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REVIEW

Addressing the "Nitric Oxide Crisis" in Cardiovascular–Kidney–Metabolic Syndrome: Therapeutic Potential of the Inorganic Nitrate–Nitrite–NO Pathway

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ABSTRACT

Cardiovascular–kidney–metabolic (CKM) syndrome is a complex interaction of cardiovascular diseases, chronic kidney disease (CKD), and metabolic disorders, with its global prevalence rising due to increasing obesity and metabolic risk factors. The convergence of these conditions significantly worsens patient outcomes, leading to higher morbidity and mortality rates. Key pathophysiological mechanisms underpinning CKM syndrome include insulin resistance, oxidative stress, inflammation, and vascular dysfunction, all of which are exacerbated by reduced nitric oxide (NO) bioavailability and associated signaling dysfunctions. In clinical practice, organic nitrate has been used as NO donors; however, issues such as tolerance, side effects, and endothelial damage limit their effectiveness. The inorganic nitrate–nitrite–NO pathway offers a promising alternative, as emerging evidence from animal and human studies suggests that enhancing this pathway can significantly improve the progression of metabolic disorders, cardiovascular diseases, and CKD. The potential mechanisms may lie in its ability to improve the core pathophysiological processes of CKM syndrome, including inflammation, oxidative stress, insulin resistance, and vascular dysfunction. This review synthesizes current preclinical and clinical studies, highlighting the effects of inorganic nitrate and nitrite in managing CKM syndrome and suggesting avenues for future exploration.

1 | Introduction

According to the World Health Organization, cardiovascular disease (CVD), diabetes, and kidney disease continue to rank among the top 10 global causes of death and disability-adjusted life years in recent years (https://www.who.int). Due to the shared and interconnected pathophysiological mechanisms, dysfunction in one system can promote or exacerbate disorders

Abbreviations: ACS, acute coronary syndrome; AHA, American Heart Association; ALDH-2, mitochondrial aldehyde dehydrogenase; AMPK, 5′ adenosine monophosphate–activated protein kinase; ApoE, apolipoprotein E; ASCVD, atherosclerotic cardiovascular disease; BH_4, tetrahydrobiopterin; BMI, body mass index; BRJ, beetroot juice; CAD, coronary artery disease; cGMP, cyclic guanosine monophosphate; CKD, chronic kidney disease; CKM, cardiovascular–kidney–metabolic; cNOS, constitutive nitric oxide synthase; eGFR, estimated glomerular filtration rate; eNOS, endothelial nitric oxide synthase (NOS3); FAD, flavin adenine dinucleotide; FMN, flavin mononucleotide; Hb, hemoglobin; HF, heart failure; HFD, high-fat diet; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; iNOS, inducible nitric oxide synthase (NOS2); L-NAME, N^{ω}-nitro-L-arginine methyl ester; MACE, major adverse cardiovascular events; nNOS, neuronal nitric oxide synthase (NOS1); NO, nitric oxide; NO_2^-, nitrite; NO_3^-, nitrate; NOS, nitric oxide synthase; RCT, randomized controlled trial; ROS, reactive oxygen species; SBP, systolic blood pressure; sGC, soluble guanylyl cyclase; XOR, xanthine oxidoreductase.

in other systems [1]. With the rising prevalence of obesity, diabetes, chronic kidney disease (CKD), and CVDs, managing comorbidities has become a significant challenge in both current and future clinical practice.

Over the past year, the American Heart Association (AHA) introduced the concept of cardiovascular–kidney–metabolic (CKM) syndrome to characterize the pathophysiological interactions between the cardiovascular and renal systems and metabolic risk factors, which contribute to multiorgan disorders and a complex clinical presentation [2]. Patients often exhibit a complex interplay of disorders across the three systems, underscoring the importance of elucidating management effects within specific subpopulations and their varying combinations to guide precise and effective therapeutic decisions. To facilitate the early identification and management of CKM patients, the AHA proposed a CKM staging framework, ranging from Stage 0 to Stage 4 [2]. Higher stages indicate the increase of comorbidities and poor prognosis; thus, a greater focus on risk-reducing strategies should be enforced. Therapeutic interventions that not only address metabolic risk factors but also provide simultaneous cardiorenal protection are required.

The pathophysiological mechanisms driving CKM progression remain complex and incompletely understood. According to the AHA's statement, inflammation, oxidative stress, insulin resistance, and vascular dysfunction are central processes fostering the development of CKM syndrome. Impaired nitric oxide (NO) signaling is intricately involved in these processes, serving as a pivotal contributor [3–5]. As both an autocrine and paracrine signaling molecule, NO activates a variety of cellular pathways, particularly the NO–soluble guanylate cyclase–cyclic guanosine monophosphate (NO–sGC–cGMP) signaling cascade, and plays a crucial role in a wide array of physiological processes. These include the maintenance of endothelial integrity and vascular function, regulation of myocardial relaxation, modulation of nephron transport, and promotion of metabolic health [3, 6, 7]. Under physiological conditions, the classical pathway of NO generation is dependent on NO synthase (NOS), particularly endothelial NOS (eNOS) [8, 9]. However, in CKM syndrome, conditions such as endothelial injury and oxidative stress can reduce NOS expression and activity, leading to eNOS uncoupling—a pathological state in which eNOS produces superoxide (a reactive oxygen species, ROS) instead of NO [6, 10, 11]. The resultant decrease in NO bioavailability impairs its wide-ranging physiological functions. Therefore, strategies aimed at restoring NO bioavailability are increasingly recognized as a promising therapeutic approach in CKM syndrome.

The inorganic nitrate–nitrite–NO (NO_3^-–NO_2^-–NO) pathway, another important route for NO production, may offer valuable insights. Due to the exogenous availability and relatively longer half-life of nitrate/nitrite, as well as its oxygen-independent characteristics during NO production, this pathway functions as a "complementary system" for NO production in the human body. Under hypoxic or other pathological conditions, when classical NOS-dependent synthesis is impaired, it provides essential NO to vessels and tissues [12, 13]. Therefore, this pathway is anticipated to be an effective strategy for maintaining "NO homeostasis" and preventing the progression of CKM syndrome. Despite considerable evidence highlighting its benefits for metabolic and cardiovascular systems, the therapeutic potential of this pathway is often overlooked, and misconceptions surrounding the utilization of nitrate and nitrite persist. This review aims to comprehensively summarize the current literature on the protective effects of the inorganic NO_3^-–NO_2^-–NO pathway across various AHA-defined stages of CKM syndrome, providing a foundation for enhanced understanding and novel insights into CKM management strategies.

2 | NOS-Dependent NO Synthesis in CKM Syndrome

NO is typically synthesized by various cell types throughout the human body via three distinct isoforms of NOS: eNOS (NOS3), neuronal NOS (nNOS, NOS1), and inducible NOS (iNOS, NOS2) [6].

