Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2026**; 31(11): 45828
https://doi.org/10.31083/FBL45828

Review

The Role of Neuronal Damage in Cardiovascular-Kidney-Metabolic Syndrome and the Therapeutic Strategy of Neuroregeneration

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Academic Editor: Moo-Ho Won
Submitted: 15 August 2025 Revised: 21 October 2025 Accepted: 29 October 2025 Published: 11 November 2026

Abstract

Cardiovascular-Kidney-Metabolic Syndrome (CKM), a concept introduced by the American Heart Association in 2023, encompasses the frequent coexistence of obesity, diabetes, chronic kidney disease, and cardiovascular disease. These conditions mutually reinforce one another and collectively contribute to CKM progression. As a critical component throughout this process, neural injury—including diabetic peripheral neuropathy, hypertension-related neurodegeneration, and uremic neuropathy—may influence disease progression through the neuroendocrine–immune axis, contributing to pathological feedback loops across target organs. Conventional interventions targeting individual organ systems may not fully address the interconnected nature of CKM. This review examines the molecular mechanisms and network dynamics of neural injury in CKM and evaluates current neural regeneration approaches—including stem cell transplantation, gene editing, neurotrophic factors, neuromodulation, and interdisciplinary therapies—for their potential to reconstruct neural architecture and support multi-organ homeostasis, together with challenges in their translational application. Overall, a comprehensive therapeutic strategy centered on neural regeneration may represent a potential approach for disrupting CKM-related pathological feedback loops and may become an important direction for future medical research.

Keywords: Cardiovascular-Kidney-Metabolic Syndrome; neurologic damage; neural regeneration; neuroendocrine-immune axis; multidimensional interventions

1. Introduction

Cardiovascular-Kidney-Metabolic Syndrome (CKM) is a concept introduced by the American Heart Association (AHA) in 2023 to address the high prevalence of chronic comorbidities. The syndrome is a complex disorder driven by the pathophysiological interplay of obesity, diabetes mellitus, chronic kidney disease, and cardiovascular diseases—including heart failure, atrial fibrillation, coronary artery disease, stroke, and peripheral arterial disease [1].

Nerve injury is now recognized as a pivotal link in the initiation and progression of CKM. It interconnects all systems involved in CKM and constitutes a central mechanism through which multiple factors interact in a complicated manner [2,3]. While the nervous system regulates the functions of the cardiovascular, renal, and metabolic systems, it is itself vulnerable to damage; neural injury can in turn injure the corresponding organs, creating a vicious cycle. Diabetic, hypertensive, and uremic neuropathies, for example, exacerbate damage to the affected organs. Critically, nerve injury further impairs cardiovascular, renal, and metabolic homeostasis by triggering immune, endocrine, and immuno-endocrine disturbances [4]. Previous studies have largely focused on single-system involvement or damage to individual organs, often overlooking the possibility that nerve injury may be a key factor throughout the entire course of CKM [3].

In the field of CKM therapeutics, innovative approaches that apply neural regeneration techniques to repair nerve damage—along with recent advances in stem-cell therapy, gene editing, and neurotrophic factors—are emerging as crucial directions for innovation [5]. However, translating these technologies into clinical practice remains challenging. Moreover, fundamental research into the pathogenesis of CKM is still scarce. For these reasons, this review aims to elucidate the impact of nerve injury on CKM, focusing on its pathogenic mechanisms and the feasibility—together with the formidable challenges—of neural regeneration, providing an objective account of these issues. By synthesizing current research advances, we seek to offer new perspectives for future clinical management of CKM.

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2. Neuro Injury Mechanisms in Cardiovascular, Renal and Metabolic Syndrome

Nerve injury participates in the initiation and progression of CKM in a multifaceted manner, establishing bidirectional causal relationships among the sympathetic nervous system, endocrine axes, and neuro-immune axis, ultimately leading to reciprocal impairment among the cardiovascular, renal, and metabolic systems. Diabetic peripheral neuropathy (DPN) suppresses nerve regeneration through hyperglycemia-induced microangiopathy, oxidative stress, and neuroinflammation, resulting in diminished sympathetic activity that damages the cardiovascular system and, via positive feedback, disrupts renal and metabolic homeostasis [4]. Hypertension intensifies neural dysfunction by increasing mural tension, injuring the endothelium, and restricting blood flow; it also directly harms the kidneys through excessive sympathetic activation while further aggravating neural injury. In line with this sympathetic–renal link, renal sympathetic denervation in patients with resistant hypertension reduces sympathetic activity, as reflected by decreased erythrocyte membrane β-adrenoreactivity [6]. End-stage chronic kidney disease (CKD) causes uremic neuropathy because of the accumulation of uremic toxins and metabolic toxicity, and this neural damage exacerbates metabolic derangements via impaired neuro-autonomic-cardiovascular reflexes [7,8]. Dysregulation of the neuroendocrine-immune (NEI) axis is pivotal in this process: the interplay among sympathetic outflow, endocrine hormones, and immune responses forms a vicious cycle that drives CKM progression (Fig. 1). The mechanisms and their interactions are discussed in detail below.

2.1 The Mechanism of DPN and Nerve Injury

Diabetes constitutes the largest component of CKM, and diabetic peripheral neuropathy (DPN) is its most common and most severe complication. DPN results from chronic hyperglycemia-driven microangiopathy, oxidative stress, neuroinflammation, and impaired nerve regeneration. Persistently high glucose increases oxidative stress at nerve terminals, generating advanced glycation end-products (AGEs) while triggering localized inflammatory responses that damage neurons and disrupt their function [4]. Accumulated AGEs engage their receptor RAGE to activate the NF-κB pathway, amplifying neuroinflammation and cellular injury. In addition, diabetes is typically accompanied by microvascular dysfunction—especially endothelial damage in small vessels—which deprives nerve terminals of adequate nutrients [9]. This ischemic insult accelerates neuronal death and functional loss.

