Beyond Compensation: Hyperinsulinemia as an Early Driver of Cardiovascular-Kidney-Metabolic Syndrome

Original articles

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ABSTRACT

Background. Cardiovascular-kidney-metabolic (CKM) syndrome encompasses obesity, type 2 diabetes, cardiovascular disease, and chronic kidney disease. Insulin resistance has traditionally been considered the primary driver, with hyperinsulinemia viewed as a compensatory response. However, emerging evidence suggests that hyperinsulinemia may precede insulin resistance in specific phenotypes and contribute to early disease mechanisms.

Methods. We conducted a narrative review of the role of hyperinsulinemia in CKM syndrome. Literature searches were performed in PubMed/MEDLINE, Embase, and Scopus through December 2025. We prioritised prospective cohort studies, meta-analyses, Mendelian randomisation studies, and randomised controlled trials, and synthesised evidence across cardiovascular, renal, and metabolic domains.

Results. Sustained hyperinsulinemia is associated with myocardial hypertrophy and fibrosis through selective preservation of mitogenic signalling, contributing to heart failure phenotypes. In the kidney, it enhances sodium and glucose reabsorption, increases intraglomerular pressure, and promotes podocyte dysfunction, potentially accelerating CKD progression. Epidemiological evidence consistently shows associations between elevated fasting insulin levels and cardiovascular events, renal outcomes, and mortality across diverse populations, with meta-analytic estimates reporting a pooled relative risk of 1.46 (95% CI 1.16–1.84) for incident cardiovascular events. However, available data are largely observational and heterogeneous in exposure definitions and adjustment models.

Conclusions. Hyperinsulinemia represents a clinically relevant and potentially modifiable component of CKM syndrome, with effects extending beyond glucose homeostasis. While causality is biologically plausible and supported by genetic and epidemiological evidence, it remains to be established through interventional studies. Recognition of hyperinsulinemia may support earlier risk stratification and mechanism-based interventions, although prospective validation is required before routine clinical implementation.

KEYWORDS: Hyperinsulinemia, Insulin resistance, Cardiovascular-kidney-metabolic syndrome, Chronic kidney disease, Obesity-related kidney disease, Heart failure, Metabolic dysfunction, Cardiorenal syndrome

List of Abbreviations

ADPKD: Autosomal Dominant Polycystic Kidney Disease
BMI: Body Mass Index
CKD: Chronic Kidney Disease
CKM: Cardiovascular-Kidney-Metabolic
CRP: C-Reactive Protein
CTGF: Connective Tissue Growth Factor
eGFR: Estimated Glomerular Filtration Rate
ENaC: Epithelial Sodium Channel
ET-1: Endothelin-1
GFR: Glomerular Filtration Rate
GLP-1: Glucagon-Like Peptide-1
GLP-1 RA: Glucagon-Like Peptide-1 Receptor Agonist
GWAS: Genome-Wide Association Studies
HbA1c: Glycated Hemoglobin A1c
HDL: High-Density Lipoprotein
HFpEF: Heart Failure with Preserved Ejection Fraction
HFrEF: Heart Failure with Reduced Ejection Fraction
HOMA-IR: Homeostatic Model Assessment for Insulin Resistance
hs-CRP: High-Sensitivity C-Reactive Protein
htTKV: Height-Adjusted Total Kidney Volume
IL-1: Interleukin-1
IL-1β: Interleukin-1 Beta
IL-6: Interleukin-6
MAPK: Mitogen-Activated Protein Kinase
MCP-1: Monocyte Chemoattractant Protein-1
nsMRA: Non-Steroidal Mineralocorticoid Receptor Antagonist
Ob-CKD: Obesity-Related Chronic Kidney Disease
OGTT: Oral Glucose Tolerance Test
PAI-1: Plasminogen Activator Inhibitor-1
PI3K/Akt: Phosphatidylinositol 3-Kinase/Protein Kinase B
RAAS: Renin-Angiotensin-Aldosterone System
SGLT2: Sodium-Glucose Cotransporter 2
SGLT2i: Sodium-Glucose Cotransporter 2 Inhibitor
SNS: Sympathetic Nervous System
SREBP-1c: Sterol Regulatory Element-Binding Protein-1c
T2DM: Type 2 Diabetes Mellitus
TGF-β: Transforming Growth Factor-Beta
TNF-α: Tumor Necrosis Factor-Alpha
UACR: Urine Albumin-to-Creatinine Ratio

Introduction

The cardiovascular-kidney-metabolic (CKM) syndrome represents a major clinical and public health challenge [1, 2]. It encompasses atherosclerotic cardiovascular disease (CVD), heart failure (HF), chronic kidney disease (CKD), and type 2 diabetes mellitus (T2DM). Insulin resistance has traditionally been considered a central pathophysiological axis. However, emerging evidence

suggests that hyperinsulinemia may act as an early and independent determinant in CKM syndrome development [3–5].

Genetic studies indicate that hyperinsulinemia may precede insulin resistance in certain contexts, supporting an alternative pathophysiological model [6, 7]. Nevertheless, the classical and emerging models should be regarded as interdependent processes whose predominance depends on genetic susceptibility, metabolic status, and environmental factors.

In this review, hyperinsulinemia is considered both as a compensatory response to insulin resistance and, in specific phenotypes, as a potential upstream driver contributing to its development, reflecting a bidirectional and context-dependent relationship.

Sustained hyperinsulinemia has been associated with endothelial dysfunction, arterial stiffness, and accelerated atherosclerosis [8, 9].

At the cardiac level, it promotes myocardial hypertrophy and fibrosis, leading to diastolic dysfunction and HF even in the absence of overt hyperglycemia [10].

At the renal level, it enhances sodium and glucose reabsorption via sodium-glucose cotransporter 2 (SGLT2), induces podocyte dysfunction, and accelerates proteinuria progression [11–13]. This is particularly relevant in obesity-related kidney disease (Ob-CKD).