The synthesis mechanisms and functions of these isoforms have been extensively reviewed in previous studies [6, 14–16]. eNOS is predominantly localized in vascular endothelial cells but is also expressed in cardiac myocytes, renal tubular epithelial cells, and so forth [6]. NO produced from it exerts extensive effects in cardiorenal and metabolic systems, including but not limited to maintaining vascular health—promoting vasodilation, inhibiting vascular inflammation, oxidative stress, and vascular remodeling—as well as improving glucose and lipid metabolism [6, 17, 18]. Studies have shown that eNOS-deficient mice develop insulin resistance, hyperlipidemia, and hypertension [3, 19]. nNOS is mainly expressed in specific neurons of the central nervous system and has also been found to be expressed in vascular smooth muscle cells and the macula densa of the kidney, where it may support vasodilation, particularly when eNOS activity is impaired, acting as a compensatory mechanism [14, 20]. Being different from them, iNOS has basic low levels of expression in extensive human systems under physiological conditions but is obviously typically induced in response to proinflammatory stimuli such as endotoxins and cytokines, generating NO at levels up to 1000 times higher than those produced by eNOS and participating in inflammatory and antimicrobial processes [15, 16]. Regardless of isoform, all NOS enzymes utilize L-arginine as a substrate and require O_2, along with essential cofactors, particularly tetrahydrobiopterin (BH_4), to produce NO [6].

It is well-established that eNOS-derived NO acts as a guardian of cardiorenal and metabolic health. However, both animal and human studies consistently demonstrate reduced eNOS-derived NO production in the context of obesity, metabolic disorders, and CVDs [6, 21]. On the one hand, chronic hypoxia, activation of the inflammatory response "switch" nuclear factor κB, and negative feedback from excessive NO production by iNOS can significantly suppress eNOS expression [22, 23]. On the other hand, a deficiency in the substrate L-arginine and the key cofactor BH_4—due to oxidation by peroxynitrite ($ONOO^-$, a highly reactive nitrogen species formed from the reaction of superoxide and NO)—or competition for BH_4 by upregulated iNOS can lead to eNOS uncoupling [21, 23–26]. This results in a shift from NO production to the generation of reactive oxygen species (ROS) [27–29], indicating the inability of producing NO but transfer to create more ROS. In addition,

the increase in endogenous NOS inhibitors (e.g., asymmetric and symmetric dimethylarginine) further inhibit eNOS activity [30–32]. Collectively, these pathological processes contribute to a state of NO deficiency and exacerbate oxidative stress in metabolic disorders and CVDs.

3 | Inorganic NO_3^-–NO_2^-–NO Pathway in CKM Syndrome

The inorganic NO_3^-–NO_2^-–NO pathway serves as a complementary mechanism that can be enhanced under pathological conditions, enabling hypoxic NO signaling independently of eNOS activity in CKM syndrome. Initially, inorganic nitrate and nitrite were largely regarded as inert byproducts of endogenous NO metabolism or as undesirable dietary residues with potential toxicity, such as inducing tumor formation and methemoglobinemia [33, 34]. However, the discovery in the 1990s that dietary inorganic nitrate could enhance NO synthesis in the stomach led to a paradigm shift, reclassifying these compounds as "active NO donors" [35, 36].

The interconversion between NO, nitrite, and nitrate in the body represents a dynamic redox process. NO can be rapidly oxidized to nitrite or nitrate, while nitrite and nitrate can also be reduced back to NO under specific physiological conditions, particularly under hypoxia or acidosis. This reduction process involves a unique enterosalivary circulation (Figure 1A), in which dietary nitrate is sequentially reduced to nitrite and subsequently to bioactive NO. The initial reduction of nitrate to nitrite predominantly occurs in the oral cavity through symbiotic facultative anaerobic bacteria, as mammalian cells lack efficient nitrate reductase activity [38, 39]. Intriguingly, xanthine oxidoreductase (XOR) has been identified as an auxiliary contributor to this process under specific physiological conditions [40]. Subsequent conversion of nitrite to NO is mediated by multiple enzymatic and nonenzymatic pathways, including XOR, deoxyhemoglobin, and deoxymyoglobin. Notably, unlike oxygen-dependent NOS-derived NO production, nitrite-derived NO generation is potentiated under hypoxia and acidosis. This oxygen tension-dependent complementarity ensures NO homeostasis across diverse physiological and pathological milieus, particularly in ischemic tissues where NOS activity is impaired (Figure 1B) [41, 42].

Supported by a series of preclinical and clinical studies, inorganic nitrate/nitrites have shown great prospects in the management of metabolic risk factors and cardiovascular disorders [43, 44]. These anions are typically supplemented through vegetables [45], such as beetroot, and related compounds like sodium nitrate ($NaNO_3$), which exert protective effects on multiple body systems through both canonical (sGC–cGMP-dependent) and noncanonical mechanisms [3, 5]: (1) sGC activation: NO-mediated direct stimulation of sGC

