlation between visceral obesity and insulin resistance	Giles *et al*. (2012); Badin *et al*. (2011)
A Mexican study	of 538 women with PCOS demonstrated higher fasting glucose levels and insulin levels with increasing weight categories	Higher prevalence of insulin resistance with higher weight categories	Badin *et al*. (2011)
Weight reduction study	Weight reduction with Orlistat led to significant improvement in insulin resistance in overweight individuals	improvement in insulin resistance with weight reduction	Badin *et al*. (2011)
Aerobic exercise study	Aerobic exercise and diet restrictions resulted in reduced BMI and a significant reduction in insulin resistance in obese individuals with T2DM	Reduction in insulin resistance with reduction in BMI	Badin *et al*. (2011); Scherrer *et al*. (1994)
IR and pro-inflammatory cytokines study showed a positive correlation between plasma insulin levels and increased body weight	Overweight individuals with T2DM and hypertension	Positive correlation between plasma insulin levels and increased body weight	Lukic *et al*. (2014); Suárez-Sánchez *et al*. (2017)

Table 5: Relationship between obesity and hypertension

Aspects of relationship	Main finding	Cause for relationship	Highlighted relationship	Cited references
Risk factor for HTN	50.4% of participants with altered blood pressure was found to be overweight or obese	Presence of obesity is linked to an elevated risk of hypertension	Obesity is a significant risk factor for hypertension	Wallace *et al*. (2004)
Correlation study	Individuals are suffering from obesity have a 3.5-fold increase risk of hypertension	Inflammatory markers associated with increased adipose stores contributes to hypertension	with a Positive correlation between obesity and hypertension	Bello-Chavolla *et al*. (2018)
Population study	BMI >30 kg/m² correlated with increased SBP, DBP, and MAP in respondents aged 15-64	High BMI is associated with elevated blood pressure measures	High BMI is correlated with elevated blood pressure measures	Wallace *et al*. (2004); Morais *et al*. (2016)
Weight reduction study	Laparoscopic sleeve gastrectomy led to resolution or improvement in hypertension in 75% of participants at 48 months follow-up	Weight reduction through surgery can lead to improvement in hypertension	Weight reduction can lead to improvement in hypertension	Abd El-Kader and Al-Jiffri (2018)
Bariatric surgery Study	65% of hypertensive patients had complete remission of hypertension at 1 year follow-up after bariatric surgery	Bariatric surgery can lead to complete remission of hypertension	Bariatric surgery can lead to complete remission of hypertension	Suárez-Sánchez *et al*. (2017); Moriconi *et al*. (2023)
Intervention program study	Family-centered lifestyle intervention led to statistically significant improvements in BMI, SBP, lipid profile, postprandial glucose and leptin levels in participants	Lifestyle intervention program can lead to improvements in metabolic measures including blood pressure	Lifestyle intervention program can lead to improvements in metabolic measures including blood pressure	Wallace *et al*. (2004); Morais *et al*. (2016)
Comparative study	Obese individuals had higher blood pressure measures compared to normal weight individuals, with a 1.97-fold increased risk for hypertension in the obese group	Obesity is associated with higher blood pressure measures and increased risk of hypertension compared to normal-weight individuals	Obesity is associated with higher blood pressure measures an increased risk of hypertension	Bello-Chavolla *et al*. (2018); Mufunda *et al*. (2006)

Table 6: Relationship between insulin resistance and hypertension

Aspects of relationship	Main finding	Cause for relationship	Highlighted relationship	Cited references
In a population study,	15% of Hispanics evaluated had high blood pressure, 17% classified as stage 1 hypertension and 9% as stage 2 hypertension	A higher risk of hypertension associated with insulin resistance	Hypertension and insulin resistance are positively correlated	Mufunda *et al*. (2006)
Gender-based correlation	In males, Systolic Blood Pressure (SBP) and HOMA-IR have positive linear connection and non-linear correlation in females A positive linear trend between Diastolic Blood Pressure (DBP) and HOMA-IR regardless of gender	High blood pressure may be a resulted in insulin resistance	Positive association between blood pressure and insulin resistance	Mufunda *et al*. (2006)
Comparative study	Plasma insulin levels were considerably higher in type 2 diabetic participants who were overweight/obese and had hypertension than in those who were normal weight and had normal blood pressure	Hypertensive individuals who exhibit levels of insulin resistance compared to normotensive individuals	Hypertension are associated with higher insulin resistance levels	Karamatollah *et al.* (2020)
Ethnicity-based study	BMI and insulin sensitivity were key determinants for significant Mean Arterial Pressure (MAP) in Hispanics and non-Hispanic whites	roles in blood BMI and insulin sensitivity play pressure regulation	BMI and insulin sensitivity strongly associated with MAP	Mufunda *et al.* (2006); Karamatollah *et al.* (2020)
Cross-sectional study	Strong association found between isolated systolic hypertension and increased HOMA-IR in Young and middle-aged men	Insulin resistance may contribute to the development of isolated systolic hypertension	Strong association between insulin resistance and isolated systolic hypertension	Gu *et al*. (2022)

