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Review Article

Integrative Determinants of Chronic Kidney Disease: Psychodynamic Stress, Nutritional Dysregulation, and Environmental Toxicity as Emerging Pharmacological Targets

Ranjna Devi[1]*, Dr. Nikhil Singh[2], Dr. Bhawana Rawat[3], Koena Saini[4]

[1] Research Scholar, Department of Pharmacy Practice, Chandigarh College of Pharmacy, Landarn, Mohali, India

[2] Associate Professor, Department of Pharmacy Practice, Chandigarh College of Pharmacy, Landarn, Mohali, India

[3] Assistant Professor, Department of Pharmacy Practice, Chandigarh College of Pharmacy, Landarn, Mohali, India

[4] Research Scholar, Department of Pharmacy Practice, Chandigarh College of Pharmacy, Landarn, Mohali, India

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For Correspondence:

Ranjna Devi, Research Scholar, Department of Pharmacy Practice, Chandigarh Group of Colleges Landarn, Mohali India;

Abstract

Even if hemodynamic and metabolic treatments for Chronic Kidney Disease (CKD) have been shown to work, there is still a significant risk of progression to End-Stage Kidney Disease. This paper asserts that the ongoing deterioration is influenced by a "integrative toxic milieu" defined by three neglected factors: psychodynamic stress, dietary dysregulation, and environmental toxicity. By combining data from important recent trials like TACT2, VALOR-CKD, and AYAME, we look at the molecular pathways that link these factors to renal fibrosis. We focus on the Psycho-Neuro-Endocrine-Immune (PNEI) and gut-kidney axes. The review also looks at how well new drugs like aldosterone synthase inhibitors, Nrf2 activators, and chelation therapies work. It makes the case for a shift in thinking toward a more comprehensive, multi-target pharmacological approach that goes beyond just the glomeruli to include the patient's overall responses to stress from their environment and their own body.

Keywords: Chronic Kidney Disease, Renal Fibrosis, Gut-Kidney Axis, PNEI Axis (Psycho-Neuro-Endocrine-Immune), Nrf2 Pathway, Environmental Nephrotoxicity

1. Introduction

1.1 The Limits of Hemodynamic Centricity and the Residual Risk

The hemodynamic paradigm has been the most essential technique to treat CKD for the past thirty years. The groundbreaking finding that intraglomerular hypertension serves as a mechanical catalyst for glomerulosclerosis resulted in the extensive utilization of Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs) as critical components of renoprotection. These medications lessen the filtration pressure and proteinuria by making the efferent arteriole wider. This makes the loss of nephrons happen more slowly. Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors have been added to this list in the last few years. They are particularly beneficial because they address tubuloglomerular feedback and affect how the body uses energy.[1] Epidemiological data and clinical trial results consistently reveal a stark reality: despite optimal blockade of the renin-angiotensin system, rigorous blood pressure control, and aggressive glucose management, a significant proportion of patients continue to experience a progressive decline in Glomerular Filtration Rate (GFR)[2]. This phenomenon, frequently referred to as the "residual risk" of CKD progression, indicates that essential pathogenic pathways are inadequately addressed by existing standard-of-care medications. The kidney has a lot of blood vessels and is quite active in metabolism. It acts as a sensor for the body's chemical environment inside and outside. It is especially susceptible to "silent" insults that do not immediately manifest as changes in serum

creatinine but rather accumulate as subclinical tubular damage, interstitial fibrosis, and vascular rarefaction over decades[3].

1.2 The Concept of the Renal Exposome

Modern nephrology has increasingly adopted the concept of the exposome to mitigate the persistent residual risk of chronic kidney disease (CKD) progression, despite sufficient hemodynamic and metabolic control. The exposome refers to the total lifetime accumulation of behavioral, endogenous, and environmental exposures, as well as the physiological responses to these exposures, that affect the onset and course of disease. In nephrology, the renal exposome provides a cohesive framework for identifying pathologic variables that traditional glomerulocentric therapeutic models inadequately address.[4] It is very important to note that the renal exposome is not an infinite thing. This review operationally identifies three exposure domains characterized by varying levels of epidemiological, mechanistic, and clinical data. These domains all come together on the same molecular damage pathways in kidney tissue.[4]

Psychodynamic stress is a novel yet growing part of the renal exposome. When the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system are always on, psychological stress creates a toxin that affects the body. This is marked by chronic inflammation, problems with the endothelium, too much catecholamine, and too much cortisol[5,6]. Even if it is currently hard to detect long-term exposure on a broad scale, it is possible to indirectly measure stress-related kidney damage using well-established physiological and biochemical surrogates as cortisol rhythm, heart-rate variability, and inflammatory biomarkers. This field currently resides in an intermediate evidence tier, characterized by substantial mechanistic plausibility and growing epidemiological validation[7].

Nutritional dysregulation is a well-known and scientifically measurable part of the renal exposome. This area also includes the generation of protein-bound uremic toxins such p-cresyl sulfate and indoxyl sulfate, metabolic acidosis, and dysbiosis of the gut microbiota.[8,9] These exposures hasten interstitial fibrosis, augment inflammation, and induce direct tubular injury. In clinical practice, components of the nutritional exposome can be directly assessed by quantifying circulating uremic toxins, assessing dietary acid load, and testing serum bicarbonate levels. These actions are supported by robust epidemiological and interventional evidence.[10]

In nephrology, environmental toxicity represents the exposome domain with the most robust validation. In various populations, the main risk factors that have been associated unambiguously with the development and progression of CKD are exposure to such toxic substances as air-borne particulate matter (PM2.5) and heavy metals such as lead and cadmium.[11,12,13] These toxic substances accumulate disproportionately in the renal cortex. A multitude of epidemiological, mechanistic, and interventional investigations validate the quantification of environmental exposures using biomonitoring, encompassing the measurement of metal levels in blood and urine[14].

The renal exposome, as employed in this review, is delineated by the integration of these three domains. The renal exposome framework serves as a tool for risk classification and therapeutic priority, facilitating the identification of predominant exposure signatures in individual patients, rather than promoting universal screening for all potential exposures. This precision-based approach provides the conceptual basis for integrating exposome-targeted pharmacological techniques, such as Nrf2 activation, chelation therapy, toxin adsorption, and aldosterone synthase inhibition into modern chronic kidney disease management[15].

