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Review

The Cardiometabolic Triad of Diabetes, Obesity, and Hypertension: Genetic and Pathophysiological Insights

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Abstract

Diabesotension, the coexistence of diabetes mellitus, obesity, and hypertension, represents an increasingly prevalent and clinically significant cardiometabolic syndrome. Epidemiological evidence highlights strong bidirectional relationships among these conditions, which together markedly elevate the risk of cardiovascular disease, stroke, nephropathy, and premature mortality. The pathophysiology of diabesotension is multifactorial, involving insulin resistance, chronic hyperglycemia, obesity-associated inflammation, endothelial dysfunction, sympathetic overactivity, and activation of the renin–angiotensin–aldosterone system (RAAS), culminating in adverse metabolic and hemodynamic interactions. Clinically, the synergistic presence of diabetes and hypertension accelerates both microvascular and macrovascular complications, leading to poorer outcomes than either condition alone. Recognizing diabesotension as a distinct clinical entity may facilitate more comprehensive care models and improved long-term outcomes, highlighting the need for continued research to refine risk stratification and optimize individualized treatment strategies. In this review, we focus on the genes implicated in key hallmarks of diabesotension, including insulin resistance, inflammation, RAAS activation, and oxidative stress, relevant clinical management strategies, and AI-based models for risk stratification of this triad of diseases.

Keywords: obesity; diabetes; hypertension; diabesotension

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1. Introduction

Diabesotension, defined as the coexistence of diabetes mellitus, obesity, and hypertension, represents a severe cardiometabolic phenotype characterized by the convergence of three major chronic diseases that frequently co-occur and share overlapping pathophysiological mechanisms. Although diabesotension shares features with broader cardiometabolic syndrome, it is defined by the co-occurrence of diabetes, obesity and hypertension, providing a clinically distinct framework for interrogating the shared and interacting mechanisms that underpin their combined disease burden. Individuals with diabesotension exhibit

elevated risk of cardiovascular disease, stroke, nephropathy, and premature mortality [1,2]. Epidemiological studies reveal that more than half of patients with type 2 diabetes develop hypertension, while individuals with hypertension are at greater risk of impaired glucose tolerance and diabetes [3,4]. This bidirectional association highlights the need to view diabesotension as a distinct entity rather than as three isolated conditions.

The pathogenesis of diabesotension is multifactorial and involves complex metabolic and hemodynamic interactions. Insulin resistance, a common feature in type 2 diabetes, plays a central role by promoting hyperinsulinemia, sympathetic overactivity, sodium retention, and endothelial dysfunction, all of which contribute to elevated blood pressure [5,6]. Chronic hyperglycemia further exacerbates vascular injury through oxidative stress and advanced glycation end-products, while obesity and low-grade systemic inflammation accelerate the progression of both disorders [7,8]. In addition, activation of the RAAS and increased arterial stiffness create a physiological environment conducive to the development and maintenance of hypertension in diabetic individuals [9].

The clinical consequences of diabesotension are profound, with patients experiencing higher rates of both microvascular and macrovascular complications compared to those with either diabetes or hypertension alone [2,10]. Hypertension accelerates the progression of diabetic nephropathy, retinopathy, and neuropathy, while diabetes worsens the vascular damage associated with high blood pressure. Together, they significantly increase the risk of coronary artery disease, stroke, heart failure, and end-stage renal disease [1]. This synergistic effect underscores the importance of early detection, aggressive risk factor modification, and comprehensive treatment strategies tailored to address both conditions simultaneously.

Effective management of diabesotension requires a holistic and multidisciplinary approach. Lifestyle modification, including dietary adjustments, physical activity, and weight reduction, serves as the foundation of therapy [11,12]. Pharmacological interventions are equally critical, with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) preferred for their renoprotective and cardioprotective properties [13,14]. Recent advances in glucose-lowering therapies, such as sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, provide additional cardiovascular and renal benefits [15]. By recognizing diabesotension as a unique clinical syndrome, healthcare systems can promote integrated care models that reduce long-term complications and improve patient outcomes.

2. Genetic Basis Underlying Diabesotension

2.1. Diabesotension-Associated Genes

Diabesotension arises from a multifactorial interplay of numerous genes that collectively influence disease susceptibility, onset, and progression. Over the past decade, thousands of genes have been identified as being associated with obesity, diabetes mellitus, and hypertension. Disease-associated genes were retrieved from the National Center for Biotechnology Information (NCBI) Gene database (https://www.ncbi.nlm.nih.gov/gene/) (accessed on 31 August 2025) [16]. Separate searches were conducted using the disease terms “obesity”, “hypertension”, and “diabetes” (date of retrieval: 30 August 2025). Genes returned as being associated with each disease term were collected and gene identifiers were standardized before comparison. After removal of duplicate entries, 2191 genes associated with obesity, 1349 genes associated with hypertension, and 2494 genes associated with diabetes were identified. The three disease-associated gene sets were intersected using Venny 2.1 (https://bioinfogp.cnb.csic.es/tools/venny/) (accessed on 31 August 2025), resulting in 443 genes common to all three conditions. These overlapping genes were defined as candidate diabesotension-related genes and were used for

subsequent analyses (Figure 1A). All 443 genes were then subjected to PANTHER v16.0 (https://www.pantherdb.org) (accessed on 31 August 2025) to categorize them into protein classes [17]. Of the 443 overlapping genes, 437 were successfully annotated (Figure 1B) and subsequently subjected to enrichment analysis using the Human Phenotype Ontology (HPO) and biological pathway databases, including KEGG, Reactome, and WikiPathways in g:Profiler (https://biit.cs.ut.ee/gprofiler/gost) (accessed on 31 August 2025) [18]. Benjamini–Hochberg FDR and p-adj value ≤ 0.05 were used to determine the statistical significance of human phenotype and biological pathways.

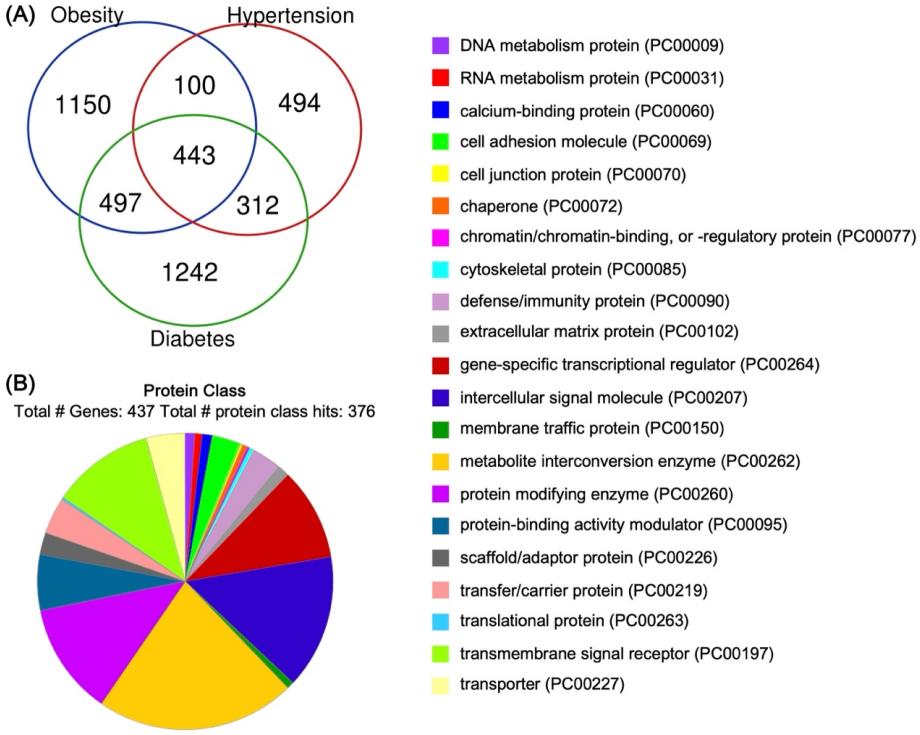


Figure 1. List of diabesotension-related genes. (**A**) A total of 443 diabesotension-related genes were retrieved from the National Center for Biotechnology Information (NCBI; https://www.ncbi.nlm.nih.gov) (accessed on 31 August 2025). (**B**) A total of 437 diabesotension-related genes were categorized into 21 primary protein classes. # represents the number.

Most of the identified genes were prominently classified as metabolite interconversion enzymes (21.8%), followed by intercellular signal molecules (14.6%) and protein-modifying enzymes (12.2%) (Figure 1B). Metabolite interconversion enzymes (MIEs), including hydrolases, lyases, oxidoreductases, and transferases, are crucial in obesity as they influence lipid, carbohydrate, and amino acid metabolism, leading to metabolic dysfunction and insulin resistance [19]. Their dysregulation is also observed in diabetes, particularly in glucokinase, which controls insulin secretion and glucose storage, and whose impaired activity can result in hyperglycemia, inflammation, and complications such as non-alcoholic fatty liver disease (NAFLD). Meanwhile, in hypertension, key MIEs include cytochrome P450 (CYP) enzymes, particularly CYP4A and CYP4F, which convert arachidonic acid to 20-hydroxyeicosatetraenoic acid (20-HETE), a molecule that elevates blood pressure [20–22]. Other important MIEs include 11β-hydroxysteroid dehydrogenases (11β-HSDs), which activate glucocorticoids, and angiotensin-converting enzyme (ACE), a known drug target that converts angiotensin I to angiotensin II [23,24].

In obesity, intercellular signals involve hormones such as leptin and insulin, inflammatory cytokines from TLR-activated adipose tissue, mitogen-activated protein kinases (ERK, JNK, p38) that regulate appetite and inflammation, and fatty acids that influence

metabolism [25,26]. Disruptions in downstream pathways, particularly PI3K/AKT and JAK/STAT, contribute to metabolic dysfunction, insulin resistance, and related complications [27,28]. In diabetes, similar mechanisms are at play, where hormones like insulin and glucagon, islet-derived paracrine factors (somatostatin and growth factors), and adipokines (TNF-α, IL-6, and resistin) regulate insulin sensitivity and islet function. Dysregulated adipokine release and paracrine signaling exacerbate insulin resistance and accelerate diabetes progression [29–32]. In hypertension, neurohormones such as angiotensin II and norepinephrine can also trigger downstream PI3K/AKT signaling via activation of G protein-coupled receptors [33]. Protein-modifying enzymes, on the other hand, contribute to obesity, diabetes, and hypertension through post-translational modifications (PTMs) that regulate metabolism, insulin signaling, lipid homeostasis, and vascular function [34]. For example, a negative regulator, Protein Tyrosine Phosphatase 1B (PTP1B), is overexpressed in obesity and disrupts insulin signaling by dephosphorylating the insulin receptor and insulin receptor substrate 1 (IRS-1) [35,36]. Likewise, histone deacetylases (HDACs) affect lipid metabolism, and dysregulation of HDAC3 and HDAC6 can promote weight gain and metabolic disorders [37,38].

2.2. Genes Involved in Hallmarks of Diabesotension

2.2.1. Insulin Resistance

The regulation of insulin sensitivity and glucose metabolism is orchestrated by a complex interplay of genetic and molecular pathways encompassing hormonal signaling, lipid metabolism, and inflammatory responses (Table 1). Among these, *AGT* modulates insulin sensitivity through renin–angiotensin system-dependent mechanisms, with specific haplotypes (such as TCG) linked to increased T2DM susceptibility [39]. Downstream of insulin receptor signaling, *AKT1* serves as a pivotal kinase in the PI3K-Akt cascade, directly promoting glucose uptake; its impaired activation contributes to insulin resistance, whereas enhanced Akt signaling improves systemic metabolic homeostasis [27,28]. The lipid transporter *CD36* regulates fatty acid uptake and oxidation, maintaining metabolic balance under physiological conditions but promoting lipid accumulation and insulin resistance in states of nutrient excess [40]. Similarly, *FOXO1*, a transcriptional regulator integrating insulin and nutrient signals, promotes hepatic gluconeogenesis and lipid oxidation while suppressing glucose uptake and insulin secretion [41].

Inflammatory mediators such as *IL6* and *TNF* disrupt insulin receptor function through SOCS3- and NF-κB-dependent mechanisms, reinforcing the inflammatory–metabolic feedback loop characteristic of obesity-associated insulin resistance [42,43]. Core components of insulin signaling, including *INS*, *INSR*, *IRS1*, and *IRS2*, are essential for maintaining glucose homeostasis; genetic or functional disruption of these elements impairs insulin secretion, receptor binding, and downstream signaling, resulting in hyperinsulinemia and glucose intolerance [44,45]. Stress-activated and nutrient-sensing kinases, MAPK8 (JNK1), MTOR, and PTEN, further modulate insulin pathway integrity, where chronic mTORC1 activation, JNK1-mediated IRS inhibition, or excessive PTEN activity converge to dampen insulin sensitivity [46].

Genes governing mitochondrial function and lipid metabolism, such as *PPARA*, *PPARGC1A*, and *SREBF1*, shape systemic insulin responsiveness through their control of oxidative and biosynthetic pathways. PPARα activation enhances fatty acid oxidation and suppresses inflammation, thereby improving insulin sensitivity, while the coactivator PGC-1α sustains mitochondrial biogenesis and thermogenesis; loss of PGC-1α function impairs lipid metabolism and promotes insulin resistance under nutrient excess [47]. Conversely, elevated *SREBP1* activity perturbs insulin receptor and Akt phosphorylation, leading to mitochondrial dysfunction and dysregulated lipid storage [48,49]. Other key modulators

include *PIK3R1*, where pathogenic variants compromise PI3K-dependent signaling [50]; *SOCS3* and *STAT3* [51,52], which inhibit *IRS1* and Akt activation in skeletal muscle; and *PTPN1 (PTP1B)*, which attenuates insulin receptor phosphorylation, contributing to cardiac insulin resistance [53]. The insulin-responsive glucose transporter *SLC2A4 (GLUT4)* remains a crucial effector of glucose uptake, with its upregulation ameliorating insulin resistance in metabolic disease contexts [54].

Finally, additional loci, including *NOS3*, *PRKAG2*, and *TRIB3*, integrate vascular, energetic, and stress responses into insulin signaling networks. *NOS3* variants influence nitric oxide-mediated endothelial and metabolic regulation [55]; *PRKAG2* mutations impair AMPK activation and myocardial glucose uptake [56]; and *TRIB3* modulates glucose-induced negative feedback on insulin action [57]. Collectively, these genes delineate a convergent regulatory framework in which inflammation, lipid handling, mitochondrial dynamics, and kinase signaling intersect to determine tissue-specific insulin sensitivity and overall glucose homeostasis.

Table 1. List of 26 diabesotension-associated genes involved in insulin resistance.

Gene Symbol	Description	Function	Evidence	References
AGT	Angiotensinogen	Modulates insulin sensitivity through altered *AGT* expression and subsequent effects on renin–angiotensin system-mediated regulation of glucose metabolism. The *AGT* haplotype TCG (rs4762) is associated with increased risk of T2DM, implicating *AGT* in insulin resistance through renin–angiotensin system-mediated mechanisms independent of other RAS loci.	GWAS	[39]
AKT1	AKT serine/threonine kinase 1	Regulates glucose uptake via the PI3K–Akt pathway; impaired Akt activation induces insulin resistance, while enhanced Akt signaling improves insulin sensitivity and metabolic outcomes.	In vivo animal	[58]
CD36	CD36 molecule	Mediates fatty acid uptake and oxidation; supports insulin sensitivity under normal diet but promotes insulin resistance under lipid overload. Facilitates fatty acid uptake and lipid accumulation during insulin resistance; membrane redistribution impairs GLUT4-mediated glucose uptake, while *CD36* inhibition restores insulin sensitivity.	In vivo animal	[59,60]
FOXO1	Forkhead box O1	Promotes hepatic glucose production and lipid utilization while suppressing glucose uptake and insulin secretion; *FOXO1* overactivation disrupts insulin signaling and contributes to systemic insulin resistance. Acts as a repressor of PPARδ in skeletal muscle; *FOXO1* deficiency enhances mitochondrial function and lipid metabolism, improving insulin sensitivity under obese conditions.	In vivo animal	[61,62]
IL6	Interleukin 6	Promotes insulin resistance through SOCS-3-mediated inhibition of insulin receptor and IRS-1 phosphorylation; chronic IL-6 elevation disrupts insulin signaling and glucose homeostasis.	Mechanistic	[63]
INS	Insulin	Regulates glucose homeostasis; *INS* gene mutations impair insulin folding, secretion, and receptor binding, leading to β-cell stress and reduced insulin sensitivity in peripheral tissues.	Genetic mutation	[64]

Table 1. *Cont.*

Gene Symbol	Description	Function	Evidence	References
INSR	Insulin receptor	Encodes the insulin receptor; loss-of-function mutations impair insulin binding and signaling, causing severe insulin resistance, hyperinsulinemia, and dysregulated glucose metabolism.	Genetic mutation	[65]
IRS1	Insulin receptor substrate 1	Mediates insulin receptor signaling via the PI3K–Akt pathway; *IRS1* deficiency impairs hepatic and muscular glucose uptake, leading to reduced insulin sensitivity and compensatory hyperinsulinemia.	In vivo animal	[66]
IRS2	Insulin receptor substrate 2	Mediates insulin signaling and β-cell maintenance; *IRS2* deficiency impairs glucose tolerance and insulin secretion, leading to β-cell dysfunction and non-obese insulin resistance.	In vivo animal	[67]
MAPK8	Mitogen-activated protein kinase 8	Impairs insulin receptor and IRS phosphorylation via stress-activated pathways; *MAPK8* dysregulation reduces insulin sensitivity and contributes to inflammation-induced insulin resistance.	Gene expression	[68]
MTOR	Mechanistic target of rapamycin kinase	Regulates insulin signaling via *mTORC1* and *mTORC2*; chronic *mTORC1* overactivation inhibits IRS-1 and impairs insulin sensitivity, while *mTORC2* promotes Akt activation and glucose homeostasis.	Mechanistic	[69]
NFKB1	Nuclear factor kappa B subunit 1	Regulates inflammation-induced inhibition of insulin signaling; *NFKB1* variants (rs7667496, rs28362491) are associated with increased T2DM risk and reduced insulin sensitivity.	Genetic association	[70]
NOS3	Nitric oxide synthase 3	Regulates nitric oxide-mediated vascular and glucose metabolism; *NOS3* variants (rs1800779) modulate endothelial function and insulin sensitivity, influencing T2DM risk.	Genetic association	[55]
PIK3R1	Phosphoinositide-3-kinase regulatory subunit 1	Encodes PI3K regulatory subunits; pathogenic variants (e.g., p.Arg649Trp) impair PI3K-dependent insulin signaling, causing severe insulin resistance and metabolic dysfunction.	Genetic mutation	[50]
PPARA	Peroxisome proliferator-activated receptor alpha	Regulates lipid oxidation and energy homeostasis; *PPARA* activation enhances mitochondrial function and suppresses inflammation, improving insulin sensitivity and mitigating metabolic dysfunction.	Mechanistic	[71]
PPARGC1A	PPARG coactivator 1 alpha	Regulates mitochondrial biogenesis and energy metabolism; promoter hypomethylation of *PPARGC1A* reduces PGC-1α expression and insulin sensitivity. Maintains mitochondrial and thermogenic activity in adipose tissue; PGC-1α deficiency impairs lipid metabolism and promotes systemic insulin resistance under high-fat conditions.	In vivo animal	[72,73]