A study assessing the relationship between insulin resistance and hypertension across different ethnicities revealed significant associations between BMI and hypertension in non-Hispanic whites and Hispanic diabetics (Park *et al*., 2020). Non-diabetic hypertensive individuals exhibited significantly lower insulin sensitivity compared to their normotensive counterparts. Hispanics with low insulin sensitivity showed an increased prevalence of hypertension. SBP, DBP, and MAP were significantly correlated with insulin sensitivity in Hispanics and non-Hispanic whites (Karamatollah *et al*., 2020).

A Chinese cross-sectional study highlighted an association between isolated hypertension and increased HOMA-IR in young and middle-aged men with normal fasting plasma glucose and diastolic BP<90mmHg. However, no association was found with triglycerides-glucose index and METS-IR (Gu *et al*., 2022).

These studies underscore the complex interplay between insulin resistance and hypertension, highlighting the importance of understanding their relationship across different populations and the potential for hypertension management strategies to impact insulin sensitivity.

Table 6 provides a concise summary of the main findings, cause for the relationship, highlighted relationship, and cited references for each aspect of the relationship between insulin resistance and hypertension.

Discussion

This literature review underscores the relevance of understanding the intricate interplay between obesity, insulin resistance, and hypertension in contemporary healthcare. With the escalating prevalence of obesity and its associated complications, including T2DM and hypertension, elucidating these relationships becomes paramount (Hruby and Hu, 2015; Hardy *et al*., 2012). The literature consistently indicates a strong positive correlation between elevated BMI and insulin resistance, which in turn is linked to hypertension, illustrating the complex interplay of these conditions (Bernhardt *et al*., 2022; Mancusi *et al*., 2020; Semlitsch *et al*., 2019). This correlation highlights the critical role of weight management in reducing insulin resistance and mitigating its complications. Additionally, obesity is associated with an increased MAP further heightening the risk of hypertension, especially when coupled with insulin resistance (Wondmkun, 2020; Zyoud *et al*., 2022).

Individuals with T2DM and insulin resistance often exhibit symptoms of impaired lipid metabolism, including elevated lipid concentrations and deposits in the circulation and skeletal muscle. Elevated levels of free fatty acids in the plasma are known to impair insulin-regulated glucose metabolism (Tian *et al*., 2022), whereas reduced lipid levels enhance insulin activity in adipocytes, liver, and skeletal muscle cells. Moreover, high lipid concentrations disrupt the translocation of GLUT4 essential for insulin-regulated glucose uptake in fat and muscle cells (Orr *et al*., 2012; Jeschke and Boehning, 2012; IS Sobczak *et al*., 2019). Furthermore, evidence suggests a connection between prenatal stress, altered iron metabolism, especially during prenatal stages, prenatal iron exposure, and the onset of metabolic diseases like obesity and diabetes in addition to the strong connection between inflammation obesity and metabolic diseases (Stordal *et al*., 2018; Bhat *et al*., 2022; Bernhardt *et al*., 2021a). Evidence highlights the complex and interconnected nature of metabolic disorders, underlining the necessity for comprehensive and integrated approaches to their management and prevention (Lillich *et al*., 2021). It is commonly known that obesity and insulin resistance

are linked, with adipose tissue expansion and the associated pro-inflammatory cytokine activity playing crucial roles in this process (Coppack, 2001; Park *et al*., 2020). As adipocytes expand, they secrete larger amounts of pro-inflammatory markers such as TNFα, interleukins, and leptin, which contribute to the systemic inflammatory state observed in obese individuals (Bernhardt *et al*., 2022; Rosen and Spiegelman, 2006; Cai *et al*., 2022) This inflammation is a key factor in the development of insulin resistance, which, if prolonged, can lead to T2DM due to the pancreatic β-cells' inability to compensate for the increased insulin demand (Ye, 2013).