1.3 Evolutionary Mismatch and the Modern Kidney

The hypothesis of evolutionary mismatch underlies these factors. Changes in human lifestyle (decreased activity level, increased stress levels, high consumption of acid-generating diets due to processed foods, and exposure to environmental toxins) have influenced the human genome that contain genes responsible for regulating kidney functions. While the Paleolithic lifestyle involved high volumes of physical activity, little psychological stress, a high consumption of plants that produce high levels of alkali, and no exposure to environmental toxins. Modern day living is characterised by sedentary lifestyles, high stress levels, low alkaline diets, and high levels of exposure to environmental toxins. This is a physiological problem that the kidneys are not able to handle.[16] This mismatch causes the long-term, low-level inflammation (inflammaging) and oxidative stress that are the main causes of CKD. The "thrifty genotype," which used to save sodium and energy, now makes people more likely to get high blood pressure and metabolic syndrome when there is too much sodium and calories. The stress response system, which was made to help people survive in life-or-death situations, is now always on because of psychosocial stressors. This causes long-term neuroendocrine dysregulation that hurts the blood vessels in the kidneys.

1.4 The Convergence of Pathogenic Mechanisms

Although stress, diet, and environment are different from one another, they still come together to these three molecular executioners in the kidney tissue that can be seen in figure 1: oxidative stress, chronic low-grade inflammation, and mitochondrial bioenergetic failure.[5,1]

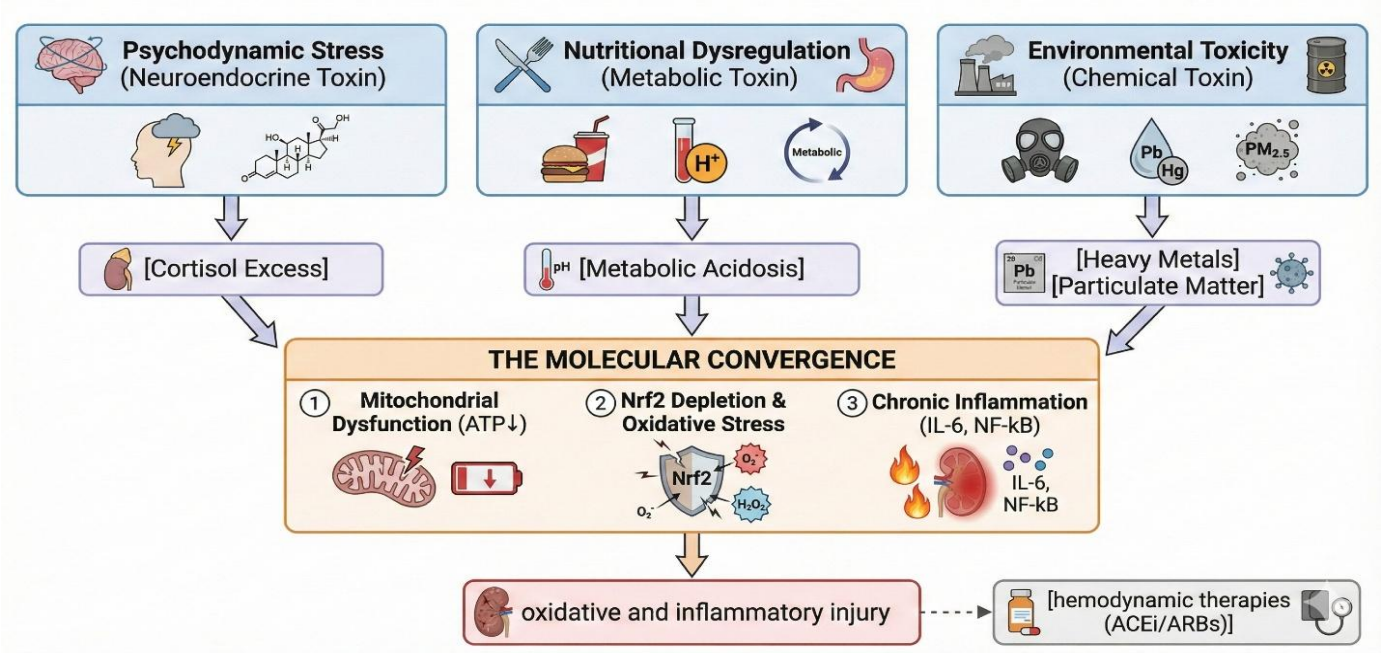

Figure 1: The Renal Exposome and Convergence of Toxicity

Figure 1 illustrates that while the inputs (stress, diet, pollution) vary, they share a final common pathway of oxidative and inflammatory injury that current hemodynamic therapies (ACEi/ARBs) do not fully address.

Psychosocial stress energetic cortisol and catecholamines, which if combined with uremic toxins coming from the gut synergistically promote endothelial dysfunction. At the same time, environmental nephrotoxins are taking away antioxidant (especially the Nrf2 pathway) reserves and thus the kidney becomes a very vulnerable organ to the acidotic stress of nutritional Dysregulation.[3,17]

2. Psychodynamic Stress and Neuroendocrine Dysregulation

The merging of psychology and nephrology has resulted in a new concept called "psychonephrology," which understands the kidney as the organ that is most affected by the brain's perception of danger. Chronic psychosocial stress, as a condition, is not only one of the factors that lead to poor medication adherence or lifestyle choices; it is a biological agent that significantly causes renal injury through the disruption of the PNEI axis[5]. The organ conversion of "stress" into "renal damage" is achieved mostly from two routes: the Hypothalamic-Pituitary-Adrenal (HPA) axis and the Sympathetic Nervous System (SNS).

2.1 The HPA Axis and Cortisol Toxicity

The HPA axis is a major neuroendocrine network in the body responsible for regulating energy homeostasis and the response to stress. After a short-term stress, the hypothalamic paraventricular nucleus releases Corticotropin-Releasing Hormone (CRH), which acts on the anterior pituitary to secrete Adrenocorticotropic Hormone (ACTH). This hormone directs the adrenal cortex (zona fasciculata) to produce cortisol. Normally, this system is controlled by an efficient negative feedback mechanism whereby high cortisol levels inhibit the release of CRH and ACTH. Nevertheless, in chronic kidney disease, this system is impaired at the core, resulting in a condition resembling 'pseudo-Cushing's' syndrome[18,19].

2.1.1 Mechanisms of Dysregulation in CKD

The HPA axis in CKD is often described as having a maladaptive "blunted" phenotype. It is represented by sustained hypercortisolism and reduced reactivity to negative feedback. There are three factors that cause this neuroendocrine imbalance, but loss of kidney function is the most important one. With decreasing glomerular filtration, the metabolic clearance of cortisol through 11β-hydroxysteroid dehydrogenase type 2 is limited, thus the half-life and tissue exposure of glucocorticoids are prolonged considerably[19].

This retention is being amplified by an inflammatory loop that goes in the forward direction, where high levels of pro-inflammatory cytokines in the blood, namely IL-6, TNF-α, and IL-1β, CRH and ACTH release are induced by crossing the blood-brain barrier and thus avoiding the standard feedback inhibition[20,21]. Besides that, the buildup of uremic toxins causes the destruction of the neural pathways that are the core of the HPA axis, hence the stress response is different from homeostatic regulation.