Table 1. *Cont.*

Gene Symbol	Description	Function	Evidence	References
PRKAG2	Protein kinase AMP-activated non-catalytic subunit gamma 2	Encodes the AMPK γ2-subunit; *PRKAG2* mutations impair AMPK signaling, reducing myocardial glucose uptake and promoting insulin resistance and cardiac metabolic dysfunction.	In vivo animal	[56]
PTEN	Phosphatase and tensin homolog	Negatively regulates PI3K–Akt signaling; altered *PTEN* expression impairs insulin action in liver, muscle, and adipose tissue, promoting systemic insulin resistance.	In vitro functional	[74]
PTPN1	Protein tyrosine phosphatase non-receptor type 1	Impairs cardiac insulin signaling; *PTPN1/PTP1B* overactivation reduces insulin receptor phosphorylation and glucose uptake, contributing to cardiac insulin resistance and dysfunction.	In vivo animal	[53]
SLC2A4	Solute carrier family 2 member 4	Mediates insulin-stimulated glucose uptake; *SLC2A4/GLUT4* enhances insulin signaling and glucose utilization, mitigating insulin resistance in gestational diabetes.	In vitro functional	[54]
SOCS3	Suppressor of cytokine signaling 3	Negatively regulates insulin signaling in skeletal muscle; *SOCS3* inhibits *IRS1* and Akt phosphorylation, promoting insulin resistance, while its deletion enhances insulin sensitivity and glucose uptake.	In vivo animal	[52]
SREBF1	Sterol regulatory element binding transcription factor 1	Regulates lipid metabolism; elevated *SREBF1/SREBP1* impairs insulin receptor and *AKT* phosphorylation, promoting mitochondrial dysfunction and insulin resistance. SREBF1 variants (rs12953299, rs4925115) modulate insulin sensitivity responses to dietary interventions.	Genetic association	[48,49]
STAT3	Signal transducer and activator of transcription 3	Mediates muscle insulin resistance; *STAT3* activation induces Fbxo40, promoting *IRS1* degradation and reducing Akt signaling, while its inhibition restores insulin sensitivity.	In vivo animal, In vitro functional	[51]
TNF	Tumor necrosis factor	Promotes adipose inflammation; TNFα activates NF-κB pathways, disrupting insulin signaling and glucose uptake, thereby contributing to obesity-associated insulin resistance.	In vitro functional	[75]
TNFRSF1A	TNF receptor superfamily member 1A	Mediates inflammation-induced insulin resistance; *TNFRSF1A* activates NF-κB and MAPK pathways, disrupting hepatic insulin signaling and metabolic homeostasis.	Transcript-omics, In vivo animal	[76]
TRIB3	Tribbles pseudokinase 3	Mediates glucose-induced insulin resistance; *TRIB3* impairs insulin-stimulated glucose uptake in skeletal muscle, and its modulation alters insulin sensitivity.	In vivo animal, In vitro functional	[57]

2.2.2. Inflammation

Inflammation constitutes a major molecular axis linking metabolic and vascular dysfunction in diabesotension. Several genes central to immune signaling, lipid metabolism, and endothelial activation contribute to this pathophysiology (Table 2). *AKT1*, a key effector of PI3K signaling, regulates acute inflammatory responses and vascular permeability by controlling leukocyte extravasation and endothelial barrier integrity [77]. *CXCL8 (IL-8)* or-

chestrates neutrophil recruitment and activation through CXCR1/2 and ACKR1 signaling, a process modulated by chemokine dimerization and post-translational modification [78]. The pro-inflammatory cytokine *IL12B* enhances insulin resistance and endothelial dysfunction, with elevated IL-12 levels linking systemic inflammation to β-cell stress and atherosclerotic risk [79]. Similarly, *IL6* serves as both a predictive and pathogenic mediator across diabetes subtypes, including type 1, type 2, and gestational diabetes, and contributes to diabetic complications such as nephropathy, neuropathy, and cognitive impairment [80].

Hyperglycemia-activated signaling cascades further amplify inflammatory injury through mitogen-activated protein kinases. *MAPK1*, *MAPK3*, and *MAPK14* (p38α) mediate stress-induced and pro-inflammatory responses in vascular and renal tissues. *MAPK1* promotes oxidative stress and cardiac remodeling, while *MAPK3* activation drives renal inflammation and fibrosis in diabetic nephropathy [81,82]. *MAPK14* functions as a central stress transducer, regulating cytokine gene expression and inflammatory signaling, and is emerging as a target for inflammation-driven metabolic disease [83]. Transcriptional regulators *NFKB1* and *TNF* integrate inflammatory signaling with metabolic dysfunction. NF-κB polymorphisms modulate cardiovascular inflammation in type 2 diabetes, particularly through interactions with other immune mediators, while TNF, secreted by adipocytes and immune cells, promotes chronic low-grade inflammation that underlies obesity-induced insulin resistance and endothelial dysfunction [84,85]. Finally, *RETN* links adipose-derived inflammation to vascular pathology by promoting arterial inflammation and atherogenesis, thereby connecting obesity, hypertension, and insulin resistance through macrophage-driven signaling [86]. Collectively, these genes delineate an inflammatory network that integrates metabolic stress with vascular remodeling, serving as a molecular bridge between diabetes and hypertension.

Table 2. List of 10 diabesotension-associated genes involved in inflammation.

Gene Symbol	Description	Function	Evidence	References
AKT1	AKT serine/threonine kinase 1	Regulates acute inflammation and vascular permeability; *Akt1* modulates leukocyte extravasation and endothelial barrier function, whereas *Akt2* has minimal effect.	In vivo animal, In vitro functional	[77]
CXCL8	C-X-C motif chemokine ligand 8	Regulates neutrophil migration and activation; *CXCL8* signals via *CXCR1/2* and *ACKR1*, with activity modulated by dimerization and post-translational modifications.	Mechanistic	[78]
IL12B	Interleukin 12B	Promotes inflammation and insulin resistance; serum *IL-12* levels are elevated and correlate with BMI, C-peptide, insulin, HOMA-IR, proinsulin, and HDL, linking *IL-12* to peripheral insulin resistance and β-cell dysfunction and atherosclerosis risk.	Correlation	[79]
IL6	Interleukin 6	Promotes inflammation and diabetes risk; elevated *IL-6* predicts T1DM, T2DM, GDM, and is associated with diabetic complications including DKD, DPN, and cognitive impairment.	Meta-analysis	[80]
MAPK1	Mitogen-activated protein kinase 1	Mediates PKC-MAPK signaling under hyperglycemia; *MAPK1* promotes oxidative stress, inflammation, and cardiac/vascular remodeling, contributing to diabetic cardiovascular complications.	Mechanistic	[81]

Table 2. *Cont.*

Gene Symbol	Description	Function	Evidence	References
MAPK14	Mitogen-activated protein kinase 14	Transduces stress and proinflammatory signals; *MAPK14*/p38α regulates gene expression and cytokine production, mediating inflammatory responses and representing a therapeutic target in stress- and inflammation-related diseases	Gene expression	[83]
MAPK3	Mitogen-activated protein kinase 3	Mediates renal inflammation in diabetic nephropathy; *MAPK3*/p38 MAPK activation promotes podocyte injury, tubular damage, fibrosis, macrophage infiltration, and Ccl2 expression.	In vivo functional	[82]
NFKB1	Nuclear factor kappa B subunit 1	Regulates inflammation-driven metabolic complications; *NFKB1* polymorphisms (e.g., rs4648068 GG) modulate risk of dyslipidemia and interact with *TLR9*, IL6R, *IL10*, and *TLR4* to influence cardiovascular inflammation in T2DM.	Genetic association	[84]
RETN	Resistin	Acts as a pro-inflammatory mediator; resistin from macrophages promotes arterial inflammation, endothelial dysfunction, and atherosclerosis, linking obesity to insulin resistance, dyslipidemia, hypertension, and cardiovascular disease.	Epidemiological, genetic mutation	[86]
TNF	Tumor necrosis factor	Acts as a pro-inflammatory cytokine; TNF-α from adipocytes and immune cells promotes chronic inflammation, linking obesity to T2DM and metabolic dysfunction, and serves as a potential biomarker and therapeutic target.	Cross-sectional study	[85]

2.2.3. Neurohormonal Regulation (RAAS)

Neurohormonal mechanisms, encompassing central insulin signaling, neurotrophic regulation, and RAAS interactions, are integral to diabesotension pathophysiology [9]. Sixteen diabesotension-associated genes have been reported to be involved in RAAS, as listed in Table 3. *AKT1* supports neuronal insulin signaling, partially restoring AS160 phosphorylation and glucose uptake when *Akt2* function is impaired, thereby influencing neuroendocrine regulation and metabolic homeostasis [87]. Transcriptional and apoptotic regulators such as *ATF4*, *BCL2*, and *FOXO3* mediate neuronal plasticity, excitability, and survival. *ATF4* controls GABAB receptor trafficking and synaptic transmission via cytoskeletal signaling [88], while the anti-apoptotic BCL-2 family maintains mitochondrial integrity in neurons under metabolic stress [89]. *FOXO3* integrates stress responses and neuronal maintenance, preventing axonal degeneration and influencing susceptibility to neurodegenerative disorders associated with metabolic imbalance [90].

Neurotrophic and insulin signaling pathways intersect through *BDNF*, *NTRK2* (TrkB), and *IRS1*. Reduced *BDNF* levels in diabetes link metabolic dysfunction to impaired neuroprotection [91], whereas *NTRK2* activation by *BDNF* triggers MAPK, PLCγ, and PI3K pathways essential for neuronal differentiation and synaptic maintenance [92]. *IRS1*, a central mediator of neuronal insulin signaling, regulates PI3K–Akt activity; its reduced function in diabetes disrupts neuronal and neurovascular integrity [93]. MAPK family members, including *MAPK1*, *MAPK3*, *MAPK8*, and *MAPK14*, also play multifaceted roles in neurohormonal regulation. *MAPK1* and *JNK3* contribute to neurotoxicity and degeneration [94]; *MAPK14* impairs autophagy and BACE1 clearance, linking metabolic

stress to neurodegeneration [95]; and *MAPK3* facilitates leptin-dependent transcriptional regulation of neuronal responses controlling appetite and energy balance [96]. Similarly, *MAPK8 (JNK1/3)* orchestrates hypothalamic POMC and AgRP neuron activity, influencing feeding behavior, thermogenesis, and systemic energy balance [97].

Inflammatory transcription factors such as *NFKB1* connect nutrient-induced stress to hypothalamic inflammation and neuroendocrine dysregulation, representing a shared pathway between metabolic and neurodegenerative disease [98]. Additional signaling regulators, including *PIK3R1*, *RAC1*, *SORT1*, and *TP53*, contribute variably to neuronal survival, synaptic remodeling, and insulin resistance-related neuroendocrine dysfunction. *PIK3R1* mutations impair AKT phosphorylation and neuronal insulin signaling [99], *RAC1* inhibition prevents hypertension and renal damage [100], *SORT1* mediates neuronal survival and death across CNS and metabolic tissues [101], and *TP53*, through its mitochondrial apoptotic activity, promotes β-cell dysfunction and neuronal vulnerability under metabolic stress [102]. Collectively, these neurohormonal regulators illustrate how metabolic and neural circuits converge through insulin, trophic, and inflammatory signaling to maintain systemic energy and vascular homeostasis.

Table 3. List of 16 diabesotension-associated genes involved in neurohormonal regulation.

Gene Symbol	Description	Function	Evidence	References
AKT1	AKT serine/threonine kinase 1	Supports neuronal insulin signaling; Akt1 partially restores AS160 phosphorylation and glucose uptake when Akt2 function is impaired, contributing to neurohormonal regulation and insulin resistance.	In vitro functional	[87]
ATF4	Activating transcription factor 4	Regulates neuronal excitability and inhibitory signaling; ATF4 controls GABAB receptor trafficking via Cdc42, modulating action potential frequency and contributing to learning, memory, and neurohormonal regulation.	In vitro functional	[88]
BCL2	BCL2 apoptosis regulator	Regulates neuronal survival via the intrinsic mitochondrial apoptosis pathway; Bcl-2 family proteins balance anti- and pro-apoptotic signals, supporting neuroprotection.	Mechanistic	[89]
BDNF	Brain-derived neurotrophic factor	Supports neuronal survival and CNS function; BDNF is reduced in diabetes, linking insulin resistance to impaired brain function, while physical activity may enhance BDNF-mediated neuroprotection.	Mechanistic	[91]
FOXO3	Forkhead box O3	Regulates neuronal survival and stress responses; FOXO3 prevents age-dependent axonal degeneration, modulates synapse function in the peripheral nervous system, and influences neurodegenerative disease susceptibility.	In vivo animal	[90]
IRS1	Insulin receptor substrate 1	Mediates neuronal insulin signaling via the IRS1-PI3K-Akt pathway; reduced IRS1 activity in diabetes impairs neuronal and neurovascular function and alters stress responses	In vivo animal	[93]

Table 3. *Cont.*

Gene Symbol	Description	Function	Evidence	References
MAPK1	Mitogen-activated protein kinase 1	MAPK1/JNK3 mediates neurodegeneration and neurotoxicity, representing a potential therapeutic target for preventing neuronal injury in diabetes.	Mechanistic	[94]
MAPK14	Mitogen-activated protein kinase 14	Negatively regulates neuronal autophagy; MAPK14/p38α impairs autophagic-lysosomal degradation, and its inhibition enhances BACE1 clearance, mitigating neurodegenerative defects in Alzheimer's disease.	In vivo functional	[95]
MAPK3	Mitogen-activated protein kinase 3	Leptin signaling activates MAPK, which contributes to the modulation of gene transcription in neurons. Through MAPK activation, leptin influences neuronal responses related to energy homeostasis and other neuroendocrine functions, highlighting MAPK as a key mediator in hypothalamic neurohormonal regulation.	Mechanistic	[96]
MAPK8	Mitogen-activated protein kinase 8	MAPK isoforms (ERK1/2, JNK1/3) regulate CNS energy balance and feeding by modulating hypothalamic POMC and AgRP neuron activity and pituitary Dio2 expression, thereby controlling appetite, thermogenesis, and metabolic homeostasis.	Mechanistic	[97]
NFKB1	Nuclear factor kappa B subunit 1	Mediates neuroinflammation in the hypothalamus; NF-κB links nutrient-induced stress to dysregulated neuroendocrine circuits, contributing to metabolic syndrome and systemic metabolic disturbances.	Mechanistic	[98]
NTRK2	Neurotrophic receptor tyrosine kinase 2	Mediates neurotrophic signaling; NTRK2/TrkB activation by BDNF triggers MAPK, PLCγ, and PI3K pathways, regulating neuronal development, survival, differentiation, and synaptic function.	Genetic association	[92]
PIK3R1	Phosphoinositide-3-kinase regulatory subunit 1	PIK3R1 mediates neuronal insulin signaling via IRS1-AKT, and mutations impair AKT phosphorylation, linking it to insulin resistance-related neuroendocrine dysfunction.	Genetic mutation	[99]
RAC1	Rac family small gtpase 1	Rac1 inhibition prevents hypertension and renal damage. No reports of a direct association with neurohormonal regulation have been published so far.	Mechanistic	[100]
SORT1	Sortilin 1	Regulates neuronal survival and death in the CNS; sortilin also functions in adipocytes, hepatocytes, and macrophages, indicating broader roles beyond neurons.	GWAS	[101]
TP53	Tumor protein p53	TP53 mediates β-cell dysfunction and insulin resistance, and the Pro72Arg variant enhances mitochondrial pro-apoptotic activity. No reports of a direct association with neurohormonal regulation have been published so far.	Genetic association	[102]

2.2.4. Oxidative Stress

Oxidative stress represents a key pathogenic mechanism linking metabolic dysfunction and vascular injury in diabesotension (Table 4). This process arises from an imbalance between reactive oxygen species (ROS) generation and antioxidant defense, governed by a complex interplay of enzymatic, signaling, and transcriptional regulators [103,104]. Central antioxidant enzymes, including CAT, GPX3, SOD1, SOD2, SOD3, and NQO1, constitute the first line of defense against oxidative damage by detoxifying ROS and maintaining cellular redox equilibrium [105–110]. Reduced activity or expression of these enzymes in diabetes or obesity enhances mitochondrial dysfunction and tissue injury, promoting insulin resistance and endothelial impairment. HMOX1, through heme degradation and carbon monoxide production, exerts cytoprotective and anti-inflammatory effects [111], while MAOA, CYBB, NOX4, and NOX5 act as major enzymatic sources of ROS, driving oxidative injury in renal, cardiac, and vascular tissues [112–115].

Transcriptional control of oxidative homeostasis is largely coordinated by *NFE2L2 (NRF2)*, a master regulator of antioxidant responses, and *NFKB1*, which integrates oxidative, inflammatory, and apoptotic signaling. Crosstalk between NRF2 and NF-κB pathways determines whether oxidative stress leads to adaptation or cellular injury [116]. Similarly, redox-sensitive kinases such as MAPK14, MAPK8, and MTOR transduce oxidative cues into metabolic and inflammatory outcomes, modulating autophagy, apoptosis, and cellular resilience [117–119]. The interplay between these kinases and mitochondrial regulators like *AKT1* and *PINK1* influences tissue-specific responses to oxidative burden, from adaptive hypertrophy to apoptosis [120,121].

Cellular stress and survival are further modulated by *BCL2*, *TP53*, and *CDKN1A*, which govern mitochondrial integrity, cell-cycle arrest, and senescence under oxidative pressure. Their dysregulation contributes to β-cell failure, adipose tissue aging, and systemic insulin resistance [89,122,123]. Pro-inflammatory cytokines and chemokines, such as *IL1A*, *IL6*, *TNF*, and *CXCL8*, amplify oxidative injury through sustained activation of NADPH oxidases and inflammatory transcription factors, perpetuating metabolic inflammation and vascular dysfunction [124–127]. Meanwhile, metabolic regulators such as *FOXO1*, *PTEN*, and *SIRT1* act as redox-sensitive switches that coordinate antioxidant gene expression and insulin signaling via PI3K–Akt and AMPK pathways [128–130]. Structural and enzymatic mediators including *ICAM1*, *PTGS2*, and *XDH* further link oxidative stress to endothelial activation, vascular remodeling, and lipid oxidation [131–133].

Together, these genes delineate a tightly interconnected redox regulatory network in which impaired antioxidant capacity, excessive ROS production, and maladaptive stress signaling converge to drive the metabolic, inflammatory, and vascular complications characteristic of diabesotension.

Table 4. List of 32 diabesotension-associated genes involved in oxidative stress.