Epidemiologically, elevated fasting insulin levels are associated with increased cardiovascular events (pooled relative risk 1.46, 95% CI 1.16-1.84), renal deterioration, and all-cause mortality, independently of glucose levels [14, 15].

In CKD, hyperinsulinemia, obesity, and metabolic dysfunction establish a pathogenic triad that may accelerate cardiovascular and renal outcomes [16, 17].

Reconsidering hyperinsulinemia as a key pathophysiological component may enable earlier interventions targeting not only glycaemic control but also overall cardiorenal risk.

This narrative review examines the evidence linking hyperinsulinemia with CKM syndrome, emphasizing molecular mechanisms, epidemiological relevance, and clinical implications for the international nephrology and cardiometabolic community.

Methods

This narrative review was designed and reported in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines. A comprehensive literature search was performed across PubMed/MEDLINE, Embase, and Scopus through December 2025, the date at which data collection was completed. Search terms used in various combinations included: “hyperinsulinemia”, “insulin resistance”, “cardiovascular disease”, “chronic kidney disease”, “heart failure”, “metabolic syndrome”, “CKM syndrome”, “obesity-related kidney disease”, “ADPKD”, “podocyte”, “SGLT2”, and “GLP-1 receptor agonist”.

Reference lists of key articles were manually screened for additional relevant publications. Studies were prioritised if they met the following criteria: prospective cohort studies and meta-analyses reporting quantitative associations between hyperinsulinemia or its surrogates (fasting insulin, HOMA-IR) and cardiovascular, renal, or metabolic outcomes; mechanistic studies elucidating molecular pathways linking insulin excess to organ damage; randomised controlled trials and large observational studies evaluating interventions modulating insulin levels and cardiorenal endpoints; genome-wide association and Mendelian randomisation studies; and major society guideline documents. Studies in English, Italian, and Spanish were eligible. Given the integrative, multidomain

nature of the topic, formal risk-of-bias assessment was not performed, as is standard practice for narrative reviews of this scope. Evidence was synthesised by pathophysiological domain, and quantitative effect estimates with 95% confidence intervals are reported where available. Special emphasis was placed on findings with direct clinical relevance to the international nephrology and cardiometabolic community.

Hyperinsulinemia and the Cardiovascular-Kidney-Metabolic Syndrome: Definitions and Pathophysiological Framework

The CKM syndrome describes the interaction between obesity, T2DM, CVD, and CKD [18–20]. These conditions share common pathophysiological pathways. Traditionally, insulin resistance has been considered the initial driver (Figure 1). Inflammation, oxidative stress, endothelial dysfunction, and metabolic disturbances mutually reinforce one another [21, 22].

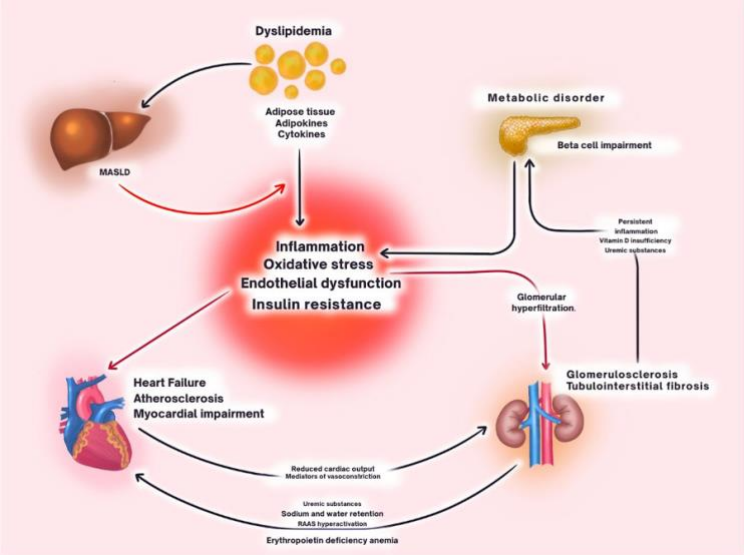

Figure 1. Cardiorenometabolic syndrome framework. The figure illustrates the interaction between inflammation, oxidative stress, insulin resistance, and endothelial dysfunction leading to cardiovascular, renal, and metabolic outcomes. Adapted from Rico Fontalvo J, et al. [20]. Distributed under the Creative Commons CC BY license.

Defining Hyperinsulinemia

Current Criteria and Challenges Despite its clinical relevance, hyperinsulinemia lacks standardized diagnostic thresholds. Current approaches include:

1. Fasting hyperinsulinemia: Insulin levels ≥15 µU/mL (moderate) or ≥25 µU/mL (severe). These cutoffs show inter-assay variability and lack age-, sex-, and ethnicity-specific adjustments [23, 24].
2. Post-challenge hyperinsulinemia: Insulin ≥75 µU/mL at 2 hours during oral glucose tolerance test (OGTT), rarely performed in routine practice [22].
3. HOMA-IR >2.5: An indirect measure of insulin resistance correlating with hyperinsulinemia, widely used for its simplicity despite limited sensitivity [23].
4. Loss of insulin pulsatility: Replacement of physiological oscillatory secretion with tonic hypersecretion, detectable only through specialized sampling, contributes to insulin receptor desensitization [24, 25].

Important limitations include lack of assay standardization, absence of reference values for CKD populations, and minimal consideration of ethnic differences in insulin secretion and clearance [11, 21].

Pathophysiological Models: Classical vs Emerging Framework

At the vascular level, hyperinsulinemia is associated with endothelial dysfunction, oxidative stress, and atherosclerotic acceleration, contributing to arterial stiffness and cardiovascular risk [7, 8].

At the cardiac level, it promotes myocardial hypertrophy and fibrosis, facilitating progression toward HF with preserved (HFpEF) and reduced (HFrEF) ejection fraction [4, 9].