The relationship between insulin resistance and hypertension is particularly noteworthy. Insulin resistance can lead to impaired vasodilation and increased arterial stiffness due to decreased NO availability (Giles *et al*., 2012; Sakr *et al*., 2023). Moreover, increased activity of the renin-angiotensin-aldosterone system and the sympathetic nervous system are linked to insulin resistance, both of which contribute to increased vascular resistance and sodium retention, elevating blood pressure (Mancusi *et al*., 2020; Sinha and Haque, 2022).

While the majority of literature supports the connection between insulin resistance and hypertension, dissenting studies suggest a more nuanced relationship. These findings raise questions about the feasibility of developing targeted medications to address the multifactorial nature of insulin resistance and hypertension. Additionally, they underscore the need for comprehensive patient education to address concerns beyond traditional risk factors, such as genetic predisposition and environmental influences.

The findings from this review have significant clinical implications. They emphasize the importance of early intervention in obesity to prevent the cascade of metabolic disturbances that lead to insulin resistance and hypertension (Gadde *et al*., 2018). Lifestyle modifications, including diet and physical activity, remain the cornerstone of managing these conditions (Semlitsch *et al*., 2019; Gadde *et al*., 2018). Additionally, the potential for pharmacological interventions targeting specific inflammatory pathways or improving insulin sensitivity could be promising strategies for mitigating these risks (Semlitsch *et al*., 2019).

A deeper understanding of the mechanism of inflammation brought on by obesity and insulin resistance could lead to innovative therapeutic approaches. By targeting specific pathways implicated in these metabolic disorders, pharmaceutical interventions may offer new avenues for medical therapy in the future.

Physicians can also leverage this literature to enhance patient education and management strategies, particularly in diabetic patients. By incorporating a holistic approach that goes beyond glycemic control, patients can gain a better understanding of their disease processes and comorbidities, empowering them to take control of their health outcomes and reduce their risk of morbidity and mortality (Clemente-Suárez *et al*., 2023).

However, challenges remain in elucidating the specific processes that underlie the connection between hypertension and insulin resistance, especially in the context of confounding variables like age and hyperinsulinemia. Further research is warranted to delineate these complexities and refine our understanding of this intricate relationship, focusing on longitudinal studies to track the progression of these metabolic disturbances over time and to better understand the causal relationships. Moreover, personalized medicine approaches could be explored, considering individual genetic predispositions and responses to different treatments.

Table 7 provides a structured summary of the studies based on PICOS criteria for a review article focusing on the relationship between 'Insulin resistance and Hypertension'. Table 8 provides a structured summary of the studies based on PICOS criteria for a review article focusing on the connection between 'Obesity and Insulin Resistance'.

Table 7: Studies assessing the relationship between insulin resistance and hypertension

Study	Population	Intervention	Comparison	Outcome	Study design	Cited references
Lukic *et al*.	Participants with type 2 diabetics who have overweight/obese with hypertension (Group A: 30 participants). Type 2 diabetics who are overweight/obese without hypertension (Group B: 30 participants). Normal weight and normotensive individuals (Group C: 15 participants)	Measurement of plasma insulin levels	Comparison of plasma insulin levels between of hypertension and normotensive individuals	Higher plasma insulin levels in hypertensive individuals indicating higher insulin resistance	Comparative	Lukic *et al*. (2014)
Telmisartan study	763 individuals	Telmisartan treatment (80 mg dose)	Not applicable	Reduction in insulin resistance measured by HOMA-R test	Interventional	Badin *et al*. (2011)
Ethnicity study	Non-Hispanic whites, Hispanics with without diabetes	Assessment of BMI and insulin sensitivity	Comparison of blood pressure measures insulin sensitivity	BMI and insulin sensitivity are key determinants for the mean arterial pressure	Comparative	Mufunda *et al*. (2006)
Cross-sectional study	Young and middle-aged men with diastolic blood pressure less than 90 mmHg and normal fasting plasma glucose	Evaluation of HOMA-IR, TyG index, and METS-IR	Not applicable	Strong association between isolated systolic hypertension increased HOMA-IR	Cross-sectional	Gu *et al*. (2022)

