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Gut-derived uremic toxins and their role in accelerating cardiovascular events in chronic kidney disease

Abstract. *Chronic kidney disease (CKD) is a long-lasting and progressive condition. It is caused by the complicated buildup of many serum uremic toxins, some of which are made by the gut flora. Two uremic toxins, indoxyl sulfate and p-cresyl sulfate, have been shown to worsen cardiovascular disease and accelerate the progression of chronic kidney disease. These toxins harm the heart over time by causing the blood arteries swell, creating oxidative stress, and making the endothelium work poorly or not at all. The relationships between uremic toxins produced in the gastrointestinal tract and cardiovascular events in individuals with CKD remain inadequately defined, especially with prospective new biomarkers that could facilitate earlier diagnosis of cardiovascular events and the commencement of treatment. This aims to conduct a systematic review and research on cardiovascular risk factors associated with specific gut-derived uremic toxins, with a particular focus on blood pressure, atherosclerosis, and arterial stiffness in individuals with CKD. This study aims to elucidate more definitions regarding the impact of these toxins on clinical events and the pathobiology of cardiovascular illnesses in individuals with chronic renal disease. Furthermore, when examining these data, we will consider treatment strategies aimed at modifying certain factors by targeting the microbiome to maintain positive clinical outcomes, as well as interventions that inhibit the production of gut-derived uremic toxins to eliminate or mitigate their adverse effects. By controlling gut-derived uremic toxins, patients' cardiovascular profiles and CKD risks can be modified, improving clinical outcomes and quality of life.*

Keywords: *chronic kidney disease; uremic toxins; gut microbiota; cardiovascular disease; indoxyl sulfate; p-cresyl sulfate; cardiovascular risk factors*

Introduction

Chronic kidney disease (CKD) is the gradual inability to eliminate bodily waste when the kidneys cease to function. Another factor influencing CKD progression is the presence of uremic toxins in the microbiome. The uremic toxins that are of significance in cardiovascular diseases among CKD patients are PCS and IS. These toxins have been linked to gut microbiome disturbance, systemic absorption, vascular inflammation, oxidative stress, and endothelial dysfunction, which are primary processes contributing to cardiovascular damage [1, 4]. The substantial quantity of research regarding the correlation between uremic retention of intestinal toxins and cardiovascular disease in individuals with CKD has yet to be sustained [8]. These toxins have been demonstrated to exacerbate cardiovascular disease by influencing risk factors such as arterial stiffness, hypertension, and atherosclerosis. It is posited that the sequestration of uremic toxins accelerates the progression of cardiovascular injury and the overall cardiovascular burden in patients with CKD [21]. They must identify a biomarker in the initial phase of this process, elucidate the biology of cardiovascular damage caused by these toxins, and develop a suitable strategy to treat and alleviate the cardiovascular load in patients with CKD [3]. The focus was deliberate on indoxyl sulfate (IS) and p-cresyl sulfate (PCS) because these are the most studied gut-derived uremic toxins with strong evidence linking them to cardiovascular outcomes. Other metabolites (e.g., TMAO, hippuric acid) were acknowledged but excluded for scope.

More recent studies have indicated that the management of gut-derived uremic toxins is also a significant component of CKD treatment. Microbiome manipulation and other methods to change the composition of the gut microbiota are possible solutions to the issue of gut-derived uremic toxins. Moreover, uremic toxin removal interventions, including hemodialysis, have been shown to lower the levels of uremic toxins in the blood, thus lowering the cardiovas-

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cular risk and burden of CKD. These methods would be incorporated into CKD treatment to help reduce the risk of cardiovascular disease [5].

Although this is our hope, a significant amount of work remains to be done to obtain a comprehensive understanding of the gut-kidney-cardiovascular nexus in the context of chronic diseases, such as CKD [7]. The role of gut-based uremic toxins in cardiovascular disease is one of the least studied areas of research. Moreover, the variances in the concentrations of toxins in patients with CKD make things more complicated [24]. It must also begin to appreciate the cardiovascular impact of individual toxins better [9]. Additional efforts to narrow down the reasonable methods for managing the effective therapeutic uremic toxin concentration would also be highly beneficial. This may provide CKD patients with an opportunity to experience positive systemic clinical and patient-reported quality of life outcomes [23]. Hence, the future of new therapeutic and diagnostic tools will be invaluable in this regard. Therefore, CKD clinical guidelines would outline an emphasis on the impact of CKD on patient well-being, emphasizing its cardiovascular risk complexity [10, 25].