At the renal level, it enhances sodium and glucose reabsorption via SGLT2, increases intraglomerular pressure, and compromises podocyte viability, promoting proteinuria and CKD progression in diabetic and non-diabetic contexts [10, 15]. Two main pathophysiological models have been proposed. The traditional model posits that insulin resistance precedes compensatory hyperinsulinemia. The emerging model proposes the opposite: hyperinsulinemia may precede and promote insulin resistance. Mendelian randomization studies support this alternative sequence [5, 6]. Figure 2 summarizes both frameworks and their implications for CKM progression.

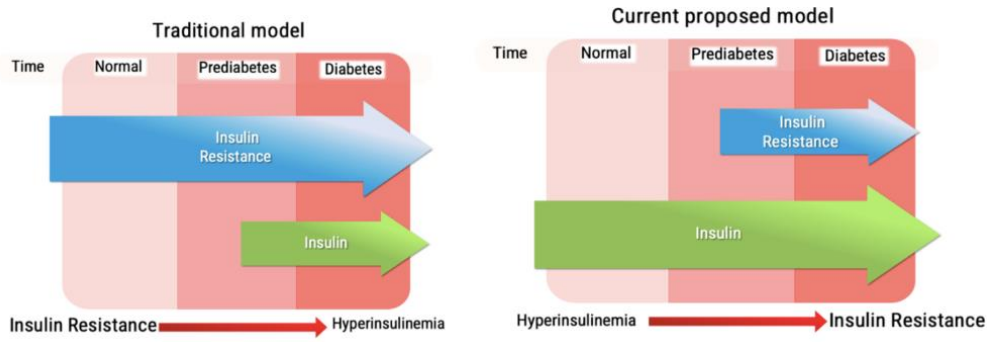

Figure 2. Comparison between the traditional and emerging models of cardiorenometabolic (CKM) syndrome pathophysiology. In the classical model, insulin resistance precedes hyperinsulinemia and progressive β-cell exhaustion. In the alternative model, hyperinsulinemia may occur early and contribute to insulin resistance development in specific phenotypes. Figure created by the authors.

These models should be considered complementary rather than mutually exclusive.

The predominant sequence likely varies according to body composition, genetic susceptibility, inflammation, and metabolic context [3].

Population-based studies have consistently demonstrated that hyperinsulinemia is associated with a higher incidence of coronary artery disease, HF, and cardiovascular mortality, irrespective of glycated hemoglobin A1c (HbA1c) or diabetes diagnosis (Table 1).

A meta-analysis reported a pooled relative risk of 1.46 (95% CI 1.16-1.84) for incident CV events in individuals with elevated fasting insulin [13].

Not all cohort data are concordant. In the Chronic Renal Insufficiency Cohort (CRIC) study, which included 1,883 non-diabetic participants with mild-to-moderate CKD, HOMA-IR was not independently associated with CKD progression, cardiovascular events, or all-cause mortality after multivariable adjustment [26]. This neutral finding highlights the heterogeneity of the available evidence and aligns with other studies reporting inconsistent associations between insulin resistance and CKD-related outcomes. Such variability likely reflects differences in insulin measurement methods, outcome definitions, CKD stage, and residual confounding by body mass index (BMI), diabetes status, and kidney function. These inconsistencies underscore the need for

standardised diagnostic thresholds and prospective interventional trials before hyperinsulinemia can be definitively established as an independent therapeutic target in CKD.

Data from the Framingham Heart Study and other population-based cohorts indicate that insulin resistance and related metabolic abnormalities predict the development of T2DM and CVD [14]. In CKD populations, hyperinsulinemia contributes to accelerated renal decline, particularly in Ob-CKD, establishing a pathogenic triad of hyperinsulinemia, visceral adiposity, and metabolic dysfunction [12, 16, 27].

Recognizing hyperinsulinemia as an early risk factor supports rethinking clinical approaches, shifting focus toward early insulin burden modulation beyond glycaemic control. This perspective is particularly relevant given that CKM syndrome represents a leading cause of global morbidity and mortality [1, 28].

Study	Population	Exposure	Outcome	Effect size
Gast et al., [13]	General population (non-diabetic adults)	Fasting insulin (highest vs lowest category)	Incident cardiovascular events	RR 1.46 (95% CI 1.16–1.84)
Xun et al., [29]	General population	Fasting insulin	Coronary heart disease	RR 1.50 (95% CI 1.28–1.77)
Erquo et al., [30]	General population cohorts	Insulin resistance (HOMA-IR)	Incident heart failure	RR 1.45 (95% CI 1.21–1.73)
Schrauben et al., [26]	CKD patients	HOMA-IR	CKD progression, CV events, mortality	Significant independent associations (adjusted models)
Chen et al., [31]	US adults (NHANES)	Insulin resistance / metabolic syndrome	CKD prevalence/incidence	Increased CKD risk (adjusted OR)
Kurella et al., [32]	Non-diabetic adults	Insulin resistance	Incident CKD	Increased risk of CKD (adjusted HR)

Table 1. Key epidemiological studies linking hyperinsulinemia with cardiovascular and renal outcomes. Selected representative cohort studies and meta-analyses reporting associations between hyperinsulinemia or insulin resistance (assessed by fasting insulin or HOMA-IR) and cardiovascular or renal outcomes across different populations. Effect estimates are reported as provided in the original studies (relative risks, hazard ratios, or odds ratios with 95% confidence intervals). Differences in exposure definitions, outcome measures, and adjustment models across studies should be considered when interpreting results.