2.1.2 Cortisol as a Uremic Toxin: The 11β-HSD2 Failure

Elevated levels of cortisol lead to a pathologic state of uremia Toxin-like effects due to inhibition (direct inhibition) of 11β-Hydroxysteroid Dehydrogenase Type 2 (11β-HSD2), the enzyme responsible for normal (selective) binding of mineralocorticoid receptors in

kidney distal tubules. The oxidative environment of CKD allows to escape their physiological inactivation and bind indiscriminately, or without selectivity, to the mineralocorticoid receptors and stimulate an "illicit" cascade of biological events similar to those produced by chronic excess of aldosterone. These events create significant damage to the circulatory system and cells in the body (causing damage to the kidneys), including hypertension (from increased blood volume), cytoskeletal Effect and death of Podocytes and system-wide metabolic disorder that contribute to inflammation.[5,19]

2.2 Sympathetic Nervous System (SNS) Overactivity: The Renorenal Reflex

The kidney has a lot of neurological connections that make a pathological feed-forward loop called the "renorenal reflex." In this loop, the failing organ is the main cause of systemic sympathetic hyperactivity[22,23]. This cycle starts when ischemia in the kidneys and the buildup of uremic metabolites activate afferent renal sensory neurons. These nerves send distress signals to the central nervous system, which causes an increase in efferent sympathetic outflow as a way to make up for the loss. This autonomic dysregulation causes three bad responses in the kidneys: afferent arteriolar vasoconstriction, β-1 adrenergic-mediated renin release (which makes the RAAS cascade worse), and direct tubular salt retention. In addition to affecting the kidneys locally, norepinephrine's systemic "spillover" causes resistant hypertension, left ventricular hypertrophy, and arrhythmogenesis. This explains why sudden cardiac mortality is so common in people with CKD[24,25].

2.3 Emerging Pharmacological Targets in the Stress Axis

The recognition of neuroendocrine dysregulation as a fundamental driver of CKD progression has spurred the development of agents that target specific nodes of this axis, moving beyond generic beta-blockade, also shown in table 1.

2.3.1 Glucocorticoid Receptor Antagonists: Mifepristone

Mifepristone (RU-486) is a potent competitive antagonist of the GR and has traditionally been used in obstetrics and in the treatment of Cushing's syndrome. It is currently under reevaluation for its therapeutic benefit in CKD, especially in patients displaying "diabetic-like" phenotypes from hypercortisolism. Mechanistically, mifepristone prevents GR activation, mitigating the metabolic consequences of excess cortisol, which leads to rapid improvements in insulin sensitivity, reduced visceral adiposity, and lower blood pressure; in the context of CKD, these systemic changes decrease the metabolic load on the nephron and decrease lipotoxicity associated with metabolic syndrome[26,27]. The clinical translatability of this approach is being investigated in the CATALYST trial (Part 2), which is focused on those patients with refractory Type 2 diabetes in conjunction with hypercortisolism to assess metabolic outcomes and renal safety and thus may provide further evidence of GR antagonism as a novel mechanism by which to break the cycle of cortisol-induced insulin resistance and kidney injury.[26] However, widespread use is problematic due to off-target effects such as blocking the progesterone receptor and the risk of adrenal insufficiency due to HPA axis instability.

Furthermore, compensatory rises in ACTH and cortisol due to blocking of GR could inadvertently cause unblocked MR to act on, leading to hypokalemia and hypertension; hence, rigid monitoring of electrolytes is required during therapy[28,29].

2.3.2 Aldosterone Synthase Inhibitors (ASIs): Baxdrostat

Aldosterone Synthase Inhibitors (ASIs), which include baxdrostat, work by a proximal mechanism, the complete inhibition of hormone synthesis[30]. Mineralocorticoid receptor antagonists (MRAs) act on the flow of hormones after they have been produced; however, after stopping the production of aldosterone, MRAs often initiate a counter-regulatory feedback loop, leading to elevated plasma levels of aldosterone. This suppression is very important since aldosterone is a direct pro-fibrotic cytokine that causes renal inflammation and collagen deposition through pathways that are not affected by systemic blood pressure. In the past, clinical translation of ASIs was difficult because aldosterone synthase (CYP11B2) and the cortisol-synthesizing enzyme 11β-hydroxylase (CYP11B1) had a 93% sequence identity. This caused first-generation agents like LCI699 to lower cortisol levels off-target. However, baxdrostat has overcome this problem by having a high selectivity (>100:1) for CYP11B2, successfully lowering aldosterone levels without affecting the cortisol stress response[31]. After the BrigHTN trial showed that resistant hypertension could be treated with a combination of baxdrostat and dapagliflozin, current Phase 3 trials are testing the idea that combining SGLT2 inhibition (to control blood flow) with upstream aldosterone suppression (to stop fibrosis) will provide extra protection for the kidneys[32,33].

2.3.3 Anti-Inflammatory Interventions: Ziltivekimab

Ziltivekimab is a fully human monoclonal antibody that specifically targets the IL-6 ligand in the PNEI axis. It is the one that effectively breaks the chain of the pro-inflammatory state that is a typical feature of chronic stress and is mainly mediated by interleukin-6 (IL-6)[34,35]. In the RESCUE trial, which was conducted on patients with Stage 3-5 CKD and high inflammatory conditions (hsCRP ≥ 2 mg/L), Ziltivekimab treatment brought about a significant decrease in one of the most important biomarkers such as hsCRP, fibrinogen, and serum amyloid A. It is worth noting that serum albumin and hemoglobin levels were also elevated, which might indicate that the catabolic and myelosuppressive effects associated with the anemia of chronic disease have been reversed[35,36]. The ongoing ZEUS trial is determining the clinical utility of this anti-inflammatory effect by asking the question as to whether IL-6 suppression leads to less cardiovascular events and less tubulointerstitial inflammation and fibrosis, thus, slowing down the decline of GFR [37].

Table 1: Summary of Stress-Axis Targets

Target Mechanism	Drug Class/Agent	Key Physiological Effect	Current Status in CKD
Cortisol Excess[27,38]	GR Antagonist (**Mifepristone**)	Blocks metabolic/adipogenic effects of cortisol; improves insulin sensitivity.	Phase 3 (CATALYST) for metabolic control; exploratory in CKD.
Aldosterone Excess[31,39]	Aldosterone Synthase Inhibitor (**Baxdrostat**)	Prevents synthesis of aldosterone; reduces fibrosis and BP; spares cortisol synthesis.	Phase 3 trials (with Dapagliflozin).
Mineralocorticoid Receptor [40,41]	Non-steroidal MRA (**Finerenone**)	Blocks inflammatory/fibrotic signaling of aldosterone without steroid side effects.	FDA Approved for CKD in T2D.
IL-6 Inflammation [35,37]	IL-6 Ligand Inhibitor (**Ziltivekimab**)	Reduces stress-induced systemic inflammation, improves anemia and albumin.	Phase 3 (ZEUS) ongoing.