Microvascular changes in diabetes further compromise neural blood supply; impaired microvascular function reduces perfusion to nerve endings, intensifying ischemic neural damage. Recent work shows that diabetic microangiopathy is closely linked to endothelial dysfunction, which disrupts the nitric oxide–endothelin balance, impairs vasodilation, and diminishes blood flow, thereby exacerbating neural injury [4,10]. Neuregulin-4 (NRG4) supports dendritic growth and branching in developing cortical neurons [11]. In high-glucose-exposed dorsal root ganglion neurons, IGF-1 activates PI3K/Akt/S6K signaling, reduces neuronal apoptosis, and restores neurite growth, highlighting its potential relevance to diabetic neuropathy [12]. Beyond diabetes, emerging evidence indicates that NRG4 also confers neuroprotection in other metabolic disorders, such as hyperlipidemia [10].

Growing evidence supports the concept that diabetic neuropathy is driven by chronic low-grade inflammation. Under sustained hyperglycemia, activated macrophages and T cells amplify local neuro-inflammation, accelerating nerve injury and promoting fibrosis [13]. Recent study has shown that modulating immune-cell activity and targeting cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) can delay neural damage; strategies that interrupt TNF-α signaling have already been shown to alleviate DPN, and the elucidation of these mechanisms is now guiding the development of novel immunomodulatory therapies [14].

Dysregulated sympathetic activation is another key contributor to DPN progression in diabetes. Excessive sympathetic outflow not only injures the cardiovascular system but also perturbs renal and metabolic functions via the intricate neuroendocrine-immune network [15]. Persistent sympathetic stimulation elevates mediators such as norepinephrine, intensifying vasoconstriction and microcirculatory impairment. The resulting reduction in blood perfusion leads to tissue hypoxia and malnutrition, disrupting neurotrophic support and ultimately causing neural dysfunction [16].

2.2 Nerve Damage Caused by High Blood Pressure

Chronic elevation of blood pressure subjects vessel walls to increased mechanical stress, provoking endothelial dysfunction and disrupting microvascular integrity. The consequent fall in organ perfusion deprives the nervous system of its trophic support and directly injures neurons [17]. Yang et al. [18] showed that silent cerebral infarcts and leukoaraiosis are common in inadequately controlled hypertensive patients, indicating that untreated hypertension is the principal driver of these covert cerebrovascular events, which progress insidiously over time. Such neural damage is not confined to the brain; comparable peripheral neuropathies develop in territories exhibiting microcirculatory failure, leading to impaired motor and sensory function [18,19]. Persistent hypertension also overactivates the sympathetic nervous system (SNS), accelerating cardiac and—most prominently—renal injury: heightened SNS tone augments renal sodium–water reabsorption and further stimulates the renin–angiotensin–aldosterone axis, increasing renal vascular resistance [20]. In metabol-