Gene Symbol	Description	Function	Evidence	References
CAT	Catalase	Protects neurons from oxidative stress; CAT decomposes H_2O_2, and reduced activity in T2DM or obesity increases ROS, mitochondrial dysfunction, and neuronal injury.	Cross-sectional study	[105]
CYBB	Cytochrome b-245 beta chain	Encodes the heavy chain of a heterodimeric transmembrane ion transporter that transfers electrons from NADPH to oxygen to generate superoxide, contributing to innate immune defense. Dysregulation of CYBB can cause oxidative stress and tissue damage, while loss of function leads to chronic granulomatous disease.	In vivo functional	[113]

Table 4. *Cont.*

Gene Symbol	Description	Function	Evidence	References
CYP1A1	Cytochrome P450 family 1 subfamily A member 1	Promotes ROS generation in mitochondria and microsomes, contributing to oxidative stress. Elevated CYP1A1 expression is associated with lipid peroxidation, oxidative damage, and pro-inflammatory cytokine production, linking it to ROS-mediated cellular injury and diabetic pathology.	Gene expression	[134]
GPX3	Glutathione peroxidase 3	GPX3 is an antioxidant enzyme that detoxifies reactive oxygen species, modulating redox signaling and protecting cells from oxidative damage. Highly expressed in kidney and lung, and to a lesser extent in adipose tissue, its expression is regulated by hypermethylation, glucocorticoid receptor, and estrogen receptor α signaling. GPX3 helps maintain adipose tissue function, particularly under conditions of oxidative stress such as obesity.	Gene expression	[106]
HMOX1	Heme oxygenase 1	HMOX1 encodes heme oxygenase-1, an inducible enzyme that responds to oxidative stress by degrading heme and producing carbon monoxide. In visceral adipose tissue, elevated HMOX1 correlates with increased HO activity, higher COHb levels, and reduced insulin resistance, suggesting a protective role against metabolic dysfunction.	Genetic association	[111]
MAOA	Monoamine oxidase A	MAOA encodes an enzyme that catalyzes monoamine degradation, generating reactive oxygen species. Its upregulation in the heart during obesity and prediabetes promotes oxidative stress and cardiac damage. Pharmacological inhibition or metformin treatment reduces ROS and MAO expression, highlighting MAOA as a key mediator of metabolic disease-associated oxidative stress and a potential therapeutic target.	Ex vivo	[112]
MAPK14	Mitogen-activated protein kinase 14	MAPK14 interacts with oxidative stress, mediating the exacerbation of acute pancreatitis (AP) under hyperlipidemia. Bidirectional causal interactions between SOD and MAPK14 highlight the role of MAPK signaling in oxidative stress-related disease progression	Transcriptomics	[117]

Table 4. *Cont.*

Gene Symbol	Description	Function	Evidence	References
NFE2L2	NFE2 like bzip transcription factor 2	NFE2L2 encodes NRF2, a transcription factor that orchestrates cellular defense against oxidative and electrophilic stress by regulating genes involved in antioxidant responses, lipid metabolism, and inflammation. Downregulation in metabolic and inflammatory conditions enhances oxidative stress and vascular dysfunction, while deficiency in knockout models or macrophages exacerbates cardiac abnormalities and atherosclerosis. NRF2 activation offers a protective strategy against metabolic disease-associated oxidative damage.	Animal knockout	[116]
NFKB1	Nuclear factor kappa B subunit 1	NFKB1 promotes oxidative stress and insulin resistance in gestational hypertension by inhibiting miR-106a and upregulating FLOT2, enhancing hepatocyte apoptosis and inflammation.	In vivo gene silencing, In vitro	[135]
NOX4	NADPH oxidase 4	Nox4 drives reactive oxygen species production in renal and cardiovascular tissues. Genetic deletion or pharmacological inhibition reduces oxidative stress, protects against renal injury, and alleviates hypertension and diabetic nephropathy, identifying Nox4 as a key mediator of oxidative stress-related organ dysfunction.	In vivo animal	[114]
NOX5	NADPH oxidase 5	NOX5, together with NOX4, is a major renal source of reactive oxygen species. Its expression and activity are regulated by NF-κB, TNF, TGF, and fibronectin. Dysregulated NOX5 promotes oxidative stress, driving proinflammatory and profibrotic responses that exacerbate kidney injury and disease progression.	Gene expression	[115]
NQO1	NAD(P)H quinone dehydrogenase 1	NQO1 catalyzes two-electron reduction in quinones, preventing redox cycling and ROS generation, thereby protecting cells from oxidative stress.	Mechanistic	[108]
SOD1	Superoxide dismutase 1	SOD1 plays a key role in mitigating oxidative stress by dismutating superoxide radicals. Its gene expression is regulated by several transcription factors responsive to redox changes and stress signals, including NF-κB (sensitive to redox state), SP1 and AP-1 (responsive to cytokines and oxidative stress), AP-2 (enhances SOD1 transcription), and CCAAT-binding proteins (C/EBP) that bind to regulatory and enhancer sequences.	Cross-sectional	[107]
SOD2	Superoxide dismutase 2	Increased SOD1 and SOD2 expression reduces oxidative stress, providing protection against insulin resistance and glucose intolerance in obesity.	In vivo gene overexpression	[109]

Table 4. *Cont.*

Gene Symbol	Description	Function	Evidence	References
SOD3	Superoxide dismutase 3	Unlike intracellular SOD1 and SOD2, SOD3 functions outside cells to maintain redox homeostasis. A mutant isoform, Arg213Gly, with reduced activity is associated with higher BMI, hypercholesterolemia, and hyperlipidemia. SOD3 levels are inversely correlated with insulin resistance in T2D. Overexpression or gene transfer of SOD3 protects pancreatic islet function from oxidative stress, promotes tissue repair, and exhibits anti-inflammatory effects.	In vivo gene overexpression	[110]
XDH	Xanthine dehydrogenase	XDH, part of the XDH/XO system, generates ROS in adipocytes. Under oxidative stress, XDH converts to XO, producing superoxide and hydrogen peroxide during purine catabolism, thereby promoting oxidative stress and cellular damage.	Mechanistic	[131]
AKT1	AKT serine/threonine kinase 1	AKT1, a PI3K downstream effector activated by insulin and IGF-I, modulates oxidative stress in a tissue-specific manner, contributing to ROS-associated cardiac hypertrophy and dysfunction or adaptive hypertrophy during physiological stimuli.	In vivo animal	[121]
BCL2	BCL2 apoptosis regulator	BCL2 regulates oxidative stress by modulating mitochondrial function, reducing ATP and ROS production, and maintaining redox balance under stress through effects on oxidative phosphorylation, ribosomal dynamics, and mitochondrial Ca^{2+} homeostasis.	Mechanistic	[89]
CDKN1A	Cyclin-dependent kinase inhibitor 1A	CDKN1A is upregulated in adipose tissue under obesity-induced oxidative stress via p53 activation, promoting cellular senescence, inflammation, and insulin resistance, thereby linking oxidative stress to adipose aging and metabolic dysfunction.	Gene expression	[123]
CXCL8	C-X-C motif chemokine ligand 8	CXCL8 is a proinflammatory chemokine upregulated by metabolic disturbances via TLR/NF-κB signaling, promoting chronic inflammation and oxidative stress that contribute to tissue dysfunction in obesity, T2DM, and gestational diabetes.	Mechanistic	[127]
FOXO1	Forkhead box O1	FOXO transcription factors (FOXO1, FOXO3, FOXO4) are activated by ROS and regulate gene expression to mediate effects on glucose metabolism, cell cycle, and apoptosis	Mechanistic	[128]
ICAM1	Intercellular adhesion molecule 1	ICAM-1 is upregulated in aortic endothelial cells by elevated LDL and oxidative stress. Induced via AP-1 and TNF-α signaling, ICAM-1 promotes endothelial activation and contributes to atherogenesis through interactions with oxidized LDL.	Cross sectional	[133]

Table 4. *Cont.*

Gene Symbol	Description	Function	Evidence	References
IL1A	Interleukin 1 alpha	In obesity, IL-1 contributes to the systemic pro-inflammatory state, which amplifies oxidative stress by promoting adipose tissue dysfunction, endothelial damage, and the dysregulation of antioxidant defenses such as Nrf2. Through this mechanism, IL-1 links inflammation to oxidative stress, contributing to metabolic complications including insulin resistance, hypertension, and impaired glucose tolerance.	Mechanistic	[124]
IL6	Interleukin 6	A proinflammatory cytokine produced by endothelial cells is upregulated by oxidative stress-induced poor glycemic control, promoting inflammation and linking oxidative stress to vascular and metabolic dysfunction in T2D.	Gene expression	[125]
MAPK8	Mitogen-activated protein kinase 8	MAPK8 (JNK1) is activated by ROS under oxidative stress, particularly in obesity, and regulates nuclear and extranuclear targets such as AP-1 and NF-κB. Activation promotes pro-inflammatory cytokine expression, impairs insulin signaling, and disrupts GLUT4 translocation, contributing to insulin resistance.	Mechanistic	[118]
MTOR	Mechanistic target of rapamycin kinase	mTOR signaling, modulated by oxidative stress, regulates cardiometabolism in diabetes, exerting cardioprotective effects through prosurvival pathways and autophagy, or causing cardiotoxicity through dysregulation, which exacerbates ischemia/reperfusion injury.	Mechanistic	[119]
PINK1	PTEN-induced kinase 1	Reduced PINK1 impairs mitochondrial protection against oxidative stress. This deficit contributes to cellular dysfunction in obesity-related T2D, affecting β-cell function and promoting insulin resistance.	Gene expression	[120]
PTEN	Phosphatase and tensin homolog	In adipocytes, insulin-stimulated ROS enhance insulin signaling by reversibly inhibiting protein tyrosine phosphatases, including PTEN, thereby promoting PI3K/Akt pathway activation.	Mechanistic	[129]
PTGS2	Prostaglandin-endoperoxide synthase 2	PTGS2, an oxidative stress-related gene, contributes to arteriovenous fistula (AVF) failure. Its elevated expression promotes oxidative stress and neointimal formation, while pharmacological inhibition reduces oxidative stress and improves hemodynamics.	Transcriptomics, In vivo	[132]

Table 4. *Cont.*

Gene Symbol	Description	Function	Evidence	References
SIRT1	Sirtuin 1	SIRT1 senses oxidative stress and mitigates vascular dysfunction by cooperating with AMPK to activate antioxidant pathways via downstream effectors including PGC-1α, FOXOs, and PPARα.	Mechanistic	[130]
TNF	Tumor necrosis factor	TNF-α is a pro-inflammatory cytokine that promotes oxidative stress by activating NADPH oxidases and increasing ROS production, linking chronic inflammation to cellular and tissue damage in metabolic and inflammatory diseases.	Mechanistic	[126]
TP53	Tumor protein p53	Oxidative stress and p53 cooperate to induce β-cell dysfunction and insulin resistance in newly diagnosed T2DM, with oxidative stress impairing β-cell function and p53 promoting insulin resistance.	Case–control study	[122]

3. The Pathogenesis of Diabesotension

Diabesotension develops through the interplay of insulin resistance, inflammation, neurohormonal dysregulation, and oxidative stress. These interconnected hallmarks form an integrated pathogenic network linking diabetes, obesity, and hypertension, as reflected by the shared and functionally interconnected genes identified (Figure 2). Several genes, such as *AKT1*, *PIK3R1* and *PTEN*, are repeatedly implicated across the hallmarks, highlighting the shared molecular basis to the pathogenesis of diabesotension. For example, dysregulation of Akt signaling impairs glucose uptake [27] and alters endothelial and inflammatory responses [136], thereby linking insulin resistance to elevated inflammation and vascular dysfunction. Similarly, pathogenic alterations in *PIK3R1* compromise PI3K-dependent insulin signaling, resulting in profound insulin resistance and metabolic dysfunction [137,138]. Overexpression of *PIK3R1* was reported to mimic glucocorticoid, a stress hormone that is known to induce insulin resistance, hyperglycemia, and dyslipidemia as long-term effects [138], linking insulin resistance to neurohormonal regulation. *PTEN*, the negative regulator of phosphatidylinositol 3-kinase (P13K), was suggested to be associated with metabolic disorder by affecting insulin sensitivity, inflammation, and neurohormonal regulation via the regulation of vagal function through vagus nerve activity. Mice with impaired efferent vagal output were found to exhibit peripheral insulin resistance, glucose intolerance, and a pro-inflammatory state in peripheral metabolic tissues and serum [139]. Collectively, these shared genes and the underlying mechanisms reveal the interconnected relationships among hallmarks, creating a permissive environment for the pathogenesis of diabesotension.

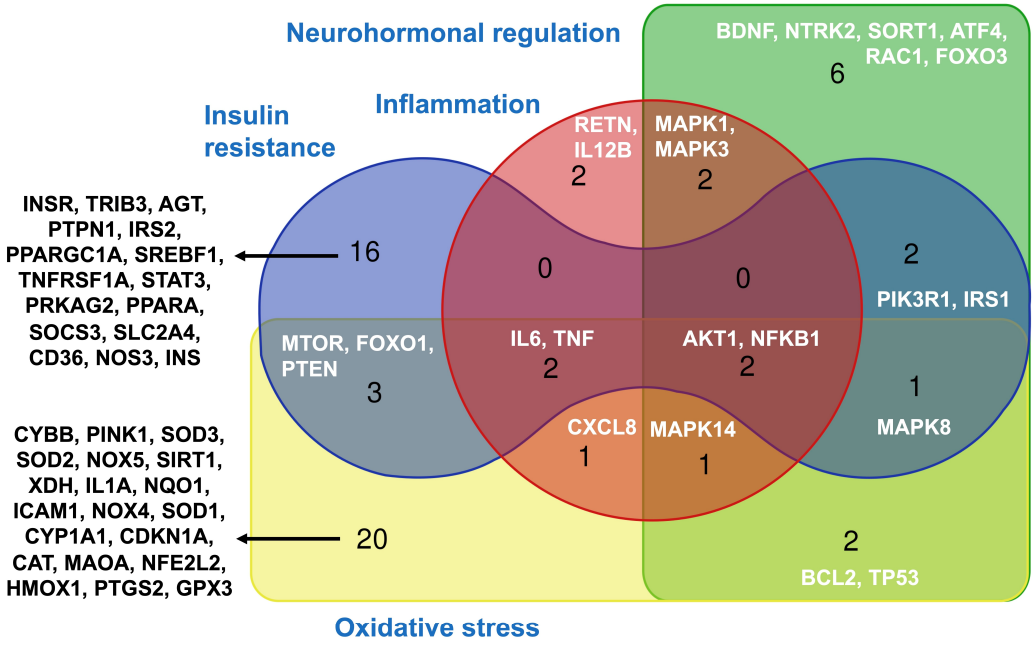


Figure 2. Convergence of genes across biological hallmarks associated with diabesotension. Venn diagram illustrating the distribution and recurrence of genes across the major biological hallmarks examined, including insulin resistance, inflammation, oxidative stress, and neurohormonal regulation. Numbers indicate the number of genes unique to or shared among the respective hallmarks, while gene symbols within overlapping regions identify recurrent genes contributing to multiple biological processes.

The hallmarks of diabesotension are suggested to be dynamically related throughout its pathogenesis (Figure 3). Insulin resistance, which represents the fundamental anomaly in metabolic disorders, particularly diabetes, acts as the initial trigger for the subsequent pathogenic events. Disruption of insulin sensitivity decreases glucose uptake in insulin-sensitive tissues, increases glycogenolysis, alters insulin secretion, and increases lipid accumulation via lipolysis in adipose tissue [140], which can lead to obesity. Moreover, insulin resistance can compromise mitochondrial function, further contributing to its severity. The decrement in mitochondrial oxidative capacity and impairment of lipid metabolism in obese and diabetic patients were reported to increase the availability of intramyocellular fatty acids, potentially being channeled towards lipotoxic lipid species biosynthesis such as ceramide and diacylglycerol, in which both are associated with insulin resistance [141]. Then, elevated adipose tissue in diabetes and obese individuals notably increased inflammatory cytokines such as *IL-6*, *IL-1β*, *MCP-1*, and *TNF-α*. These cytokines produced by adipose tissues are found to increase dyslipidemia and further contribute to insulin resistance [142]. Prolonged insulin resistance further alters vascular and renal sodium handling by altering neurohormonal regulation via RAAS activity. Overactive RAAS can increase angiotensin II and aldosterone release, which will eventually raise sodium reabsorption and blood pressure [143,144]. Furthermore, the PI3K pathway is impaired in an insulin-resistant state, which can cause vasoconstriction and elevate blood pressure, since insulin plays a profound role in vasodilation by activating the P13K pathway, which can promote endothelial nitric oxide production [145].

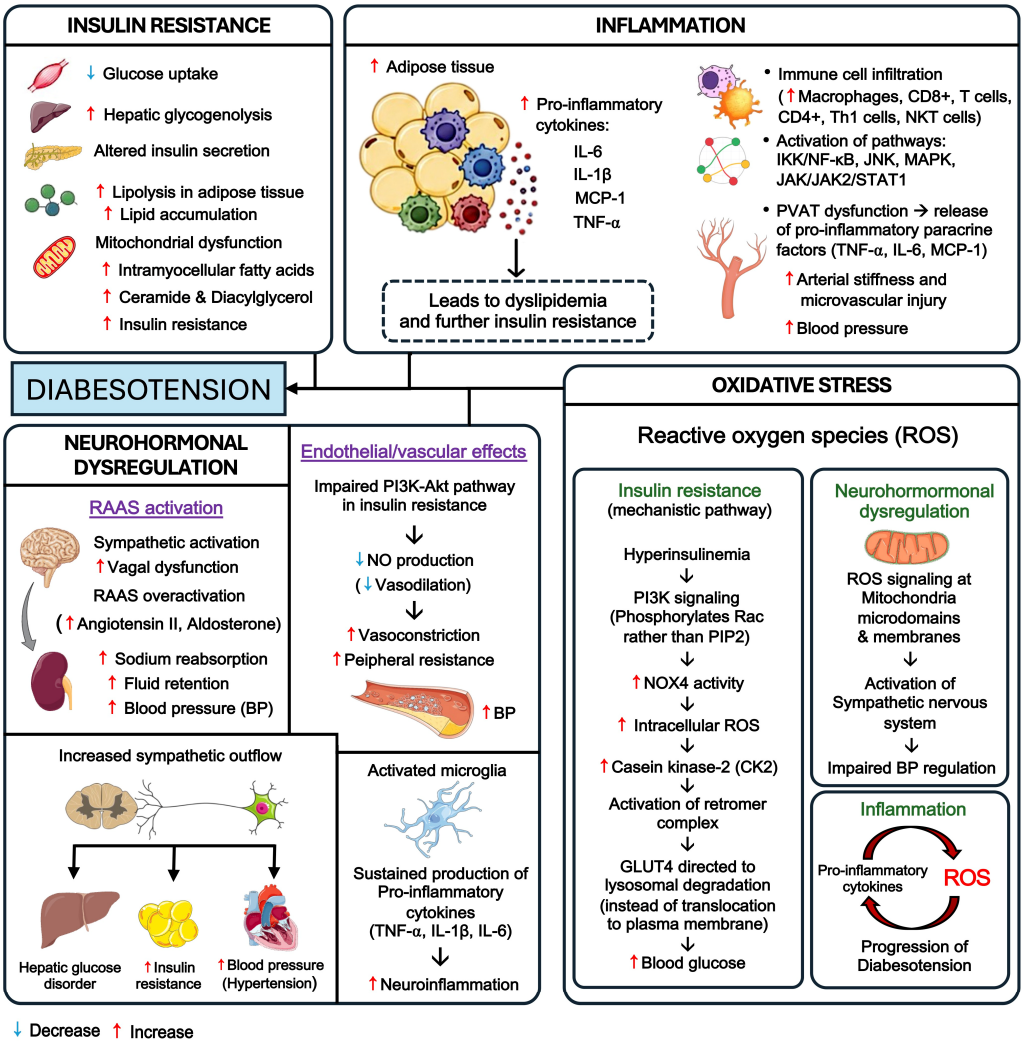


Figure 3. A schematic diagram illustrating the hallmarks of diabesotension, highlighting the interplay among insulin resistance, inflammation, RAAS/neurohormonal dysregulation, and oxidative stress. The figure was created using Microsoft PowerPoint, with icons obtained from Servier Medical Art (https://smart.servier.com) (accessed on 1 September 2026) and Bioicons (https://bioicons.com) (accessed on 1 September 2026).

Low-grade chronic inflammation observed in obese individuals serves as a significant catalyst that sustains and exacerbates insulin resistance while facilitating vascular dysfunction [142,146]. Studies have found that both innate and adaptive immune cells contribute to obesity-linked insulin resistance by promoting inflammation, particularly in adipose tissue. They found that increased adipose tissue macrophages, T cells (particularly $CD8^+$ effector/effector memory T cells, and $CD4^+$ Th1 cells), and natural killer T cells are associated with the development of insulin resistance [147–150]. Mechanistically, these immune cells cause insulin resistance through the release of type 1 cytokines, such as IL-1β, TNFα, and IFNγ [151], and activation of IKK/NF-kB, JNK, MAPK, and JAK/JAK2/STAT1 pathways [146]. Inflammation is also associated with hypertension via the dysfunction of perivascular adipose tissue (PVAT), particularly under conditions of obesity and insulin resistance. *PVAT* dysfunction eventually increased the release of pro-inflammatory paracrine factors, contributing to vascular dysregulation and elevated blood pressure [152,153]. Examples of paracrine factors secreted by *PVAT* include adipokines, cytokines, and chemokines, with TNF-α and interleukins (ILs) being known to induce endothelial dysfunction, arterial stiffness, and microvascular injury hypertension [153,154], all of which are key patholog-

ical features of hypertension. Notably, the secretion of adiponectin, an important anti-inflammatory adipokine, is reduced in the *PVAT* of obese and diabetic individuals [155], thereby creating a permissive environment that favors vascular inflammation and dysfunction. Inflammation also creates a self-sustaining inflammatory metabolic feedback loop by intensifying oxidative stress in diabesotension. Adipose tissue accumulation induces the synthesis of pro-inflammatory cytokines [142], which consequently increases the generation of reactive oxygen species (ROS) [156]. ROS production further induces the release of pro-inflammatory cytokines [157], causing damage to the cellular components driving the progression of diabesotension. Moreover, prolonged inflammation sustains sympathetic nervous system (SNS) activation, promoting renal sodium reabsorption, impairing pressure natriuresis, and elevating blood pressure [143,144,158]. Specifically, stimulation of TNF-α and IL-1β in the paraventricular nucleus of the hypothalamus was shown to increase the release of adrenocorticotropic hormone, responsible for enhancing cardiac sympathetic afferent reflexes and outflow, both of which are significant factors for the development of hypertension [159]. Collectively, inflammation plays a profound role in the progression of diabesotension as it dynamically interacts with insulin resistance, oxidative stress, and neurohormonal regulation.