3. Nutritional Dysregulation: The Gut-Kidney Axis and Metabolic Acidosis

The dietary factors leading to CKD have gone beyond the traditional focus of just reducing dietary sodium and controlling protein intake. The current knowledge of renal nutrition is heavily reliant on the two main pathological mechanisms: the "Gut-Kidney Axis," whereby the microbiome becomes a major source of nephrotoxins, and "Metabolic Acidosis," a catabolic state that not only depletes muscle and bone but also causes renal fibrosis to progress rapidly[42].

3.1 The Gut-Kidney Axis: Dysbiosis and Uremic Toxins

In individuals with good health, the gut microbiome lives in a symbiotic relationship with the host, thus it helps the body with nutrient absorption, vitamin synthesis, and immune regulation. In CKD, this relationship turns into dysbiosis, which is marked by the excessive growth of proteolytic bacteria (e.g., *Enterobacteriaceae*, *Clostridiaceae*) and a dramatic decrease of saccharolytic (fiber-fermenting) species (e.g., *Bifidobacterium*, *Lactobacillus*). The shift is caused by the arrival of urea in the gut lumen, changed intestinal pH, and dietary restrictions that are usually imposed on patients (low potassium diets that often mean low fruit/vegetable fiber intake)[9,43].

3.1.1 Mechanisms of Toxin Generation

The dysbiotic microbiome in CKD is comparable to a toxic metabolic organ that metabolically instigates the disease by eating into food proteins that are left undigested for a long time in the colon. The colonic microbiota converts both tyrosine and tryptophan, which are two aromatic amino acids, to phenols and indoles, respectively. These are then absorbed into the body through the portal vein. After the liver takes them up, phenolics such as p-cresyl sulfate (PCS) and indoxyl sulfate (IS) undergo enzymatic reactions that lead to the formation of uremic toxins (PBUTs) as well as other substances like trimethylamine-N-oxide (TMAO) and phenylsulfate[9,44]. These uremic toxins have damaging effects in the renal proximal tubule, where they are taken up by the renal tubule via organic anion transporters (OATs) at a high rate, as a result of which they cause ire. This further leads to the activation of NADPH oxidase that generates oxidative stress and TGF-β and PAI-1 dependent EMT that results in fibrosis. Besides that, IS and PCS enable kidney injury to continue by interacting with and hence turning on NF-κB signaling, which in turn results in the release of pro-inflammatory cytokines.[45]

3.1.2 The "Leaky Gut" Phenomenon

Besides, chronic kidney disease is related to swelling of the intestinal wall and changes in the epithelium junctions. The union of the epithelial cells is the most affected one, so it is thus considered the weakest link. This penetration of the barrier function leads the bacterial endotoxins (Lipopolysaccharide, LPS) and viable bacteria to move from the gut to the systemic circulation. This "endotoxemia" mobilizes an immune reaction of low intensity and of great duration which is responsible for the cardiovascular disease aggravation and for an increase of renal inflammation rate. The inflammation originated in the gut also participates in the inhibition of red blood cell formation (anemia) and causes insulin resistance[46].

3.2 Metabolic Acidosis: A Silent Catabolic Driver

As nephron mass falls, the kidney's ability to remove the daily non-volatile acid load from dietary proteins and make adequate bicarbonate to restore body buffers is weakened. The resulting metabolic acidosis is a significant, undetectable factor contributing to deteriorating clinical outcomes and accelerated disease progression, rather than only a transient biochemical irregularity[8,47,48].

3.2.1 Pathophysiology of Acid-Mediated Injury

Three distinct detrimental mechanisms contribute to

the pathophysiology of acid-mediated injury. Acidosis activates the ATP-dependent ubiquitin-proteasome system and caspase-3 in muscle cells. This is the initial step in a powerful catabolic signal. This mechanism breaks down muscle protein to free up glutamine for the kidneys to use to make ammonia. This is a trade-off that helps get rid of acid but also leads to loss of lean muscle mass and contributes to sarcopenia and frailty[8,49]. Second, the body tries to buffer extra protons by breaking down bone material. This process makes CKD-Mineral and Bone Disorder (CKD-MBD) worse and causes vascular calcification by putting calcium into the circulation.[50] Lastly, the adaptive maximizing of ammoniagenesis by surviving nephrons activates the alternative complement pathway (C3, C5b-9), which causes high levels of ammonia in the renal interstitium. This maladaptive reaction leads to direct tubulointerstitial inflammation and fibrosis, thereby leading the kidney to "burn out" its remaining tissue to maintain systemic pH balance.[50,51]

3.3 Emerging Pharmacological Targets in Nutrition

3.3.1 Novel Acid Binders: Veverimer

Oral sodium bicarbonate has been used in the past to treat metabolic acidosis in people with CKD. But this method is limited by the amount of sodium that comes with it, which makes high blood pressure and fluid retention worse. Veverimer is a non-absorbed, counterion-free polymer that selectively binds protons and chloride in the gastrointestinal tract. This causes a systemic "chloride shift" that makes new bicarbonate without changing the balance of sodium[52,53] Veverimer's main clinical use is as a targeted treatment for the musculoskeletal problems that come with acidosis in people who can't handle sodium, not as a disease-modifying treatment for GFR stabilization. This is because Phase 3 trials showed that it worked to normalize serum bicarbonate and improve physical function by reversing acid-mediated muscle catabolism. The premature cessation of the VALOR-CKD trial indicated that this metabolic correction did not result in a reduction in the progression of CKD[52,54,55].

Accordingly, veverimer's therapeutic profile is best understood when benefits and limitations are considered in parallel (Table 2).

Table 2: Benefits and Risks of Veverimer in Chronic Kidney Disease.