Hyperinsulinemia and heart failure

Patients with HF, including those with HFpEF and HFrEF, frequently exhibit hyperinsulinemia or insulin resistance, even without overt diabetes [2, 4, 9]. This association is particularly prominent in HFpEF, where metabolic dysfunction and obesity represent major phenotypic determinants [2, 17]. Excess circulating insulin activates intracellular signaling pathways, PI3K/Akt (metabolic) and MAPK (mitogenic), promoting cardiomyocyte hypertrophy, collagen deposition, and interstitial fibrosis [4, 7]. In insulin resistance, the metabolic arm (PI3K/Akt) becomes impaired while the mitogenic arm (MAPK) remains active or enhanced, creating “selective insulin resistance”. This favors trophic and profibrotic effects over metabolic homeostasis, contributing to adverse cardiac remodeling [3]. Clinically, these alterations translate into myocardial stiffness, diastolic dysfunction, and elevated risk of symptomatic heart failure [9]. Epidemiologically, hyperinsulinemia is associated with worse prognosis, higher hospitalization rates, and increased cardiovascular mortality, independently of diabetes status [8, 13]. Therapeutically, interventions reducing insulin burden, including SGLT2 inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RA), have demonstrated cardiorenal benefits, supporting hyperinsulinemia modulation as a potential treatment target beyond glycaemic control [33]. While these agents reduce insulin burden, their cardiorenal benefits are likely multifactorial and cannot be solely attributed to hyperinsulinemia modulation.

Hyperinsulinemia and obesity

Visceral obesity is associated with subclinical hyperinsulinemia from early stages, establishing a bidirectional relationship that amplifies cardiometabolic risk [28, 34].

Excess visceral adipose tissue promotes low-grade inflammation, lipotoxicity, and release of proinflammatory cytokines (including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 (IL-1)) which induce peripheral insulin resistance. In response, pancreatic β-cells increase insulin secretion to maintain euglycemia, sustaining a chronic hyperinsulinemic state [3, 5].

This excess insulin favors a self-perpetuating cycle characterized by increased lipid storage, enhanced adipocyte differentiation, and persistent metabolic dysfunction. Hyperinsulinemia stimulates lipogenesis through sterol regulatory element-binding protein-1c (SREBP-1c) activation and lipolysis suppression, further promoting visceral fat accumulation [35, 36].

This vicious cycle (wherein obesity drives hyperinsulinemia, which exacerbates obesity) represents a central mechanism in CKM syndrome development. Central obesity acts as a central modulator of the CKM axis. Hyperinsulinemia exerts local and systemic effects on the endothelium, myocardium, and kidney [20, 37].

At the renal level, perivisceral fat accumulation and sustained hyperinsulinemia promote glomerular hyperfiltration, podocyte injury, oxidative stress, and renin-angiotensin-aldosterone system (RAAS) activation, contributing to Ob-CKD [12, 27]. These mechanisms accelerate the transition from metabolic dysfunction to overt CKD, particularly without diabetes.

Hyperinsulinemia often precedes dysglycemia and independently predicts progression to T2DM, CVD, and renal deterioration in obesity [13, 14]. Early detection may identify high-risk individuals before diabetes or cardiovascular events, supporting the potential utility of hyperinsulinemia as a screening target [3]. These approaches require prospective validation before routine clinical implementation.

Hyperinsulinemia functions as a central pathobiological node linking obesity, aging, and cardiometabolic risk, reinforcing its role as a modifiable therapeutic target [3]. Figure 3 summarizes these mechanisms: visceral adiposity induces inflammation and insulin resistance; hyperinsulinemia perpetuates metabolic dysfunction, promotes cardiac and renal remodeling, and establishes a common pathogenic axis for T2DM, CVD, and Ob-CKD.

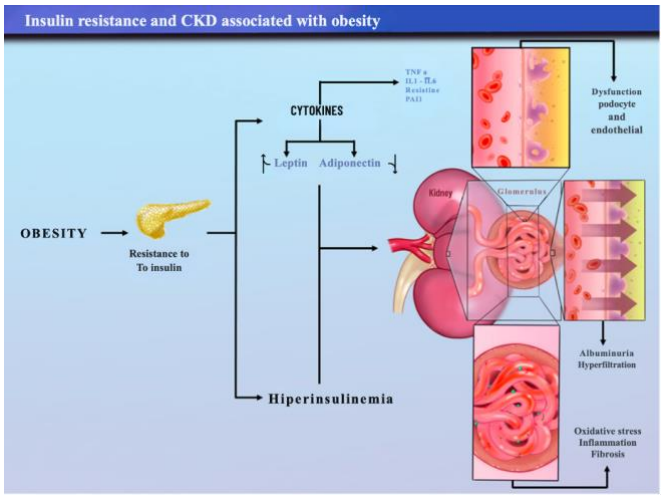

Figure 3. Insulin resistance in CKD associated with obesity. Pathophysiological mechanisms linking insulin resistance and obesity-associated chronic kidney disease (Ob-CKD). TNF-α: tumor necrosis factor alpha; IL-6: interleukin 6; IL-1: interleukin 1; PAI-1: plasminogen activator inhibitor-1. Adapted from Rico Fontalvo J, et al. [20]. Distributed under the Creative Commons CC BY license.

Hyperinsulinemia and diabetes

Clinically relevant hyperinsulinemia can be assessed using several methods:

1. Fasting insulin levels: Simple and widely available, though interpretation is complicated by lack of standardized assays and reference values [21].
2. HOMA-IR: Calculated as (fasting insulin × fasting glucose)/22.5, with values >2.5 indicating insulin resistance. While convenient, HOMA-IR is indirect and may not reflect dynamic insulin secretion [23].
3. Euglycaemic-hyperinsulinemic clamp: The reference standard for quantifying insulin sensitivity, though complexity and cost limit routine use [21].
   Interpretation should be contextualized according to metabolic phenotype, body composition, ethnicity, and CKM risk profile. The absence of universally accepted thresholds represents a significant limitation.