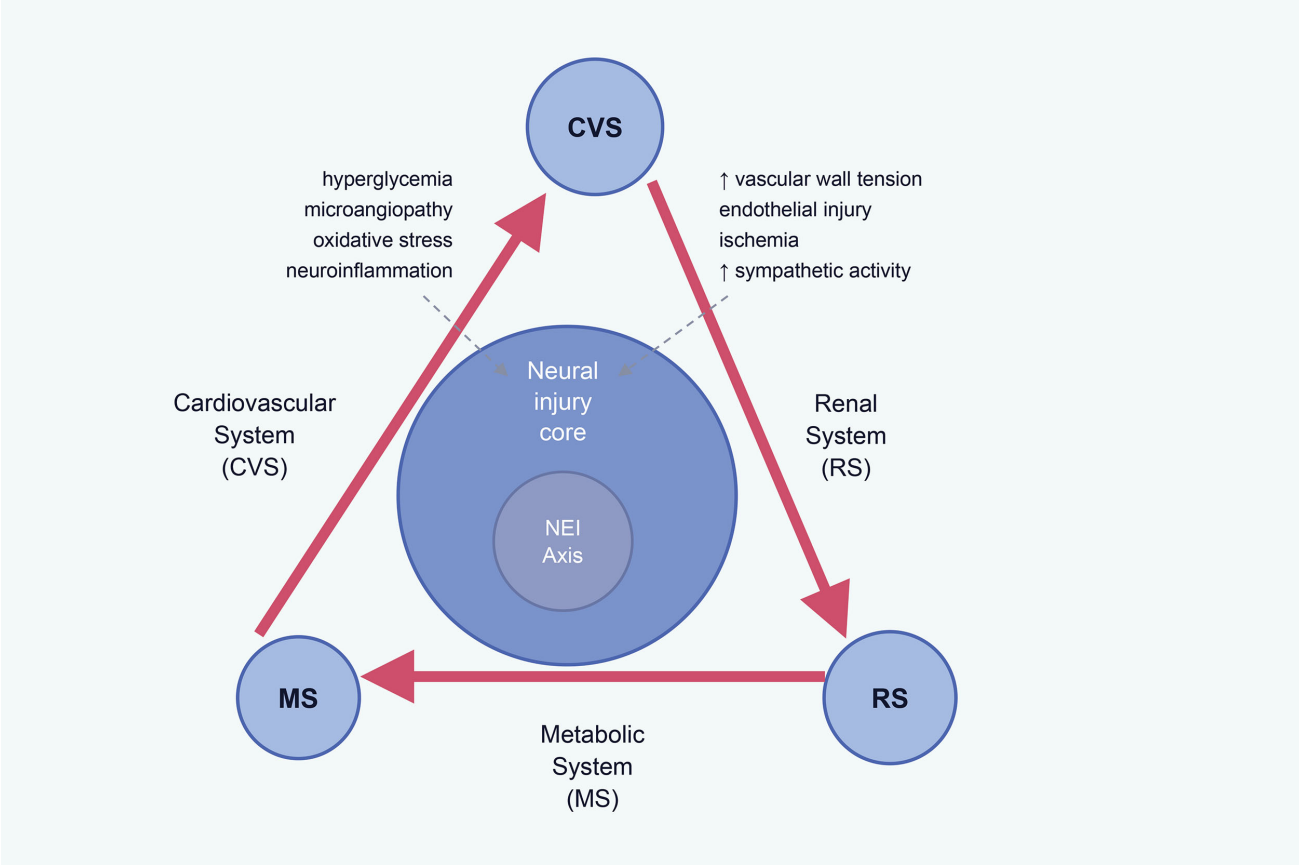


Fig. 1. The cardiovascular system (CVS), renal system (RS), and metabolic system (MS) interact through interconnected pathological pathways, collectively influencing the central nervous system. The central region represents the neural injury core and the neuroendocrine–immune (NEI) axis within it. Cardiovascular factors include increased vascular wall tension, endothelial injury, ischemia, and heightened sympathetic activity, whereas metabolic factors include hyperglycemia, microangiopathy, oxidative stress, and neuroinflammation. Solid red arrows indicate the interactions among the three peripheral systems and the direction of their feedback loop; dashed arrows indicate the potential effects of peripheral pathological processes on the neural injury core. CVS, cardiovascular system; RS, renal system; MS, metabolic system; NEI, neuroendocrine–immune.

ically dysregulated hypertensive individuals, progressive deterioration of peripheral nerve conduction closely parallels SNS overdrive and declining renal function.

Hypertension-induced vascular dysfunction impedes neural repair and regeneration through microcirculatory insufficiency and endothelial damage, thereby intensifying neurodegeneration. This effect is amplified by hypertension-triggered release of reactive oxygen species (ROS) and pro-inflammatory cytokines; ROS compromise neural tissue integrity and render the blood–brain barrier (BBB) more vulnerable to ischemic insult [21]. Moreover, hypertension increases BBB permeability, allowing neurotoxic substances to enter the brain, thereby exacerbating neural injury and accelerating cognitive decline [19]. Chronic hypertension also inflicts damage on the peripheral nervous system, giving rise to sensorimotor deficits. Longitudinal study now demonstrates that sustained hypertension induces peripheral-nerve demyelination and axonal degeneration, manifesting as neuropathic pain and functional impairment [22]. Oliveira-Sales et al. [23] identified neuroinflammation and oxidative stress as central drivers of the sensorimotor dysfunction elicited by hypertension. Pharmacological modulation of oxidative-stress markers not only halted progression but actually reversed the deficits: in their hypertensive mouse model, treated animals regained baseline neurological performance.

2.3 Nerve Disease of Uremia

In CKM, nerve injury is neither merely a complication nor a secondary event; it is a pivotal driver of disease progression. Once CKD reaches end-stage renal disease, profound cardio-renal-metabolic dysregulation triggers a characteristic uremic neuropathy. Metabolic toxins activate the neuronal NLRP3 inflammasome, increasing secretion of pro-inflammatory cytokines such as IL-1β and IL-18, which generate local inflammation, promote neuronal apoptosis, and thereby intensify neural damage [7]. Additional studies show that uremic toxins can activate en-

dothelial inflammatory pathways (e.g., MAPK and NF-κB), disrupt the blood–brain barrier, and further exacerbate the neurodegenerative process. These toxins not only destabilize the neuronal membrane but also elicit oxidative stress that activates p38MAPK, JNK, and related signaling cascades, ultimately leading to loss of neurological function [8].

As renal failure progresses, the circulating levels of protein-bound uremic toxins—such as indoxyl sulfate and p-cresyl sulfate—rise sharply. Among these toxins, indoxyl sulfate has been shown to trigger oxidative stress in peripheral nerve tissue and to contribute to peripheral nerve dysfunction in patients with chronic kidney disease [24]; other protein-bound uremic toxins may exert additional neurotoxic effects, but their specific contributions to axonal injury and Schwann-cell dysfunction remain to be fully characterized. Moreover, metabolic toxicity activates MAPK and NF-κB pathways, provoking demyelinating inflammation and shifting the injury from a static to a dynamic process. Critically, this form of damage exhibits "systemic projection": even if central nervous structures are not directly exposed to uremic toxins, feedback through the autonomic nervous system can still disrupt heart-rate variability, vasomotor reflexes, and renin–angiotensin–aldosterone system (RAAS) regulation [25].

Most patients with chronic kidney disease (CKD) are in a state of chronic, low-grade systemic inflammation. Circulating pro-inflammatory mediators—including IL-6, TNF-α, and CRP—are elevated and can traverse the blood–nerve barrier, thereby activating local neuro-immune responses. Studies have shown that activation of the TLR4 receptor, via a MyD88-dependent pathway, potentiates microglial activation, promotes neuronal apoptosis, and drives demyelination. These events collectively sustain neuroinflammatory cascades and neuronal injury, leading to long-term neurological sequelae [26]. Both renal anemia and hyperhomocysteinemia compromise oxygen delivery to neural tissue and impair endothelial function, aggravating microcirculatory deficits within peripheral nerves [27]. Thus, a pathological loop of "metabolic toxicity → immune activation → neural damage" is established, accelerating the emergence of neurological complications in cardio-renal-metabolic (CKM) syndrome.

More critically, autonomic dysfunction is now recognized as a key driver in the initiation and progression of uremic neuropathy [25,27]. Reduced heart-rate variability (HRV) serves as an early and sensitive marker of autonomic impairment, often manifesting before overt CKD is diagnosed [28]. Sympathetic overactivity not only precipitates hypertension and left-ventricular hypertrophy but also activates the renin–angiotensin–aldosterone system (RAAS), promoting sodium and water retention and thereby accelerating CKD progression. In addition, sympathetic-mediated lipolysis intensifies insulin resistance and lipotoxicity, providing a metabolic substrate for neural injury. These intertwined mechanisms convert isolated nerve damage into a systemic, self-reinforcing cycle that perpetuates whole-body metabolic dysregulation in CKD [29].