Key contributions:

1. The indoxyl sulfate and p-cresyl sulfate types of gut-derived uremic toxins are underscored in this study as contributing to the extracardiac complications of patients with chronic kidney disease.

2. There was a strong correlation between increased levels of these toxins and worsening cardiovascular risk factors, including deteriorating arterial stiffness, hypertension, and negative changes in the blood lipids, which help highlight the toxins' cardiovascular toxic effects.

3. In this case, the patients suffering from chronic kidney disease and the uremic toxins, especially those suffering from uremic toxin syndrome, cardiovascular incidents were proven to be the dominant factor, which further showed that these unhealthy toxins were high contributors to disease progression.

4. This is the first research to show that manipulation of the microbiome, and the techniques of the removal of such toxins, might be able to lower the high cardiovascular risk factors which are becoming more and more common in patients suffering from chronic kidney disease, and this opens the doors for new lines of treatment.

This paper is designed to investigate the relationship between gut-developed uremic toxins, in particular indoxyl and p-cresyl sulfate, and cardiovascular events in patients with chronic kidney disease. Section 2 reviews the available literature to draw up the profile of cardiovascular pathologies for which these toxins can be held responsible. Method 3.1 estimating the link between toxins and CVD risk factors in CKD section discusses the technique used to estimate the association between the toxins and CVD risk factors within CKD patients. The results and implications on the relation between the level of toxins and increasing cardiovascular risk are further discussed in section 4. This includes factors that can be modulated therapeutically, such as the removal of toxins in the gut, which influence the microbiome. Section 5 gives final recommendations regarding the necessity of better-designed research in the field of patient care, especially concerning the more complex matters of cardiovascular disease.

Literature survey

One of the leading causes of cardiovascular disease (CVD) in people with CKD is the production of toxins in the gut [6]. The role of gut microbial metabolites, indoxyl and p-cresyl sulphates, has been established. After making it past the intestinal wall and into the bloodstream, they trigger the inflammatory and oxidative stress responses that ultimately lead to heart problems. Research on these uremic toxins has been conducted on individuals with chronic renal disease [22]. Because of endothelial dysfunction and atherosclerosis, they may hasten the beginning of CVD [11]. Because their buildup worsens the prognosis of chronic renal disease patients, they are of special interest to researchers in the cardiology sector. To develop new medical diagnostics and treatments, comprehensive research is required to investigate the impact of these toxins on the cardiovascular system in chronic renal disease [12, 13]. The production of indoxyl sulfate and p-cresyl sulfate is closely linked to the composition of the gut microbiota. Dysbiosis, characterized by the overgrowth of proteolytic bacteria, enhances the generation of these toxins, which subsequently accumulate in the circulation. Several studies demonstrate that microbiome-targeted therapies, including probiotics, prebiotics, and synbiotics, can reduce toxin levels and improve cardiovascular outcomes. This highlights the central role of microbiota composition in toxin production and disease progression.

Over the years, several therapeutic approaches have been undertaken with an emphasis on modulation of the gut microbiome to reduce gut-derived uremic toxins. Patients with CKD have benefited from the significant reduction in the cardiovascular complications that uremic toxin overload can cause as a result of modifications in gut microbiota composition. Probiotic, prebiotic, and specific dietary approaches have emerged as the first-line, low-risk, non-invasive interventions that can reduce the uremic toxin burden and its cardiovascular consequences [14]. Moreover, within the uremic toxin framework, there is interest in the development of so-called step therapies that resolve the toxin triage, such as dialysis techniques that selectively remove the toxins of predominant clinical concern, provided that such approaches do not induce greater overall toxicity [15]. They may also directly lessen the cardiovascular complications of CKD, broadening the therapeutic range that can be used for the disease. There is a growing body of clinical evidence to support such microbiome-based therapies for favorable cardiovascular outcomes in CKD [16, 17].