- Therapeutic Implications: Several drug classes demonstrate benefits in reducing insulin burden and improving cardiorenal outcomes:

1. *Metformin* improves peripheral insulin sensitivity and reduces hepatic glucose production. It enhances endothelial function and reduces oxidative stress, making it first-line in insulin resistance [38].
2. *GLP-1 receptor agonists* enhance glucose-dependent insulin secretion, improve insulin sensitivity, and promote weight loss. Major trials demonstrated cardiovascular and renal benefits, including reduced adverse cardiovascular events and slowed albuminuria progression [39, 40].
3. *SGLT2 inhibitors* reduce insulin burden by inducing glucosuria independently of insulin, decreasing glucotoxicity and preserving β-cell function. Landmark trials showed significant reductions in heart failure hospitalizations, cardiovascular death, and CKD progression across glycaemic status [41, 42].

- Lifestyle interventions remain fundamental: Regular physical activity, particularly combined aerobic and resistance training, reduces insulin levels, improves insulin sensitivity, and decreases abdominal adiposity [32].
  Caloric restriction and 5-10% weight loss significantly reduce fasting insulin and delay type 2 diabetes progression.

This integrated approach, combining lifestyle modification with targeted pharmacological therapies, can slow progression from subclinical hyperinsulinemia to overt diabetes and reduce cardiovascular-kidney- metabolic risk, particularly when initiated early.

Hyperinsulinemia and arterial hypertension

Hyperinsulinemia, with insulin resistance and chronic hyperglycemia, acts as a central mediator in arterial hypertension development [34, 43]. This involves integrated vascular, renal, and autonomic mechanisms, resulting in sustained vasoconstriction, volume expansion, and elevated blood pressure. The relationship is particularly evident in metabolic syndrome and obesity, where insulin resistance amplifies the hypertensive effects of excess insulin [15].

- Vascular Mechanisms: Excess insulin stimulates endothelin-1 (ET-1) production through MAPK pathway activation, promoting arterial stiffness, vasoconstriction, and increased peripheral resistance [43]. The imbalance between PI3K/Akt (metabolic) and MAPK

(mitogenic) signaling reduces nitric oxide bioavailability and impairs endothelium-dependent vasodilation.
The net effect is sustained vasoconstriction and reduced vascular compliance [32]. This adverse vascular milieu is amplified by proinflammatory mediators (including plasminogen activator inhibitor-1 (PAI-1), monocyte chemoattractant protein-1 (MCP-1), interleukins, TNF-α, and C-reactive protein (CRP)) which perpetuate endothelial inflammation and oxidative stress [8].
These inflammatory pathways contribute to endothelial dysfunction, atherosclerosis progression, and increased cardiovascular risk.

- Renal Mechanisms: Hyperinsulinemia activates RAAS and directly increases epithelial sodium channel (ENaC) activity in the distal nephron, promoting sodium retention, volume expansion, and sustained blood pressure elevation [34, 43]. Additionally, insulin enhances renal sodium reabsorption through Na-K-ATPase and Na-H exchanger activity, further contributing to volume overload.
  In CKD, the interplay between hyperinsulinemia, sodium retention, and volume expansion is particularly pronounced, contributing to resistant hypertension and accelerated cardiovascular-renal progression [15, 16].
  This is especially relevant in Ob-CKD, where central adiposity, hyperinsulinemia, and RAAS activation converge to establish an adverse hemodynamic profile [12].
- Autonomic Mechanisms: Chronic sympathetic nervous system (SNS) activation, secondary to insulin resistance and hyperinsulinemia, increases vasomotor tone, cardiac output, and heart rate, contributing to metabolic hypertension [44].
  Hyperinsulinemia stimulates central sympathetic outflow through hypothalamic effects, while peripheral insulin resistance prevents normal vasodilatory actions, creating sympathetic overactivity coupled with impaired vascular relaxation.
- Clinical Implications: These mechanisms illustrate how hyperinsulinemia integrates metabolic dysregulation with vascular dysfunction, renal sodium handling, and autonomic imbalance, consolidating its role as a modifiable determinant of hypertension within CKM syndrome.
  Therapeutic interventions reducing insulin levels, including weight loss, SGLT2 inhibitors, and GLP-1 receptor agonists, have demonstrated blood pressure benefits [41, 45].
  Recognition of hyperinsulinemia as a hypertension contributor helps explain the clustering of elevated blood pressure with obesity, insulin resistance, and metabolic syndrome, supporting an integrated approach to CKM risk reduction.

Hyperinsulinemia and Chronic Kidney Disease

Hyperinsulinemia is highly prevalent across all CKD stages and etiologies, including diabetic and non-diabetic kidney disease [11, 39]. This reflects a bidirectional relationship: kidney dysfunction impairs insulin clearance and promotes insulin resistance, while sustained hyperinsulinemia accelerates CKD progression through multiple mechanisms [16].

Insulin resistance and compensatory hyperinsulinemia are present even in early CKD with preserved eGFR, suggesting metabolic dysregulation may precede measurable renal impairment [40].

The pathophysiological impact of hyperinsulinemia on the kidney operates across three distinct anatomical compartments. At the glomerular level, excess insulin promotes hyperfiltration through afferent arteriolar vasodilation and increased intraglomerular pressure, a haemodynamic alteration

that, while initially adaptive, ultimately accelerates glomerulosclerosis and proteinuria [10]. Insulin also directly compromises podocyte integrity by inducing cytoskeletal reorganisation and increasing albumin permeability. With chronic exposure, it further promotes podocyte apoptosis and epithelial-mesenchymal transition, contributing to progressive loss of the filtration barrier [39].

At the tubular level, hyperinsulinemia enhances sodium reabsorption through ENaC and Na-K-ATPase upregulation, promoting volume expansion and hypertension [46]. Simultaneously, insulin stimulates proximal tubular SGLT2 activity, increasing glucose reabsorption and sustaining a cycle in which hyperinsulinemia drives sodium retention while impaired renal insulin clearance in CKD perpetuates systemic hyperinsulinemia [15]. At the interstitial level, insulin activates the profibrotic mediators transforming growth factor-beta (TGF-β) and connective tissue growth factor (CTGF), promoting extracellular matrix deposition, tubular atrophy, and interstitial fibrosis [11]. These effects converge with insulin-mediated oxidative stress and mitochondrial dysfunction, contributing to chronic endothelial inflammation and accelerating vascular calcification and arteriolosclerosis.