2.4 Neuroendocrine-Immune Axis Regulation

The neuroendocrine-immune (NEI) axis is a regulatory network that integrates the sympathetic nervous system (SNS), the endocrine system, and the immune system. During the development of cardio-renal-metabolic (CKM) syndrome, dysregulation of the NEI axis amplifies injury to the cardiovascular, renal, and metabolic systems through multiple converging pathways [30]. Excessive sympathetic drive elevates circulating stress hormones—cortisol, epinephrine, and norepinephrine—leading to endocrine imbalance and hyper-inflammatory immune responses. These factors reinforce one another in a positive-feedback loop, creating a vicious cycle that accelerates the onset and progression of CKM [25,31]. Beyond these canonical pathways, NEI-axis dysregulation is also linked to alterations in the gut microbiota and their immunomodulatory effects; reduced microbial diversity has been significantly correlated with sympathetic activation and immune dysfunction, offering a novel perspective on CKM pathogenesis [32]; conversely, gut-microbiota-targeted interventions, such as probiotic supplementation, have shown favorable effects on cardiometabolic parameters in experimental models [33].

The SNS is the principal effector arm of the NEI axis. It releases neurotransmitters such as norepinephrine and epinephrine to orchestrate cardiac, renal, and metabolic functions. Chronic sympathetic hyperactivity directly precipitates hypertension, imposes excessive cardiac workload, and reduces renal perfusion, thereby hastening cardiovascular deterioration. It also promotes insulin resistance and dysregulated lipid metabolism, exacerbating metabolic syndrome [34]. Sympathetic activation further stimulates the renin–angiotensin–aldosterone system (RAAS), leading to volume expansion, sodium and water retention, edema, and sustained hypertension. Recent evidence indicates that prolonged SNS activation up-regulates systemic pro-inflammatory cytokines such as interleukin-6 (IL-6), amplifying whole-body inflammation and aggravating cardiometabolic disease [35]. Additionally, persistent sympathetic stimulation drives renal tubular-interstitial fibrosis, enhances oxidative stress, and fuels intrarenal inflammation, perpetuating a self-amplifying injury cycle [36]. Beyond RAAS activation, chronic SNS excitation elevates plasma ACTH, norepinephrine, and catecholamine levels through diverse neurotransmitters, cytokines, and signaling cascades, sustaining low-grade systemic inflammation and immune activation that progressively damage multiple organ systems [37].

Patients with cardio-renal-metabolic (CKM) syndrome are locked in a chronic stress state that chronically activates the endocrine system, elevating circulating cortisol and norepinephrine (NE) [38]. Cortisol, the prototypical

stress hormone, is released in excess and directly impairs insulin action, precipitating insulin resistance and attendant obesity. Simultaneously, it aggravates cardiovascular injury by raising blood glucose, increasing vascular tone, and provoking endothelial dysfunction [39]. Clinical data show that sustained hypercortisolaemia drives metabolic dysregulation, induces oxidative damage in endothelial cells, and accelerates atherogenesis [40]. Epinephrine and norepinephrine amplify sympathetic output: heightened levels sensitize the myocardium to stress and promote renal sodium–water retention, fuelling hypertension and oedema [41].

Immune responses are equally pivotal in CKM pathogenesis. Cytokines and chemokines orchestrate endothelial injury, thrombosis, and atherogenesis, while initiating tubular inflammation and driving interstitial fibrosis that worsen renal damage [42]. Sympathetic nerves directly modulate immune-cell function via neurotransmitter release; activated immunity, in turn, feeds back cytokine signals that re-excite sympathetic and endocrine circuits, perpetuating a vicious cycle. Recent work highlights T-cell subsets as critical integrators within the neuroendocrine-immune (NEI) axis: distinct T-cell programs sustain and amplify adaptive immunity [43], while macrophage polarization toward a reparative phenotype—dependent on efferocytosis and fatty-acid oxidation—determines whether injury resolves or progresses to chronic inflammation, tissue damage, and fibrosis [44]; dysregulation of these programs may thereby accelerate CKM progression. Thus, the NEI axis operates as a highly interactive network in which sympathetic, endocrine, and immune systems reinforce one another, collectively fuelling the initiation and evolution of CKM (Fig. 2).

3. Research Progress of Nerve Regeneration and CKM Treatment Strategy

Neuroregeneration constitutes an intrinsic self-repair mechanism that can be therapeutically augmented after injury. Interventions such as stem-cell transplantation, gene editing, administration of neurotrophic factors, neural stimulation, and pharmacotherapy are employed to promote axonal regrowth, synaptic remodeling, and functional restoration [45]. By repairing damaged neural architecture and re-establishing neurotransmission, these strategies improve the function of affected organ systems and break the multisystem vicious cycle initiated by nerve injury. In the peripheral nervous system, dedifferentiated Schwann cells secrete neurotrophic factors (e.g., NGF and BDNF) and clear axonal debris, thereby fostering axonal regeneration and synaptic plasticity. This restores autonomic balance, stabilizes heart rate, blood pressure, and vascular tone, and reduces cardiovascular workload [46,47]. Concurrently, re-establishing sympathetic–parasympathetic equilibrium enhances renal perfusion and filtration, while re-normalizing endocrine and metabolic homeostasis—alleviating insulin resistance and dyslipidaemia. Advanced tools such as stem cells and gene editing further amplify regenerative efficiency, ensuring coordinated recovery of cardiac, renal, and metabolic functions. Neural stimulation may modulate neuroplasticity and autonomic function [48,49], while antioxidant and anti-inflammatory pharmacological interventions may help reduce oxidative stress and neuroinflammation [50,51]. Thus, neuroregeneration is not merely a localized repair process; it represents the reconstitution of the neuroendocrine-immune network that underpins global restoration of cardiovascular, renal, and metabolic health (Table 1, Ref. [52,53,54,55,56,57,58,59,60]).