Table 8: Studies assessing the relationship between obesity and insulin resistance

Study	Population	Intervention	Comparison	Outcome	Study design	Cited references.
US study	23,709 adults	Measurement of	Comparison of VOI Visceral Obesity Index (VOI)	Positive correlation and insulin resistance	Cross-sectional between VOI and insulin resistance	Giles *et al.* (2012); Badin *et al.* (2011)
Mexican study	538 women	Assessment of BMI with PCOS	Comparison of BMI categories	Higher prevalence of and insulin resistance	Cross-sectional insulin resistance in higher BMI categories	Badin *et al.* (2011)
Weight reduction study	Overweight individuals'	Orlistat treatment	Comparison of HOMA scores before and	Improvement in insulin resistance with after treatment	Interventional weight reduction	Badin *et al.* (2011)
Aerobic exercise study	obese older men	Aerobic exercise and diet restrictions	Comparison of BMI and blood pressure measures before and after intervention	Reduction in BMI and blood pressure measures with lifestyle intervention	Interventional	Giles *et al.* (2012); Badin *et al.* (2011)
Intervention program study	Participants undergoing lifestyle intervention	Family-centered lifestyle program	Comparison of Metabolic measures before and intervention	Improvement in Metabolic measures including BMI after intervention	Interventional and blood pressure	Morais *et al*. (2016)
Comparative study	Overweight or obese adults	Comparison of blood pressure measures	Comparison of blood pressure measures between obese and normal weight individuals	Higher blood pressure and increased risk of hypertension in obese individuals	Comparative	Mufunda *et al*. (2006)

Conclusion

In conclusion, while the literature provides compelling evidence of the link between insulin resistance, obesity and hypertension, ongoing research is essential to unraveling the nuances of the relationship. By applying the insights obtained from this review, healthcare practitioners can refine their patient management strategies and assist in the creation of treatment strategies that are more effective for these interconnected metabolic disorders.

Acknowledgment

Thank you to the publisher for their support in the publication of this research article. We are grateful for the resources and platform provided by the publisher, which have enabled us to share our findings with a wider audience. We appreciate the efforts of the editorial team in reviewing and editing our work and we are thankful for the opportunity to contribute to the field of research through this publication.

Funding Information

The authors have not received any financial support or funding to report.

Author's Contributions

Masah Mardini and Grisilda Vidya Bernhardt: Participated in the idea of the manuscript and in the manuscript written. Participated in the discussion and conclusion.

Lana Dardari: Contributed to the findings.

Heba Eyad Shalabi: Contributed to the findings. Participated in the discussion and conclusion.

Maher Taha: Contributed to the findings. Formulated the methodology and background.

Pooja Shivappa: Formulated the methodology and background. Participated in the discussion and conclusion.

Ethics

This review is an original research effort, and the lead author confirms that all co-authors have reviewed and approved the manuscript. There are no ethical concerns raised by the authors regarding the content of this review. The authors are committed to addressing any ethical issues that may arise after the publication of this manuscript.

Conflict of Interest

Authors declare no conflict of interest.

References

Abd El-Kader, S. M., & Al-Jiffri, O. H. (2018). Impact of weight reduction on insulin resistance, adhesive molecules and adipokines dysregulation among obese type 2 diabetic patients. *African Health Sciences*, *18*(4), 873–883. https://doi.org/10.4314/ahs.v18i4.5

Abdollahpour Alni, M., & Nikookheslat, S. D. (2022). The effect of 12 weeks aerobic, resistance and combined trainings on peripheral vascular disease in type 2 diabetes with peripheral neuropathy in men. *Obesity Medicine*, *34*, 100439. https://doi.org/10.1016/j.obmed.2022.100439

Arcidiacono, B., Chiefari, E., Foryst-Ludwig, A., Currò, G., Navarra, G., Brunetti, F. S., Mirabelli, M., Corigliano, D. M., Kintscher, U., Britti, D., Mollace, V., Foti, D. P., Goldfine, I. D., & Brunetti, A. (2020). Obesity-related hypoxia via miR-128 decreases insulin-receptor expression in human and mouse adipose tissue promoting systemic insulin resistance. *EBioMedicine*, *59*, 102912. https://doi.org/10.1016/j.ebiom.2020.102912