Neurohormonal pathways serve as a critical bridge through which insulin resistance, inflammation, and oxidative stress translate into sustained diabesotension. For example, adipose tissue can induce endothelial dysfunction by secreting paracrine signals and hormones, known as adipokines [152]. Excessive secretion of vasoactive adipokines such as angiotensinogen, angiotensin II, and aldosterone, as well as increased plasma renin activity, is observed in obesity, which can alter endothelial integrity [160,161]. Notably, endothelial dysfunction is also contributed to by parasympathetic and sympathetic regulation. Parasympathetic tone of the autonomic nervous system was shown to be reduced in obese individuals, leading to increased heart rate and reduced baroreflex sensitivity [161]. Meanwhile, sympathetic outflow increases, causing hepatic glucose disorder, alteration in insulin resistance, and increased blood pressure or hypertension [159]. In addition, neuroinflammation of the hypothalamus can also cause diabesotension. This neurohormonal dysregulation happens as immune cells that reside in the CNS, particularly microglia, produce sustained pro-inflammatory cytokines in response to TNF stimulation by adipose tissue, increased saturated fatty acids, and glucocorticoids [162]. Increased hypothalamic neuroinflammation further exacerbates diabesotension by increasing oxidative stress, endoplasmic reticulum stress, neurodegeneration, insulin resistance, and leptin resistance [159,163]. Besides the hypothalamus, *in vivo* studies have reported that a high-fat diet can increase pro-inflammatory cytokines such as *IL-1β*, *IL-6*, and *TNF-α* in other brain regions, including the cerebellum [163], hippocampus [164], amygdala, and brainstem [165], suggesting widespread involvement of brain regions in the facilitation of neuroinflammation-induced metabolic diseases. Briefly, obesity-driven adipokine, autonomic nervous system dysregulation, and central neuroinflammation–oxidative stress represent the downstream effects of pathogenic neurohormonal dysregulation. These factors also interact with insulin resistance, inflammation, and oxidative stress during the development of diabesotension.

Oxidative stress occurs when the generation of free radicals exceeds the antioxidant defenses, leading to disruption of redox signaling and molecular damage [166]. Oxidative stress represents both a downstream consequence and an upstream driver of diabesotension hallmarks. For instance, inflammation is a downstream consequence of oxidative stress, as it is able to induce monocyte and macrophage activation and increases procytokine expression [167,168]. This was proven in the case of hyperglycemia in diabetes patients, where oxidative stress-induced inflammation occurred physiologically [169,170]. This condition is exacerbated in obese individuals, as excess adipose tissue secretes proinflam-

matory molecules, particularly adipokines [152]. Likewise, insulin resistance is also linked to oxidative stress. Studies have observed a direct role of ROS damage in the etiology of many chronic diseases, including insulin resistance in diabetes patients [171,172]. Hyperinsulinemia, one of the features of insulin resistance, causes the PI3-kinase signaling pathway to phosphorylate Rac rather than PIP2, leading to enhanced NOX4 activity [173]. Eventually, this leads to elevated intracellular ROS production. The increased ROS subsequently activates casein kinase-2 (CK2), which in turn stimulates the retromer complex [174]. Activation of the retromer promotes downstream signaling to the trans-Golgi network, causing GLUT4 to be targeted to lysosomal degradation rather than being translocated to the plasma membrane [175]. Consequently, glucose levels remain elevated under oxidative conditions. ROS have also been involved with neurohormonal dysregulation, especially in hypertension and heart failure [176,177]. It is reported that ROS signaling at mitochondria-associated neuronal microdomains and membranes contributes to the activation of the sympathetic nervous system, which has been previously explained as a cause of hypertension [177]. In addition, excessive ROS levels also impair synaptic plasticity, especially within autonomic regions such as the brainstem and hypothalamus. Such alteration effects neuronal signal transmission, leading to imbalance between the parasympathetic and sympathetic nervous systems [178], whose balance is crucial for normal blood pressure regulation of the human body.

4. The Interplay Between Gene–Environment and Gene–Gene Interactions in Diabesotension-Related Genes

Diabesotension is a complex multifactorial phenotype in which genetic susceptibility interacts with environmental and behavioral exposures to shape the shared pathophysiology of obesity, T2D and hypertension. One of the earliest studies on diabesotension-related genes, as summarized in Table 1, investigated the association between *SREBF1* variants and the insulin sensitivity response [48]. Gene–diet interactions have also been reported for *SREBF1*, a transcriptional regulator involved in lipid and glucose metabolism. In a 6-week fish oil supplementation study of 210 adults, three *SREBF1* variants (rs12953299, rs4925118, and rs4925115) were associated with differences in the insulin response to supplementation, while rs12953299 and rs4925115 were additionally associated with changes in insulin sensitivity. Notably, these variants were not associated with fasting insulin concentrations or insulin sensitivity at baseline, suggesting that their metabolic effects may become apparent in response to specific dietary exposures. These findings provide evidence that *SREBF1* genetic variation may modify the metabolic response to omega-3 fatty acid intake. However, given the relatively small sample size and short intervention period, replication in larger and more diverse populations is needed to establish the robustness and potential clinical relevance of these gene–diet interactions [48].

Potential gene–environment interplay in T2DM has also been suggested for genetic variation within the NF-κB inflammatory pathway. In a cohort of 487 elderly individuals, two *NFKB1* variants, rs7667496 and rs28362491, were associated with an increased risk of T2DM (OR = 1.68 and 1.67, respectively) [70]. Importantly, these associations remained significant after adjustment for age, sex, hypertension, BMI, and cholesterol, indicating that the genetic effects were independent of several established demographic and metabolic risk factors. Given the central role of NF-κB signaling in inflammatory responses to metabolic and environmental stimuli, these findings raise the possibility that *NFKB1* variation may influence individual susceptibility to T2DM in the presence of obesity, hypertension, dyslipidemia, or other pro-inflammatory exposures [70]. However, no formal gene–environment interaction was tested. Therefore, further studies are required to determine whether these factors modify the effects of *NFKB1* variants on T2DM risk.

Genetic variation in *NTRK2* has also been implicated in inter-individual differences in renal function, a phenotype closely influenced by metabolic and cardiovascular factors (Table 3). In 848 Mexican American participants, the *NTRK2* variants rs1036915 and rs1187274, which were in perfect linkage disequilibrium, were significantly associated with eGFR ($p = 0.017$). Carriers of the minor G allele of rs1036915 exhibited higher eGFR than carriers of the major A allele (104 versus 98 mL/min/1.73 m^2). Notably, this association persisted after accounting for age, sex, diabetes, diabetes duration, systolic blood pressure, and antihypertensive medication, suggesting an independent contribution of *NTRK* variation to renal function in the presence of important metabolic and cardiovascular exposures [92].

For gene–gene interactions, a case–control study investigated the potential gene–gene interactions among genetic variants in three renin–angiotensin system (RAS) genes, *ACE*, *AGT*, and *AGTR1*, in relation to T2D risk [39]. The study included 290 patients with T2DM and 267 control participants. Significant differences in allele frequencies between cases and controls were observed for *AGT* variants, whereas no significant associations were detected for *ACE* or *AGTR1*. The TCG haplotype of *AGT* was associated with an increased risk of T2DM (OR = 1.92, 95% CI: 1.15-3.20). However, interaction analyses found no evidence of significant gene–gene interactions among *ACE*, *AGT*, and *AGTR1*. Instead, the associations between *AGT* variants and T2DM appeared to be independent, suggesting that genetic variation within the RAS, particularly in *AGT*, may modestly contribute to T2DM susceptibility [39].

A study of 452 patients with T2DM investigated the individual and combined effects of genetic variants within the NF-κB1 inflammatory pathway on susceptibility to hypertension and dyslipidemia [84]. Polymorphisms in *TLR2*, *TLR4*, *TLR9*, *NF-κB1*, *IL6*, *IL6R*, *IL10*, and *ICAM1* were evaluated among patients with T2DM alone, T2DM with hypertension, and T2DM with both hypertension and dyslipidemia. The *TLR9* rs352140 CT genotype was associated with an approximately 2.8–2.94 fold increased risk of hypertension and hypertension with dyslipidemia, whereas the *NF-κB1* rs4648068 GG genotype was associated with a 64.8% reduction in dyslipidemia risk. Analysis of combined genetic effects showed that the *TLR9/IL6R/NF-κB* G-C-T risk haplotype was associated with a 3.26-fold increased risk of hypertension, while the *IL10/TLR4/NF-κB1* G-T-A protective haplotype was associated with an 82% reduction in dyslipidemia risk. These findings suggest that interactions among genetic variants within inflammatory signaling pathways may synergistically influence susceptibility to hypertension and dyslipidemia in patients with T2DM [84].

5. AI-Driven Prediction of Diabesotension Risk

Recent advances in ML and AI have enabled increasingly sophisticated risk prediction and stratification models for metabolic disorders via integration of multi-omics and clinical data. However, none of the studies identified in this review developed a unified predictive model specifically for the diabesotension triad of obesity, T2D, and hypertension. Instead, existing models have predominantly focused on individual diseases, particularly T2D and hypertension, or their associated complications, while obesity remains comparatively underrepresented in integrated predictive modeling. Table 5 summarizes 26 studies employing AI-based approaches in T2D and hypertension research. Previously, ensemble and gradient-boosting approaches, particularly XGBoost, have demonstrated strong performance in detecting high-risk subgroups of T2D using polygenic risk scores (PRS), metabolic risk score (MRS), imaging-derived features, and demographics as variables [179–181]. Meanwhile, a study by [182] applied a multi-omics sparse regression model to predict diabetes risk, achieving discrimination even among individuals without overt prediabetes by integrating genome-wide polygenic scores with proteomic and metabolomic profiles. Complementing genetic risk, epigenetic and methylation-based tree-ensemble models have shown added

predictive value when integrated with standard clinical variables, thereby improving long-term T2D prediction across independent cohorts [183].

Table 5. List of ML-driven prediction models for T2DM, hypertension, or obesity from 2016 to 2026.

Model	Features	Outcome	References
XGBoost ensemble (eXtreme Gradient Boosting)	Polygenic risk scores, multi-image risk scores, age, sex, family history	The AI model integrated genetic markers, medical imaging features, and demographic variables to enable early detection and risk stratification of T2D. PRS and MRS were key contributors in accurately identifying high-risk subgroups for T2D.	[179]
LASSO sparse regression (multi-omics)	Genome-wide variants, proteome, metabolome, clinical biomarkers	Integration of multiple omics layers improved T2D prediction beyond current clinical standards. PRS were the most informative, enhancing risk discrimination in individuals without prediabetes.	[182]
Deep metric learning (DML) on EHR	Longitudinal EHR variables, demographics, labs	DML predicted T2D onset and identified future T2D subtypes using routinely available HER data. The model enabled early risk stratification and interpretable patient subtyping, outperforming standard diagnostic tests and supporting automated, scalable screening.	[184]
DNA-methylation score (tree-ensemble)	Blood-based CpG methylation sites	Development and validation of DNA methylation based risk scores that, when added to conventional clinical variables, improved 10-year type 2 diabetes (T2D) prediction in two European cohorts.	[183]
Deep-learning digital biomarker (DP) from CGM	Continuous glucose monitor time series	A deep learning-derived digital biomarker (DP) for dysglycemia was developed and evaluated for type 2 diabetes detection. The DP model achieved high sensitivity/specificity, demonstrating accurate discrimination between diabetic and non-diabetic participants.	[185]
Random-forest with gPRS + metabolites	Genome-wide polygenic risk score, selected metabolites, demographics	The model integrated genome-wide polygenic risk scores, selected metabolomic features, and demographic variables. Significantly enhanced discriminative performance compared with clinical factors alone, demonstrating improved classification of individuals at high risk for future T2D.	[180]
Meta-prediction framework for CAD	Demographics, lifestyle, labs, medication, 15 meta-features including multiple PRSs	The framework combined demographic, lifestyle, laboratory, medication data, and multiple polygenic risk-derived meta-features to predict 10-year incident coronary artery disease, highlighting the added value of incorporating multiple PRSs into comprehensive cardiovascular risk stratification with robust external validation.	[186]

Table 5. *Cont.*

Model	Features	Outcome	References
Multimodal AI correlates of glucose spikes	EHR, CGM, lab, imaging, lifestyle data	The multimodal AI identified age, diet, physical activity, sleep, microbiome composition, stress, comorbidities, and genetics as major contributors to spike variability, demonstrating that a holistic multimodal approach can substantially improve understanding of individual glucose dynamics and the basis of post prandial spikes.	[187]
Two-stage PRS-integrated ML (screening)	PRS + clinical risk (stage 1); PRS + glycemic measures (stage 2)	A two-stage machine learning pipeline presented for personalized T2D screening; both stages maintains robust performance across subgroups and cost-effectiveness analysis projected savings compared to the ADA risk test.	[188]
Context-informed CNN	Genotype + genomic-context annotations	A genomic context-informed genotype approach with within-model ancestry adjustment, showing that incorporating functional priors can boost polygenic prediction accuracy by roughly 5 % over standard models.	[189]
Neural Network and Ensemble Model	Routine clinical variables (HighChol, BMI, Smoking, Physical Activity, sex, Age)	The machine learning models used common clinical parameters to predict hypertension in patients with diabetes. Age, BMI, and high cholesterol were identified as the most important predictors, indicating the potential for automated hypertension risk prediction to support diabetes management.	[190]
Random Forest and Boosting Model	Clinical and lab risk factors (age. SBP, HbA1c, lipids)	Machine learning models were applied to identify risk factors for diabetic nephropathy (DN) in patients with T2DM, with the random forest classifier showing the best performance. The model identified 18 important predictive factors, supporting ML-based risk assessment to improve DN screening and monitoring in TD2M patients.	[191]
Gradient-Boosting Risk Model (XGBoost + SHAP)	Clinical, lifestyle, and laboratory variables. Uses XGBoost and CatBoost with SMOTE class-balancing and SHAP explainability	The ML model combined XGBoost and CatBoost with explainable AI techniques to predict Type 2 diabetes risk. Key predictors included fasting blood sugar, fatty liver, urolithiasis, red blood cell indices, and lifestyle factors. SHAP analyses enhanced interpretability and enabled individualized risk assessment.	[181]
SVM Model	Fasting blood glucose, systolic and diastolic blood pressure, age, body mass index (BMI)	The SVM model integrated clinical and physiological parameters, including blood glucose measurements, blood pressure readings, anthropometric variables, and demographic factors, to enable early classification and risk identification of diabetes and hypertension status.	[192]

Table 5. *Cont.*

Model	Features	Outcome	References
Tree-Based ML for Hypertension Risk	Age, BP metrics, waist circumference, diabetes status, BMI, lifestyle factors.	Enabled large-scale hypertension risk prediction using non-laboratory and semi-laboratory features, with tree-based ML models, particularly XGBoost, that demonstrate superior performance in identifying hypertensive individuals.	[193]
Deep Learning (T-BEHRT transformer)	Full electronic health record time series, baseline SBP, medication, comorbidities	A deep learning model (T-BEHRT) applied to large scale HER data showed that patients with diabetes and systolic BP <120mm Hg has the lowest cardiovascular risk. The model outperformed conventional approaches by capturing known and latent confounders, supporting the "lower, the better" BP paradigm.	[194]
K-means and logistic regression algorithm for high-risk T2DM	Blood glucose level, blood pressure, heart rate, pregnancy, plasma glucose concentration, body mass index (BMI), age	K-means and classification algorithm model that predicts whether a person is diabetic or not. Higher model accuracy was achieved compared to other experiments using the same dataset but with different algorithms. Model consisted of cluster and class method to enhance prediction accuracy.	[195]
Supervised machine learning algorithms for T2DM risk predictions	Pregnancy, plasma glucose, diastolic blood pressure, triceps skin fold, serum insulin, BMI, diabetes pedigree, age	Machine learning algorithms such as SVM-linear, radial basis function (RBF), kernel support vector machine, k-nearest neighbor (k-NN), artificial neural network (ANN), multifactor dimensionality reduction (DMR) used to develop trends and detect patterns among diabetic patients.	[196]
Linear SVM and radial SVM to predict Hypertension risk	Gene expression data, rare variants, age, sex, pedigree structure, smoking status	Supervised machine learning methods, linear SVM and radial SVM were integrated with gene expression data and rare variants to predict risk of hypertension. Linear SVM was found to perform better than radial SVM and logistic regression.	[197]
AI detection of Diabetic retinopathy (more than mild diabetic retinopathy (mtmDR))	Nonmydriatic imaging, ophthalmoscopy, fundus photography	EyeArt Artificial Intelligence system had better mtmDR detection, sensitivity, and specificity compared to general ophthalmologists or retina specialists.	[198]
GlucoNet-MM: Personalized and explainable blood glucose forecasting	Physiological and behavioral data, continuous glucose monitoring (CGM), insulin dosage, carbohydrate intake, physical activity	Interpretable deep learning framework that combines multi-task learning (MTL) and decision transformer (DT) for patient-specific blood glucose forecasting. Temporal visualizations and integrated gradient-based attribution to provide interpretability.	[199]

Table 5. *Cont.*

Model	Features	Outcome	References
Machine learning-based prediction method for hypertension outcomes	Sex, age, height, weight, BMI, number of antihypertensive drugs at discharge	Classification algorithms such as support vector machine (SVM), C4.5 decision tree, random forest (RF), and extreme gradient boosting (XGBoost) were used to accurately predict outcomes of hypertension patients based on physical examination indicators of patients. Ten-fold cross validation shows that C4.5, RF, XGBoost achieves excellent prediction results with a small number of features.	[200]
Automatic classification of Hypertension using C4.5 decision tree algorithm, random forest, linear discriminant analysis, linear support vector machine.	Sex, age, BMI, weight, height, heart rate, systolic blood pressure, diastolic blood pressure	Machine learning-based method used to classify hypertension types using personal data. Eight features were used to train four classifier algorithms. Outcomes can be classified into four categories: healthy, prehypertension, stage-1 hypertension, stage-2 hypertension. Best methods to classify hypertension are C4.5 decision tree and random forest.	[201]
Predict risk of Hypertension using ANN, RF, XGBoost, SHAP	27 factors including personal information, physical activity, salt, fat, vegetable intake, diabetes, history of hypertension	Automated system to predict the risk of patients developing hypertension. Boruta-based feature selection showed 10 of the 27 features were the high contributing factors of developing hypertension. XGBoost performed better than the other models.	[202]
Wavelet Scattering Transform (WST), SVM, KNN and LR in predicting risk of Hypertension	Clinical and demographic data, systolic and diastolic blood pressure, photoplethysmography signal segments	WST was used to extract features from PPG signals to predict normotension and prehypertension together with clinical data using algorithms such as logistic regression, KNN, SVM. SVM model had better training and testing accuracy compared to the other models.	[203]
RF, CatBoost, MLP neural network, logistic regression to predict	Age, BMI, occupation, gender, history of diseases, physical activity, psychological pressure	Predicting the risk of hypertension using easy-to-collect factors. Four machine learning algorithms were trained. Random forest model had better performance with higher accuracy and sensitivity. Four primary risk factors of hypertension were identified: BMI, age, family history and waist circumference.	[204]

Deep learning approaches have also been applied to longitudinal electronic health records (EHRs) and continuous glucose monitoring (CGM) data in order to predict temporally resolved risk, patient subtyping, and digital biomarker development [184]. Ref. [194], on the other hand, applied a deep learning model called T-BEHRT on a large-scale HER dataset to facilitate scalable, automated screening and refined cardiovascular risk assessment in individuals with diabetes. A study by [185] also applied DL on the CGM datasets, where the model achieved high sensitivity and specificity for dysglycemia detection, demonstrating accurate discrimination between diabetic and non-diabetic participants. The author of [199] developed GlucoNet-MM, an interpretable DL model that integrates multi-task

learning (MTL) and decision transformer (DT) for patient-specific blood glucose monitoring. A multimodal AI model integrating EHRs, CGM, lifestyle, microbiome, imaging, and genetic data further revealed the multifactorial determinants of post-prandial glucose variability, supporting a holistic and personalized view of glycemic regulation in normal, pre-diabetic and T2D patients [187].