Domain	Observed Benefits	Risks / Limitations	Clinical Interpretation
Metabolic Effects [56]	Sustained increase in serum bicarbonate levels	Does not address upstream causes of acid generation	Effective biochemical correction of acidosis
Muscle & Physical Function [57,58]	Improved muscle strength and physical performance	Benefits are functional rather than structural	Reversal of acid-mediated muscle catabolism
Electrolyte Balance [59]	Sodium- and potassium-neutral mechanism	No impact on volume overload drivers beyond acidosis	Advantageous in sodium-sensitive patients
Renal Outcomes [52]	—	No reduction in eGFR decline, ESKD, or renal death (VALOR-CKD)	Not disease-modifying for CKD progression
Cardiovascular Safety[60]	Avoids sodium-related hypertension and fluid retention	Does not mitigate inflammatory or fibrotic signaling	Safer alternative to bicarbonate in high-risk patients
Target Population [61,62]	Advanced CKD with metabolic acidosis and sodium intolerance	Limited utility in early CKD or fibrosis-driven progression	Best suited as adjunctive supportive therapy

Clinical Positioning in the Framework of the renal exposome, metabolic acidosis acts more as a catabolic-stressor rather than the overriding fibrotic force following the onset of CKD. This confirms that, despite the improvement observed in resistance to disease and overall health status, the VALOR-CKD study that inhibition of urease does not independently affect the underlying pathophysiology of the kidneys[52.] Accordingly, the optimal positioning of veverimer would be that of a supportive/symptom-modifying drug and particularly useful within the subgroup of sodium-sensitive and heart failure-prone individuals with CKD. To achieve maximum beneficial effect, however, veverimer would be most appropriately used together with disease-modifying therapies against inflammation, oxidative stress, mitochondrial damage, and toxic exposures.[63]

3.3.2 Targeting the Gut-Kidney Axis: Adsorbents and Synbiotics

New ways to treat people focus on stopping toxin precursors from getting into the intestines so that the

body doesn't have to deal with as many gut-derived toxins. Activated bamboo charcoal (ABC) works like "oral dialysis" because its porous structure is perfect for adsorbing precursors like indole and p-cresol before they are turned into anything else in the liver. This approach has been shown to lower serum levels of indoxyl sulfate and p-cresyl sulfate compared to controls. In patients with Stage 3 CKD, it also stabilized eGFR (+4.6%)[44].

Another cutting-edge therapy concept entails changing the microbiome makeup to those bacteria that break down sugars (non-toxin producing) by using synbioticsa synergistic combination of prebiotics (fermentable fibers such as inulin and resistant starch) and probiotics (live beneficial bacteria like *Bifidobacterium* and *Lactobacillus*). Conclusive human studies point to the ability of synbiotics to lower serum p-cresyl sulfate (PCS) and indoxyl sulfate (IS) concentrations by a significant margin. In fact, by adding fermentable carbohydrates, prebiotics hamper bacteria from proteolytic fermentation and thus reduce the generation of nitrogenous toxins; at the same time, this metabolic change leads to the increased formation of Short Chain Fatty Acids (SCFAs) such as butyrate which are the energy source for colonocytes and help to restore gut barrier function thus, lowering endotoxemia [9,64]

4. Environmental Toxicity: The Silent Nephrotoxins

During the era of industrialization, the "Renal Exposome" consists of a wide variety of environmental pollutants that accumulate biologically in the kidney. The renal cortex, due to its rich blood supply and active transport capability, is a major site of heavy metals and particulate matter. These environmental agents should not be considered as past events; they are alive, extensively, and overwhelmingly influential factors of CKD progression in the present-day world.[11]

4.1 Mechanisms of Environmental Nephrotoxicity

4.1.1 Heavy Metals (Lead and Cadmium)

Lead (Pb) and cadmium (Cd) are prevalent contaminants in the environment that can damage the kidneys in diverse ways that add up. Lead primarily functions as a calcium molecular mimic, disrupting intracellular signaling and accumulating in the proximal tubule, resulting in mitochondrial hypertrophy and obstructing the electron transport chain. The clinical "lead nephropathy" triad hypertension, hyperuricemia (saturnine gout), and tubulointerstitial nephritis arises from its inhibition of enzymes such as ferrochelatase and endothelial nitric oxide synthase[65]. Lead being sequestered in bone can serve as a body source that enables the release of lead back into the body via the blood system when the amount of activity in bone increases (such as during acidosis or as a result of menopause). The above mechanisms have been thought to be a significant factor in the ongoing health issues that people experience as a result of lead exposure. Cadmium is toxic due to the fact that it binds to hepatocyte metallothionein, which is then filtered through the glomerulus and taken back up by the proximal tubule. There, lysosomal breakdown produces free cadmium ions, which lead to apoptosis and significant oxidative damage. Because cadmium stays in renal tissue for 10 to 30 years, the harm it causes is still primarily based on how much exposure someone has had over time rather than how much they get at once[66].

4.1.2 Air Pollution (Particulate Matter)

New eras of epidemiological studies have found a strong correlation between the inception of CKD and exposure to fine particulate matter (PM2.5) through both systemic and local direct pathways. Inhalation of PM2.5 brings about a body response of inflammation, which is reflected in raised levels of TNF-α, CRP, and IL-6. This, along with oxidative stress in the whole body, makes the renal vascular system less stable. Direct nephrotoxins are ultrafine particles (less than 0.1 μm) that move into the blood directly from the alveoli of the lungs. The glomerulus removes them, and they impinge on podocytes and tubular epithelial cells directly, thus causing glomerulosclerosis and focal tissue damage[13,67]

4.1.3 The Unifying Mechanism: Nrf2 Depletion

The usual route of the environment-caused nephrotoxic side effect is to generate Reactive Oxygen Species (ROS) and exhaust the kidney's antioxidant defenses. The poisons to the kidneys specifically hamper or dominate Nrf2 (Nuclear factor erythroid 2-related factor 2), which is the main transcriptional regulator of antioxidant genes (e.g., HO-1, NQO1). In CKD, Nrf2 is very often downregulated or only partially active because it is bound by the repressor Keap1, which makes the organ susceptible to the oxidative attack of environmental pollutants.[68,69]

4.2 Emerging Pharmacological Targets in Environmental Defense

4.2.1 Chelation Therapy: The TACT Trials

Disodium EDTA (Na_2EDTA) chelation therapy works by bonding with divalent and trivalent heavy metals, particularly lead (Pb) and cadmium (Cd), and thus promoting the urinary excretion of these metals. Owing to the presence of the kidney as a main site of toxic heavy metal accumulation and redox damage, chelation therapy has remained a potential targeted therapeutic intervention with implications for the domain of environmental toxicity of the exposome of the kidney[70]. The Trial to Assess Chelation Therapy (TACT1) was the first large, NIH-sponsored, randomized controlled trial to demonstrate clinical benefit from EDTA-based chelation. TACT1 enrolled 1,708 post-myocardial-infarction patients, many of whom had diabetes and were exposed to higher environmental metal burdens characteristic of the late 20th century. In the trial, a 41% relative risk reduction in major adverse cardiovascular events was found in the patients with diabetes, which was attributed mechanistically to the elimination of the vasculotoxic metals contributing to oxidative stress, endothelial dysfunction, and mitochondrial damage[71,72].