Ob-CKD represents perhaps the clearest paradigm of hyperinsulinemia-driven renal injury. Visceral adiposity establishes a direct pathogenic link between metabolic dysfunction and progressive nephropathy [12, 27], mediated by adipokine dysregulation (reduced adiponectin, elevated leptin), RAAS activation, lipotoxicity from ectopic renal fat deposition, and chronic inflammation driven by TNF-alpha, IL-6, and IL-1beta [37]. Hyperinsulinemia amplifies each of these pathways by promoting renal lipid accumulation, enhancing oxidative stress, and directly stimulating mesangial cell proliferation and podocyte injury, contributing to glomerular hyperfiltration, albuminuria, and accelerated eGFR decline even without diabetes [20, 47, 48]. Ob-CKD manifests with a characteristic phenotype comprising proteinuria (often nephrotic-range), glomerulomegaly, and progressive eGFR loss histologically distinct from classical diabetic nephropathy. Interventions targeting visceral fat reduction and insulin burden demonstrate significant renoprotection in this population [27, 49, 50].

The clinical relevance of hyperinsulinemia extends well beyond Ob-CKD. In non-diabetic CKD, elevated fasting insulin levels are independently associated with albuminuria and accelerated eGFR decline, indicating that hyperinsulinemia may contribute to renal injury through mechanisms distinct from hyperglycaemia [31, 32]. ADPKD, the most common inherited kidney disease, represents a unique genetic and metabolic model in which early insulin resistance and metabolic dysfunction are already evident, potentially mediated through polycystin expression in pancreatic beta-cells and hepatic tissues [40, 51]. In this context, disease-specific features such as massive cystic organomegaly complicate nutritional assessment by masking early malnutrition and sarcopenia, highlighting the need for specialised body composition evaluation [52, 53]. Hormonal factors, including the role of female sex steroids in hepatic cystogenesis, further contribute to the metabolic complexity of ADPKD [54, 55], while the psychosocial burden of the disease underscores the importance of an integrated and holistic management approach [56]. Collectively, these features make ADPKD a clinically relevant framework for understanding the interplay between hyperinsulinemia, metabolic dysfunction, and CKD progression beyond classical metabolic phenotypes.

Epidemiologically, hyperinsulinemia predicts both incident CKD and progression of established kidney disease, with elevated fasting insulin associated with increased new-onset CKD risk (hazard ratio 1.5-2.0) and accelerated eGFR decline independently of diabetes, hypertension, and obesity [31, 32]. Hyperinsulinemia correlates with higher albuminuria and predicts progression from microalbuminuria to macroalbuminuria in both diabetic and non-diabetic populations. In established CKD, it associates with worse cardiovascular outcomes, higher hospitalisation rates, and increased mortality, underscoring its role as a modifiable prognostic factor [16, 57]. The interaction between hyperinsulinemia, uraemia, and CVD creates an adverse phenotype characterised by

accelerated atherosclerosis, left ventricular hypertrophy, and elevated sudden cardiac death risk. Anaemia of CKD further amplifies cardiovascular risk in this population and requires integrated haematological management [58, 59]. Uremic toxin accumulation drives vascular calcification through pathways that intersect with and are potentiated by chronic hyperinsulinemia, compounding cardiorenal risk [60].

Integrating metabolic assessment (including fasting insulin, HOMA-IR, and body composition analysis) into routine CKD management may facilitate risk stratification and guide targeted interventions.

Integrated Clinical Approach and Future Directions

Phenotypic Stratification Within the CKM Continuum

Recognition of hyperinsulinemia as a multiorgan pathophysiological driver necessitates an integrated approach to CKM syndrome transcending traditional organ-specific boundaries [1, 17].

Four principal hyperinsulinemia-driven phenotypes may be distinguished:

1. Cardio-predominant: Heart failure with preserved ejection fraction, diastolic dysfunction, and myocardial fibrosis. Clinical markers include elevated natriuretic peptides and echocardiographic impaired relaxation [2, 9].
2. Reno-predominant: Albuminuria, glomerular hyperfiltration, and accelerated eGFR decline, particularly in Ob-CKD [12, 27]. Clinical markers include persistent albuminuria (urine albumin-to-creatinine ratio [UACR] >30 mg/g) and rapid eGFR decline (>3 mL/min/1.73m^2/year).
3. Adipose-predominant: Visceral obesity, adipocyte dysfunction, and chronic inflammation. Biochemical markers include elevated high-sensitivity C-reactive protein (hs-CRP), hypertriglyceridemia, reduced high-density lipoprotein (HDL), and hepatic steatosis [3, 28].
4. Glucometabolic: Progressive dysglycemia, impaired β-cell function, and sustained compensatory insulin hypersecretion [23, 61].

These phenotypes are not mutually exclusive; identification of the predominant pattern may guide diagnostic and therapeutic prioritization.

Risk Stratification and Screening Strategies:

Targeted screening for hyperinsulinemia may be considered in selected high-risk populations:

1. Obesity with metabolic syndrome (BMI ≥30 kg/m^2 or abdominal adiposity)
2. Early-stage CKD (G1-G3a) with metabolic dysfunction
3. HFpEF, particularly with obesity
4. Normoglycaemic individuals with family history of diabetes or prediabetes
5. ADPKD patients with metabolic risk factors [40].

Screening methodologies may include fasting insulin measurement (≥15 µU/mL suggests moderate hyperinsulinemia), HOMA-IR calculation (>2.5 indicates insulin resistance), and oral glucose tolerance testing with serial insulin measurements when feasible [21, 23]. Body composition assessment through bioelectrical impedance or waist circumference measurement provides complementary information on central adiposity [52].