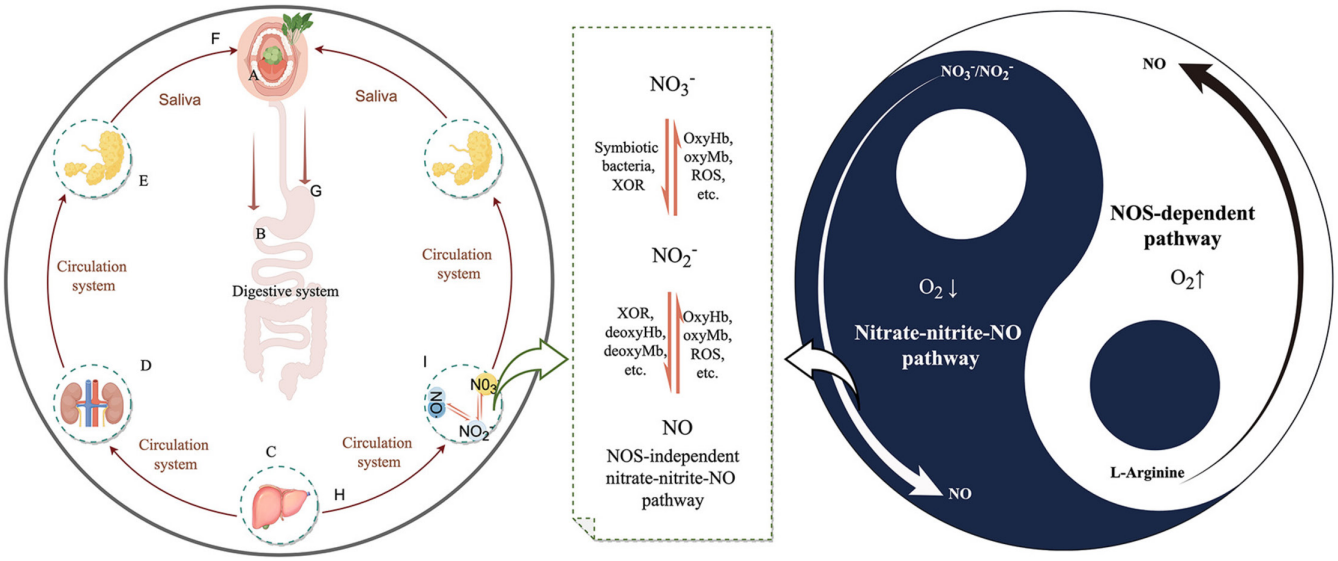

FIGURE 1 | Enterosalivary circulation of nitrate and the complementary NO synthesis pathways. The left panel illustrates the enterosalivary circulation of NO_3^-, while the right panel depicts the Taiji diagram, symbolizing the relationship of mutual independence yet mutual complementarity between the two NO synthesis pathways. (A) Dietary nitrate intake: NO_3^- is consumed through dietary sources. (B) Absorption: After oral ingestion, NO_3^- enters the digestive tract. (C) First-pass metabolism bypass: NO_3^- bypasses first-pass metabolism and is almost entirely absorbed into the bloodstream. (D) Excretion: Approximately two-thirds of NO_3^- is excreted unchanged via the kidneys. (E) Recycling: The remaining one-third is transported to the salivary glands via sialin, a nitrate transporter. (F) Salivary secretion: NO_3^- is secreted from the salivary glands into the oral cavity as nitrate-rich saliva. In the presence of accumulated NO_3^-, anaerobic bacteria (including Staphylococcus, Streptococcus, Veronococcus, and Rhodococcus [37]) in the mouth utilize NO_3^- as an alternative electron acceptor during respiration. These bacteria also produce reductase enzymes that convert NO_3^- into NO_2^-. (G) Swallowing: NO_2^- is swallowed. (H) Reduction in the stomach: In the acidic environment of the stomach, nitrite undergoes further reduction to NO. (I) Circulation: In the bloodstream, NO can rapidly oxidize to NO_2^- in the presence of oxyHb/oxyMb or reactive oxygen species. NO_2^- can be further oxidized to NO_3^-. And, under conditions such as hypoxia, acidosis, and the presence of XOR, deoxyhemoglobin, vitamin C, and cytochrome P450, NO_2^- is more likely to be reduced to NO. deoxyHb: deoxyhemoglobin; deoxyMb: deoxymyoglobin; NO: nitric oxide; NO_2^-: nitrite; NO_3^-: nitrate; NOS: nitric oxide synthase; O_2: oxygen; oxyHb: oxyhemoglobin; oxyMb: oxymyoglobin; ROS: reactive oxygen species; XOR: xanthine oxidoreductase.

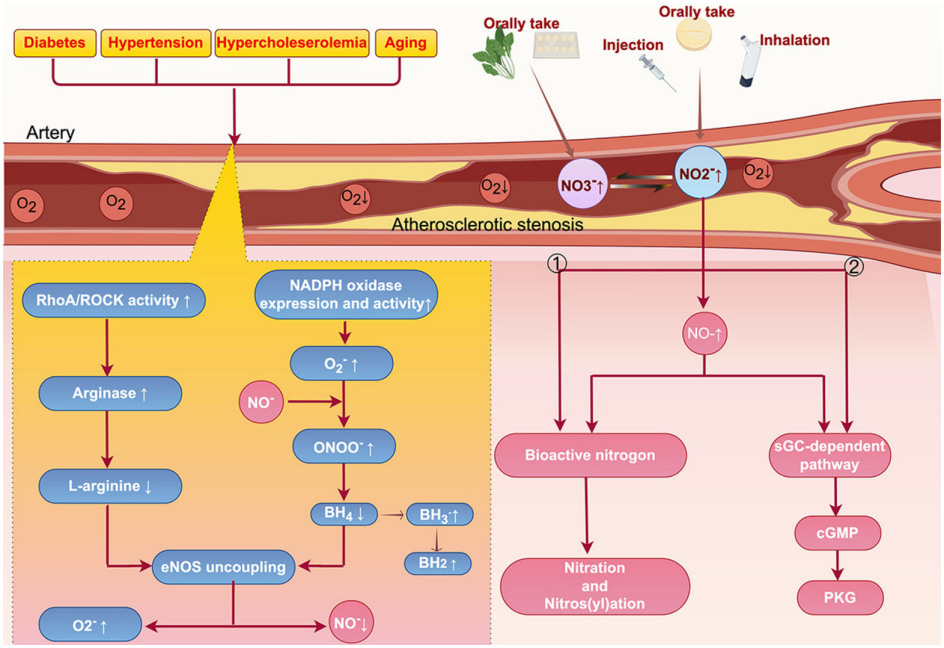

FIGURE 2 | Impaired NOS-dependent pathway in the ischemic–hypoxic environment and the role of the nitrate–nitrite–NO pathway in CKM syndrome. Key pathological factors, including diabetes, hypertension, hypercholesterolemia, and aging, contribute to eNOS uncoupling, resulting in reduced NO bioavailability and increased oxidative stress. In this context, inorganic nitrate/nitrite supplementation provides an alternative pathway to sustain NO homeostasis. Notably, unlike the NOS-dependent pathway, which requires high oxygen availability for NO synthesis, the nitrate–nitrite–NO pathway is upregulated under ischemic–hypoxic conditions, acting as a crucial compensatory mechanism for NO production in CKM syndrome. Abbreviations: BH_4: tetrahydrobiopterin; cGMP: cyclic guanosine monophosphate; eNOS: endothelial nitric oxide synthase; NADPH: nicotinamide adenine dinucleotide phosphate; NO: nitric oxide; NO_2^-: inorganic nitrite; NO_3^-: inorganic nitrate; O_2: oxygen; O_2^-: superoxide anion; RhoA/ROCK: Ras homolog family member A/Rho-associated protein kinase; sGC: soluble guanylate cyclase.

TABLE 1 | Key differences between inorganic nitrate/nitrite and organic nitrates.

Differences	Inorganic nitrate–nitrite–NO (NO_3^-–NO_2^-–NO)	Organic nitrate (R-ONO_2)
Sources	Diet: Vegetables rich in nitrate (such as spinach and lettuce), some drinking water, and certain meats. Pharmaceuticals: KNO_X and $NaNO_X$.	Common drugs: Nitroglycerin, isosorbide dinitrate, isosorbide-5-mononitrate, pentaerithrityl tetranitrate, and so forth.
NO synthesis conditions	Conversion of nitrate to nitrite: Mainly rely on commensal anaerobic bacteria in the oral cavity, gastrointestinal tract, and so forth. XOR has also been found to reduce nitrate. Conversion of nitrite to NO: Involves deoxyhemoglobin, deoxymyoglobin, XOR, mitochondrial complexes, liver cytochromes, and so forth.	Primarily catalyzed by mitochondrial ALDH-2. Cytochrome P450 enzymes, XOR, glutathione-*S*-transferase, glyceraldehyde-3-phosphate dehydrogenase, and other ALDH isoforms with relatively lower potency are also involved.
Advantages	Convenient access: Can be obtained through daily diet. Good tolerance: Less likely to develop obvious tolerance and has a lower probability of causing side effects such as headache and hypotension.	Rapid onset of action: Nitroglycerin can quickly exert effects such as vasodilation. Diverse formulations: There are various dosage forms available, facilitating clinical use.
Limitations	Long-term or high-dose use: May have potential carcinogenic risks and may cause methemoglobinemia, but the relevant conclusions are still controversial. Susceptible to oral health: Changes in the oral microbiota or oral diseases may affect its metabolic conversion process.	Prominent tolerance issue: Prone to developing tolerance during long-term use, leading to reduced efficacy. Obvious side effects: Commonly accompanied by adverse reactions such as lightheadedness, postural hypotension, flushing, and lightheadedness. And they may also cause endothelial dysfunction.