3.1 Stem Cells and Gene Therapy

In recent years, stem-cell therapy and gene-editing technologies have made notable advances in neural repair and now show considerable promise for cardio-renal-metabolic (CKM) disorders. CKM is often characterized by widespread systemic nerve injury, encompassing autonomic dysfunction, cognitive decline, and neurodegenerative changes [61]. Such damage not only compromises basic neural functions but also accelerates cardiovascular decompensation, renal failure, and metabolic dysregulation [62]. Neural stem cells (NSCs) and induced pluripotent stem cells (iPSCs) provide new avenues for neural repair. Their regenerative capacity lies in sustained self-renewal, directed differentiation into neurons, astrocytes, or oligodendrocytes, and paracrine secretion of neurotrophic factors that foster axonal regrowth and synaptic remodeling at the site of injury [63,64]. Beyond replacement, stem cells modulate immunity and dampen inflammation, thereby improving cardiac and renal performance while stabilizing metabolic homeostasis [65]. In a preclinical study, intravenous administration of iPSC-derived endothelial progenitor cells attenuated ischemic acute kidney injury and the associated cardiac dysfunction in mice, demonstrating that stem-cell therapy can concurrently protect the kidney and the heart [52]. Nevertheless, clinical translation faces hurdles: low post-graft cell survival, imprecise lineage commitment, and potential immune rejection [66]. Thus, optimizing cell sources, devising robust immune-tolerance strategies, and enhancing engraftment efficiency remain urgent priorities.

Complementary to tissue-engineered stem-cell approaches, CRISPR/Cas9 and other ultra-precise gene-editing platforms offer heritable specificity for neural repair. Correcting key molecular drivers—such as inserting or up-regulating neurotrophic-factor genes (BDNF, NGF, etc.)—is a promising strategy for neural repair; its rationale is supported by evidence that BDNF can modulate inflammatory cytokine secretion in macrophages [67] and by the characterization of axonal degeneration pathways, such as acrylamide-induced noradrenergic axon degeneration, that editing-based approaches may ultimately target [68]. Editing of inflammatory mediators such as TNF-α and

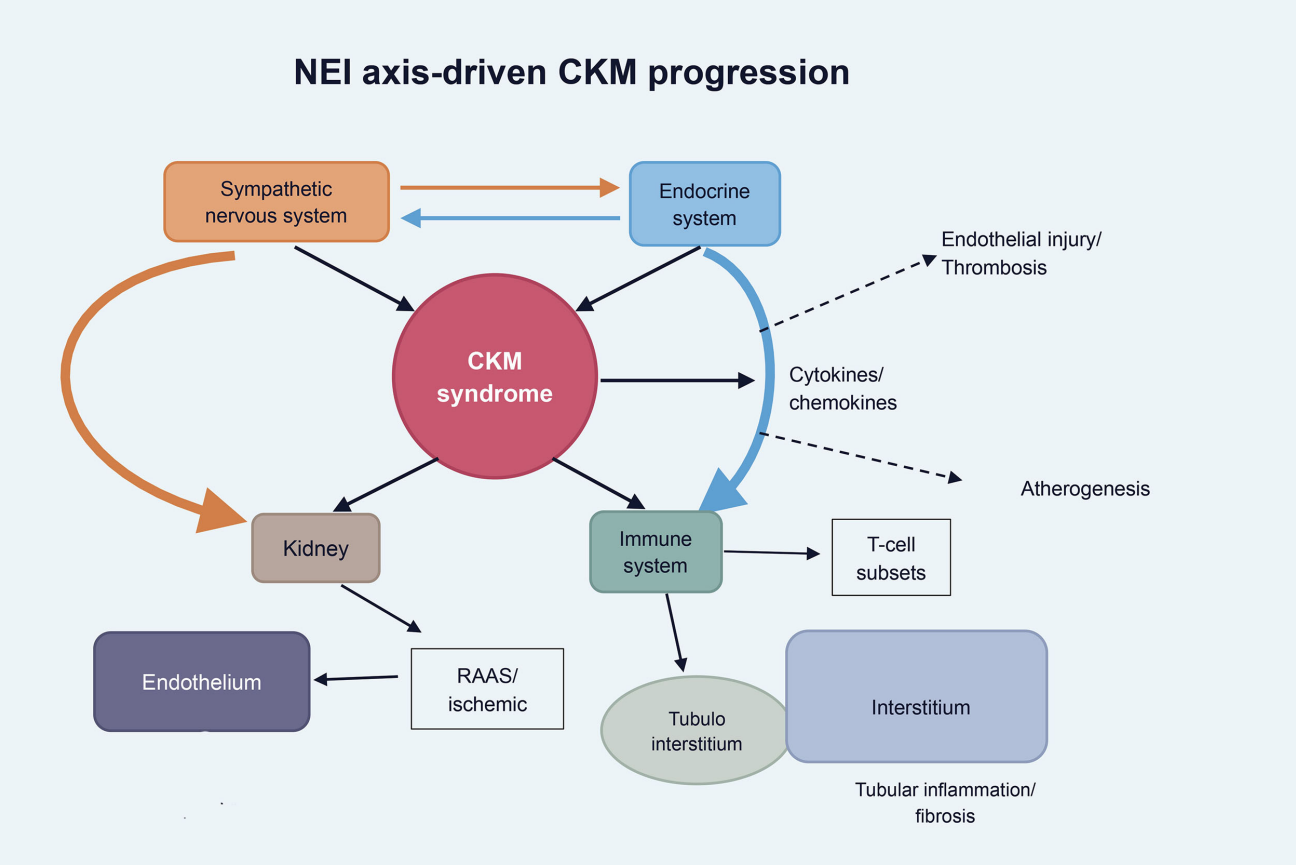


Fig. 2. NEI-axis–driven progression of Cardiovascular-Kidney-Metabolic (CKM) syndrome. Sympathetic and endocrine signals first induce endothelial injury, leading to thrombosis. Damaged endothelium and injured tissues release cytokines/chemokines that activate and recruit immune cells, with T-cell subsets playing a central role. Activated immunity amplifies tubular inflammation via the renin–angiotensin–aldosterone system (RAAS) and triggers an ischemic reflex and fibrosis. Fibrosis, in turn, worsens tubulo-interstitial injury, perpetuating CKM progression. Critically, inflammatory mediators released by immune cells feed back to re-excite sympathetic and endocrine circuits, establishing a self-reinforcing vicious cycle within the neuroendocrine-immune (NEI) axis that accelerates CKM evolution.

IL-1β to remodel the neuro-immune microenvironment represents an additional potential avenue, although direct evidence in neural repair settings is still emerging. Additionally, correcting metabolic or neurodegeneration-associated mutations represents a longer-term goal of gene-editing approaches to neural repair [64].