In this regard, the lack of efficacy of TACT2 (2024),

designed and attempted to replicate this outcome, failed to show a significant reduction of cardiovascular events[59]. Such discrepancy can now be rationally explained by the difference in baseline intensity of exposure, rather than ineffectiveness of therapy. Lead doses in the 30–40% reduction of baseline levels, due to successful public health measures over the decades (namely, lead-free gasoline and paints), meant that subjects of the TACT2 trial had insubstantial enough lead exposures that could provide a clear therapeutic effect of chelation therapy, effectively muddying the therapeutic effects. These observations highlight an important tenet of clinical translation: chelation therapy is a function of exposure and cannot be considered a universal treatment modality. Small clinical trials and meta-analyses have already shown the use of EDTA chelation treatment to stabilize or slightly increase the estimated glomerular filtration rate (eGFR) of patients with CKD and high-normal to elevated serum levels of lead[73,74].

Clinical Positioning within the Renal Exposome Model, the disparate results of TACT1 and TACT2 trials shed new light on the fact that chelation therapy has to be utilized in its role as a precision treatment in patients with proven accumulation of heavy metals, but it should never be utilized in its broad-spectrum treatment era. In the renal exposome model, it has been noted that environmental nephrotoxicity has the exacerbating effect of oxidative as well as mitochondrial damage. Thus, EDTA chelation therapy can be applied, based on careful patient selection, particularly with patients with CKD and exposure to lead and/or cadmium, and concurrently considering other therapeutic approaches like pathways involving inflammation, fibrosis, and mitochondrial dysfunction. The precision medicine paradigm helps to bring order amidst the conflicting results and aligns the use of chelation therapy with the paradigm shift of exposomics and nephrology.

4.2.2 Nrf2 Activators: Bardoxolone Methyl and Omaveloxolone

There appears to be a convergence on a particular pathogenic mechanism for the role of environmental nephrotoxins, including heavy metals and particulate matter, in chronic kidney disease that involves the inhibition of the Nrf2 gene, the chief regulator of the antioxidant response. There seems to be sound justification for its pharmacologic reexpression, which may offer a means of addressing the issue of antioxidant defenses triggered by the toxicity of the environment, an aspect of the renal exposome.[75]

Bardoxolone methyl was a novel synthetic triterpenoid Nrf2 inducer that provided first-in-class proof of concept but highlighted necessary safety caveats. The phase III trial in patients with late diabetic nephropathy was prematurely interrupted due to an incision in hospitalizations for heart failure. Follow-up mechanism of action studies attributed a toxicity effect to endothelin-induced salt and water retention rather than cardiotoxicity. It is important to note that these follow-on studies afforded improvements in patient recruitment and defined the therapeutic candidate, bardoxolone.[76] TSUBAKI and AYAME trial patients were meticulously selected and excluded for pre-existing heart failure or large sensitivity,[77,78] and these two trials showed highly significant and durable elevations in estimated glomerular filtration rate (eGFR) with no re-appearance of the adverse cardiovascular signal observed in the BEACON trial[79]. These improvements were mechanistically linked to mesangial cell relaxation, leading to increased filtration surface area, along with suppression of inflammatory and oxidative pathways downstream of Nrf2 activation.[80,81] Nonetheless, the eGFR rise remains mechanistically debated, with ongoing discussion as to whether it reflects beneficial hemodynamic remodeling versus functional hyperfiltration.

The clinical evolution of bardoxolone has informed the development of next-generation Nrf2 activators, most notably omaveloxolone, a structurally related but pharmacokinetically distinct analog. Omaveloxolone has recently gained regulatory approval in Friedreich's ataxia and has provided safety in the setting of an mitochondrially mediated disorder[82]. There are preclinical kidney studies that indicate omaveloxolone has an effect in improving mitochondrially mediated bioenergetics, ATP, and redox, with an increased therapeutic index with less fluid retention than bardoxolone [81,83,84]. The characteristics make it an agent of interest to be tested in CKD in the future, especially when an exposome factor is prominent.

Clinical Positioning within the Renal Exposome Framework, The depletion of Nrf2 in the renal exposome model has been identified as the final common endpoint within which environmental toxins increase oxidative and mitochondrial damage. The role of bardoxolone methyl has already shown in the TSUBAKI and AYAME trials that Nrf2 activation can lead to clinical relevant changes in renal function parameters, but its limitations emphasize the utilization of risk adjustment strategies for cardiovascular risk.[85,86]

Omaveloxolone, which leverages the strengths of Nrf2 activation and mitochondrial stabilization along with possibly improved safey, truly represents the next logical step in the development of exposome-targeted therapies for renal disorders. Future studies should focus on enrichment for those patients who have high levels of oxidative stress, exposure to environmental toxins, and mitochondrial disease and examine the role of Nrf2 activators within the context of multitargeted therapies[87].

4.2.3 Mitochondrial Targeted Antioxidants: Elamipretide

The fact that traditional systemic antioxidants (such Vitamin C and E) have failed in CKD trials in the past is mostly because they can't reach the inner mitochondrial membrane, where the most Reactive Oxygen Species (ROS) are generated. Elamipretide (SS-31) gets around this problem by using a "precision medicine" approach. It works as a tetrapeptide that specifically targets and

binds to cardiolipin, a special phospholipid that is important for the shape of cristae and the organization of electron transport chain supercomplexes.

In diseases where cardiolipin oxidation causes cytochrome c release and electron leakage, elamipretide stabilizes the lipid structure to stop apoptotic collapse and improve bioenergetic efficiency. This lowers the amount of ROS that is generated at its source. Preclinical studies show that it can keep ATP generation and GFR up by keeping organelle integrity instead of just getting rid of free radicals in the blood. This is shown in models of ischemia injury, renal artery stenosis, and diabetic nephropathy[88,89].

5. Integrative Cross-Talk: The Convergence of Determinants

The "siloed" view of these determinants fails to capture the reality of the patient experience. In vivo, stress, diet, and environment interact in complex feed-forward loops that amplify renal injury, also shown in table 3.

Table 3: Cross-Talk and Therapeutic Synergy

Determinant A	Determinant B	Mechanism of Crosstalk	Therapeutic Implication
Psychodynamic Stress [43,90]	**Nutritional Dysregulation**	Stress → Leaky Gut → Endotoxemia	Stress reduction may lower uremic toxin burden.
Environmental Toxicity[91]	**Nutritional Dysregulation**	Heavy metals alter microbiome composition (Dysbiosis)	Chelation might restore healthy microbiome diversity.
Nutritional Dysregulation [92,93]	**Psychodynamic Stress**	Uremic toxins cause neuroinflammation/cognitive decline	Adsorbents (ABC) may improve cognitive/mental status.
Environmental Toxicity [94,95]	**Mitochondrial Function**	Metals/Pollutants block Nrf2 and damage ETC	Nrf2 activators (Bardoxolone) counteract environmental oxidative stress.
Genetic Susceptibility [96,97]	**Environmental Stress**	APOL1 risk alleles exacerbated by inflammation (IFN-γ)	Anti-inflammatory (Ziltivekimab) may blunt genetic risk.