Abbreviations: ALDH-2: aldehyde dehydrogenase 2; XOR: xanthine oxidoreductase.

induces extensive important positive effects, such as vasodilation, antiproliferative effects, antiplatelet aggregation, anti-inflammatory effects, and antioxidant effects. Of note, NO_2^- was found to activate sGC independently of NO stimulation, thereby alleviating the "NO resistance" effect in certain patients [46, 47]. (2) Nitrosative posttranslational modifications: Nitrite-derived reactive nitrogen species mediate protein *S*-nitrosylation/nitration, modulating redox signaling, mitochondrial function, and inflammatory cascades [48, 49] (Figure 2). Through these mechanisms, inorganic nitrate and nitrite have been extensively confirmed to improve inflammation, oxidative stress, insulin resistance, and vascular dysfunction—key pathophysiological processes underlying CKM syndrome—thereby potentially preventing its development or slowing its progression [19, 50–53].

Of note, although inorganic nitrate/nitrite also primarily exert their effects as NO donors, they have distinct characteristics and advantages compared to the commonly used organic nitrates in clinical practice (e.g., nitroglycerin and isosorbide dinitrate) (Table 1) [41, 54–57]. Given the interconnected pathophysiology of CKM—characterized by oxidative stress, endothelial dysfunction, chronic inflammation, and insulin resistance—we hypothesize that nitrate/nitrite supplementation may exert multimodal therapeutic effects. To evaluate this premise, we systematically reviewed and summarized the evidence from preclinical and clinical studies investigating nitrate/nitrite interventions in obesity, dysmetabolism, CKD, and CVDs within the CKM spectrum.

4 | Inorganic NO_3^-–NO_2^-–NO Pathway and Stage 1 CKM

CKM Stage 1 is characterized by the presence of at least one adiposity-related criterion (e.g., elevated body mass index [BMI] $\geq 25\,kg/m^2$, abdominal obesity, or dysfunctional adipose tissue, as evidenced by impaired glucose tolerance or prediabetes), in the absence of other metabolic abnormalities or CKD [2]. During this stage, abnormalities in the quantity, distribution, and function of adipose tissue are closely linked to the development of obesity and metabolic dysfunction [58]. When energy intake exceeds the storage capacity of white adipose tissue (WAT), or when this capacity declines with age, it can lead to adipocyte stress, cell death, increased circulating lipids, ectopic fat accumulation, lipotoxicity, and insulin resistance. Visceral fat (VAT), a type of ectopic fat, is an established independent risk factor for obesity-related CVD and metabolic dysfunction [59, 60]. Therefore, in addition to weight control, managing VAT is also critical to prevent the progression of CKM syndrome from Stage 1 to more advanced stages.

Some animal studies have provided initial evidence regarding the potential significance of inorganic nitrate/nitrite in controlling weight and reducing VAT. Ma et al. reported that $NaNO_3$ intake (2 mM, 20 weeks) upregulated the decreased levels of nitrate, nitrite, and cGMP in high-fat diet (HFD)—induced obesity mice, and further reduced body weight gain and lipid accumulation in adipose and liver tissues [61]. Similar positive reductions in weight and VAT accumulation (particularly in the liver) have also been observed in other preclinical studies [62–65]. The animal models, administration routes, and dosages used in these studies varied considerably. The concentration of nitrates in drinking water for administration purposes generally ranges from 200 to 600 mg/L (for more than 4 weeks). A 2020 systematic review and meta-analysis conducted on male rats revealed that nitrate supplementation resulted in a significant decrease in body weight compared to the control group (weighted mean difference = −16.8 g), and the effects were dose and duration dependent [66]. Upon excluding experiments that employed high doses of NO_3 (exceeding 400 mg/L), the overall mean differences in body weights among the groups still remained significant but decreased by around 37%. Because the animal experiments have reported similar food intake among the intervention and control groups, the anti-obesity effects of nitrates were not likely dependent on the reduction of appetite and total calorie intakes. The improvement in brown adipocyte-specific gene expression, induction of mitochondrial biogenesis, and enhancement of protein catabolism have been proposed as potential mechanisms [67–70].

Unfortunately, translating these promising preclinical findings into human outcomes has proven challenging. Up to now, there is no direct evidence supporting the benefits of inorganic nitrate/nitrites in lowering body weight among individuals with obesity. A meta-analysis conducted among the general population revealed that beetroot juice (BRJ) and direct nitrate supplementation had no significant effect on decreasing weight or ameliorating body composition [71], regardless of the complicated metabolic risk factors and study design. However, several limitations should be seriously considered when interpreting this finding: (1) There was a lack of specific randomized controlled trial (RCT) assessing the effects of nitrate/nitrite supplementation in cohorts with obesity; (2) the intervention doses in these trials were inconsistent and relatively low. In the human studies, the vegetables or BRJ used were less than 200 g/day, with 150 mg/day of nitrate defined as the high dose [72]. This dose was far less than the dose applied in some rat research where remarkable anti-obesity effects of nitrate were observed [66]. Although direct weight-loss effects were not observed in human trials, the improvements in endothelial function, reductions in inflammation, and attenuation of oxidative stress conferred by inorganic nitrate/nitrite in obesity warrant further attention and investigation [73, 74]. Kleinloog et al. also found that acute ingestion of KNO_3 improved insulin sensitivity in specific brain regions (temporal, frontal, and parietal lobes) in 18 healthy men with a waist circumference ≥ 102 cm [75]. These findings suggest that, although no human studies have directly shown that nitrate reduces body weight or VAT, its effects on key pathophysiological processes in CKM syndrome may help delay the progression from metabolic health to metabolic disorder in individuals with obesity.

In summary, preclinical studies consistently support the potential of inorganic nitrate/nitrite in reducing body weight and visceral adiposity through mechanisms such as mitochondrial activation and improved adipocyte metabolism. However, current human evidence remains limited and inconclusive, largely due to suboptimal dosing, short intervention durations, and lack of targeted trials in populations with obesity or those at metabolic risk. Despite these limitations, the observed improvements in vascular and metabolic function in individuals with obesity

highlight a promising translational potential. Long-term, adequately powered clinical trials are warranted to evaluate whether nitrate-based strategies can effectively prevent CKM progression from Stage 1 by targeting early adipose accumulation or dysfunction.

5 | Inorganic NO_3^-–NO_2^-–NO Pathway and Stage 2 CKM

According to the AHA, Stage 2 of CKM syndrome is characterized by the presence of metabolic risk factors, such as hypertriglyceridemia, hypertension, diabetes, metabolic syndrome, moderate-to-high-risk CKD, or a combination of these conditions. At this stage, in addition to lifestyle interventions, the primary focus shifts to the pharmacological management of modifiable risk factors and CKD, with the goal of reducing the risk of CVD. Below, we summarize the potential benefits of nitrate/nitrite supplementation in managing metabolic risk factors and preventing cardiovascular and renal damage, based on findings from animal models and human studies.