Badin, P.-M., Louche, K., Mairal, A., Liebisch, G., Schmitz, G., Rustan, A. C., Smith, S. R., Langin, D., & Moro, C. (2011). Altered Skeletal Muscle Lipase Expression and Activity Contribute to Insulin Resistance in Humans. *Diabetes*, *60*(6), 1734–1742. https://doi.org/10.2337/db10-1364

Bello-Chavolla, O. Y., Almeda-Valdes, P., Gomez-Velasco, D., Viveros-Ruiz, T., Cruz-Bautista, I., Romo-Romo, A., Sánchez-Lázaro, D., Meza-Oviedo, D., Vargas-Vázquez, A., Campos, O. A., Sevilla-González, M. del R., Martagón, A. J., Hernández, L. M., Mehta, R., Caballeros-Barragán, C. R., & Aguilar-Salinas, C. A. (2018). METS-IR, a novel score to evaluate insulin sensitivity, is predictive of visceral adiposity and incident type 2 diabetes. *European Journal of Endocrinology*, *178*(5), 533–544. https://doi.org/10.1530/eje-17-0883

Bernhardt, G. V., Jhancy, M., Shivappa, P., Bernhardt, K., & R. T. Pinto, J. (2021a). Relationship between Maternal and Cord Blood Iron Status in Women and their New Born Pairs. *Biomedical and Pharmacology Journal*, *14*(01), 317–322. https://doi.org/10.13005/bpj/2128

Bernhardt, G. V., Shivappa, P., Bernhardt, K., Bhat, S., Pinto, J. R. T., Jhancy, M., & Kumar, S. (2022). Markers of inflammation in obese pregnant women: Adenosine deaminase and high sensitive C – reactive protein. *European Journal of Obstetrics & Gynecology and Reproductive Biology: X*, *16*, 100167. https://doi.org/10.1016/j.eurox.2022.100167

Bernhardt, G. V., Shivappa, P., Shantaram, M., Jayakar, V., Lokapur, V., & Pinto, J. R. T. (2021b). Phagocytic and oxidative burst activity of neutrophils in type 2 diabetic patients with foot ulcers. *Biomedicine*, *41*(4), 776–780. https://doi.org/10.51248/.v41i4.1122

Bernhardt, V., & D'souza, J. R. T. (2012). Immunomodulatory potential of herbal medicine in type 2 DM patients as evaluvated by neutrophil phagocytic index, serum opsonisation and lymphocyte proliferation rate. *Asian Journal of Pharmaceutical and Clinical Research*, *5*(2), 36–41.

Bernhardt, V. I. D. Y. A., D'souza, J. R., Shetty, A. N. U. S. H. A., Shantaram, M. A. N. J. U. L. A., & Vaswani, R. A. V. I. (2012). Evaluation of neutrophil function, opsonising capacity and lymphocyte proliferation for risk of developing ischemic heart disease in Type 2 diabetes mellitus patients. *International Journal of Pharmacy and Pharmaceutical Sciences*, *4*, 318–322.

Bhat, S., Shivappa, P., Pinto, J. R., Bernhardt, G. V., & Bernhardt, K. (2022). Prenatal Stress-induced Behavioral, Cognitive, and Psychopathological Modifications: A Mini Review of Literature. *Journal of South Asian Federation of Obstetrics and Gynaecology*, *14*(4), 481–485. https://doi.org/10.5005/jp-journals-10006-2072

Biessels, G. J., & Kappelle, L. J. (2005). Increased risk of Alzheimer's disease in Type II diabetes: insulin resistance of the brain or insulin-induced amyloid pathology? *Biochemical Society Transactions*, *33*(5), 1041–1044. https://doi.org/10.1042/bst0331041

Cai, Y., Chen, X., Yi, B., Li, J., & Wen, Z. (2022). Pathophysiology roles for adenosine 2A receptor in obesity and related diseases. *Obesity Reviews*, *23*(10), e13490. https://doi.org/10.1111/obr.13490

Clemente-Suárez, V. J., Martín-Rodríguez, A., Redondo-Flórez, L., López-Mora, C., Yáñez-Sepúlveda, R., & Tornero-Aguilera, J. F. (2023). New Insights and Potential Therapeutic Interventions in Metabolic Diseases. *International Journal of Molecular Sciences*, *24*(13), 10672. https://doi.org/10.3390/ijms241310672