Beyond T2D, machine learning models have been widely applied to hypertension and diabetes-related complications, including nephropathy, retinopathy, and cardiovascular disease. Tree-based and ensemble methods, particularly random forest and XGBoost, consistently outperformed linear classifiers in predicting hypertension risk using a combination of demographic, anthropometric, lifestyle, and clinical features, while offering interpretable feature importance through SHAP-based explainability [193,202,204]. Support vector machines, neural networks, and hybrid clustering-classification methods have similarly demonstrated robust performance across diverse populations, leveraging both clinical variables and higher-dimensional molecular data [195–197]. Notably, AI-driven imaging systems called EyeArt have achieved specialist-level performance in detecting diabetic retinopathy, highlighting the clinical readiness of AI models for large-scale deployment. However, the clinical translation of AI models more broadly remains dependent on robust external validation across diverse populations and healthcare settings, appropriate regulatory evaluation, and successful integration into existing clinical workflows. Differences in patient demographics, imaging protocols, healthcare infrastructure, data availability, and model performance across populations may limit generalizability, while implementation challenges related to cost, interoperability, clinician acceptance, data privacy, and ongoing performance monitoring must also be addressed before widespread deployment.

Despite these advances, the current evidence highlights a substantial gap between disease-specific AI prediction and an integrated diabesotension model. A true diabesotension prediction framework would need to model obesity, T2D, and hypertension simultaneously rather than treating each condition as an isolated outcome. Such a framework would ideally integrate longitudinal anthropometric, glycemic, blood-pressure, biochemical, lifestyle, medication, and demographic data with genomic and other multi-omics information to capture the shared and interacting biological mechanisms underlying the three conditions. Multi-task learning or multimodal architectures may be particularly suitable, as they could accommodate correlated outcomes while identifying both shared and disease-specific predictors. Importantly, model development would require adequate representation of individuals across different disease trajectories, combinations of obesity, T2D, and hypertension, and diverse ancestral populations, followed by external validation in independent multi-ancestry cohorts. For models incorporating genetic information, ancestry-specific allele frequencies, effect sizes, and the cross-population transferability of PRS should also be explicitly evaluated. Evaluation should extend beyond discrimination to include calibration, interpretability, clinical utility, and the ability to predict progression from a single metabolic disorder to coexisting diabesotension. Developing such an integrated framework represents an important direction for future research and may enable earlier identification of individuals at risk of developing the interconnected metabolic triad.

6. Clinical Management Strategies

The clinical management of diabetes, hypertension, and obesity requires an integrated approach because these conditions frequently coexist and share metabolic and cardiovascular risk factors. Pharmacological treatment remains a central component of disease management, although the therapeutic strategies differ substantially across the three conditions. FDA-approved DrugBank data demonstrate considerable diversity in the pharmacological classes used for diabetes and hypertension, whereas a comparatively smaller range of

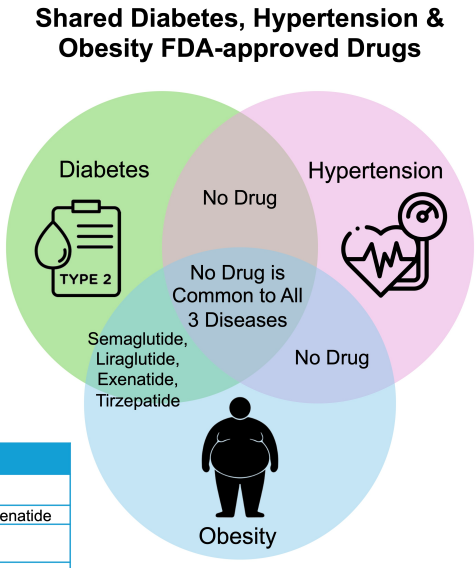
drugs is indicated for obesity (Figure 4) [205]. Notably, there was no overlap between antihypertensive drugs and those used for either diabetes or obesity, highlighting the largely distinct pharmacological mechanisms currently targeted in hypertension management.

Diabetes Drugs

Drug class	Drugs
Biguanides	Metformin
SGLT2 Inhibitors	Bexagliflozin, Dapagliflozin, Canagliflozin, Ertugliflozin, Empagliflozin
Dual SGLT1/SGLT2 Inhibitor	Sotagliflozin
Sulfonylureas	Glipizide, Glimepiride, Gliquidone, Glyburide, Gliclazide, Tolbutamide, Tolazamide
Meglitinides	Repaglinide, Nateglinide
Thiazolidinediones	Pioglitazone, Rosiglitazone
DPP-4 Inhibitors	Vildagliptin, Saxagliptin, Linagliptin, Sitagliptin, Alogliptin
GLP-1 Receptor Agonists	Semaglutide, Dulaglutide, Liraglutide, Exenatide, Lixisenatide
Dual GIP/GLP-1 Receptor Agonist	Tirzepatide
a-Glucosidase Inhibitors	Acarbose, Miglitol

Obesity Drugs

Drug class	Drugs
GLP-1 Receptor Agonists	Semaglutide, Liraglutide, Exenatide
Dual GIP/GLP-1 Receptor Agonist	Tirzepatide
GI Lipase Inhibitor	Orlistat
Melanocortin-4 Receptor Agonist	Setmelanotide
Sympathomimetic Anorectic Agents	Phentermine, Diethylpropion, Benzphetamine, Phendimetrazine, Phenmetrazine
Combination (Anti-Obesity)	Topiramate (used in combination with phentermine)



Hypertension Drugs

Drug class	Drugs
ACE Inhibitors	Captopril, Enalapril, Enalaprilat, Lisinopril, Benazepril, Perindopril, Ramipril, Fosinopril, Trandolapril, Cilazapril, Spirapril, Moexipril, Quinapril
Angiotensin II Receptor Blockers (ARBs)	Losartan, Valsartan, Telmisartan, Irbesartan, Olmesartan, Candesartan cilexetil, Eprosartan, Azilsartan medoxomil
Direct Renin Inhibitor	Aliskiren
B1-Selective Beta Blockers	Atenolol, Bisoprolol, Betaxolol, Acebutolol, Nebivolol
Non-Selective Beta Blockers	Propranolol, Nadolol, Pindolol, Timolol, Carteolol
Combined a/B Blockers	Carvedilol, Labetalol
Dihydropyridine CCBs	Amlodipine, Levamlodipine, Felodipine, Nisoldipine, Isradipine, Nilvadipine, Nicardipine, Nitrendipine
Non-Dihydropyridine CCBs	Diltiazem, Verapamil
Thiazide Diuretics	Hydrochlorothiazide, Bendroflumethiazide, Benzthiazide, Cyclothiazide, Quinethazone
Thiazide-like Diuretics	Chlorthalidone, Indapamide, Metolazone
Potassium-sparing Diuretic	Triamterene
Mineralocorticoid Receptor Antagonist	Spironolactone
Aldosterone Synthase Inhibitor	Baxdrostat
al-Adrenergic Blockers	Prazosin, Doxazosin, Terazosin
Central a2-Adrenergic Agonists	Clonidine, Methyldopa, Guanfacine
Direct Vasodilators	Hydralazine, Minoxidil
Dopamine D1 Receptor Agonist	Fenoldopam
Endothelin Receptor Antagonist	Aprocitentan
Adrenergic Neuron Blockers	Bethanidine, Guanadrel
Ganglionic Blockers	Mecamylamine, Pentolinium, Trimethaphan

Figure 4. Overview and overlap of drugs associated with diabetes, hypertension, and obesity from the DrugBank database (accessed on 30 August 2026). Drugs identified from the three drug datasets were classified according to their major pharmacological classes and therapeutic indications. The Venn diagram illustrates shared drugs among diabetes, hypertension, and obesity. Four drugs, semaglutide, liraglutide, exenatide, and tirzepatide, were shared between the diabetes and obesity datasets. No shared drugs were identified between diabetes and hypertension or between hypertension and obesity, and no drug was common to all three conditions. Drugs explicitly classified as withdrawn or discontinued in the respective datasets were excluded.

In contrast, an important therapeutic overlap was observed between diabetes and obesity. Four drugs, semaglutide, liraglutide, exenatide, and tirzepatide, were shared between the diabetes and obesity datasets. Semaglutide, liraglutide, and exenatide act through glucagon-like peptide-1 receptor (GLP-1R) signaling, while tirzepatide targets both glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors. According to a study by Mayer et al. (2024) [206], semaglutide effectively lowered BMI, body weight and HbA1c, and liraglutide has been reported to improve glycemic control and reduce body weight in adults with T2DM [207]. The convergence of these therapies across diabetes and obesity reflects the close biological relationship between glucose homeostasis, appetite regulation, energy balance, and adiposity. However, meta-analysis studies reported that liraglutide significantly reduced systolic blood pressure (SBP) compared with placebo in individuals with or without pathoglycemia, with greater reductions observed at higher doses, although the effect was attenuated beyond one year of treatment [208]. Similarly, semaglutide was associated with clinically meaningful blood pressure reductions in normotensive individuals without diabetes [209].

Both exenatide and tirzepatide have also demonstrated beneficial effects on body weight and metabolic control. One year of exenatide treatment resulted in significant

weight reduction and improved glycemic control, accompanied by decreased postprandial glucagon, active GLP-1, and total GIP levels [210]. Similarly, tirzepatide produced statistically significant and clinically meaningful weight reduction compared with placebo, with particularly pronounced effects among individuals with overweight or obesity without diabetes, while maintaining an acceptable safety profile [211]. However, Gill et al. (2010) reported that 12-week exenatide treatment had minimal effects on heart rate but showed trends toward improved blood pressure, weight loss, and systolic blood pressure [212]. Meanwhile, the SURMOUNT-1 ambulatory blood pressure monitoring substudy demonstrated that tirzepatide reduced 24-hour ambulatory blood pressure in adults with overweight and above [213]. These findings suggest that GLP-1 receptor agonists may contribute to blood pressure reduction, potentially through their effects on excess body weight. However, the efficacy of all four drugs specifically in individuals with both obesity and hypertension remains to be established.

7. Conclusions

In summary, diabesotension constitutes a genetically and biologically unified cardiometabolic continuum, underpinned by shared polygenic architectures, pleiotropic regulatory networks and gene–environment interactions that converge on insulin resistance, adipose dysfunction and vascular dysregulation. Moving forward, translational studies should prioritize functional validation of shared susceptibility genes implicated across T2D, obesity, and hypertension, particularly those involved in insulin signaling, adipogenesis, inflammation, lipid metabolism, and vascular homeostasis, using CRISPR-based perturbation, organoid models, and relevant in vivo systems. Concurrently, predictive models should progress beyond single-omic approaches toward integrative architectures, such as multimodal deep neural networks, graph neural networks, and transformer-based models, capable of jointly incorporating multi-omics, clinical, and lifestyle data to predict the diabesotension triad and its progression. These models should undergo external validation across ancestrally and geographically diverse populations, followed by prospective evaluation of their clinical utility. Ultimately, biomarker- or genotype-stratified prospective trials comparing pathway-guided interventions with conventional risk-factor-based management will be necessary to determine whether multi-omic risk stratification improves prevention, treatment selection, and long-term cardiometabolic outcomes. Such studies would provide a practical framework for translating genetic and multi-omic discoveries into the precise prevention and treatment of diabesotension.

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References

1. Petrie, J.R.; Guzik, T.J.; Touyz, R.M. Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms. *Can. J. Cardiol.* **2018**, *34*, 575–584. [CrossRef]
2. Abdullah-Zawawi, M.-R.; Abdul Jalal, M.I.; Afiqah-Aleng, N.; Kamal-Chinakarppen, S.-J.; Md Shahri, N.A.A.; Sulaiman, S.A.; Chin, S.F.; Mohamed-Hussein, Z.-A.; Jamal, R.; Abdul Murad, N.A. Bioinformatics-Led Identification of Pathophysiological Hallmark Genes in Diabesotension via Graph Clustering Method. *J. Diabetes Metab. Disord.* **2025**, *24*, 141. [CrossRef]
3. El Alami, H.; Bouqdayr, M.; Errafii, K.; Lkhider, M.; Al Idrissi, N.; Ghazal, H.; Wakrim, L.; Abidi, O.; Khlil, N.; Naamane, A.; et al. Risk Factors for Hypertension in Patients with Type 2 Diabetes Mellitus in the Casablanca-Settat Region, Morocco: A Cross-Sectional Study. *Pan Afr. Med. J.* **2025**, *51*, 38. [CrossRef]
4. Yuan, Y.; Isasi, C.R.; Al-Rousan, T.; Ghosh, A.K.; Mullachery, P.H.; Palta, P.; Makarem, N. Associations of Concurrent Hypertension and Type 2 Diabetes With Mortality Outcomes: A Prospective Study of U.S. Adults. *Diabetes Care* **2025**, *48*, 1241–1250. [CrossRef]
5. Sinha, S.; Haque, M. Insulin Resistance Is Cheerfully Hitched with Hypertension. *Life* **2022**, *12*, 564. [CrossRef]
6. Guo, H.; Wu, H.; Li, Z. The Pathogenesis of Diabetes. *Int. J. Mol. Sci.* **2023**, *24*, 6978. [CrossRef]
7. Hussain, A. Chronic Hyperglycemia and Cardiovascular Dysfunction: An in-Depth Exploration of Metabolic and Cellular Pathways in Type 2 Diabetes Mellitus. *Cardiovasc. Diabetol. Endocrinol. Rep.* **2025**, *11*, 39. [CrossRef]
8. Li, Y.; Liu, Y.; Liu, S.; Gao, M.; Wang, W.; Chen, K.; Huang, L.; Liu, Y. Diabetic Vascular Diseases: Molecular Mechanisms and Therapeutic Strategies. *Signal Transduct. Target. Ther.* **2023**, *8*, 152. [CrossRef]
9. Hsueh, W.A.; Wyne, K. Renin-Angiotensin-Aldosterone System in Diabetes and Hypertension. *J. Clin. Hypertens.* **2011**, *13*, 224–237. [CrossRef]
10. Roy, B. Pathophysiological Mechanisms of Diabetes-Induced Macrovascular and Microvascular Complications: The Role of Oxidative Stress. *Med. Sci.* **2025**, *13*, 87. [CrossRef]
11. Elhag, W.; El Ansari, W. Medical Weight Management: A Multidisciplinary Approach. In *Weight Management—Challenges and Opportunities*; IntechOpen: London, UK, 2022.
12. Thalia, O.P. Lifestyle Interventions for Managing Diabetes and Hypertension: A Holistic Approach. *IDOSR J. Biochem. Biotechnol. ALLIED FIELDS* **2024**, *9*, 13–17. [CrossRef]
13. Sobhy, M.; Eletriby, A.; Ragy, H.; Kandil, H.; Saleh, M.A.; Farag, N.; Guindy, R.; Bendary, A.; Nayel, A.M.E.; Shawky, A.; et al. ACE Inhibitors and Angiotensin Receptor Blockers for the Primary and Secondary Prevention of Cardiovascular Outcomes: Recommendations from the 2024 Egyptian Cardiology Expert Consensus in Collaboration with the CVREP Foundation. *Cardiol. Ther.* **2024**, *13*, 707–736. [CrossRef]
14. Avula, A.; Johal, L.K.; Ali, F.; Amir, S.; Yadav, S.; Murtuza, M.; Zia, U.; Janjua, F.F.; Raza, A.; Lal, K.; et al. ACE Inhibitors and ARBs in Chronic Kidney Disease: A Systematic Review of Randomized Controlled Trials on Albuminuria Reduction, EGFR Decline, and Safety. *Cureus* **2025**, *17*, e93707. [CrossRef]
15. Liakos, A.; Karagiannis, T.; Avgerinos, I.; Bekiari, E. SGLT-2 Inhibitors and GLP-1 Receptor Agonists as Combination Therapy in Type 2 Diabetes. *Curr. Diab. Rep.* **2026**, *26*, 1. [CrossRef]
16. Sayers, E.W.; Beck, J.; Bolton, E.E.; Bourexis, D.; Brister, J.R.; Canese, K.; Comeau, D.C.; Funk, K.; Kim, S.; Klimke, W.; et al. Database Resources of the National Center for Biotechnology Information. *Nucleic Acids Res.* **2021**, *49*, D10–D17. [CrossRef]
17. Mi, H.; Ebert, D.; Muruganujan, A.; Mills, C.; Albou, L.-P.; Mushayamaha, T.; Thomas, P.D. PANTHER Version 16: A Revised Family Classification, Tree-Based Classification Tool, Enhancer Regions and Extensive API. *Nucleic Acids Res.* **2021**, *49*, D394–D403. [CrossRef]
18. Raudvere, U.; Kolberg, L.; Kuzmin, I.; Arak, T.; Adler, P.; Peterson, H.; Vilo, J. G:Profiler: A Web Server for Functional Enrichment Analysis and Conversions of Gene Lists (2019 Update). *Nucleic Acids Res.* **2019**, *47*, W191–W198. [CrossRef]
19. Čolak, E.; Pap, D. The Role of Oxidative Stress in the Development of Obesity and Obesity-Related Metabolic Disorders. *J. Med. Biochem.* **2021**, *40*, 1–9. [CrossRef]
20. Roman, R.J. 20-HETE and Hypertension. *Hypertension* **2024**, *81*, 2012–2015. [CrossRef]