Despite encouraging pre-clinical results, clinical deployment is limited by off-target effects, durability concerns, and ethical constraints [69]. Within the CKM context, gene editing must be executed with exquisite precision—tightly controlling molecular switches to avoid systemic toxicity or collateral impairment of other organs—before it can safely enter human therapeutics.

The synergistic use of stem-cell therapy and gene editing offers a more precise and comprehensive strategy for neural repair. By genetically enhancing stem-cell function, it becomes possible to achieve superior targeted differentiation at injury sites and to improve post-transplant cell survival [53]. In a 2019 study, CRISPR-based activation of endogenous neurotrophic genes in adipose-derived stem cell sheets was used to stimulate peripheral nerve regeneration; the engineered cell sheets promoted axonal regrowth, remyelination, and functional recovery in a rat model of sciatic nerve injury, pointing to a promising new direction for repairing neural damage [53]. Combined stem-cell and gene-editing approaches may therefore become a pivotal therapeutic modality for CKM-related neural injury and its complications; however, significant technical hurdles and ethical concerns still need to be resolved.

3.2 Neural Stimulation and Regulation

Cardio-renal-metabolic (CKM) syndrome is frequently accompanied by neural dysfunction—most notably dysautonomia—which not only aggravates cardiovascular, renal, and metabolic derangements but also worsens overall prognosis. Neuromodulation and neurostimulation techniques have emerged as important therapeutic modalities for neurological disorders and are equally applicable to

Table 1. Multi-system restorative effects of neuro-regenerative strategies in CKM syndrome.

Intervention	Mechanisms & actions	Cardiovascular effects	Renal effects	Metabolic effects	Representative studies/technologies
Stem-cell therapy	NSC/iPSC differentiation, paracrine release of BDNF/NGF, immunomodulation	Improves cardiac performance; lowers sympathetic tone; stabilizes heart rate & blood pressure	Restores renal perfusion & filtration; reduces inflammation	Ameliorates insulin resistance; normalizes lipid metabolism	Intravenous administration of iPSC-derived endothelial progenitor cells attenuated renal ischemia–reperfusion injury and associated cardiac dysfunction in mice [52]
Gene editing	CRISPR/Cas9-mediated up-regulation of BDNF/NGF; down-regulation of TNF-α, IL-1β	Potential to support autonomic balance and cardiovascular function	Potential to modulate renal injury through neuro-immune pathways	Potential to support metabolic homeostasis	CRISPRa-enhanced adipose-derived stem cell sheets promoted axonal regeneration, remyelination, and functional recovery in a rat model of sciatic nerve injury [53]
Neural stimulation	Electrical modulation of central/peripheral circuits; network re-patterning	Stabilizes BP & HRV; reduces cardiac workload	Enhances renal blood flow & filtration	Re-balances neuro-endocrine axis to restore metabolic homeostasis	2025 review: case-based evidence that DBS targeting the ventrolateral periaqueductal gray lowered BP in severe drug-resistant hypertension, potentially via reduced sympathetic outflow [54]
Pharmacotherapy	Antioxidant, anti-inflammatory, and neurotrophic factor supplementation	Reduces oxidative stress; improves cardiac function	Decreases neuro-inflammation; protects nephron integrity	Improves insulin sensitivity; lowers serum lipids	NGF implicated in metabolic complications and neurodegeneration, with potential relevance to CKM [55]
Cross-disciplinary integrated therapy	Synergistic combination of stem cells + CV drugs + metabolic agents targeting multiple nodes; ACEI + NSCs combination proposed based on RAS–neurodegeneration crosstalk, although direct experimental validation is still awaited [56]	2024 trial: semaglutide reduced clinically important kidney outcomes in patients with type 2 diabetes and CKD [60]	Not yet established.	GLP-1 agonists improved glycaemic control and conferred neuroprotection [57,58,59]	2024 trial: semaglutide reduced clinically important kidney outcomes in patients with type 2 diabetes and CKD [60]

NSC, Neural stem cells; iPSC, induced pluripotent stem cells; IL, interleukin; HRV, heart-rate variability; CKM, Cardiovascular-Kidney-Metabolic Syndrome; DBS, deep brain stimulation; TMS, Transcranial magnetic stimulation; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; CRISPR, clustered regularly interspaced short palindromic repeats; TNF-α, tumor necrosis factor-alpha; CV, cardiovascular; BP, blood pressure; MI, myocardial infarction; ACEI, angiotensin-converting enzyme inhibitor; GLP, glucagon-like peptide.

CKM. Deep brainstem stimulation, transcranial magnetic stimulation (TMS), sympathetic nerve modulation, and deep brain stimulation (DBS) all show promising efficacy [70].

Transcranial magnetic stimulation (TMS) delivers focused magnetic pulses through the scalp to modulate cortical neuronal activity. Over the past few years, TMS has achieved major breakthroughs in neural repair: it improves cognitive and mood disturbances, enhances cortical neuroplasticity, and—critically—exerts powerful sympathomodulatory effects [71]. By targeting specific cortical areas, TMS can rebalance autonomic control, thereby stabilizing blood-pressure fluctuations and heart-rate variability, reducing cardiac workload, and exerting cardioprotective effects. Concomitantly, renal function benefits from this autonomic recalibration [48]. Although the exact mechanisms remain incompletely defined, extensive clinical and pre-clinical evidence confirms that TMS provides multifaceted benefits—neural repair, cardiovascular regulation, and metabolic equilibrium—through neuromodulation [49].