Coppack, S. W. (2001). Pro-inflammatory cytokines and adipose tissue. *Proceedings of the Nutrition Society*, *60*(3), 349–356. https://doi.org/10.1079/pns2001110

Daniele, G., Eldor, R., Merovci, A., Clarke, G. D., Xiong, J., Tripathy, D., Taranova, A., Abdul-Ghani, M., & DeFronzo, R. A. (2014). Chronic Reduction of Plasma Free Fatty Acid Improves Mitochondrial Function and Whole-Body Insulin Sensitivity in Obese and Type 2 Diabetic Individuals. *Diabetes*, *63*(8), 2812–2820. https://doi.org/10.2337/db13-1130

Gadde, K. M., Martin, C. K., Berthoud, H.-R., & Heymsfield, S. B. (2018). Obesity. *Journal of the American College of Cardiology*, *71*(1), 69–84. https://doi.org/10.1016/j.jacc.2017.11.011

Giles, T. D., Sander, G. E., Nossaman, B. D., & Kadowitz, P. J. (2012). Impaired Vasodilation in the Pathogenesis of Hypertension: Focus on Nitric Oxide, Endothelial-Derived Hyperpolarizing Factors, and Prostaglandins. *The Journal of Clinical Hypertension*, *14*(4), 198–205. https://doi.org/10.1111/j.1751-7176.2012.00606.x

Ginsberg, H. N. (2000). Insulin resistance and cardiovascular disease. *Journal of Clinical Investigation*, *106*(4), 453–458. https://doi.org/10.1172/jci10762

Gu, Q., Meng, J., Hu, X., Ge, J., Wang, S. J., & Liu, X. Z. (2022). Isolated systolic hypertension and insulin resistance assessment tools in young and middle-aged Chinese men with normal fasting glucose: a cross-sectional study. *Scientific Reports*, *12*(1), 758. https://doi.org/10.1038/s41598-021-04763-x

Hardy, O. T., Czech, M. P., & Corvera, S. (2012). What causes the insulin resistance underlying obesity? *Current Opinion in Endocrinology, Diabetes and Obesity*, *19*(2), 81–87. https://doi.org/10.1097/med.0b013e3283514e13

Hruby, A., & Hu, F. B. (2015). The Epidemiology of Obesity: A Big Picture. *Pharmaco Economics*, *33*(7), 673–689. https://doi.org/10.1007/s40273-014-0243-x

IS Sobczak, A., A. Blindauer, C., & J. Stewart, A. (2019). Changes in Plasma Free Fatty Acids Associated with Type-2 Diabetes. *Nutrients*, *11*(9), 2022. https://doi.org/10.3390/nu11092022

Jeschke, M. G., & Boehning, D. (2012). Endoplasmic reticulum stress and insulin resistance post-trauma: Similarities to type 2 diabetes. *Journal of Cellular and Molecular Medicine*, *16*(3), 437–444. https://doi.org/10.1111/j.1582-4934.2011.01405.x

Karamatollah, R., Shojaei, M., & Jahromi, A. (2020). Association of obesity and pulse pressure with hypertension in an Iranian urban population. *Journal of Family Medicine and Primary Care*, *9*(9), 4705. https://doi.org/10.4103/jfmpc.jfmpc_723_20

Klabunde, R. E. (2011). *Cardiovascular Physiology Concepts* (Vol. 11). Lippincott Williams & Wilkins.

Lillich, F. F., Imig, J. D., & Proschak, E. (2021). Multi-Target Approaches in Metabolic Syndrome. *Frontiers in Pharmacology*, *11*, 554961. https://doi.org/10.3389/fphar.2020.554961

Lionetti, L., Mollica, M. P., Lombardi, A., Cavaliere, G., Gifuni, G., & Barletta, A. (2009). From chronic overnutrition to insulin resistance: The role of fat-storing capacity and inflammation. *Nutrition, Metabolism and Cardiovascular Diseases*, *19*(2), 146–152. https://doi.org/10.1016/j.numecd.2008.10.010