The association between gut microbiota and uremic toxins, as well as cardiovascular disease in CKD, has limited data with several unanswered questions. However, emerging data suggest that these potential therapeutic targets can be effective [2]. The wide range of toxins in the CKD patient population makes it challenging to develop a standard therapy protocol. The exact pathway through which the dangerous blooms damage the cardiovascular system is

under investigation. The diagnostics for toxins are limited, and research into more specific treatment options is also restricted. Understanding the gut-kidney-cardiovascular axis, it will be able to predict that the capable of more effectively treating CKD and the cardio-renal manifestations in the future due to scientific inquiry, the ability to alter clinical pathways, and create new treatments [18]. There is ongoing active research aimed at studying microbiome-based therapeutics and detoxification methods, which is encouraging improvements in patient care and outcomes [19, 20].

Materials and methods

This paper focuses on uremic gut-derived toxins as compared to cardiovascular disease and CKD. This study adopted a mixed approach, combining a systematic review of existing literature with a prospective observational cohort of 150 patients with CKD. Patient-level data were collected and analyzed for associations between gut-derived uremic toxin levels and cardiovascular risk factors, thereby strengthening the clinical correlations. The accumulation of toxic waste, such as microbial toxins, is one of the more challenging complications of CKD. In this instance, indoxyl sulfate and p-cresyl sulfate are poisonous byproducts and are produced by the gut and added to the cardiovascular system, overburdening patients with CKD. The cardiotoxicity of these uremic toxins has been measured with well-designed studies in which the patients are prospectively enrolled (oriented towards future cardiovascular events) in which events have been properly monitored over time and in which proper plans have been used to describe the patients and their events; information on cardiovascular events has been gathered with adjudication of the data. It is so far to the best of our knowledge, the first study to present this story as far as determine it, with the mediators of cardiovascular and management over the uremic toxins. The observed period is 12 months being, this time, sufficient to offset the association (or the lack thereof) and the other confounding factors where the cardiovascular system uremic events are controlled. The aim of the study is to give deeper explanations regarding the dose of uremic cardiovascular event and CKD and to find superior therapies with regard to the individual patient who is carrying the high cardiovascular systemic disease.

Study population

People with chronic kidney disease that are 18 years or older and in stage 1 to stage 5 will be the focus of the study and will be recruited from different healthcare facilities. The inclusion criteria of the study will be confirmed CKD whereas the exclusion criteria will include acute kidney injury, people that are currently on dialysis or have undergone a kidney transplant. Examination will be carried out over the course of 12 months, with the first, second, and last evaluations taking place at the beginning, 6 months, and 12 months respectively. This study will focus on the impact of gut-derived uremic toxins on cardiovascular events in the population during the course of the 12 months. To ensure demographic data, (age, gender, comorbidity, and, of course, the stage of CKD) will be collected during the study so that the data variables can be analyzed properly which will be done seamlessly and with the highest accuracy.

Assessment of gut-derived uremic toxins

The gut produces two principal uremic toxins, indoxyl sulfate and p cresyl sulfate, which are the focus of the formal study. These poisons will be measured using HPLC and mass spectrometry. At the start of the trial and every three months throughout the twelve-month period, patients will have their blood and urine sampled. Toxin concentrations will be correlated with the cardiovascular markers which include blood pressure, stiffness of arteries and the lipid profile. The study will explain the role of the composition of the microbiome in the production of these uremic toxins from gut microbiome. It will examine the production and or changes to the gut microbiome that might influence associated changes to the levels of these uremic toxins. The study anticipates that by controlling or altering the parameters of the uremic toxins and the cardiovascular parameters over time, it will be able to pronounce the relationship of the derived uremic toxins from the gut and the cardiovascular disease that accompany chronic kidney disease in the patients.