5.1 The Stress-Microbiome-Toxin Loop

"Stress-Microbiome-Toxin Loop" is a two-way pathogenic axis that alters the gut environment in a very deep manner by vagal and hormonal signals. Stress-induced catecholamines, for instance, directly elevate the virulence of toxin-producing bacteria via bacterial adrenergic sensors. At the same time, Corticotropin-Releasing Factor (CRF) compromises intestinal mucosa ("leaky gut"), thus facilitating the systemic translocation of lipopolysaccharides (LPS) and environmental metals. The loop, however, keeps going as the uremic toxins that are derived from it, indoxyl sulfate and p-cresyl sulfate, pass the blood-brain barrier and cause neuroinflammation, which results in the exacerbation of the patient's mental disorder. Therefore, healing treatments are bilateral: adsorbents or synbiotics not only help by stabilizing the stomach but also protecting the brain. On the other hand, stress-reduction methods such as mindfulness and beta-blockers reinforce the gut barrier and decrease the flow of toxins[43,90]

5.2 The Toxin-Mitochondria-Acidosis Loop

When ambient heavy metals and uremic toxins (IS/PCS) come together on the mitochondria of the proximal tubule, they start a harmful cycle called the "Toxin-Mitochondria-Acidosis Loop." When mitochondria don't work right, they can't make enough ATP for active transport. This is especially true for the energy-intensive H+-ATPases that secrete protons. This lack of energy makes metabolic acidosis worse, which shows up as an acquired form of Renal Tubular Acidosis. On the other hand, the ensuing acidosis changes the pH inside cells, which makes enzymes work less well and makes mitochondrial damage worse. This mechanism shows that there is a synergistic therapeutic potential: drugs like Elamipretide that stabilize mitochondrial bioenergetics may improve the ability to get rid of acid, while drugs like Veverimer that bind to acid could protect mitochondrial mass by reducing the metabolic workload and catabolic stress on the tubule.[50,88]

6. Detailed Analysis of Emerging Pharmacological Agents

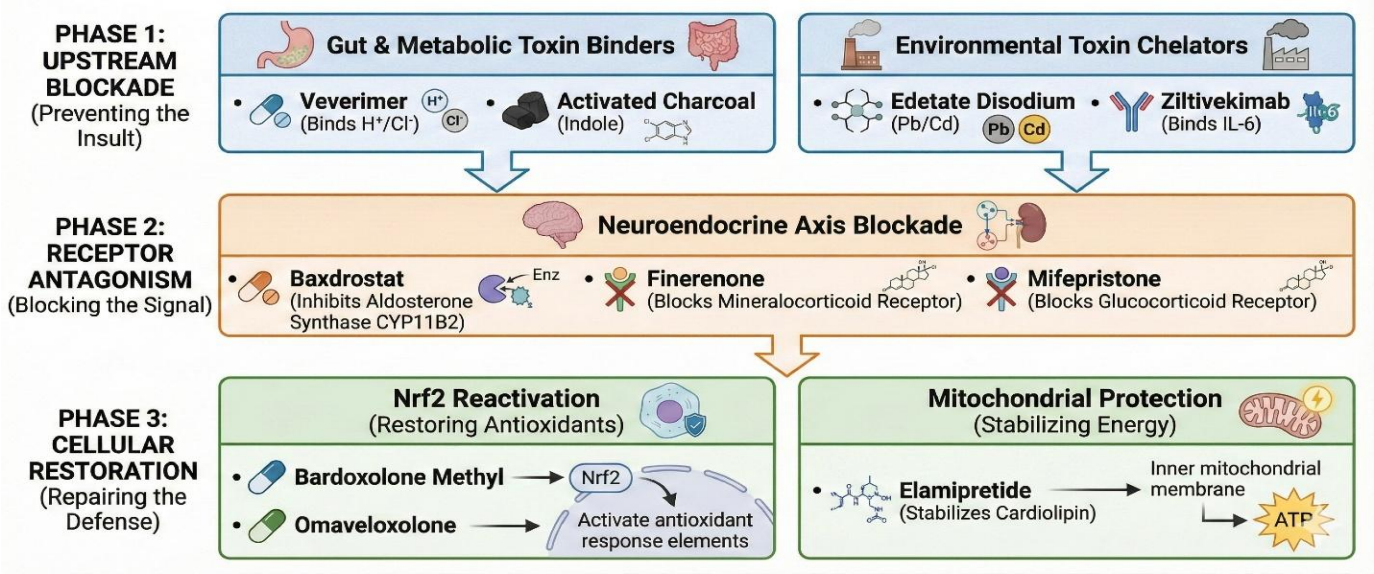

Figure 2: Therapeutic Interception of the Toxic Milieu

Figure 2 demonstrates the shift from purely hemodynamic management to a multi-tiered approach targeting toxin accumulation, receptor signaling, and cellular bioenergetics.

6.1 Aldosterone Synthase Inhibitors: The Case of Baxdrostat

Baxdrostat is an emerging therapy for mineralocorticoid excess, targeting an entirely different origin than current product types. Unlike spironolactone or finerenone (which are mineralocorticoid receptor antagonists) and prevent receptor activation, Baxdrostat prevents aldosterone synthesis by blocking the enzyme responsible for converting deoxycorticosterone to aldosterone (CYP11B2). This is a primary difference between the two therapies, with the latter leading to elevated plasma aldosterone levels as a side effect of their ability to block mineralocorticoid receptor activation. This may lead to a more complete blockage of pro-fibrotic signaling that happens later on. The BrigHTN trial showed a significant, dose-dependent decline in systolic blood pressure (-20 mmHg) in those with resistant hypertension, which gives it clinical validity. Phase 3 studies are now evaluating whether the removal of the aldosterone ligand, particularly in conjunction with SGLT2 inhibitors, enhances anti-fibrotic protection and renal outcomes, as opposed to receptor blockade alone[31,98].

6.2 Nrf2 Activators: Navigating the Safety-Efficacy Balance

The "Bardoxolone Paradox" currently defines the clinical application of Nrf2 activators: while the agent consistently elevates eGFR in trials for diabetic kidney disease, such as TSUBAKI and AYAME, the underlying mechanism remains contentious, with advocates suggesting a beneficial enhancement of filtration surface area through anti-inflammatory mesangial cell relaxation, and detractors attributing the phenomenon to maladaptive hyperfiltration[80,81]. Omaveloxolone, a second-generation drug, has come out at the same time as this discussion. It has a different pharmacokinetic profile but the same Nrf2-activating power as the first drug. Its recent licensure for Friedreich's ataxia has generated interest in "neuro-renal" protection trials aimed at the mitochondrial abnormalities common to both neurons and podocytes[83].