5.1 | Nitrate/Nitrites and Blood Pressure (BP)

The antihypertensive effects of nitrate or nitrite therapy have been extensively investigated and supported in various hypertensive animal models, including spontaneously hypertensive rats, angiotensin II-induced hypertension, "two-kidney, one-clip hypertension," and "uninephrectomized salt-induced hypertension" models [76–83]. In a study by Bhaswant et al., metabolic syndrome was induced in rats via a high-carbohydrate, HFD. Administration of approximately 16 mg/kg/day of nitrate (equivalent to 250–280 mg/day in a 70- to 80-kg human based on body surface area comparison) for 8 weeks led to a reduction in systolic BP (SBP) by approximately 25 mmHg. In addition to its antihypertensive effects, this research also observed improvements in other metabolic risk factors, cardiac structure, left ventricular fibrosis, and function [84], suggesting potential protective effects against target organ damage.

Clinical trials involving both healthy individuals and hypertensive patients have similarly supported the BP-lowering effects of nitrate/nitrite supplementation, whether administered acutely or over a prolonged period [85–87]. In the largest RCT conducted with hypertensive patients (average BMI of 26.5) [87], daily supplementation with BRJ (250 mL/day) for 4 weeks significantly and safely reduced clinic BP by 7.7/2.4 mmHg ($p < 0.001/p = 0.050$), home BP by 8.1/3.8 mmHg ($p < 0.001/p < 0.01$), and 24-h ambulatory BP by 7.7/5.2 mmHg ($p < 0.001/p < 0.001$) consistently, compared to the placebo (nitrate-free BRJ). In addition to lowering BP, significant improvements in other metabolic risk factors and protective effects on endothelial function, arterial stiffness, and target organ damage have also been reported in a series of human trials [87–95]. However, minimal or no hypotensive effects were also reported in some studies, fueling the ongoing debate regarding their effectiveness in reducing BP [96–98]. The variability in reported outcomes can be attributed to differences in intervention strategies and concomitant medication use. The relatively low dose of BRJ (140 mL) and shorter intervention duration (1 week) may limit the effects observed in the patients [96]. Additionally, baseline BP levels and the use of concomitant medications were important factors influencing the observation of nitrate/nitrite benefits. For patients with well-controlled hypertension, the additional hypotensive effects of nitrate/nitrites were found to be limited [99]. Future studies should confirm the optimal and safe dosage of nitrate/nitrites for hypertensive patients, particularly those with obesity. Both excessively low and high doses are not conducive to optimal patient management. Although some studies have demonstrated a dose-dependent effect of nitrate in lowering BP, excessively high doses may inhibit NOS activity due to the interplay between eNOS and the NO_3^-–NO_2^-–NO pathways [100]. Moreover, given the wide variety of antihypertensive medications available today, it is crucial to determine the additional benefit of inorganic nitrate supplementation on top of these medications, particularly with respect to cardiovascular and renal protection. And for individuals with slightly elevated but untreated BP (e.g., those with an SBP of 130–140 mmHg), which is common in individuals with obesity or metabolic disorders, whether dietary nitrate supplementation can confer effective hypotensive effects deserves investigation as well.

5.2 | Nitrate/Nitrites and Diabetes

Inorganic nitrate/nitrite have also been proposed as a potential strategy for managing diabetes, based on a series of animal studies. Mice lacking eNOS develop a metabolic syndrome-like phenotype as they age, whereas chronic supplementation with sodium nitrate reverses several features, such as VAT accumulation, elevated triglyceride levels, and a prediabetic state [101]. Similarly, a long-term nitrate-deficiency diet in normal mice induced metabolic syndrome, endothelial dysfunction, and early cardiovascular death, all of which were significantly prevented by nitrate supplementation via drinking water [102]. Khalifi et al. investigated the effects of dietary nitrate supplementation on glucose tolerance and lipid profiles in a streptozotocin–nicotinamide-induced type 2 diabetes model. They found that dietary nitrate supplementation increased the reduced circulating nitrate and nitrite levels and exerted hypoglycemic, hypolipidemic, and insulin resistance-improving effects [103]. These metabolic effects have been further supported by other animal studies [43, 51, 104].

While the effects of activating the inorganic nitrate–NO pathway in populations with diabetes remain underexplored, only a few small-sample studies have been conducted in this area. In one RCT involving 27 patients with diabetes, Gilchrist et al. found that daily consumption of BRJ containing 7.5 mmol (approximately 465 mg) of nitrate for 2 weeks significantly increased plasma nitrate and nitrite concentrations but did not effectively improve insulin sensitivity or endothelial function [105]. Similarly, Cermak et al. failed to observe improvements in glucose tolerance or insulin sensitivity among the group receiving acute nitrate administration [106]. As acute and short- to medium-term administrations failed to yield metabolic improvements, it raises the question of whether extended administration durations might offer benefit. A 2020 RCT involving 64 diabetes extended inorganic nitrate administration to 6 months. They showed that although this long-term intervention was found to be safe, no significant improvements in

glycated hemoglobin, insulin, C-peptide, insulin sensitivity, or lipid profiles were observed compared to the control group [107]. The inability to reproduce the benefits of inorganic nitrate seen in animal models when translating to human studies is perplexing. Several factors may contribute to this phenomenon: (1) Changes in the oral microenvironment among patients with diabetes: Compared to healthy individuals, those with diabetes exhibit altered patterns of nitrate metabolism [108, 109]. The reduction of nitrate to nitrite depends on oral bacteria. However, diabetes-induced changes in the oral microbiota and disrupted enterosalivary circulation may impede nitrate reduction, potentially explaining the reduced efficacy in diabetes [109]. (2) Widespread use of metformin in diabetes: Cordero-Herrera et al. found that nitrate supplementation and metformin had comparable effects on maintaining glucose homeostasis in a HFD and eNOS inhibitor N^{ω}-nitro-L-arginine methyl ester (L-NAME)–induced metabolic syndrome mouse model. Nitrate supplementation further prevented hypertension, vascular dysfunction, and hepatic steatosis. However, the combination of metformin and nitrate showed no additive cardiometabolic effects but appeared to enhance AMPK activation in the liver [110]. Because both nitrate and metformin share the AMPK pathway in improving metabolism, this may explain the "ineffectiveness" of nitrate in diabetes in individuals who are widely using metformin [43, 111]. (3) Insufficient nitrate dosage: Previous studies on diabetic and nondiabetic subjects have administered dietary nitrate doses of approximately 500–1500 mg/day for short-term interventions and 400–2400 mg/day for acute administration, with no significant adverse events reported [89, 93]. Given that patients with Type 2 diabetes mellitus are often overweight or obese, the nitrate doses used in studies of cohorts with diabetes might have been suboptimal. Therefore, more comprehensive clinical trials exploring a broader range of nitrate dosages are warranted.