Knowledge Gaps and Research Priorities Critical unresolved questions include:

1. Diagnostic standardization: Validated, population-specific hyperinsulinemia thresholds accounting for age, sex, ethnicity, body composition, and CKD stage; insulin immunoassay standardization for cross-study comparisons.
2. Mechanistic clarification: Insulin pulsatility restoration as therapeutic target [24, 25]; genetic determinants of hyperinsulinemia-first versus insulin-resistance-first phenotypes [6, 62]; tissue-specific insulin signaling defects.
3. Interventional trials: Pragmatic RCTs with hyperinsulinemia reduction as primary endpoint and hard cardiovascular-renal outcomes; comparison of lifestyle intervention, SGLT2 inhibitors, GLP-1 receptor agonists, and combination approaches; duration ≥3-5 years across diverse CKM populations.
4. Composite biomarkers: Integration of insulin dynamics with endothelial function, inflammatory markers, and organ damage indicators; composite scores for improved risk stratification.
5. Precision medicine: Genetic polymorphisms and phenotypic characteristics predicting differential response to insulin-lowering interventions; machine learning for personalized algorithms.
6. Health economics: Cost-effectiveness of hyperinsulinemia screening; budget impact of widespread SGLT2i/GLP-1 RA adoption; optimal delivery models for lifestyle interventions.

Implications for Clinical Practice

Recognition of hyperinsulinemia as a modifiable CKM component supports several paradigm shifts:

1. earlier identification and intervention during hyperinsulinemic, normoglycaemic phases when organ damage may be preventable;
2. mechanism-based therapeutic selection guided by predominant phenotype rather than glucose-centric targets alone;
3. integration of hyperinsulinemia screening and body composition analysis into routine practice;
4. personalized treatment algorithms accounting for phenotypic heterogeneity and patient preferences.

These principles facilitate a comprehensive approach to CKD prevention and management, with particular attention to Ob-CKD and metabolic dysfunction in CKD populations.

Implementation of hyperinsulinemia-focused strategies represents an opportunity to move toward truly preventive, mechanism-based medicine addressing upstream metabolic drivers before irreversible complications.

Discussion

The evidence synthesised in this review supports a reconceptualisation of hyperinsulinemia within CKM syndrome: not merely a compensatory response to insulin resistance, but a potential early and independent pathogenic driver with direct, clinically relevant consequences for the heart, kidney, and adipose tissue, beyond overt hyperglycaemia. Although causality is biologically plausible and supported by genetic and epidemiological evidence, definitive proof from interventional trials is still

lacking. This perspective has important mechanistic, epidemiological, and therapeutic implications that deserve critical appraisal. At the myocardial level, the concept of selective insulin resistance provides a compelling mechanistic link between hyperinsulinemia and HFpEF. When the metabolic arm of insulin signalling (PI3K/Akt) becomes impaired while the mitogenic arm (MAPK) remains active, the net result is a shift toward trophic and profibrotic effects, promoting cardiomyocyte hypertrophy and interstitial fibrosis [2, 4, 9]. Major cardiorenal outcome trials with SGLT2 inhibitors and GLP-1 receptor agonists demonstrate benefits extending beyond glycaemic control, consistent with insulin burden reduction as a shared therapeutic mechanism [33, 45]. In the kidney, the convergence of glomerular haemodynamic stress, tubular sodium-glucose reabsorption, podocyte injury, and interstitial fibrosis driven by chronic hyperinsulinemia collectively accelerates CKD progression across a spectrum of aetiologies [10, 11, 16]. The mechanisms and clinical consequences of hyperinsulinemia in visceral obesity are summarised in Table 2, and the principal therapeutic strategies are presented in Table 3.

Pathophysiological axis	Mechanism involved	Clinical consequences
Metabolic	Compensatory hyperinsulinemia in response to peripheral insulin resistance; increased lipogenesis and adipocyte differentiation	Metabolic dysfunction, progressive weight gain, subclinical hyperglycemia
Inflammatory	Release of TNF-α, IL-6, PAI-1 and MCP-1 by visceral adipose tissue; chronic low-grade inflammation	Oxidative stress, systemic insulin resistance
Endothelial and vascular	Activation of MAPK pathways and decrease in PI3K/Akt signal; nitric oxide reduction and endothelin-1 increase	Endothelial dysfunction, hypertension, adverse cardiac remodeling
Renal	Activation of the renin–angiotensin–aldosterone system; glomerular hyperfiltration, tubulointerstitial fibrosis	Obesity-associated kidney disease, progression of subclinical CKD
Integrator (CKM syndrome)	Interaction of the metabolic, inflammatory and endothelial axes	Increased risk of type 2 diabetes, CVD and CKD

Table 2. Pathophysiological mechanisms and clinical consequences of hyperinsulinemia in obesity-related CKD and CKM syndrome. Summary of the main pathophysiological pathways through which hyperinsulinemia contributes to metabolic, inflammatory, vascular, and renal dysfunction within the cardiovascular-kidney-metabolic (CKM) continuum.

The temporal relationship between hyperinsulinemia and insulin resistance remains a subject of active investigation. Genome-wide association and Mendelian randomisation data are consistent with, though do not yet prove, a hyperinsulinemia-first sequence in certain phenotypes [5, 6, 62]. Prospective epidemiological data provide corroborating evidence: elevated fasting insulin is consistently associated with incident cardiovascular events (pooled RR 1.46, 95% CI 1.16-1.84) [13], coronary heart disease (RR 1.50, 95% CI 1.28-1.77) [29], incident HF (RR 1.45, 95% CI 1.21-1.73) [30], and renal deterioration [31, 32], all independently of glycaemia. These associations challenge the traditional glucose-centric view and support recognition of hyperinsulinemia as an independent, measurable, and modifiable risk factor.