Deep brain stimulation (DBS) involves surgically implanting electrodes to deliver targeted electrical pulses to specific brain nuclei. Originally validated for Parkinson's disease and other neurodegenerative disorders [72], DBS is now being investigated in cardio-renal-metabolic (CKM) syndrome to modulate the cross-talk among neural, cardiovascular, renal, and metabolic pathways. Studies demonstrate that stimulation of the basal ganglia, thalamus, or related autonomic hubs can markedly correct dysautonomia, re-establish physiologic heart-rate and blood-pressure variability, and thereby ameliorate both cardiac and renal dysfunction [73,74]. A 2025 review discussed emerging case-based evidence that deep brain stimulation targeting the ventrolateral periaqueductal gray may reduce blood pressure in severe drug-resistant hypertension, potentially by decreasing sympathetic outflow to the vasculature [54]. By electrically re-patterning neuronal activity and re-balancing network function, DBS simultaneously protects the cardiovascular system and fosters neural repair and functional recovery [75]. Nevertheless, long-term safety profiles, optimal stimulation parameters, and truly individualized DBS protocols remain to be rigorously defined.

Sympathetic neuromodulation has achieved a therapeutic breakthrough in CKM. Chronic sympathetic overactivity is tightly linked to cardiovascular disease, renal impairment, and metabolic dysregulation; conversely, precise sympathetic inhibition (or targeted activation) improves cerebral–cardiac perfusion, enhances glomerular filtration, and normalizes glucose–lipid metabolism [76,77]. In line with the therapeutic potential of sympathoinhibition, pharmacological blockade of sympathetic vascular tone with the α1-adrenoceptor antagonist doxazosin reduced ambulatory blood pressure and sympathetic nervous activity in hypertensive patients with type 2 diabetes and overt nephropathy [78]. By titrating sympathetic drive with high precision, this technology not only stabilizes the cardiovascular system but also re-calibrates whole-body metabolic and endocrine balance. Sympathetic neuromodulation therefore offers a promising route toward personalized, multi-organ therapy in CKM syndrome, delivering synchronous benefits across the heart, kidneys, and metabolic circuitry.

3.3 Drug Therapy Strategy

In CKM, oxidative stress, chronic low-grade inflammation, and neurodegeneration not only injure the nervous system but also precipitate cardiac, renal, and metabolic dysfunction [79]. Consequently, many commercially available neuroprotective drugs possess antioxidant properties that are equally applicable to CKM; by scavenging free radicals they attenuate oxidative damage and facilitate neural recovery. Studies show that antioxidant formulations, such as nutriosomes loaded with grape-pomace phytochemicals, exert antioxidant and neuroprotective effects in models of oxidative stress and in a mouse model of Parkinson's disease [50], supporting the broader potential of antioxidant strategies to reduce neural injury.

Persistent inflammation is another key driver of neural damage in CKM. Anti-inflammatory agents—non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and selected immunosuppressants—are therefore integral to pharmacological neuroprotection. In a 2018 mouse study of traumatic brain injury, combined pharmacological blockade of interleukin-1α (IL-1α) and IL-1β signaling protected mice from cognitive dysfunction after injury [51]. These findings underscore the principle that anti-inflammatory therapy can curb neural inflammation and foster repair, although prolonged use risks immunosuppression; thus, dosing must be tightly controlled.

Neurotrophic factors—such as BDNF, NGF, and FGF—constitute a key class of agents that foster neuronal survival, growth, and differentiation, thereby accelerating neural repair [80]. Beyond their trophic effects, modulation of intracellular signaling pathways—such as adenylate cyclase signaling, which can be targeted to promote neurogenesis—may offer additional pharmacological opportunities for protecting the nervous system [81]. NGF has been implicated in metabolic complications and in neurodegenerative processes such as Alzheimer's disease, supporting its potential relevance to both the metabolic and neurological components of CKM [55]. BDNF, acting through TrkB receptor activation, safeguards neurons and promotes their regeneration; extensive pre-clinical evidence confirms its ability to improve cognition and overall neurological status in CKM [82]. Despite these encouraging findings, translating these agents to the clinic remains challenging. Therapeutic efficacy is influenced by inter-individual variability, disease stage, and the precise selection of molecular targets. Future work must therefore concentrate on achieving

Table 2. Nerve injury and regeneration in Cardiovascular-Kidney-Metabolic (CKM) syndrome.

Module	Key point	Mechanism/discovery	Representative intervention	Reference(s)
Definition	CKM Syndrome (AHA 2023)	Clustering of obesity, diabetes, CKD, and CVD that mutually exacerbate one another	Multidisciplinary, integrated management required	[1]
Nerve Injury Mechanisms	Diabetic Peripheral Neuropathy (DPN)	Chronic hyperglycemia → microangiopathy, AGEs–RAGE axis, NF-κB activation	Neuregulin-4, BDNF, anti-inflammatory agents (e.g., IL-1β blockade)	[4,9,14,90]
	Hypertension-related Neurodegeneration	Endothelial damage, BBB disruption, sympathetic over-activation	Antioxidants, β-blockers, neuromodulation	[17,20,22,23]
	Uremic Neuropathy	Accumulated uremic toxins → NLRP3 inflammasome, oxidative stress, demyelination	Toxin removal, anti-inflammatory, neuro-protective agents	[7,24,26,29]
Master Regulator	Neuroendocrine-Immune (NEI) Axis	Sympathetic hyperactivity → RAAS activation, cortisol excess, chronic inflammation	Neuromodulation, anti-inflammatory therapy, β-blockers	[30,31,36,43]
Regenerative Strategies	Stem-Cell Therapy	iPSC/NSC transplantation → neuronal differentiation, paracrine release of BDNF, NGF	CRISPR-enhanced stem cells to boost survival and targeting	[52,53,63]
	Gene Editing	CRISPR-mediated up-regulation of BDNF/NGF and down-regulation of TNF-α/IL-1β	Precise neural repair, modulation of neuro-immune milieu	[53,67,68]
	Neuromodulation Techniques	TMS, DBS, sympathetic nerve stimulation	Restore autonomic balance, improve cardiac & renal indices	[49,54,70,77]
	Pharmacotherapy	Antioxidants, neurotrophic factors, GLP-1R agonists, ACEI/ARB	Multi-target synergy: anti-inflammatory, antioxidant, metabolic control	[55,57,60,79]
Interdisciplinary Integration	Multi-Organ Concurrent Intervention	Simultaneous targeting of neural, cardiac, renal, and metabolic systems	Combination: stem cells + ACEI + GLP-1RA + antioxidants	[56,60,83,87]

AHA, American Heart Association; CKD, chronic kidney disease; AGEs, advanced glycation end-products; RAGE, Receptor for AGEs; BBB, blood–brain barrier; RAAS, renin–angiotensin–aldosterone system; DBS, deep brain stimulation; ARB, angiotensin II receptor blocker; CVD, cardiovascular disease; NF-κB, nuclear factor kappa B; NLRP3, NLR family pyrin domain containing 3.

precise drug localization, optimizing dosing regimens, and minimizing adverse effects.