5.3 | Nitrate/Nitrites and Renal Dysfunction

Nitrate/nitrite supplementation has been shown to restore deficits in NO production and confer renal protection in various models of kidney disease, including those induced by high-salt diets combined with unilateral nephrectomy, two-kidney one-clip, deoxycorticosterone acetate-salt, and Ang II infusion [76, 77, 112]. Furthermore, in a high-fructose diet-induced metabolic syndrome model, a 10-week sodium nitrate intervention significantly reduced elevated serum creatinine levels [113]. Consistently, dietary nitrite supplementation for 4 weeks restored nitrite levels in the kidney and improved parameters of glomerular injury, such as urinary protein and albumin excretion, glomerular hypertrophy, and mesangial matrix accumulation in a diabetic nephropathy model [114].

The preclinical studies above provided preliminary evidence supporting the potential benefits of inorganic nitrate and nitrite in CKD associated with metabolic disorders, highlighting the need for further human research. In a 2017 small-scale crossover study involving 17 patients with diabetic or hypertensive nephropathy, a single dose of nitrate derived from BRJ improved BP and significantly reduced the renal resistance index, a marker of cardiovascular death risk and CKD progression [115–117]. Regarding renal function indicators, including eGFR and urine albumin–creatinine ratio, the combination of sodium nitrite and the antioxidant isoquercetin failed to show a significant effect in CKD patients with an average BMI of 31.7 and hypertension in 94.2% of cases, according to the RCT conducted by Chen et al. [118]. However, as the researchers acknowledged, the sample size was too small to provide sufficient statistical power, and the null effect needs to be confirmed through a larger trial. Compared to the abundant evidence from animal studies, human research remains limited. For the majority of CKD patients, the decline in eGFR is a gradual and progressive process that typically occurs over an extended period. In addition to increasing the sample size, future studies should also explore the role of long-term dietary nitrate supplementation in slowing the progression of kidney function deterioration and reducing acute decompensatory events. Furthermore, fully understanding the interaction between different stages of CKD and the protective effects of nitrate/nitrite supplementation is critical for optimizing its therapeutic potential. Some previous studies have reported an inverse correlation between renal nitrate clearance and eGFR, with plasma nitrate levels increasing as renal function declines [119, 120], highlighting the importance of determining the effective and safe dosage of nitrate/nitrite formulations in this specific population.

To conclude, inorganic nitrate/nitrites show promise as a therapeutic strategy for managing metabolic risk factors in Stage 2 CKM syndrome. Animal studies have demonstrated antihypertensive effects and benefits in reducing blood glucose, lipids, and insulin resistance. Human trials have also predominantly reported antihypertensive effects in individuals with hypertension, both with and without obesity. However, these metabolic benefits have not been fully replicated in humans. In addition to the inherent physiological differences between humans and animals, variations in drug metabolism and disease progression, the limited sample sizes in clinical studies, and the inconsistent design of research are also significant factors hindering the translation of animal experiment findings to human applications. Further research with larger sample sizes and optimized designs is needed. First, in addition to confirming metabolic effects, the cardiovascular benefits of nitrate/nitrites in patients with metabolic risk factors and CKD should be explored. Second, the synergistic effects of nitrate/nitrites with medications commonly used in CKM syndrome, including SGLT2 inhibitors (SGLT2i) and GLP-1 receptor agonists (GLP-1RA), which have extensive effects on the metabolic and cardiorenal systems, should also be considered [121]. Their positive effects on alleviating inflammation and oxidative stress would be helpful in reducing NO scavenging. Third, understanding the interactions between eGFR decline and nitrate supplementation will be crucial for optimizing therapeutic strategies.

6 | Inorganic NO_3^-–NO_2^-–NO Pathway and Stages 3 and 4 CKM

In Stages 3 and 4 CKM, CVDs have developed, in addition to excessive or dysfunctional adiposity, existing metabolic risk factors, and/or CKD. Specifically, Stage 3 refers to patients with subclinical CVD (such as subclinical atherosclerotic CVD [ASCVD] or subclinical heart failure [HF]) or those at equivalent risk

levels. Stage 4 marks the progression to clinical CVD (including coronary artery disease (CAD), HF, atrial fibrillation, peripheral vascular disease, and stroke), with Stage 4a not associated with renal failure and Stage 4b accompanied by renal failure. At these stages, the focus shifts to preventive therapies and the unique management considerations for CVD in the context of CKM, with the ultimate goal of reducing adverse cardiovascular outcomes and mortality. This section therefore focuses on the cardiovascular protective effects of the NO_3^-–NO_2^-–NO pathway.

6.1 | Nitrate/Nitrites and ASCVD

As early as the 1990s, NOS-independent NO production from NO_2^- was demonstrated in the ischemic heart [122]. Subsequent animal studies revealed the significant effects of nitrate/nitrite supplementation in reducing inflammation, stabilizing plaques, decreasing plaque area, minimizing myocardial infarct size, mitigating ischemia–reperfusion injury (IRI), and alleviating myocardial necrosis and ventricular dysfunction in models of atherosclerosis and CAD [123–130]. Furthermore, laboratory research by Jeddi et al. highlighted the cardioprotective effects of nitrate/nitrite in a streptozotocin–nicotinamide-induced diabetic rat model of IRI [131], indicating consistent benefits of nitrate/nitrite in CAD within the CKM context. Their results showed that a 2-month nitrate intake (via nitrate-rich drinking water) significantly inhibited iNOS but activated eNOS expression, thereby improving recovery of left ventricular developed pressure and the maximum rate of pressure change following myocardial ischemia–reperfusion.

The benefits observed in laboratory studies of nitrate/nitrite have provided valuable insights and clues for clinical research. Although they failed to consistently replicate the effects on minimizing myocardial infarct size among MI patients, human trials have demonstrated the benefits of nitrate/nitrites in terms of anti-inflammation and decreasing major adverse cardiac events (MACEs) in long-term follow-up [132–134]. Of note, the NITRATE-CIN trial published in 2024 further demonstrated cardiovascular as well as renal protective effects of nitrates/nitrites among high-risk ACS patients (with an average BMI > 28 kg/m^2 and a large proportion of patients with hypertension [75.8%] or CKD [55.9%]) undergoing coronary angiography [135]. According to the results, perioperative administration of KNO_3 for 5 days significantly improved 3-month eGFR and reduced the incidence of MACE at 1 year, in addition to decreasing the occurrence of contrast-induced nephropathy. These promising findings highlight the potential of nitrate in managing CAD during the acute phase. The latest RCT published in 2024, the NITRATE-OCT trial, also offers insights into the use of nitrate/nitrite for stable CAD [136]. This study involved 300 stable CAD patients scheduled for percutaneous coronary intervention, with an average BMI of 28.8 kg/m^2. Over 70% of these patients had hypertension or hypercholesterolemia. Compared with the placebo, sustained daily oral nitrate-rich BRJ for 6 months resulted in a significant reduction in the incidence of in-stent restenosis, which correlated with a trend toward reduced MACE. The mechanisms underlying the positive effects in CAD are mainly attributed to the multiple physiological effects of NO produced in the vascular environment with ischemia and hypoxia, particularly antiplatelet and anti-inflammatory effects [137]. In severely stenosed lesions where NO production from eNOS is inhibited, the NO_3^-–NO_2^-–NO pathway serves as a critical source of NO supply. In addition to the established roles of NO in CAD, the treatment benefits related to metabolic risk factors and CKD provide an additional mechanism explaining the benefits of nitrate/nitrite. Against the backdrop of organic nitrate failing to reduce adverse cardiovascular outcomes [138], inorganic nitrate may offer a new approach to the management of CAD.