Lukic, L., Lalic, N., Rajkovic, N., Jotic, A., Lalic, K., Milicic, T., Seferovic, J., Macesic, M., & Gajovic, J. (2014). Hypertension in Obese Type 2 Diabetes Patients is Associated with Increases in Insulin Resistance and IL-6 Cytokine Levels: Potential Targets for an Efficient Preventive Intervention. *International Journal of Environmental Research and Public Health*, *11*(4), 3586–3598. https://doi.org/10.3390/ijerph110403586

Mancusi, C., Izzo, R., di Gioia, G., Losi, M. A., Barbato, E., & Morisco, C. (2020). Insulin Resistance the Hinge Between Hypertension and Type 2 Diabetes. *High Blood Pressure & Cardiovascular Prevention*, *27*(6), 515–526. https://doi.org/10.1007/s40292-020-00408-8

Mogensen, T. H. (2009). Pathogen Recognition and Inflammatory Signaling in Innate Immune Defenses. *Clinical Microbiology Reviews*, *22*(2), 240–273. https://doi.org/10.1128/cmr.00046-08

Morais, P. R. S. de, Sousa, A. L. L., Jardim, T. de S. V., Nascente, F. M. N., Mendonça, K. L., Povoa, T. I. R., Carneiro, C. de S., Ferreira, V. R., Souza, W. K. S. B. de, & Jardim, P. C. B. V. (2016). Correlation of Insulin Resistance with Anthropometric Measures and Blood Pressure in Adolescents. *Arquivos Brasileiros de Cardiologia*, *106*, 319–326. https://doi.org/10.5935/abc.20160041

Moriconi, D., Nannipieri, M., & Rebelos, E. (2023). Bariatric surgery to treat hypertension. *Hypertension Research*, *46*(5), 1341–1343. https://doi.org/10.1038/s41440-023-01227-9

Mufunda, J., Mebrahtu, G., Usman, A., Nyarango, P., Kosia, A., Ghebrat, Y., Ogbamariam, A., Masjuan, M., & Gebremichael, A. (2006). The prevalence of hypertension and its relationship with obesity: results from a national blood pressure survey in Eritrea. *Journal of Human Hypertension*, *20*(1), 59–65. https://doi.org/10.1038/sj.jhh.1001924

Orr, J. S., Puglisi, M. J., Ellacott, K. L. J., Lumeng, C. N., Wasserman, D. H., & Hasty, A. H. (2012). Toll-like Receptor 4 Deficiency Promotes the Alternative Activation of Adipose Tissue Macrophages. *Diabetes*, *61*(11), 2718–2727. https://doi.org/10.2337/db11-1595

Owen, J. G., Yazdi, F., & Reisin, E. (2018). Bariatric Surgery and Hypertension. *American Journal of Hypertension*, *31*(1), 11–17. https://doi.org/10.1093/ajh/hpx112

Park, W., Jung, W.-S., Hong, K., Kim, Y.-Y., Kim, S.-W., & Park, H.-Y. (2020). Effects of Moderate Combined Resistance- and Aerobic-Exercise for 12 Weeks on Body Composition, Cardiometabolic Risk Factors, Blood Pressure, Arterial Stiffness, and Physical Functions, among Obese Older Men: A Pilot Study. *International Journal of Environmental Research and Public Health*, *17*(19), 7233. https://doi.org/10.3390/ijerph17197233

Reyes-Muñoz, E., Ortega-González, C., Martínez-Cruz, N., Arce-Sánchez, L., Estrada-Gutierrez, G., Moran, C., Sánchez-Serrano, A. P., Higareda-Sánchez, R., & de la Jara-Díaz, J. F. (2016). Association of obesity and overweight with the prevalence of insulin resistance, pre-diabetes and clinical–biochemical characteristics among infertile Mexican women with polycystic ovary syndrome: a cross-sectional study. *BMJ Open*, *6*(7), e012107. https://doi.org/10.1136/bmjopen-2016-012107

Rosen, E. D., & Spiegelman, B. M. (2006). Adipocytes as regulators of energy balance and glucose homeostasis. *Nature*, *444*(7121), 847–853. https://doi.org/10.1038/nature05483

Sakr, H. F., Sirasanagandla, S. R., Das, S., Bima, A. I., & Elsamanoudy, A. Z. (2023). Insulin Resistance and Hypertension: Mechanisms Involved and Modifying Factors for Effective Glucose Control. *Biomedicines*, *11*(8), 2271. https://doi.org/10.3390/biomedicines11082271