21. Wu, C.-C.; Gupta, T.; Garcia, V.; Ding, Y.; Schwartzman, M.L. 20-HETE and Blood Pressure Regulation. *Cardiol. Rev.* **2014**, *22*, 1–12. [CrossRef]
22. Froogh, G.; Garcia, V.; Schwartzman, M.L. The CYP/20-HETE/GPR75 Axis in Hypertension. *Adv. Pharmacol.* **2022**, *94*, 1–25. [CrossRef]
23. Sandeep, T.C.; Walker, B.R. Pathophysiology of Modulation of Local Glucocorticoid Levels by 11β-Hydroxysteroid Dehydrogenases. *Trends Endocrinol. Metab.* **2001**, *12*, 446–453. [CrossRef]
24. Gomez-Sanchez, E.P.; Gomez-Sanchez, C.E. 11β-Hydroxysteroid Dehydrogenases: A Growing Multi-Tasking Family. *Mol. Cell. Endocrinol.* **2021**, *526*, 111210. [CrossRef]
25. Rogero, M.; Calder, P. Obesity, Inflammation, Toll-Like Receptor 4 and Fatty Acids. *Nutrients* **2018**, *10*, 432. [CrossRef]
26. Jin, X.; Qiu, T.; Li, L.; Yu, R.; Chen, X.; Li, C.; Proud, C.G.; Jiang, T. Pathophysiology of Obesity and Its Associated Diseases. *Acta Pharm. Sin. B* **2023**, *13*, 2403–2424. [CrossRef]
27. Savova, M.S.; Mihaylova, L.V.; Tews, D.; Wabitsch, M.; Georgiev, M.I. Targeting PI3K/AKT Signaling Pathway in Obesity. *Biomed. Pharmacother.* **2023**, *159*, 114244. [CrossRef]
28. Huang, X.; Liu, G.; Guo, J.; Su, Z. The PI3K/AKT Pathway in Obesity and Type 2 Diabetes. *Int. J. Biol. Sci.* **2018**, *14*, 1483–1496. [CrossRef]
29. Kwon, H.; Pessin, J.E. Adipokines Mediate Inflammation and Insulin Resistance. *Front. Endocrinol.* **2013**, *4*, 71. [CrossRef]
30. Onyango, A.N. Mechanisms of the Regulation and Dysregulation of Glucagon Secretion. *Oxid. Med. Cell. Longev.* **2020**, *2020*, 3089139. [CrossRef]
31. Ruan, H.; Lodish, H.F. Insulin Resistance in Adipose Tissue: Direct and Indirect Effects of Tumor Necrosis Factor-α. *Cytokine Growth Factor Rev.* **2003**, *14*, 447–455. [CrossRef]
32. Dunmore, S.J.; Brown, J.E.P. The Role of Adipokines in β-Cell Failure of Type 2 Diabetes. *J. Endocrinol.* **2013**, *216*, T37–T45. [CrossRef]
33. Zhang, F.; Armando, I.; Jose, P.A.; Zeng, C.; Yang, J. G Protein-Coupled Receptor Kinases in Hypertension: Physiology, Pathogenesis, and Therapeutic Targets. *Hypertens. Res.* **2024**, *47*, 2317–2336. [CrossRef]
34. Yang, Y.; Wu, J.; Zhou, W.; Ji, G.; Dang, Y. Protein Posttranslational Modifications in Metabolic Diseases: Basic Concepts and Targeted Therapies. *MedComm* **2024**, *5*, e752. [CrossRef]
35. Kołodziej-Sobczak, D.; Sobczak, Ł.; Łączkowski, K.Z. Protein Tyrosine Phosphatase 1B (PTP1B): A Comprehensive Review of Its Role in Pathogenesis of Human Diseases. *Int. J. Mol. Sci.* **2024**, *25*, 7033. [CrossRef]
36. Venable, C.L.; Frevert, E.U.; Kim, Y.B.; Fischer, B.M.; Kamatkar, S.; Neel, B.G.; Kahn, B.B. Overexpression of Protein-Tyrosine Phosphatase-1B in Adipocytes Inhibits Insulin-Stimulated Phosphoinositide 3-Kinase Activity without Altering Glucose Transport or Akt/Protein Kinase B Activation. *J. Biol. Chem.* **2000**, *275*, 18318–18326. [CrossRef]
37. Sun, Z.; Miller, R.A.; Patel, R.T.; Chen, J.; Dhir, R.; Wang, H.; Zhang, D.; Graham, M.J.; Unterman, T.G.; Shulman, G.I.; et al. Hepatic Hdac3 Promotes Gluconeogenesis by Repressing Lipid Synthesis and Sequestration. *Nat. Med.* **2012**, *18*, 934–942. [CrossRef]
38. Li, Z.; Song, Y.; Li, Z.; Liu, S.; Yi, S.; Zhang, Z.; Yu, T.; Li, Y. Role of Protein Lysine Acetylation in the Pathogenesis and Treatment of Obesity and Metabolic Syndrome. *Curr. Obes. Rep.* **2025**, *14*, 24. [CrossRef]
39. Joyce-Tan, S.M.; Zain, S.M.; Abdul Sattar, M.Z.; Abdullah, N.A. Renin-Angiotensin System Gene Variants and Type 2 Diabetes Mellitus: Influence of Angiotensinogen. *J. Diabetes Res.* **2016**, *2016*, 1–7. [CrossRef]
40. Garcia, N.; Mellergaard, M.; Salomon, C.; Sepulveda, P.; Kristensen, P.; Handberg, A. CD36 and Its Role in Obesity. *Obes. Rev.* **2026**, *27*, e70039. [CrossRef]
41. Lee, S.; Dong, H.H. FoxO Integration of Insulin Signaling with Glucose and Lipid Metabolism. *J. Endocrinol.* **2017**, *233*, R67–R79. [CrossRef]
42. Tanti, J.-F.; Ceppo, F.; Jager, J.; Berthou, F. Implication of Inflammatory Signaling Pathways in Obesity-Induced Insulin Resistance. *Front. Endocrinol.* **2012**, *3*, 181. [CrossRef]
43. McArdle, M.A.; Finucane, O.M.; Connaughton, R.M.; McMorrow, A.M.; Roche, H.M. Mechanisms of Obesity-Induced Inflammation and Insulin Resistance: Insights into the Emerging Role of Nutritional Strategies. *Front. Endocrinol.* **2013**, *4*, 52. [CrossRef]
44. Guo, S. Insulin Signaling, Resistance, and Metabolic Syndrome: Insights from Mouse Models into Disease Mechanisms. *J. Endocrinol.* **2014**, *220*, T1–T23. [CrossRef]
45. Mir, M.M.; Jeelani, M.; Alharthi, M.H.; Rizvi, S.F.; Sohail, S.K.; Wani, J.I.; Sabah, Z.U.; BinAfif, W.F.; Nandi, P.; Alshahrani, A.M.; et al. Unraveling the Mystery of Insulin Resistance: From Principle Mechanistic Insights and Consequences to Therapeutic Interventions. *Int. J. Mol. Sci.* **2025**, *26*, 2770. [CrossRef]
46. Stanciu, S.M.; Jinga, M.; Miricescu, D.; Stefani, C.; Nica, R.I.; Stanescu-Spinu, I.-I.; Vacaroiu, I.A.; Greabu, M.; Nica, S. MTOR Dysregulation, Insulin Resistance, and Hypertension. *Biomedicines* **2024**, *12*, 1802. [CrossRef]

47. Supruniuk, E.; Mikłosz, A.; Chabowski, A. The Implication of PGC-1α on Fatty Acid Transport across Plasma and Mitochondrial Membranes in the Insulin Sensitive Tissues. *Front. Physiol.* **2017**, *8*, 923. [CrossRef]
48. Bouchard-Mercier, A.; Rudkowska, I.; Lemieux, S.; Couture, P.; Pérusse, L.; Vohl, M.-C. SREBF1 Gene Variations Modulate Insulin Sensitivity in Response to a Fish Oil Supplementation. *Lipids Health Dis.* **2014**, *13*, 152. [CrossRef]
49. Peng, Y.; Yang, X.; Luo, X.; Liu, C.; Cao, X.; Wang, H.; Guo, L. Novel Mechanisms Underlying Anti-Polycystic Ovary like Syndrome Effects of Electroacupuncture in Rats: Suppressing SREBP1 to Mitigate Insulin Resistance, Mitochondrial Dysfunction and Oxidative Stress. *Biol. Res.* **2020**, *53*, 50. [CrossRef]
50. Thauvin-Robinet, C.; Auclair, M.; Duplomb, L.; Caron-Debarle, M.; Avila, M.; St-Onge, J.; Le Merrer, M.; Le Luyer, B.; Héron, D.; Mathieu-Dramard, M.; et al. PIK3R1 Mutations Cause Syndromic Insulin Resistance with Lipoatrophy. *Am. J. Hum. Genet.* **2013**, *93*, 141–149. [CrossRef]
51. Zhang, L.; Chen, Z.; Wang, Y.; Tweardy, D.J.; Mitch, W.E. Stat3 Activation Induces Insulin Resistance via a Muscle-Specific E3 Ubiquitin Ligase Fbxo40. *Am. J. Physiol. Endocrinol. Metab.* **2020**, *318*, E625–E635, Erratum in *Am. J. Physiol. Endocrinol. Metab.* **2022**, *322*, E330. https://doi.org/10.1152/ajpendo.00480.2019_COR. [CrossRef]
52. Jorgensen, S.B.; O'Neill, H.M.; Sylow, L.; Honeyman, J.; Hewitt, K.A.; Palanivel, R.; Fullerton, M.D.; Öberg, L.; Balendran, A.; Galic, S.; et al. Deletion of Skeletal Muscle SOCS3 Prevents Insulin Resistance in Obesity. *Diabetes* **2013**, *62*, 56–64. [CrossRef]
53. Nguyen, T.D.; Schwarzer, M.; Schrepper, A.; Amorim, P.A.; Blum, D.; Hain, C.; Faerber, G.; Haendeler, J.; Altschmied, J.; Doenst, T. Increased Protein Tyrosine Phosphatase 1B (PTP1B) Activity and Cardiac Insulin Resistance Precede Mitochondrial and Contractile Dysfunction in Pressure-Overloaded Hearts. *J. Am. Heart Assoc.* **2018**, *7*, e008865. [CrossRef]
54. Jin, Y.; Cheng, X.; Wu, J.; Zhu, Y.; Xu, H.; Cao, C. Enhanced SLC2A4 Expression Mitigates Insulin Resistance in Gestational Diabetes Mellitus via the FoxO Signaling Pathway in Vitro. *Exp. Ther. Med.* **2025**, *30*, 1–9. [CrossRef]
55. Garme, Y.; Saravani, R.; Galavi, H.R. Association of Nitric Oxide Synthase 3 Gene Polymorphism with the Risk of Type 2 Diabetes. *Biomed. Rep.* **2017**, *7*, 85–89. [CrossRef]
56. Thorn, S.L.; Gollob, M.H.; Harper, M.-E.; Beanlands, R.S.; deKemp, R.A.; DaSilva, J.N. Chronic AMPK Activity Dysregulation Produces Myocardial Insulin Resistance in the Human Arg302Gln-PRKAG2 Glycogen Storage Disease Mouse Model. *EJNMMI Res.* **2013**, *3*, 48. [CrossRef]
57. Zhang, W.; Liu, J.; Tian, L.; Liu, Q.; Fu, Y.; Garvey, W.T. TRIB3 Mediates Glucose-Induced Insulin Resistance via a Mechanism That Requires the Hexosamine Biosynthetic Pathway. *Diabetes* **2013**, *62*, 4192–4200. [CrossRef]
58. Zhang, Z.; Liu, H.; Liu, J. Akt Activation: A Potential Strategy to Ameliorate Insulin Resistance. *Diabetes Res. Clin. Pract.* **2019**, *156*, 107092. [CrossRef]
59. Glatz, J.F.C.; Angin, Y.; Steinbusch, L.K.M.; Schwenk, R.W.; Luiken, J.J.F.P. CD36 as a Target to Prevent Cardiac Lipotoxicity and Insulin Resistance. *Prostaglandins Leukot. Essent. Fat. Acids* **2013**, *88*, 71–77. [CrossRef]
60. Goudriaan, J.R.; Dahlmans, V.E.H.; Teusink, B.; Ouwens, D.M.; Febbraio, M.; Maassen, J.A.; Romijn, J.A.; Havekes, L.M.; Voshol, P.J. CD36 Deficiency Increases Insulin Sensitivity in Muscle, but Induces Insulin Resistance in the Liver in Mice. *J. Lipid Res.* **2003**, *44*, 2270–2277. [CrossRef]
61. Park, S.; Cha, H.-N.; Shin, M.-G.; Park, S.; Kim, Y.; Kim, M.-S.; Shin, K.-H.; Thoudam, T.; Lee, E.J.; Wolfe, R.R.; et al. Inhibitory Regulation of FOXO1 in PPARδ Expression Drives Mitochondrial Dysfunction and Insulin Resistance. *Diabetes* **2024**, *73*, 1084–1098. [CrossRef]
62. Teaney, N.A.; Cyr, N.E. FoxO1 as a Tissue-Specific Therapeutic Target for Type 2 Diabetes. *Front. Endocrinol.* **2023**, *14*, 1286838. [CrossRef]
63. Rehman, K.; Akash, M.S.H.; Liaqat, A.; Kamal, S.; Qadir, M.I.; Rasul, A. Role of Interleukin-6 in Development of Insulin Resistance and Type 2 Diabetes Mellitus. *Crit. Rev. Eukaryot. Gene Expr.* **2017**, *27*, 229–236. [CrossRef]
64. Kushi, R.; Hirota, Y.; Ogawa, W. Insulin Resistance and Exaggerated Insulin Sensitivity Triggered by Single-Gene Mutations in the Insulin Signaling Pathway. *Diabetol. Int.* **2021**, *12*, 62–67. [CrossRef]
65. Rojek, A.; Wikiera, B.; Noczynska, A.; Niedziela, M. Syndrome of Congenital Insulin Resistance Caused by a Novel INSR Gene Mutation. *J. Clin. Res. Pediatr. Endocrinol.* **2023**, *15*, 312–317. [CrossRef]
66. Toyoshima, Y.; Nakamura, K.; Taguchi, Y.; Tokita, R.; Takeuchi, S.; Osawa, H.; Teramoto, N.; Sugihara, H.; Yoshizawa, F.; Yamanouchi, K.; et al. Deletion of IRS-1 Leads to Growth Failure and Insulin Resistance with Downregulation of Liver and Muscle Insulin Signaling in Rats. *Sci. Rep.* **2025**, *15*, 649. [CrossRef]
67. Hirose, M.; Inoue, K.; Matoba, S.; Tatebe, T.; Tokita, S.; Dodo, Y.; Tomishima, T.; Hasegawa, A.; Honda, A.; Ozaki, M.; et al. Disruption of Insulin Receptor Substrate 2 (IRS2) Causes Non-Obese Type 2 Diabetes with β-Cell Dysfunction in the Golden (Syrian) Hamster. *Sci. Rep.* **2024**, *14*, 17450. [CrossRef]
68. Turkyilmaz, A.; Akin, M.N.; Kasap, B.; Ozdemİr, C.; Demirtas Bilgic, A.; Edgunlu, T.G. AKT1 and MAPK8: New Targets for Gestational Diabetes Mellitus? *Fetal Pediatr. Pathol.* **2024**, *43*, 427–435. [CrossRef]
69. Yoon, M.-S. The Role of Mammalian Target of Rapamycin (MTOR) in Insulin Signaling. *Nutrients* **2017**, *9*, 1176. [CrossRef]

70. Coto, E.; Díaz-Corte, C.; Tranche, S.; Gómez, J.; Alonso, B.; Iglesias, S.; Reguero, J.R.; López-Larrea, C.; Coto-Segura, P. Gene Variants in the NF-KB Pathway (NFKB1, NFKBIA, NFKBIZ) and Their Association with Type 2 Diabetes and Impaired Renal Function. *Hum. Immunol.* **2018**, *79*, 494–498. [CrossRef]
71. Lin, Y.; Wang, Y.; Li, P. PPARα: An Emerging Target of Metabolic Syndrome, Neurodegenerative and Cardiovascular Diseases. *Front. Endocrinol.* **2022**, *13*, 1074911. [CrossRef]
72. Kleiner, S.; Mepani, R.J.; Laznik, D.; Ye, L.; Jurczak, M.J.; Jornayvaz, F.R.; Estall, J.L.; Chatterjee Bhowmick, D.; Shulman, G.I.; Spiegelman, B.M. Development of Insulin Resistance in Mice Lacking PGC-1α in Adipose Tissues. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 9635–9640. [CrossRef]
73. Santos, J.L.; Krause, B.J.; Cataldo, L.R.; Vega, J.; Salas-Pérez, F.; Mennickent, P.; Gallegos, R.; Milagro, F.I.; Prieto-Hontoria, P.; Riezu-Boj, J.I.; et al. PPARGC1A Gene Promoter Methylation as a Biomarker of Insulin Secretion and Sensitivity in Response to Glucose Challenges. *Nutrients* **2020**, *12*, 2790. [CrossRef]
74. Li, Y.Z.; Di Cristofano, A.; Woo, M. Metabolic Role of PTEN in Insulin Signaling and Resistance. *Cold Spring Harb. Perspect. Med.* **2020**, *10*, a036137. [CrossRef]
75. Mohallem, R.; Aryal, U.K. Regulators of TNFα Mediated Insulin Resistance Elucidated by Quantitative Proteomics. *Sci. Rep.* **2020**, *10*, 20878. [CrossRef]
76. Wang, Q.; Li, X.; Wushoulaji, K.; Wang, J.; Wan, L.; Yang, Y.; Gong, X. Exploring the Biological Functions and Immune Regulatory Roles of IRAK3, TNFRSF1A, CX3CR1, and JUNB in T2DM Combined with MAFLD: Integrated Bioinformatics and Single-Cell Analysis. *Front. Immunol.* **2025**, *16*, 1587225. [CrossRef]
77. Di Lorenzo, A.; Fernández-Hernando, C.; Cirino, G.; Sessa, W.C. Akt1 Is Critical for Acute Inflammation and Histamine-Mediated Vascular Leakage. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 14552–14557. [CrossRef]
78. Cambier, S.; Gouwy, M.; Proost, P. The Chemokines CXCL8 and CXCL12: Molecular and Functional Properties, Role in Disease and Efforts towards Pharmacological Intervention. *Cell. Mol. Immunol.* **2023**, *20*, 217–251. [CrossRef]
79. Wegner, M.; Winiarska, H.; Bobkiewicz-Kozłowska, T.; Dworacka, M. IL-12 Serum Levels in Patients with Type 2 Diabetes Treated with Sulphonylureas. *Cytokine* **2008**, *42*, 312–316. [CrossRef]
80. Jin, Z.; Zhang, Q.; Liu, K.; Wang, S.; Yan, Y.; Zhang, B.; Zhao, L. The Association between Interleukin Family and Diabetes Mellitus and Its Complications: An Overview of Systematic Reviews and Meta-Analyses. *Diabetes Res. Clin. Pract.* **2024**, *210*, 111615. [CrossRef]
81. Jubaidi, F.F.; Zainalabidin, S.; Taib, I.S.; Abdul Hamid, Z.; Mohamad Anuar, N.N.; Jalil, J.; Mohd Nor, N.A.; Budin, S.B. The Role of PKC-MAPK Signalling Pathways in the Development of Hyperglycemia-Induced Cardiovascular Complications. *Int. J. Mol. Sci.* **2022**, *23*, 8582. [CrossRef]
82. Lim, A.K.H.; Nikolic-Paterson, D.J.; Ma, F.Y.; Ozols, E.; Thomas, M.C.; Flavell, R.A.; Davis, R.J.; Tesch, G.H. Role of MKK3–P38 MAPK Signalling in the Development of Type 2 Diabetes and Renal Injury in Obese Db/Db Mice. *Diabetologia* **2009**, *52*, 347–358. [CrossRef]
83. Madkour, M.M.; Anbar, H.S.; El-Gamal, M.I. Current Status and Future Prospects of P38α/MAPK14 Kinase and Its Inhibitors. *Eur. J. Med. Chem.* **2021**, *213*, 113216. [CrossRef]
84. Zuo, C.; Cheng, J.; Yang, D.; Liu, Y.; Chen, H.; Lu, X.; Guo, M.; Yang, Z.; Wang, Z.; Wang, Y.; et al. Synergistic Effects of NF-KB1 and Inflammatory Pathway Polymorphisms on Hypertension and Dyslipidemia Susceptibility in Type 2 Diabetes. *Diabetol. Metab. Syndr.* **2025**, *17*, 269. [CrossRef]
85. Alzamil, H. Elevated Serum TNF-α Is Related to Obesity in Type 2 Diabetes Mellitus and Is Associated with Glycemic Control and Insulin Resistance. *J. Obes.* **2020**, *2020*, 1–5. [CrossRef]
86. Park, H.K.; Kwak, M.K.; Kim, H.J.; Ahima, R.S. Linking Resistin, Inflammation, and Cardiometabolic Diseases. *Korean J. Intern. Med.* **2017**, *32*, 239–247. [CrossRef]
87. Sharma, M.; Dey, C.S. Role of Akt Isoforms in Neuronal Insulin Signaling and Resistance. *Cell. Mol. Life Sci.* **2021**, *78*, 7873–7898. [CrossRef]
88. Corona, C.; Pasini, S.; Liu, J.; Amar, F.; Greene, L.A.; Shelanski, M.L. Activating Transcription Factor 4 (ATF4) Regulates Neuronal Activity by Controlling GABABR Trafficking. *J. Neurosci.* **2018**, *38*, 6102–6113. [CrossRef]
89. Perez-Serna, A.A.; Guzman-Llorens, D.; Dos Santos, R.S.; Marroqui, L. Bcl-2 and Bcl-XL in Diabetes: Contributions to Endocrine Pancreas Viability and Function. *Biomedicines* **2025**, *13*, 223. [CrossRef]
90. Santo, E.E.; Paik, J. FOXO in Neural Cells and Diseases of the Nervous System. *Curr. Top. Dev. Biol.* **2018**, *127*, 105–118. [CrossRef]
91. Rozanska, O.; Uruska, A.; Zozulinska-Ziolkiewicz, D. Brain-Derived Neurotrophic Factor and Diabetes. *Int. J. Mol. Sci.* **2020**, *21*, 841. [CrossRef]
92. Thameem, F.; Voruganti, V.S.; Blangero, J.; Comuzzie, A.G.; Abboud, H.E. Evaluation of Neurotrophic Tyrosine Receptor Kinase 2 (NTRK2) as a Positional Candidate Gene for Variation in Estimated Glomerular Filtration Rate (EGFR) in Mexican American Participants of San Antonio Family Heart Study. *J. Biomed. Sci.* **2015**, *22*, 23. [CrossRef]
93. Lavin, D.P.; White, M.F.; Brazil, D.P. IRS Proteins and Diabetic Complications. *Diabetologia* **2016**, *59*, 2280–2291. [CrossRef]