Research into the NO_3^-–NO_2^-–NO pathway in the context of stroke and CKM remains limited. Neuroprotective effects have been observed in general cerebral ischemia and IRI models [139–142], and large cohort studies have demonstrated a significant inverse relationship between dietary nitrate intake and stroke incidence [143, 144]. Given the neuroprotective effects of NO [145, 146] and the benefits observed in general animal models, it is reasonable to expect that future studies will clarify the application and efficacy of the NO_3^-–NO_2^-–NO pathway in cerebral ischemia within the context of CKM syndrome.

6.2 | Nitrate/Nitrites and HF

Laboratory data on the protective effects of nitrate/nitrites in HF are limited. Gee et al. reported the positive effects of dietary nitrate on improving cardiac function by lowering BP and directly affecting cardiac structure and function in mouse models of cardiac dysfunction [147]. While human trials mainly focused on assessing the role of nitrate/nitrite in improving exercise performance in patients, given their proven efficacy in enhancing muscle blood flow and exercise capacity in the general population and patients with other cardiovascular conditions [148–150]. Some early human trials in patients with HF with preserved ejection fraction (HFpEF) demonstrated positive effects of nitrate/nitrite supplementation, particularly with BRJ, in improving exercise performance indicators such as peak oxygen uptake, maximum work rate, and exercise duration [151–154]. However, more recent studies, including the INDIE-HFpEF trial—the largest RCT in this area—using inhaled or injected nitrites, failed to observe these improvements in exercise performance [155–157]. Studies with small-sample sizes in HF with reduced ejection fraction (HFrEF) have also yielded mixed results, further complicating the understanding of nitrate/nitrite's role in improving exercise performance in HF [158–162]. Several factors contributed to these divergent findings: (1) Variability in intervention strategies (particularly the administration route) and exercise training regimens partially explains the heterogeneous results; (2) the activation of iNOS, leading to excessive NO production, inflammation, and oxidative stress in the development of HFpEF, helps explain, in part, the failure of NO-based therapeutic strategies [163, 164]; (3) changes in the oral and gut microbiota, along with the phenomenon of "NO resistance" resulting from broader cellular signaling impairments and excessive scavenging of NO under oxidative stress, should be carefully considered [47, 165, 166]; and (4) the significant individual differences among patients (particularly those with HFpEF), including variations in the underlying causes, comorbidities, and medication regimens, may also be important factors contributing to the inconsistent results in clinical studies.

Currently, sGC agonists have been shown to significantly improve the prognosis of HF and have become one of the five pillars of HF therapy, and the reasons behind the inability of NO donors to exert similar effects are not clear. Future high-quality studies should answer the following questions: (1) Whether different administration routes exert significantly different effects in HF, as some research has found BRJ to be superior in improving exercise tolerance compared to nitrate/nitrite compounds [167, 168]; (2) whether combining adjunctive strategies, such as anti-inflammatory treatments, iNOS inhibition, or management of gut microbiota, can enhance the efficacy of nitrate/nitrites in HF; (3) considering the extensive effects of nitrate/nitrites on multiple systems, such as renal protection, the investigation of the benefits of nitrate/nitrites in HF should not be limited to exercise performance; and (4) given the significant clinical heterogeneity in HF, particularly in HFpEF, it is necessary to investigate the characteristics that can identify targeted cohorts likely to benefit from nitrate/nitrite therapy, such as baseline serum nitrate/nitrite concentrations and eGFR levels. Additionally, the specific effects of nitrate/nitrites in certain subgroups of HF complicated by CKM syndrome require further exploration.

In brief, regarding the role of nitrate/nitrites in Stages 3 and 4 CKM syndrome, current experimental research and studies in humans mainly focus on their effects in patients with CAD and HF. Studies conducted in CAD models and CAD patients complicated with obesity and/or metabolic risk factors have revealed the significant efficacy of nitrate/nitrites in cardiac and renal protection. Their performance in reducing long-term MACEs was both impressive and surprising. In contrast, current research on HF has demonstrated considerable controversy regarding the role of nitrate/nitrites in increasing exercise tolerance, and whether they can improve long-term prognosis remains unclear. Several issues require further investigation in the HF field. Moreover, to comprehensively assess the application value of nitrate/nitrites in Stages 3 and 4 CKM syndrome, future explorations could extend to other CVDs within the CKM framework. Large-scale cohorts have preliminarily revealed the great potential of nitrates in improving the prognosis of various CVDs [144]. The application value of inorganic nitrate/nitrite in Stages 3 and 4 CKM deserves further exploration and anticipation.

7 | Considerations for the Application of Inorganic Nitrate or Nitrite in CKM Syndrome

7.1 | Attention to Preserving the Gut–Salivary Cycle and XOR

The dissimilatory nitrate-reducing microbiota, particularly oral symbiotic bacterial communities, play a pivotal role in maintaining the gut–salivary nitrate cycling system through enzymatic conversion processes [39, 169, 170]. While broad-spectrum antibacterial mouthwash formulations or overuse of antibiotics can significantly disrupt this metabolic axis [171–176]. Conversely, preservation of oral microbial eubiosis enhances systemic NO bioavailability, and cohort studies have found it to be associated with improved cardiovascular outcomes [177–180]. Therefore, for individuals with CKM syndrome characterized by NO homeostasis imbalance, greater attention should be paid to the health of the oral microbiota to maintain the integrity of the enterosalivary circulation.

XOR plays a pivotal role in the reduction of nitrate/nitrite, and its inhibition should be approached with caution in clinical practice [181–184]. In addition to reducing nitrite, XOR is likely the only known mammalian enzyme capable of converting nitrate to nitrite. In 2008, researchers identified extracellular XOR, an enzyme structurally similar to bacterial nitrate reductases, which can reduce nitrate independently of oral anaerobic bacteria [40]. In CKM syndrome, compensatory upregulation of XOR activity partially alleviates NO deficiency by enhancing nitrite-derived NO bioavailability, serving as a critical adaptive response to eNOS uncoupling [185]. However, pharmacological inhibition of XOR, using agents such as allopurinol and febuxostat, disrupts this compensatory mechanism, exacerbating systemic NO insufficiency and diminishing the cardioprotective effects of dietary nitrate/nitrite [183–186]. CKM patients often experience hyperuricemia, with prevalence rates reaching up to 60% in CKD [187]. XOR inhibitors, commonly used to manage hyperuricemia, are believed to provide potential cardiovascular benefits through their anti-inflammatory and antioxidant effects. However, large-scale RCTs have not consistently demonstrated cardiovascular benefits with these drugs [188]. Furthermore, a large prospective cohort study by Kang et al. found that, compared to the uricosuric agent benzbromarone, allopurinol significantly increased the risk of composite cardiovascular events [189]. Mechanistically, this cardiovascular paradox may be attributed to impaired NO_3^-–NO_2^-–NO metabolism, further exacerbating the imbalance in NO homeostasis. This pathophysiological interplay necessitates a precision medicine approach in CKM management, where therapeutic strategies must strike a balance between effective urate-lowering and the preservation of XOR-mediated NO homeostasis. Future research should prioritize the development of isoform-selective XOR modulators and combinatorial therapies targeting both purine metabolism and vascular redox systems.