3.4 Cross-Disciplinary Treatment Model

Cross-disciplinary, integrative therapy represents a newly emerging paradigm that offers unique value for cardio-renal-metabolic (CKM) syndrome. By simultaneously targeting neural regeneration, cardiovascular modulation, renal protection, and metabolic intervention, such multidimensional regimens act synergistically across organ systems to markedly enhance therapeutic efficacy.

Neural regeneration serves as the entry point for this integrated model. Neural stem cells (NSCs) and neurotrophic factors have already entered clinical use for nerve-injury repair [83]. NSCs secrete BDNF, NGF and other trophic molecules that foster neuronal growth and repair while re-balancing the neuro-endocrine network to improve cardiac and metabolic function [84]. The renin–angiotensin system (RAS) is increasingly recognized as a bridge between cardiovascular regulation and neurodegenerative processes, and RAS-targeting agents such as angiotensin-converting enzyme inhibitors may therefore extend their benefits beyond hemodynamic control to neural protection [56]. On this rationale, combined strategies pairing NSC-based neural regeneration with ACE inhibition represent a promising avenue for multi-system repair in CKM, although direct experimental evidence is still awaited.

Parallel advances have been achieved in cardiovascular and renal therapeutics. β-blockers, calcium-channel blockers, antioxidants, IL-1β antagonists and other anti-inflammatory agents are standard tools in cardiology; beyond their hemodynamic benefits, they attenuate myocardial workload, suppress oxidative stress, and modulate systemic inflammation—each of which supports neural recovery [85,86]. In rats with myocardial infarction, post-infarct cognitive impairment has been linked to altered mitochondrial dynamics, suggesting that preserving mitochondrial

function after MI may help protect cognition [87]. Likewise, SOD, vitamin E and related antioxidants scavenge free radicals, inhibit neuronal injury, and thereby enhance neural repair [88].

Metabolic control is a linchpin for overall therapeutic success in cardio-renal-metabolic (CKM) syndrome. Diabetes, obesity, and other metabolic derangements are now recognized as major drivers of both its onset and progression [89]. Recent data show that integrating metabolic therapy with neuroprotection and cardiovascular support yields greater efficacy than any single-domain approach. In patients with type 2 diabetes, GLP-1 receptor agonists such as liraglutide have demonstrated substantial cardiovascular and cardio-renal benefits, as shown by network meta-analyses of cardio-renal outcomes [57]; mechanistic work continues to define the receptor-mediated pathways underlying these pleiotropic metabolic effects [58]. Beyond glycaemic and weight control, GLP-1 receptor agonists are also being evaluated for pain treatment and other neurological indications, suggesting additional neuroprotective potential that may help mitigate neural damage [59].

Cross-disciplinary care leverages precisely this synergy: cardiovascular drugs can be paired with neuroregenerative stem-cell therapy so that stem-cell–derived neurotrophic factors reinforce myocardial recovery; concurrently, antioxidants, anti-inflammatory agents, and metabolic modulators can be combined to attack the CKM pathological network at multiple nodes. In the clinical setting, a 2024 randomized trial demonstrated that the GLP-1 receptor agonist semaglutide reduced the risk of clinically important kidney outcomes in patients with type 2 diabetes and chronic kidney disease, illustrating how metabolic agents can confer multi-organ protection in CKM [60].

4. Future Research Direction and Clinical Prospect

Multidimensional intervention is poised to become a cornerstone of future neuro-repair strategies. By integrating pharmacotherapy, stem-cell therapy, gene editing (notably CRISPR platforms), and neuromodulation (TMS, DBS, etc.), we can simultaneously drive neural regeneration and markedly enhance CKM outcomes. Stem-cell and gene-editing approaches are especially powerful for correcting injury-related genes, while neuromodulatory techniques further accelerate axonal regrowth and circuit re-balancing. Within a comprehensive CKM framework, such layered therapies are better able to address the syndrome's multifactorial pathophysiology, yielding superior, system-wide benefits (Table 2, Ref. [1,4,7,9,14,17,20,22,23,24,26,29,30,31,36,43,49,52,53,54,55,56,57,60,63,67,68,70,77,79,83,87,90]).

However, translating these advances from the laboratory to the clinic still presents several unresolved issues: Can therapeutic efficacy be objectively quantified? Will there be toxic or off-target effects on patients' normal tissues? What will the long-term outcomes of the disease be? For gene editing and stem-cell therapies in particular, ensuring therapeutic precision and preventing potential adverse effects remain the most pressing challenges.

5. Conclusion

Multidimensional interventions integrating pharmacotherapy, stem-cell therapy, gene editing, and neuromodulation offer a promising strategy to promote neural repair and improve cardiovascular–kidney–metabolic (CKM) outcomes. Clinical translation requires rigorous evaluation of therapeutic efficacy, precision, safety, and long-term outcomes.

Author Contributions

MK and QL wrote the manuscript, and contributed to the conceptualization and design of the study. SS, XZ and HY were responsible for the conceptualization and design of the review framework. ZY, XG, JZ and CZ performed the systematic literature search and screening. All authors read and approved the final version of the manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This work was supported by National Natural Science Foundation of China (Grant Nos. U23A20398; Grant Nos. 82030007), Noncommunicable Chronic Diseases-National Science and Technology Major Project (Grant Nos. 2024ZD0537707), Open Research Projects of the Ministry of Education Innovation Center for Basic Medical Research on Metabolic Cardiovascular Diseases (Grant Nos. xnykdxcxzx-2024-13).

Conflicts of Interest

The authors declare no conflicts of interest.

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