94. Sidarala, V.; Kowluru, A. The Regulatory Roles of Mitogen-Activated Protein Kinase (MAPK) Pathways in Health and Diabetes: Lessons Learned from the Pancreatic β-Cell. *Recent Pat. Endocr. Metab. Immune Drug Discov.* **2017**, *10*, 76–84. [CrossRef]
95. Alam, J.; Scheper, W. Targeting Neuronal MAPK14/P38α Activity to Modulate Autophagy in the Alzheimer Disease Brain. *Autophagy* **2016**, *12*, 2516–2520. [CrossRef]
96. Kalil, G.Z.; Haynes, W.G. Sympathetic Nervous System in Obesity-Related Hypertension: Mechanisms and Clinical Implications. *Hypertens. Res.* **2012**, *35*, 4–16. [CrossRef]
97. Wen, X.; Zhang, B.; Wu, B.; Xiao, H.; Li, Z.; Li, R.; Xu, X.; Li, T. Signaling Pathways in Obesity: Mechanisms and Therapeutic Interventions. *Signal Transduct. Target. Ther.* **2022**, *7*, 298, Correction in *Signal Transduct. Target. Ther.* **2022**, *7*, 369. https://doi.org/10.1038/s41392-022-01188-4. [CrossRef]
98. Cai, D.; Liu, T. Inflammatory Cause of Metabolic Syndrome via Brain Stress and NF-KB. *Aging* **2012**, *4*, 98–115. [CrossRef]
99. Huang-Doran, I.; Tomlinson, P.; Payne, F.; Gast, A.; Sleigh, A.; Bottomley, W.; Harris, J.; Daly, A.; Rocha, N.; Rudge, S.; et al. Insulin Resistance Uncoupled from Dyslipidemia Due to C-Terminal PIK3R1 Mutations. *JCI Insight* **2016**, *1*, e88766. [CrossRef]
100. Parvanova, A.; Reseghetti, E.; Abbate, M.; Ruggenenti, P. Mechanisms and Treatment of Obesity-Related Hypertension—Part 1: Mechanisms. *Clin. Kidney J.* **2024**, *17*, sfad282. [CrossRef]
101. Su, X.; Chen, X.; Wang, B.; Chen, L.; Dai, C. Emerging Roles of Sortilin in Affecting the Metabolism of Glucose and Lipid Profiles. *Bosn. J. Basic Med. Sci.* **2021**, *22*, 340. [CrossRef]
102. Guo, D.; Fang, L.; Yu, X.; Wang, C.; Wang, Y.; Guo, W. Different Roles of TP53 Codon 72 Polymorphism in Type 2 Diabetes and Its Complications: Evidence from a Case-Control Study on a Chinese Han Population. *Int. J. Gen. Med.* **2021**, *14*, 4259–4268. [CrossRef]
103. Caturano, A.; Rocco, M.; Tagliaferri, G.; Piacevole, A.; Nilo, D.; Di Lorenzo, G.; Iadicicco, I.; Donnarumma, M.; Galiero, R.; Acierno, C.; et al. Oxidative Stress and Cardiovascular Complications in Type 2 Diabetes: From Pathophysiology to Lifestyle Modifications. *Antioxidants* **2025**, *14*, 72. [CrossRef]
104. An, Y.; Xu, B.-T.; Wan, S.-R.; Ma, X.-M.; Long, Y.; Xu, Y.; Jiang, Z.-Z. The Role of Oxidative Stress in Diabetes Mellitus-Induced Vascular Endothelial Dysfunction. *Cardiovasc. Diabetol.* **2023**, *22*, 237. [CrossRef]
105. Abu Khadra, K.M.; Bataineh, M.I.; Khalil, A.; Saleh, J. Oxidative Stress and Type 2 Diabetes: The Development and the Pathogenesis, Jordanian Cross-Sectional Study. *Eur. J. Med. Res.* **2024**, *29*, 370. [CrossRef]
106. Langhardt, J.; Flehmig, G.; Klöting, N.; Lehmann, S.; Ebert, T.; Kern, M.; Schön, M.R.; Gärtner, D.; Lohmann, T.; Dressler, M.; et al. Effects of Weight Loss on Glutathione Peroxidase 3 Serum Concentrations and Adipose Tissue Expression in Human Obesity. *Obes. Facts* **2018**, *11*, 475–490. [CrossRef]
107. Dzięgielewska-Gęsiak, S.; Wysocka, E.; Fatyga, E.; Muc-Wierzgoń, M. Relationship of SOD-1 Activity in Metabolic Syndrome and/or Frailty in Elderly Individuals. *Metabolites* **2024**, *14*, 514. [CrossRef]
108. Lee, W.-S.; Ham, W.; Kim, J. Roles of NAD(P)H:Quinone Oxidoreductase 1 in Diverse Diseases. *Life* **2021**, *11*, 1301. [CrossRef]
109. Liu, Y.; Qi, W.; Richardson, A.; Van Remmen, H.; Ikeno, Y.; Salmon, A.B. Oxidative Damage Associated with Obesity Is Prevented by Overexpression of CuZn- or Mn-Superoxide Dismutase. *Biochem. Biophys. Res. Commun.* **2013**, *438*, 78–83. [CrossRef]
110. Cui, R.; Gao, M.; Qu, S.; Liu, D. Overexpression of Superoxide Dismutase 3 Gene Blocks High-Fat Diet-Induced Obesity, Fatty Liver and Insulin Resistance. *Gene Ther.* **2014**, *21*, 840–848. [CrossRef]
111. Abraham, N.G.; Junge, J.M.; Drummond, G.S. Translational Significance of Heme Oxygenase in Obesity and Metabolic Syndrome. *Trends Pharmacol. Sci.* **2016**, *37*, 17–36. [CrossRef]
112. Merce, A.P.; Ionică, L.N.; Bînă, A.M.; Popescu, S.; Lighezan, R.; Petrescu, L.; Borza, C.; Sturza, A.; Muntean, D.M.; Creţu, O.M. Monoamine Oxidase Is a Source of Cardiac Oxidative Stress in Obese Rats: The Beneficial Role of Metformin. *Mol. Cell. Biochem.* **2023**, *478*, 59–67. [CrossRef]
113. Turgeon, J.; Haddad, P.; Dussault, S.; Groleau, J.; Maingrette, F.; Perez, G.; Rivard, A. Protection against Vascular Aging in Nox2-Deficient Mice: Impact on Endothelial Progenitor Cells and Reparative Neovascularization. *Atherosclerosis* **2012**, *223*, 122–129. [CrossRef]
114. Pavlov, T.S.; Palygin, O.; Isaeva, E.; Levchenko, V.; Khedr, S.; Blass, G.; Ilatovskaya, D.V.; Cowley, A.W.; Staruschenko, A. NOX4-dependent Regulation of ENaC in Hypertension and Diabetic Kidney Disease. *FASEB J.* **2020**, *34*, 13396–13408. [CrossRef]
115. Mallik, S.; Paria, B.; Firdous, S.M.; Ghazzawy, H.S.; Alqahtani, N.K.; He, Y.; Li, X.; Gouda, M.M. The Positive Implication of Natural Antioxidants on Oxidative Stress-Mediated Diabetes Mellitus Complications. *J. Genet. Eng. Biotechnol.* **2024**, *22*, 100424. [CrossRef]
116. Gutiérrez-Cuevas, J.; Galicia-Moreno, M.; Monroy-Ramírez, H.C.; Sandoval-Rodriguez, A.; García-Bañuelos, J.; Santos, A.; Armendariz-Borunda, J. The Role of NRF2 in Obesity-Associated Cardiovascular Risk Factors. *Antioxidants* **2022**, *11*, 235. [CrossRef]
117. Qiu, M.; Huang, Y.; Zhou, X.; Yu, J.; Li, J.; Wang, W.; Zippi, M.; Fiorino, S.; Hong, W. Hyperlipidemia Exacerbates Acute Pancreatitis via Interactions between P38MAPK and Oxidative Stress. *Cell. Signal.* **2025**, *125*, 111504. [CrossRef]

118. Feng, J.; Lu, S.; Ou, B.; Liu, Q.; Dai, J.; Ji, C.; Zhou, H.; Huang, H.; Ma, Y. The Role of JNk Signaling Pathway in Obesity-Driven Insulin Resistance. *Diabetes Metab. Syndr. Obes.* **2020**, *13*, 1399–1406. [CrossRef]
119. Zhao, D.; Yang, J.; Yang, L. Insights for Oxidative Stress and MTOR Signaling in Myocardial Ischemia/Reperfusion Injury under Diabetes. *Oxid. Med. Cell. Longev.* **2017**, *2017*, 6437467. [CrossRef]
120. Almeida, E.A.; Mehndiratta, M.; Madhu, S.V.; Kar, R.; Puri, D. PINK1 and Oxidative Stress in Lean and Obese Patients with Type 2 Diabetes Mellitus. *J. Diabetes Complicat.* **2023**, *37*, 108542. [CrossRef]
121. Fernandez-Twinn, D.S.; Blackmore, H.L.; Siggens, L.; Giussani, D.A.; Cross, C.M.; Foo, R.; Ozanne, S.E. The Programming of Cardiac Hypertrophy in the Offspring by Maternal Obesity Is Associated with Hyperinsulinemia, AKT, ERK, and MTOR Activation. *Endocrinology* **2012**, *153*, 5961–5971. [CrossRef]
122. Al-Baqeri, A.; AL-Habori, M.; Al-Eryani, E.; Saif-Ali, R. The Interplay of Tumor Suppressor P53 and Oxidative Stress in Pancreatic β-Cell Apoptosis and Insulin Resistance in Newly Diagnosed Type 2 Diabetes Mellitus. *Diabetol. Metab. Syndr.* **2025**, *17*, 402. [CrossRef]
123. Wondmkun, Y.T. Obesity, Insulin Resistance, and Type 2 Diabetes: Associations and Therapeutic Implications. *Diabetes Metab. Syndr. Obes.* **2020**, *13*, 3611–3616. [CrossRef]
124. Masenga, S.K.; Kabwe, L.S.; Chakulya, M.; Kirabo, A. Mechanisms of Oxidative Stress in Metabolic Syndrome. *Int. J. Mol. Sci.* **2023**, *24*, 7898. [CrossRef]
125. Oguntibeju, O.O. Type 2 Diabetes Mellitus, Oxidative Stress and Inflammation: Examining the Links. *Int. J. Physiol. Pathophysiol. Pharmacol.* **2019**, *11*, 45–63.
126. Manna, P.; Jain, S.K. Obesity, Oxidative Stress, Adipose Tissue Dysfunction, and the Associated Health Risks: Causes and Therapeutic Strategies. *Metab. Syndr. Relat. Disord.* **2015**, *13*, 423–444. [CrossRef]
127. Saucedo, R.; Ortega-Camarillo, C.; Ferreira-Hermosillo, A.; Díaz-Velázquez, M.F.; Meixueiro-Calderón, C.; Valencia-Ortega, J. Role of Oxidative Stress and Inflammation in Gestational Diabetes Mellitus. *Antioxidants* **2023**, *12*, 1812. [CrossRef]
128. Ponugoti, B.; Dong, G.; Graves, D.T. Role of Forkhead Transcription Factors in Diabetes-Induced Oxidative Stress. *Exp. Diabetes Res.* **2012**, *2012*, 1–7. [CrossRef]
129. Olivares-Vicente, M.; Herranz-López, M. The Interplay Between Oxidative Stress and Lipid Composition in Obesity-Induced Inflammation: Antioxidants as Therapeutic Agents in Metabolic Diseases. *Int. J. Mol. Sci.* **2025**, *26*, 8544. [CrossRef]
130. Meng, T.; Qin, W.; Liu, B. SIRT1 Antagonizes Oxidative Stress in Diabetic Vascular Complication. *Front. Endocrinol.* **2020**, *11*, 568861. [CrossRef]
131. Świątkiewicz, I.; Wróblewski, M.; Nuszkiewicz, J.; Sutkowy, P.; Wróblewska, J.; Woźniak, A. The Role of Oxidative Stress Enhanced by Adiposity in Cardiometabolic Diseases. *Int. J. Mol. Sci.* **2023**, *24*, 6382. [CrossRef]
132. Hu, K.; Guo, Y.; Li, Y.; Zhou, S.; Lu, C.; Cai, C.; Yang, H.; Li, Y.; Wang, W. Identification and Validation of PTGS2 Gene as an Oxidative Stress-Related Biomarker for Arteriovenous Fistula Failure. *Antioxidants* **2023**, *13*, 5. [CrossRef]
133. Widjaja, N.A.; Caesar, L.A.; Nova, S.; Ardianah, E. Beyond the Scale: Investigating Adiponectin, ICAM-1, and VCAM-1 as Metabolic Markers in Obese Adolescents with Metabolic Syndrome. *J. Obes.* **2023**, *2023*, 1–11. [CrossRef]
134. Bae, C.-S.; Lee, Y.; Ahn, T. Therapeutic Treatments for Diabetes Mellitus-Induced Liver Injury by Regulating Oxidative Stress and Inflammation. *Appl. Microsc.* **2023**, *53*, 4. [CrossRef]
135. Guo, Y.; Liu, Z.; Wang, M. NFKB1-Mediated Downregulation of MicroRNA-106a Promotes Oxidative Stress Injury and Insulin Resistance in Mice with Gestational Hypertension. *Cytotechnology* **2021**, *73*, 115–126. [CrossRef]
136. García-Prieto, C.F.; Hernández-Nuño, F.; Del Rio, D.; Ruiz-Hurtado, G.; Aránguez, I.; Ruiz-Gayo, M.; Somoza, B.; Fernández-Alfonso, M.S. High-Fat Diet Induces Endothelial Dysfunction through a down-Regulation of the Endothelial AMPK-PI3K-Akt-ENOS Pathway. *Mol. Nutr. Food Res.* **2015**, *59*, 520–532. [CrossRef]
137. Winnay, J.N.; Solheim, M.H.; Dirice, E.; Sakaguchi, M.; Noh, H.-L.; Kang, H.J.; Takahashi, H.; Chudasama, K.K.; Kim, J.K.; Molven, A.; et al. PI3-Kinase Mutation Linked to Insulin and Growth Factor Resistance in Vivo. *J. Clin. Invest.* **2016**, *126*, 1401–1412. [CrossRef]
138. Tsay, A.; Wang, J.-C. The Role of PIK3R1 in Metabolic Function and Insulin Sensitivity. *Int. J. Mol. Sci.* **2023**, *24*, 12665. [CrossRef]
139. Li, Y.Z.; Son, J.E.; Vo, N.; Bellisimo, C.; Lee, J.H.; Rapps, J.; Pollock-Tahiri, E.; Ghebreselassie, M.; Chen, C.T.; Bazinet, R.P.; et al. PTEN Regulates Vagal-Insulin Signaling to Optimize Autonomic Output Determining Peripheral Inflammatory and Metabolic Homeostasis. *Nat. Commun.* **2025**, *17*, 774. [CrossRef]
140. Gonzalez-Franquesa, A.; Patti, M.-E. Insulin Resistance and Mitochondrial Dysfunction. *Mitochondrial Dyn. Cardiovasc. Med.* **2017**, *982*, 465–520. [CrossRef]
141. Sergi, D.; Naumovski, N.; Heilbronn, L.K.; Abeywardena, M.; O'Callaghan, N.; Lionetti, L.; Luscombe-Marsh, N. Mitochondrial (Dys)Function and Insulin Resistance: From Pathophysiological Molecular Mechanisms to the Impact of Diet. *Front. Physiol.* **2019**, *10*, 532. [CrossRef]
142. Uti, D.E.; Atangwho, I.J.; Omang, W.A.; Alum, E.U.; Obeten, U.N.; Udeozor, P.A.; Agada, S.A.; Bawa, I.; Ogbu, C.O. Cytokines as Key Players in Obesity Low Grade Inflammation and Related Complications. *Obes. Med.* **2025**, *54*, 100585. [CrossRef]