Cardiovascular event monitoring

Detailed definitions of particular cardiovascular events, such as myocardial infarction, stroke, and heart failure (where present), will also be determined during the study. A patient's medical record will be evaluated for any cardiovascular events, and standard imaging tests, such as an echocardiogram/ECG, will be conducted for clinical purposes. The cardiovascular risk profile, which includes blood pressure, cholesterol levels, and arterial stiffness, will also be noted. "These are going to be compared to blood levels of gut-derived uremic toxins to determine whether there is an increased rate of cardiovascular events in people with high levels of these toxins". These events will be monitored from the start of the trial until the twelve-month follow-up to see whether any acceptable conclusions can be drawn about the function of uremic toxins on the cardiovascular system in patients with chronic renal disease. Another goal is to determine the degree of endothelial dysfunction, a key component of cardiovascular damage in chronic renal disease, by measuring the current level of endothelial function.

Data analysis

Statistical methods will analyze how the levels of uremic toxins derived from the gut, affect the outcomes of the cardiovascular system. Regression will estimate how cardiovascular biomarkers react to changes in the uremic toxin concentration while age, sex, or existing conditions (diabetes, hypertension) will be treated as extraneous variables. For the sake of cardiovascular health, cardiovascular multivariate analysis will be applied, while survival analysis will be applied to evaluate the specific time and conditions cardiovascular outcomes (such as myocardial infarctions or strokes) occur. Cardiovascular outcomes and the level of uremic toxins will be illustrated using scatter plots and histograms to show the prevalence of cardiovascular risk factors, thus determining the existing cardiovascular burdens and obtain-

ing the proper knowledge to aid in bypassing the danger of uremic toxins among CKD patients.

Therapeutic interventions

This study examines the gut-associated uremic toxins and the cardiovascular outcomes attending to the study while trying to develop strategies to minimize the level of toxins. Certain probiotics and prebiotics will be dosed for the gut having excess uremic toxins within the focus of the powdered dose, and the constituent dietary interventions also aim to minimize the intake of gut bacterial toxins promoting foods. Comparing the cardiovascular health and the concentration of toxins before and after the intervention will provide evidence for which, in determining the outcomes of cardiovascular physiology, the outcomes clearly illustrate the lose intervention in the treated and untreated groups. This study will employ the statistical approach, and it contributes within a framework to understand how they are able to advance and undue the accumulated risk to the cardiovascular system for cardiovascular in the population specifically individuals with chronic kidney diseases. This is suggested in the study approximation towards the goal of primary chronic kidney disease. Its objective is to examine the diet and probiotics population direct translation with a number of evidence in cardiovascular risk reduction and kidney homeostasis preservation.

Beyond conventional approaches such as dialysis and phosphate binders, several alternative strategies have been investigated. These include modulation of the gut microbiome through probiotics, prebiotics, and synbiotics, dietary interventions aimed at reducing protein fermentation, and oral adsorbents that selectively bind uremic toxin precursors in the gut. Such approaches represent promising adjuncts to standard care, targeting the root of toxin generation.

Fig. 1 illustrates an overview of how gut-derived uremic toxins play a role in cardiovascular injury in CKD patients. The cycle begins with gut bacteria producing toxins, such as indoxyl sulfate, and p-cresyl sulfate, that leak into the circulation, which subsequently accumulates in the kidneys and heart. Fig. 1 illustrates important intermediate consequences of the toxins, such as vascular inflammation, oxidative stress, and endothelial dysfunction, and how those lead to cardiovascular injury, myocardial infarction, stroke, and cardiovascular diseases. In Fig. 1, arrows connect each stage back to the uremic toxins which shows the ways in which cardiovascular risk is significantly increased for patients with CKD and how this risk can be treated.

Results and discussion

The research included 150 patients of chronic kidney disease (CKD) who had boys and girls equally divided. The average age was 58.4 ± 12.3 years, and patients with stages 2, 3, and 4 CKD were part of the group. The population also had a significant amount of comorbidities, that being hypertension (72 %) and diabetes (63 %). Patients had high concentrations of indoxyl sulfate and p-cresyl sulfate, which are classified as gut bacteria-derived uremic toxins. Table 1 presents CKD study population's baseline characteristics and the distribution of study population corresponding to these toxins.