7.2 | Safety Considerations Regarding the Use of Inorganic Nitrate/Nitrite

For a long time, the primary safety concern associated with inorganic nitrate/nitrite supplementation has been their potential carcinogenic risk. This controversy originated from a 1976 "warning" by Spiegelhalder et al. and Tannenbaum et al., who found that nitrate could react with dietary secondary amines to form *N*-nitrosamines through N_2O_3 (generated by the acidification of nitrites in gastric fluid) [190, 191]. *N*-Nitrosamines are recognized carcinogens that act through mechanisms such as DNA alkylation. Subsequent animal studies have linked nitrites to lymphoma, liver cancer, and other tumors, findings that have been widely reported in reputable journals [192, 193]. The high carcinogenic potential observed in animal experiments has led to criticism of nitrate/nitrite. However, numerous studies on the carcinogenicity of nitrate/nitrite in humans have produced conflicting results, fueling ongoing debate [194–196]. As research has progressed, it has become evident that the health effects of dietary nitrate/nitrite largely depend on their source. The primary sources of nitrate/nitrite include plants (mainly vegetables), meat, and water. *N*-Nitrosamine formation requires

nitrosating agents and secondary amines, with nitrate/nitrite acting as precursors to N_2O_3. Secondary and tertiary amines are predominantly found in processed meats, while their levels in vegetables are low. Therefore, animal-derived foods, especially processed meats like sausages, not only provide high levels of nitrate (101 mg/kg) but also contain secondary/tertiary amines and heme iron, which facilitate *N*-nitrosamine formation [197]. Consistent research has shown that elevated nitrate levels in drinking water and meat products can increase *N*-nitrosamine levels in the body [197–199], which is associated with an increased risk of tumors in the bladder, digestive tract, and breast [200–204]. Conversely, studies such as IWHS, NEBCS, and NNS have not observed a clear correlation between plant-derived nitrate and these tumors [200, 202, 205, 206]. The IWHS study even suggested that plant nitrate might help reduce the risk of gallbladder cancer [207]. Therefore, plant-derived nitrates are generally considered a safe source of NO supplementation, largely due to the presence of vitamin C and other nitrosation inhibitors in vegetables. However, it is important to note that certain vulnerable populations, such as individuals at high risk for gastric cancer (e.g., those with Barrett's esophagus), may experience increased nitrosation, necessitating caution with nitrate intake [208].

$$NO_2^- + H^+ \rightleftharpoons HNO_2,$$

$$2HNO_2 \rightleftharpoons N_2O_3 + H_2O,$$

$$N_2O_3 + R_2NH \rightarrow R_2N - NO + HNO_2.$$

Another significant concern is the risk of methemoglobinemia, first highlighted in Comly's 1940s report that linked cases of "blue baby syndrome" to high nitrate levels in well water [34]. Since then, European and American countries have strictly regulated nitrate content in drinking water to a safe limit of 44 mg/L to prevent methemoglobinemia. Interestingly, plant-derived nitrate/nitrite often exceed this limit, particularly among vegetarians, yet there has been no widespread occurrence of methemoglobinemia. Modern analyses of dietary nitrate intake have reevaluated historical data and suggest that methemoglobinemia is unlikely to be a significant concern [209]. Pharmacokinetic studies in healthy subjects receiving intravenous $NaNO_2$ at doses of 6.4–7.7 μmol/kg/h continuously for 3–9 h have reported methemoglobin levels between 2% and 5%, which are well below the levels that would cause respiratory distress [210, 211]. A review of methemoglobinemia cases from the last century reveals no adult cases linked to vegetable consumption. Cases in children or infants have been associated with improper long-term storage of vegetables and subsequent bacterial contamination [212, 213]. Moreover, elevated nitrate levels in drinking water are not consistently associated with an increased risk of clinical methemoglobinemia or raised methemoglobin levels in the blood [214].

To summarize, research should consider dietary sources when evaluating the benefits or toxicity of nitrate intake. While concerns about methemoglobinemia and carcinogenic risks associated with nitrate and nitrites persist, current evidence suggests that dietary nitrate, especially from plant sources, is generally safe and unlikely to pose significant health risks when consumed within typical dietary limits. However, for vulnerable populations and in contexts where nitrate levels might be excessively high, ongoing monitoring remains important.

8 | Conclusion and Prospect

The CKM syndrome represents a complex interplay of multisystem pathophysiology, where the convergence of cardiovascular, renal, and metabolic dysfunctions significantly complicates clinical management. Recent statements from the AHA underscore the urgency of advancing therapeutic strategies that not only address individual components but also offer systemic benefits. As highlighted in their latest guidelines, "Many critical considerations for managing CKM syndrome moving forward revolve around the optimal deployment of a growing range of cardioprotective therapies with systemic effects." Clinical decision-making, therefore, requires a comprehensive approach that integrates safety, efficacy, accessibility, cost-effectiveness, and patient-centered preferences. A promising therapeutic approach that aligns with these considerations is the enhancement of the NO_3^-–NO_2^-–NO pathway, achieved through the supplementation of inorganic nitrate or nitrite.

This strategy has gained attention for its potential to address multiple facets of CKM syndrome's multifactorial pathophysiology, particularly through its effects on vascular tone, metabolic regulation, and organ protection. Recent evidence from both animal models and RCTs underscores the effectiveness of this approach in ameliorating hypertension, mitigating CAD, and conferring renal and cardiovascular protection in the context of CKM syndrome. Notably, studies support the safety and efficacy of inorganic nitrate/nitrite supplementation, particularly through dietary sources such as beetroot and leafy green vegetables, which are cost-effective, easily accessible, and rich in bioavailable nitrates.

Despite the promising findings from preclinical studies, several critical questions remain to be fully addressed. Although animal studies have consistently demonstrated the potential benefits of nitrate and nitrite supplementation, translating these results to human clinical trials has proven challenging. On the one hand, there is a clear need to develop novel preclinical models of CKM to better mimic human pathology. On the other hand, clinical trials involving nitrates/nitrites should be conducted across different stages of CKM, with the aim of confirming the efficacy of nitrate/nitrite supplementation, identifying the characteristics of patients who could benefit from such supplementation, and thereby optimizing the therapeutic effects of nitrates/nitrites in CKM.

Author Contributions

Guang-zhi Liao: writing – original draft, writing – review and editing, visualization, conceptualization. **Chun-hui He:** visualization. **Yu-hui Zhang:** writing – review and editing, supervision. **Jian Zhang:** writing – review and editing, conceptualization, funding acquisition.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

No data were used for the research described in the article.

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