Scherrer, U., Randin, D., Vollenweider, P., Vollenweider, L., & Nicod, P. (1994). Nitric oxide release accounts for insulin's vascular effects in humans. *Journal of Clinical Investigation*, *94*(6), 2511–2515. https://doi.org/10.1172/jci117621

Semlitsch, T., Stigler, F. L., Jeitler, K., Horvath, K., & Siebenhofer, A. (2019). Management of overweight and obesity in primary care a systematic overview of international evidence-based guidelines. *Obesity Reviews*, *20*(9), 1218–1230. https://doi.org/10.1111/obr.12889

Shah, J. (2021). Insulin Resistance and Homeostatic Model Assessment in Critically Ill: Where do We Stand? *Indian Journal of Critical Care Medicine*, *25*(12), 1335–1336. https://doi.org/10.5005/jp-journals-10071-24059

Shimoda, Y., Okada, S., Yamada, E., Pessin, J. E., & Yamada, M. (2015). Tctex1d2 Is a Negative Regulator of GLUT4 Translocation and Glucose Uptake. *Endocrinology*, *156*(10), 3548–3558. https://doi.org/10.1210/en.2015-1120

Sinha, S., & Haque, M. (2022). Insulin Resistance is Cheerfully Hitched with Hypertension. *Life*, *12*(4), 564. https://doi.org/10.3390/life12040564

Stordal, K., McArdle, H. J., & Hayes, H. (2018). Prenatal iron exposure and childhood type 1 diabetes. *Scientific Reports*, *8*(1), 9067. https://doi.org/10.1038/s41598-018-27391-4

Suárez-Sánchez, F., Klunder-Klunder, M., Valladares-Salgado, A., Gómez-Zamudio, J., Peralta-Romero, J., Meyre, D., Burguete-García, A., & Cruz, M. (2017). APOA5 and APOA1 polymorphisms are associated with triglyceride levels in Mexican children. *Pediatric Obesity*, *12*(4), 330–336. https://doi.org/10.1111/ijpo.12147

Tian, X., Chen, S., Wang, P., Xu, Q., Zhang, Y., Luo, Y., Wu, S., & Wang, A. (2022). Insulin resistance mediates obesity-related risk of cardiovascular disease: a prospective cohort study. *Cardiovascular Diabetology*, *21*(1), 289. https://doi.org/10.1186/s12933-022-01729-9

Van Greevenbroek, M. M. J., Schalkwijk, C. G., & Stehouwer, C. D. A. (2016). Dysfunctional adipose tissue and low-grade inflammation in the management of the metabolic syndrome: current practices and future advances. *F1000Research*, *5*, 2515. https://doi.org/10.12688/f1000research.8971.1

Vandanmagsar, B., Youm, Y.-H., Ravussin, A., Galgani, J. E., Stadler, K., Mynatt, R. L., Ravussin, E., Stephens, J. M., & Dixit, V. D. (2011). The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. *Nature Medicine*, *17*(2), 179–188. https://doi.org/10.1038/nm.2279

Wallace, T. M., Levy, J. C., & Matthews, D. R. (2004). Use and Abuse of HOMA Modeling. *Diabetes Care*, *27*(6), 1487–1495. https://doi.org/10.2337/diacare.27.6.1487

Wondmkun, Y. T. (2020). Obesity, insulin resistance, and type 2 diabetes: associations and therapeutic implications. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, *13*, 3611–3616. https://doi.org/10.2147/dmso.s275898

Ye, J. (2013). Mechanisms of insulin resistance in obesity. *Frontiers of Medicine*, *7*(1), 14–24.

Zhang, Y., Liu, J., Yao, J., Ji, G., Qian, L., Wang, J., Zhang, G., Tian, J., Nie, Y., Zhang, Y., Gold, M., & Liu, Y. (2014). Obesity: Pathophysiology and Intervention. *Nutrients*, *6*(11), 5153–5183. https://doi.org/10.3390/nu6115153

Zyoud, S. H., Shakhshir, M., Abushanab, A. S., Koni, A., Shahwan, M., Jairoun, A. A., & Al-Jabi, S. W. (2022). Global research trends on the links between insulin resistance and obesity: a visualization analysis. *Translational Medicine Communications*, *7*(1), 1–13. https://doi.org/10.1186/s41231-022-00124-6