143. Artunc, F.; Schleicher, E.; Weigert, C.; Fritsche, A.; Stefan, N.; Häring, H.-U. The Impact of Insulin Resistance on the Kidney and Vasculature. *Nat. Rev. Nephrol.* **2016**, *12*, 721–737. [CrossRef]
144. Brosolo, G.; Da Porto, A.; Bulfone, L.; Vacca, A.; Bertin, N.; Scandolin, L.; Catena, C.; Sechi, L.A. Insulin Resistance and High Blood Pressure: Mechanistic Insight on the Role of the Kidney. *Biomedicines* **2022**, *10*, 2374. [CrossRef]
145. Das, U.N. Renin-Angiotensin-Aldosterone System in Insulin Resistance and Metabolic Syndrome. *J. Transl. Int. Med.* **2016**, *4*, 66–72. [CrossRef]
146. Wu, H.; Ballantyne, C.M. Metabolic Inflammation and Insulin Resistance in Obesity. *Circ. Res.* **2020**, *126*, 1549–1564. [CrossRef]
147. Shin, K.C.; Hwang, I.; Choe, S.S.; Park, J.; Ji, Y.; Kim, J.I.; Lee, G.Y.; Choi, S.H.; Ching, J.; Kovalik, J.-P.; et al. Macrophage VLDLR Mediates Obesity-Induced Insulin Resistance with Adipose Tissue Inflammation. *Nat. Commun.* **2017**, *8*, 1087. [CrossRef]
148. McLaughlin, T.; Liu, L.-F.; Lamendola, C.; Shen, L.; Morton, J.; Rivas, H.; Winer, D.; Tolentino, L.; Choi, O.; Zhang, H.; et al. T-Cell Profile in Adipose Tissue Is Associated with Insulin Resistance and Systemic Inflammation in Humans. *Arterioscler. Thromb. Vasc. Biol.* **2014**, *34*, 2637–2643. [CrossRef]
149. Khan, I.M.; Perrard, X.Y.; Brunner, G.; Lui, H.; Sparks, L.M.; Smith, S.R.; Wang, X.; Shi, Z.-Z.; Lewis, D.E.; Wu, H.; et al. Intermuscular and Perimuscular Fat Expansion in Obesity Correlates with Skeletal Muscle T Cell and Macrophage Infiltration and Insulin Resistance. *Int. J. Obes.* **2015**, *39*, 1607–1618. [CrossRef]
150. Wensveen, F.M.; Jelenčić, V.; Valentić, S.; Šestan, M.; Wensveen, T.T.; Theurich, S.; Glasner, A.; Mendrila, D.; Štimac, D.; Wunderlich, F.T.; et al. NK Cells Link Obesity-Induced Adipose Stress to Inflammation and Insulin Resistance. *Nat. Immunol.* **2015**, *16*, 376–385. [CrossRef]
151. Wu, H.; Ballantyne, C.M. Skeletal Muscle Inflammation and Insulin Resistance in Obesity. *J. Clin. Investig.* **2017**, *127*, 43–54. [CrossRef]
152. Padilla, J.; Vieira-Potter, V.J.; Jia, G.; Sowers, J.R. Role of Perivascular Adipose Tissue on Vascular Reactive Oxygen Species in Type 2 Diabetes: A Give-and-Take Relationship. *Diabetes* **2015**, *64*, 1904–1906. [CrossRef]
153. Koenen, M.; Hill, M.A.; Cohen, P.; Sowers, J.R. Obesity, Adipose Tissue and Vascular Dysfunction. *Circ. Res.* **2021**, *128*, 951–968. [CrossRef]
154. Nosalski, R.; Guzik, T.J. Perivascular Adipose Tissue Inflammation in Vascular Disease. *Br. J. Pharmacol.* **2017**, *174*, 3496–3513. [CrossRef]
155. Aghamohammadzadeh, R.; Unwin, R.D.; Greenstein, A.S.; Heagerty, A.M. Effects of Obesity on Perivascular Adipose Tissue Vasorelaxant Function: Nitric Oxide, Inflammation and Elevated Systemic Blood Pressure. *J. Vasc. Res.* **2015**, *52*, 299–305. [CrossRef]
156. Daiber, A.; Steven, S.; Vujacic-Mirski, K.; Kalinovic, S.; Oelze, M.; Di Lisa, F.; Münzel, T. Regulation of Vascular Function and Inflammation via Cross Talk of Reactive Oxygen and Nitrogen Species from Mitochondria or NADPH Oxidase-Implications for Diabetes Progression. *Int. J. Mol. Sci.* **2020**, *21*, 3405. [CrossRef]
157. Marseglia, L.; Manti, S.; D'Angelo, G.; Nicotera, A.; Parisi, E.; Di Rosa, G.; Gitto, E.; Arrigo, T. Oxidative Stress in Obesity: A Critical Component in Human Diseases. *Int. J. Mol. Sci.* **2014**, *16*, 378–400. [CrossRef]
158. Hall, J.E.; Mouton, A.J.; da Silva, A.A.; Omoto, A.C.M.; Wang, Z.; Li, X.; do Carmo, J.M. Obesity, Kidney Dysfunction, and Inflammation: Interactions in Hypertension. *Cardiovasc. Res.* **2021**, *117*, 1859–1876. [CrossRef]
159. Han, C.; Rice, M.W.; Cai, D. Neuroinflammatory and Autonomic Mechanisms in Diabetes and Hypertension. *Am. J. Physiol. Endocrinol. Metab.* **2016**, *311*, E32-41. [CrossRef]
160. Ferreira, N.S.; Tostes, R.C.; Paradis, P.; Schiffrin, E.L. Aldosterone, Inflammation, Immune System, and Hypertension. *Am. J. Hypertens.* **2021**, *34*, 15–27. [CrossRef]
161. Fatima, N.; Patel, S.N.; Hussain, T. Angiotensin II Type 2 Receptor: A Target for Protection Against Hypertension, Metabolic Dysfunction, and Organ Remodeling. *Hypertension* **2021**, *77*, 1845–1856. [CrossRef]
162. Lohmeier, T.E.; Iliescu, R. The Sympathetic Nervous System in Obesity Hypertension. *Curr. Hypertens. Rep.* **2013**, *15*, 409–416. [CrossRef]
163. Alexaki, V.I. The Impact of Obesity on Microglial Function: Immune, Metabolic and Endocrine Perspectives. *Cells* **2021**, *10*, 1584. [CrossRef]
164. Kang, E.-B.; Koo, J.-H.; Jang, Y.-C.; Yang, C.-H.; Lee, Y.; Cosio-Lima, L.M.; Cho, J.-Y. Neuroprotective Effects of Endurance Exercise Against High-Fat Diet-Induced Hippocampal Neuroinflammation. *J. Neuroendocrinol.* **2016**, *28*. [CrossRef]
165. Almeida-Suhett, C.P.; Graham, A.; Chen, Y.; Deuster, P. Behavioral Changes in Male Mice Fed a High-Fat Diet Are Associated with IL-1β Expression in Specific Brain Regions. *Physiol. Behav.* **2017**, *169*, 130–140. [CrossRef]
166. Griendling, K.K.; Camargo, L.L.; Rios, F.J.; Alves-Lopes, R.; Montezano, A.C.; Touyz, R.M. Oxidative Stress and Hypertension. *Circ. Res.* **2021**, *128*, 993–1020. [CrossRef]
167. Bae, H.; Jeong, C.H.; Cheng, W.N.; Hong, K.; Seo, H.G.; Han, S.G. Oxidative Stress-Induced Inflammatory Responses and Effects of N-Acetylcysteine in Bovine Mammary Alveolar Cells. *J. Dairy Res.* **2017**, *84*, 418–425. [CrossRef]

168. Elmarakby, A.A.; Sullivan, J.C. Relationship between Oxidative Stress and Inflammatory Cytokines in Diabetic Nephropathy. *Cardiovasc. Ther.* **2012**, *30*, 49–59. [CrossRef]
169. Zhang, Y.; Yuan, D.; Yao, W.; Zhu, Q.; Liu, Y.; Huang, F.; Feng, J.; Chen, X.; Huang, Y.; Chi, X.; et al. Hyperglycemia Aggravates Hepatic Ischemia Reperfusion Injury by Inducing Chronic Oxidative Stress and Inflammation. *Oxid. Med. Cell. Longev.* **2016**, *2016*, 3919627. [CrossRef]
170. Kumar, P.; Swain, M.M.; Pal, A. Hyperglycemia-Induced Inflammation Caused down-Regulation of 8-OxoG-DNA Glycosylase Levels in Murine Macrophages Is Mediated by Oxidative-Nitrosative Stress-Dependent Pathways. *Int. J. Biochem. Cell Biol.* **2016**, *73*, 82–98. [CrossRef]
171. Pieri, B.L.d.S.; Rodrigues, M.S.; Farias, H.R.; Silveira, G.d.B.; Ribeiro, V.d.S.G.d.C.; Silveira, P.C.L.; De Souza, C.T. Role of Oxidative Stress on Insulin Resistance in Diet-Induced Obesity Mice. *Int. J. Mol. Sci.* **2023**, *24*, 12088. [CrossRef]
172. Ore, A.; Adewale, A.A.; Kehinde, S.A.; Faniyi, T.O.; Oladeji, A.D.; Rufus, P.C.; Akande, A.A.; Chukwuemeka, I.E. Potential Roles of Oxidative Stress and Insulin Resistance in Diisononyl Phthalate Induced Dyslipidemia and Hepatosteatosis in BALB/c Mice. *Adv. Redox Res.* **2022**, *5*, 100038. [CrossRef]
173. Campa, C.C.; Ciraolo, E.; Ghigo, A.; Germena, G.; Hirsch, E. Crossroads of PI3K and Rac Pathways. *Small GTPases* **2015**, *6*, 71–80. [CrossRef]
174. Ma, J.; Nakagawa, Y.; Kojima, I.; Shibata, H. Prolonged Insulin Stimulation Down-Regulates GLUT4 through Oxidative Stress-Mediated Retromer Inhibition by a Protein Kinase CK2-Dependent Mechanism in 3T3-L1 Adipocytes. *J. Biol. Chem.* **2014**, *289*, 133–142. [CrossRef]
175. Hurrle, S.; Hsu, W.H. The Etiology of Oxidative Stress in Insulin Resistance. *Biomed. J.* **2017**, *40*, 257–262. [CrossRef]
176. Gallo, G.; Rubattu, S.; Volpe, M. Mitochondrial Dysfunction in Heart Failure: From Pathophysiological Mechanisms to Therapeutic Opportunities. *Int. J. Mol. Sci.* **2024**, *25*, 2667. [CrossRef]
177. Wang, R.; Wang, M.; Du, D.; Shan, Z.; Bi, L.; Chen, Q.-H. Brain-Targeted Reactive Oxygen Species in Hypertension: Unveiling Subcellular Dynamics, Immune Cross-Talk, and Novel Therapeutic Pathways. *Antioxidants* **2025**, *14*, 408. [CrossRef]
178. Beckhauser, T.F.; Francis-Oliveira, J.; De Pasquale, R. Reactive Oxygen Species: Physiological and Physiopathological Effects on Synaptic Plasticity. *J. Exp. Neurosci.* **2016**, *10*, 23–48. [CrossRef]
179. Huang, Y.-J.; Chen, C.; Yang, H.-C. AI-Enhanced Integration of Genetic and Medical Imaging Data for Risk Assessment of Type 2 Diabetes. *Nat. Commun.* **2024**, *15*, 4230. [CrossRef]
180. Hahn, S.-J.; Kim, S.; Choi, Y.S.; Lee, J.; Kang, J. Prediction of Type 2 Diabetes Using Genome-Wide Polygenic Risk Score and Metabolic Profiles: A Machine Learning Analysis of Population-Based 10-Year Prospective Cohort Study. *EBioMedicine* **2022**, *86*, 104383. [CrossRef]
181. Rafie, Z.; Talab, M.S.; Koor, B.E.Z.; Garavand, A.; Salehnasab, C.; Ghaderzadeh, M. Leveraging XGBoost and Explainable AI for Accurate Prediction of Type 2 Diabetes. *BMC Public Health* **2025**, *25*, 3688. [CrossRef]
182. Carrasco-Zanini, J.; Pietzner, M.; Wheeler, E.; Kerrison, N.D.; Langenberg, C.; Wareham, N.J. Multi-Omic Prediction of Incident Type 2 Diabetes. *Diabetologia* **2024**, *67*, 102–112. [CrossRef]
183. Cheng, Y.; Gadd, D.A.; Gieger, C.; Monterrubio-Gómez, K.; Zhang, Y.; Berta, I.; Stam, M.J.; Szlachetka, N.; Lobzaev, E.; Wrobel, N.; et al. Development and Validation of DNA Methylation Scores in Two European Cohorts Augment 10-Year Risk Prediction of Type 2 Diabetes. *Nat. Aging* **2023**, *3*, 450–458. [CrossRef]
184. Jin, Q.; Zhang, H.; Szczerbinski, L.; Zhu, J.; Gerych, W.; Xu, X.; Wang, K.; Hsu, S.; Mandla, R.; Deutsch, A.J.; et al. Opportunistic Screening of Type 2 Diabetes with Deep Metric Learning Using Electronic Health Records. *Sci. Rep.* **2025**, *15*, 41892. [CrossRef]
185. Shao, J.; Pan, Y.; Xue, J.; Pan, H.; Wang, J.; Li, S.; Nie, Z.; Li, Y.; Tian, Z.; Zhao, Y.; et al. A Deep Learning-Derived Digital Biomarker of Dysglycemia and Its Association with Genetic Risk of Type 2 Diabetes. *Npj Metab. Health Dis.* **2025**, *3*, 46. [CrossRef]
186. Chen, S.-F.; Lee, S.E.; Sadaei, H.J.; Park, J.-B.; Khattab, A.; Chen, J.-F.; Henegar, C.; Wineinger, N.E.; Muse, E.D.; Torkamani, A. Meta-Prediction of Coronary Artery Disease Risk. *Nat. Med.* **2025**, *31*, 2277–2288, Correction in *Nat. Med.* **2025**, *31*, 3204. https://doi.org/10.1038/s41591-025-03925-y. [CrossRef]
187. Carletti, M.; Pandit, J.; Gadaleta, M.; Chiang, D.; Delgado, F.; Quartuccio, K.; Fernandez, B.; Raygoza Garay, J.A.; Torkamani, A.; Miotto, R.; et al. Multimodal AI Correlates of Glucose Spikes in People with Normal Glucose Regulation, Pre-Diabetes and Type 2 Diabetes. *Nat. Med.* **2025**, *31*, 3121–3127. [CrossRef]
188. Khattab, A.; Chen, S.-F.; Sadaei, H.J.; Wineinger, N.; Torkamani, A. A Two-Stage Machine Learning Approach for Personalized Type 2 Diabetes Screening Across Diverse Populations. *Preprint* **2024**. [CrossRef]
189. Barnett, E.J.; Zhang-James, Y.; Hess, J.L.; Glatt, S.J.; Faraone, S.V. Using Genomic Context Informed Genotype Data and Within-Model Ancestry Adjustment to Classify Type 2 Diabetes. *Commun. Med.* **2025**, *5*, 479. [CrossRef]
190. Alqahtani, S.A.M. Comparative Machine Learning Models for Hypertension Prediction in a Cohort of Patients with Diabetes Using Routine Clinical Variables. *Arch. Endocrinol. Metab.* **2025**, *69*, 1–8. [CrossRef]
191. Hosseini Sarkhosh, S.M.; Esteghamati, A.; Hemmatabadi, M.; Daraei, M. Predicting Diabetic Nephropathy in Type 2 Diabetic Patients Using Machine Learning Algorithms. *J. Diabetes Metab. Disord.* **2022**, *21*, 1433–1441. [CrossRef]

192. Okwudili, U.H.; Ukachukwu, O.O.; Chijindu, V.C.; Ezea, M.O.; Ishaq, B. An Improved Performance Model for Artificial Intelligence-Based Diabetes Prediction. *J. Electr. Syst. Inf. Technol.* **2025**, *12*, 25. [CrossRef]
193. Ji, W.; Zhang, Y.; Cheng, Y.; Wang, Y.; Zhou, Y. Development and Validation of Prediction Models for Hypertension Risks: A Cross-Sectional Study Based on 4,287,407 Participants. *Front. Cardiovasc. Med.* **2022**, *9*, 928948. [CrossRef]
194. Rao, S.; Li, Y.; Nazarzadeh, M.; Canoy, D.; Mamouei, M.; Hassaine, A.; Salimi-Khorshidi, G.; Rahimi, K. Systolic Blood Pressure and Cardiovascular Risk in Patients With Diabetes: A Prospective Cohort Study. *Hypertension* **2023**, *80*, 598–607. [CrossRef]
195. Wu, H.; Yang, S.; Huang, Z.; He, J.; Wang, X. Type 2 Diabetes Mellitus Prediction Model Based on Data Mining. *Inform. Med. Unlocked* **2018**, *10*, 100–107. [CrossRef]
196. Kaur, H.; Kumari, V. Predictive Modelling and Analytics for Diabetes Using a Machine Learning Approach. *Appl. Comput. Inform.* **2022**, *18*, 90–100. [CrossRef]
197. Held, E.; Cape, J.; Tintle, N. Comparing Machine Learning and Logistic Regression Methods for Predicting Hypertension Using a Combination of Gene Expression and Next-Generation Sequencing Data. *BMC Proc.* **2016**, *10*, 34. [CrossRef]
198. Lim, J.I.; Regillo, C.D.; Sadda, S.R.; Ipp, E.; Bhaskaranand, M.; Ramachandra, C.; Solanki, K.; Dubiner, H.; Levy-Clarke, G.; Pesavento, R.; et al. Artificial Intelligence Detection of Diabetic Retinopathy. *Ophthalmol. Sci.* **2023**, *3*, 100228. [CrossRef]
199. Maqsood, S.; Sarwar, M.A.; Belousovienė, E.; Maskeliūnas, R. GlucoNet-MM: A Multimodal Attention-based Multi-task Learning Framework with Decision Transformer for Personalised and Explainable Blood Glucose Forecasting. *Diabetes Obes. Metab.* **2025**, *27*, 7416–7430. [CrossRef]
200. Chang, W.; Liu, Y.; Xiao, Y.; Yuan, X.; Xu, X.; Zhang, S.; Zhou, S. A Machine-Learning-Based Prediction Method for Hypertension Outcomes Based on Medical Data. *Diagnostics* **2019**, *9*, 178. [CrossRef]
201. Nour, M.; Polat, K. Automatic Classification of Hypertension Types Based on Personal Features by Machine Learning Algorithms. *Math. Probl. Eng.* **2020**, *2020*, 2742781, Corrigendum in *Math. Probl. Eng.* **2020**, *2020*, 8986139. https://doi.org/10.1155/2020/8986139. [CrossRef]
202. Islam, M.M.; Alam, M.J.; Maniruzzaman, M.; Ahmed, N.A.M.F.; Ali, M.S.; Rahman, M.J.; Roy, D.C. Predicting the Risk of Hypertension Using Machine Learning Algorithms: A Cross Sectional Study in Ethiopia. *PLoS ONE* **2023**, *18*, e0289613. [CrossRef]
203. Martinez-Ríos, E.; Montesinos, L.; Alfaro-Ponce, M. A Machine Learning Approach for Hypertension Detection Based on Photoplethysmography and Clinical Data. *Comput. Biol. Med.* **2022**, *145*, 105479. [CrossRef]
204. Zhao, H.; Zhang, X.; Xu, Y.; Gao, L.; Ma, Z.; Sun, Y.; Wang, W. Predicting the Risk of Hypertension Based on Several Easy-to-Collect Risk Factors: A Machine Learning Method. *Front. Public Health* **2021**, *9*, 619429. [CrossRef]
205. Wishart, D.S.; Knox, C.; Guo, A.C.; Cheng, D.; Shrivastava, S.; Tzur, D.; Gautam, B.; Hassanali, M. DrugBank: A Knowledgebase for Drugs, Drug Actions and Drug Targets. *Nucleic Acids Res.* **2008**, *36*, D901–D906. [CrossRef]
206. Mayer, C.S.; Fontelo, P. Semaglutide Use in People with Obesity and Type 2 Diabetes from Real-World Utilization Data: An Analysis of the All of US Program. *Diabetes Obes. Metab.* **2024**, *26*, 4989–4995. [CrossRef]
207. Yousef, C.C.; Thomas, A.; Matar, M.A.; Ghandoura, L.; Aldossary, I.; Almuhanna, S.M.; Alhussain, F.; AL Bisher, F.B.; Aljohani, R.M.; Balubaid, A.N.; et al. Liraglutide Effects on Glycemic Control and Weight in Patients with Type 2 Diabetes Mellitus: A Real-World, Observational Study and Brief Narrative Review. *Diabetes Res. Clin. Pract.* **2021**, *177*, 108871. [CrossRef]
208. Zhao, X.; Huang, K.; Zheng, M.; Duan, J. Effect of Liraglutide on Blood Pressure: A Meta-Analysis of Liraglutide Randomized Controlled Trials. *BMC Endocr. Disord.* **2019**, *19*, 4. [CrossRef]
209. Kennedy, C.; Hayes, P.; Salama, S.; Hennessy, M.; Fogacci, F. The Effect of Semaglutide on Blood Pressure in Patients without Diabetes: A Systematic Review and Meta-Analysis. *J. Clin. Med.* **2023**, *12*, 772. [CrossRef]
210. Kishimoto, M.; Noda, M. Effects of Exenatide in a Morbidly Obese Patient with Type 2 Diabetes. *Diabetes Ther.* **2014**, *5*, 323–332. [CrossRef]
211. Cerchi, E.; Santo, P.A.d.E.; de Oliveira, M.C.; Janovsky, C.C.P.S.; Halpern, B. Effects of Tirzepatide on Weight Management in Patients with and without Diabetes: A Systematic Review and Meta-Analysis. *Int. J. Obes.* **2025**, *49*, 2415–2425. [CrossRef]
212. Gill, A.; Hoogwerf, B.J.; Burger, J.; Bruce, S.; Macconell, L.; Yan, P.; Braun, D.; Giaconia, J.; Malone, J. Effect of Exenatide on Heart Rate and Blood Pressure in Subjects with Type 2 Diabetes Mellitus: A Double-Blind, Placebo-Controlled, Randomized Pilot Study. *Cardiovasc. Diabetol.* **2010**, *9*, 6. [CrossRef]
213. de Lemos, J.A.; Linetzky, B.; le Roux, C.W.; Laffin, L.J.; Vongpatanasin, W.; Fan, L.; Hemmingway, A.; Ahmad, N.N.; Bunck, M.C.; Stefanski, A. Tirzepatide Reduces 24-Hour Ambulatory Blood Pressure in Adults With Body Mass Index $\geq$27 Kg/m ^{2}: SURMOUNT-1 Ambulatory Blood Pressure Monitoring Substudy. *Hypertension* **2024**, *81*, e41–e43. [CrossRef]

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