A major constraint on clinical implementation is the absence of validated, population-specific thresholds for hyperinsulinemia. Variability among insulin immunoassays, the lack of age-, sex-, and ethnicity-adjusted cutoffs, the absence of CKD-specific reference values, and the limited routine availability of dynamic insulin secretion measures collectively impede translation from mechanistic insight to clinical practice [21, 23].

The additional dimension of pulsatile insulin secretion, whose physiological disruption contributes independently to receptor desensitisation, remains accessible only through research protocols [24, 25]. Addressing these diagnostic gaps is a prerequisite for any meaningful clinical implementation strategy.

Intervention	Mechanism on insulin burden	Key trial(s)	Main cardiorenal benefit	Evidence
SGLT2 inhibitors	Reduce circulating insulin via glucosuria; suppress NLRP3 inflammasome; reduce intraglomerular pressure	DAPA-CKD [41], CREDENCE [63], EMPEROR-Reduced [64], EMPEROR-Preserved [65]	Reduced kidney failure, CV death, HF hospitalisation across CKD stages	A
GLP-1 receptor agonists	Improve insulin sensitivity; reduce hepatic insulin resistance; attenuate postprandial hyperinsulinaemia	LEADER [45], SELECT [66], FLOW [67]	Reduced major CV events; 22-24% reduction in composite kidney endpoints	A
Finerenone (nsMRA)	Blocks mineralocorticoid receptor-mediated fibrosis; attenuates aldosterone-driven insulin resistance	FIDELIO-DKD [68], FIGARO-DKD [69]	Reduced albuminuria and CKD progression in diabetic kidney disease	A
Metformin	Improves hepatic/peripheral insulin sensitivity; activates AMPK; reduces hepatic glucose output	UKPDS [70], DPP [71]	Reduced T2DM progression; cardiovascular benefit; endothelial improvement	B
Bariatric / metabolic surgery	Profound reduction of insulin secretion and resistance through weight-independent mechanisms	STAMPEDE [49], SLEEVEPASS [50]	Significant reduction in albuminuria, glomerular hyperfiltration, T2DM remission in Ob-CKD	B
Lifestyle: aerobic + resistance training	Reduces fasting insulin and HOMA-IR; improves muscle insulin signalling; decreases visceral adiposity	Look AHEAD [72], DPP [71]	Reduced insulin burden; 31% lower risk of very-high-risk CKD; delayed T2DM	B
Dietary modification (caloric restriction)	Reduces postprandial insulin demand; decreases visceral fat; attenuates compensatory hyperinsulinaemia	DiRECT [73], DPP [71]	5-10% weight loss reduces fasting insulin; T2DM remission in 46% at 1 year (DiRECT)	B

Table 3. Therapeutic strategies targeting hyperinsulinemia and their cardiorenal effects in CKM syndrome. Overview of pharmacological and lifestyle interventions that reduce insulin burden or improve insulin sensitivity, with corresponding evidence from major clinical trials and their impact on cardiovascular and renal outcomes. Evidence levels: A = strong (multiple randomized controlled trials or meta-analyses); B = moderate (single randomized controlled trial or large observational studies).

Several critical knowledge gaps remain to be addressed through future research. Population-specific hyperinsulinemia thresholds accounting for age, sex, ethnicity, body composition, and CKD stage are urgently needed, along with harmonised insulin immunoassay protocols. On the mechanistic side, whether restoration of pulsatile insulin secretion constitutes a viable therapeutic target remains to be established. Most importantly, pragmatic randomised controlled trials with hyperinsulinemia reduction as the primary therapeutic endpoint, and hard cardiovascular and renal outcomes as co-primary measures, are currently absent. Such trials should compare lifestyle interventions, SGLT2 inhibitors, GLP-1 receptor agonists, and their combinations across diverse CKM populations over at least three to five years of follow-up. Development of composite biomarkers integrating insulin dynamics with markers of endothelial function, inflammation, and early organ damage would further enhance risk stratification, and health-economic analyses of screening programmes are needed to inform implementation policy.

This review has inherent limitations. As a narrative synthesis, it lacks a pre-registered protocol and formal risk-of-bias assessment. Reverse causality is a major concern, particularly in CKD populations where reduced insulin clearance may itself contribute to hyperinsulinemia. Residual confounding, especially by adiposity, diabetes status, and baseline kidney function, cannot be excluded despite adjustment in observational studies. Heterogeneity of insulin assays, study populations, and outcome definitions across the included literature precludes definitive meta-analytic conclusions. The causal relationship between primary hyperinsulinemia and insulin resistance, while biologically plausible and supported by genetic epidemiological data, has not yet been established through

direct interventional evidence. These limitations notwithstanding, the convergent mechanistic, epidemiological, and therapeutic evidence reviewed here supports recognising hyperinsulinemia as a clinically relevant and potentially modifiable component of CKM syndrome.

Hyperinsulinemia represents a central and often under-recognised component of CKM syndrome, exerting effects on cardiac remodelling, renal function, and adipose tissue metabolism beyond overt hyperglycaemia. Emerging genetic and epidemiological evidence challenges the traditional view of hyperinsulinemia as purely compensatory, suggesting that it may act as an early contributor to disease development in specific phenotypes. Mechanistically, selective insulin resistance, profibrotic signalling, tubular sodium retention, and metabolic amplification pathways collectively shape the CKM phenotype across organ systems. Epidemiological data consistently support associations between elevated fasting insulin and adverse cardiovascular and renal outcomes, although causality remains unproven.

Important knowledge gaps persist, including the lack of standardised diagnostic thresholds and the absence of interventional trials specifically targeting hyperinsulinemia with hard cardiorenal outcomes. Nevertheless, integrating metabolic assessment including fasting insulin and HOMA-IR, into clinical evaluation may improve risk stratification and support a more mechanism-based approach to CKM management. Future research should prioritise prospective studies, standardisation of diagnostic criteria, and pragmatic trials translating mechanistic insights into clinically actionable strategies.

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