6.3 Novel Binders and Adsorbents

To avert nutritional depletion associated with prior, non-specific binders, therapeutic innovation in the regulation of gut-derived toxins is transitioning towards heightened specificity. Activated bamboo charcoal (ABC) is a good example of this strategy. It is meant to specifically target the colonic precursors of p-cresyl sulfate (p-cresol) and indoxyl sulfate (indole). Pilot data showing a 29% drop in serum indoxyl sulfate shows that it could lower direct tubular toxicity[44]. Even if the VALOR-CKD study ended early, veverimer is still a useful "sodium-free alkali" for stage 4–5 CKD patients whose salt retention makes it impossible for them to take bicarbonate therapy. However, correcting acidosis in advanced disease may work more as a palliative treatment for musculoskeletal health rather than a disease-modifying strategy, as seen by the observed discrepancy between improved functional status and the absence of effect on disease progression[55].

7. Conclusion and Future Directions

Management of CKD is moving towards a different direction. The period when CKD had to be treated only as a hemodynamic complication of diabetes and hypertension is coming to an end. Now we are moving towards an era of Integrative Nephrology where the "Renal Exposome" that includes the patient's stress levels, gut health, and the environment contaminated with toxins is considered the main cause of residual risk is acknowledged, also shown in table 3.

Table 3. Emerging Pharmacological Targets Across Renal Exposome Determinants: Mechanisms, Evidence Boundaries, and Clinical Positioning

Determinant Category	Therapeutic Target	Drug Name(s)	Primary Mechanism of Action	Key Benefits	Risks / Limitations	Evidence Level & Clinical Positioning
Psychodynamic Stress	Aldosterone Synthase [99,100]	**Baxdrostat**	Selective inhibition of CYP11B2 → suppression of aldosterone synthesis	Anti-fibrotic, BP reduction independent of RAAS escape	Limited long-term renal outcome data	Phase 3; promising disease-modifying adjunct, best in stress-hyperaldosteronism phenotype
	Glucocorticoid Receptor [101,102]	**Mifepristone**	Competitive GR antagonism → reduces cortisol-mediated metabolic and renal stress	Improves insulin resistance, metabolic load	Risk of adrenal axis dysregulation, hypokalemia	Phase 3 (metabolic); supportive therapy in hypercortisolemic phenotype
	Mineralocorticoid Receptor [103]	**Finerenone**	Non-steroidal MR blockade → anti-inflammatory, anti-fibrotic	Proven renal & CV protection in T2D-CKD	Hyperkalemia risk	Approved; disease-modifying cornerstone therapy
	IL-6 Ligand[37]	**Ziltivekimab**	Neutralization of IL-6–mediated inflammatory signaling	Reduces systemic inflammation, improves anemia	Long-term renal fibrosis impact under study	Phase 3 (ZEUS); adjunct for inflammatory-stress phenotype
Nutritional Dysregulation	Metabolic Acidosis [104]	**Veverimer**	Non-absorbed GI HCl binder → endogenous bicarbonate generation	Improves bicarbonate levels, muscle function	No effect on CKD progression (VALOR-CKD)	Post-Phase 3; supportive, symptom-modifying therapy
	Uremic Toxins[44]	**Activated Bamboo Charcoal**	Adsorbs indole & p-cresol precursors in colon	Reduces IS/PCS; potential eGFR stabilization	Limited large-scale outcome data	Pilot/Phase 2; exposome-targeted adjunct
	Gut Microbiome [105,106]	**Synbiotics**	Shift from proteolytic to saccharolytic fermentation	Reduces toxin generation; improves gut barrier	Variable strain-specific efficacy	Exploratory; supportive and preventive role
Environmental Toxicity	Nrf2 Pathway	**Bardoxolone Methyl[86]**	Nrf2 activation → antioxidant, anti-inflammatory gene transcription	Improves eGFR in selected patients (TSUBAKI, AYAME)	Fluid retention in HF-prone patients (BEACON)	Phase 3; precision-selected, non-HF populations

		Omaveloxolone [83,107]	Nrf2 activation with enhanced mitochondrial bioenergetics	Improved redox balance; potential safer profile	Renal outcome data still emerging	Approved (FA); preclinical/early CKD translation
	Heavy Metals[108]	**Edetate Disodium**	Chelation of Pb/Cd → urinary excretion	Reduces oxidative metal burden	Ineffective in low-exposure populations	Phase 3 completed; biomarker-guided precision therapy
	Mitochondrial ROS[109]	**Elamipretide**	Cardiolipin stabilization → reduced mitochondrial ROS	Preserves ATP production, organelle integrity	Limited CKD-specific outcome trials	Phase 2/3; promising mitochondrial-targeted adjunct

7.1 Actionable Insights for the Future

In the future, nephrology will evolve toward precision medicine through the development of patient-specific toxicity profiles that will allow for the periodic assessment of exposure to both heavy metals (lead and cadmium) and uremic toxins (indoxyl sulfate and p-cresyl sulfate). Identifying individuals who will benefit from targeted chelation or adsorption therapy will be made easier by developing these tailored toxicity profiles. Additionally, in evaluating the risk for CKD, it is important to consider the psychodynamic parameters of heart rate variability and cortisol levels, both of which are markers for the sympathetic nervous system tone. These parameters are especially important for patients identified as having a specific "stress phenotype." In these patients, treatment with either mineralocorticoid receptor antagonists (MRAs) or aldosterone synthase inhibitors (ASIs) may provide superior outcomes. Ultimately, a "quintuple" approach to treatment will likely become the next standard of care. This quintuple approach will systematically incorporate GLP-1 receptor agonists, selective acid binders (veverimer), and either non-steroidal MRAs or ASIs to help regulate anti-fibrotic properties, as well as mechanism-specific agents including Nrf2 activators, such as bardoxolone, and chelation therapy for addressing specific exposome issues. This will also enhance the efficacy of SGLT2 and RAS inhibition therapy.

7.2 Final Thought

The kidneys are the body's most important chemical sensors. They break down not only the glucose we eat, but also the tension we feel and the air we breathe. We are getting closer to stopping the evolution of this severe disease by adding more drugs to our arsenal that target psychological stress, nutritional imbalance, and environmental toxins. The arrival of drugs like baxdrostat, veverimer, and omaveloxolone shows that this new area is not only a theory, but is about to become a reality.

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