The cardiovascular impact of gut-derived uremic toxins occurs through multiple overlapping pathways. Indoxyl sulfate and p-cresyl sulfate induce oxidative stress and proinflammatory signaling, which result in endothelial dysfunction. This dysfunction contributes to increased arterial stiffness, hypertension, and atherosclerotic plaque formation. The cascade of endothelial damage, inflammation, and vascular remodeling explains how these toxins accelerate cardiovascular risk in CKD patients.

There were 150 patients with CKD who were part of the trial. Table 1 displays their clinical and demographic data, including age, sex, stage of CKD, comorbidities, and average levels of indoxyl sulphate and p-cresyl sulphate. To investigate the target population and to stack galaxies for future studies, they are the initial steps, and they are crucial. Arterial stiffness, blood pressure, and reduced levels of indoxyl and p-cresyl sulphate — markers of cardiovascular risk — were connected by an astonishingly steep curve. Toxin levels of arterial stiffness ($r = 0.72$, $p < 0.01$) and systolic blood pressure ($r = 0.65$, $p < 0.01$) were also elevated. The toxins had an inverse correlation with cholesterol levels, indicating that they may also impact athe-

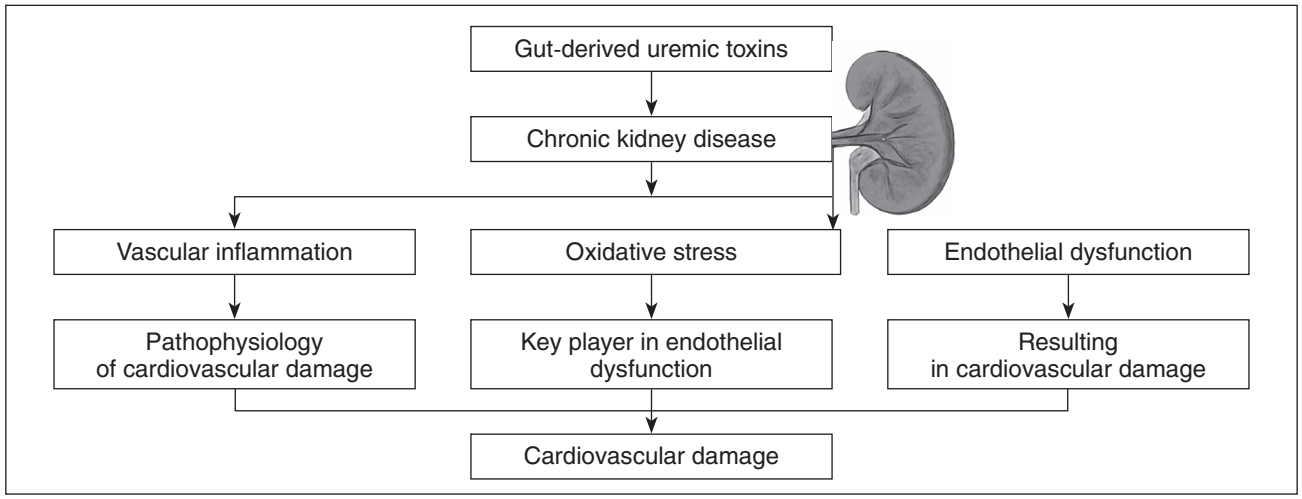

Figure 1. Role of gut-derived uremic toxins in accelerating cardiovascular events in chronic kidney disease

rosclerosis and endothelial dysfunction to some extent. These findings point to a critical role for gut-derived uremic toxins in the acceleration of cardiovascular damage in CKD patients. What follows is Table 2 summarizing these relationships.

Table 2 illustrates the association of the indoxyl sulfate and p-cresyl sulfate with the components of the cardiovascular system (including arterial stiffness, pressure, and cholesterol) and their respective risks with p-cresyl sulfate. Independent of the other risk factors, arterial stiffness and systolic blood pressure were positively correlated. HDL cholesterol had a negative correlation with the toxins which suggests a tainted conduit system due to indoxyl sulfate and p-cresyl sulfate.

The 12-month monitoring period noted that there were more heart attacks, strokes, and heart failures amongst the patients with higher levels of uremic toxins. Of the patients with a high concentration of indoxyl sulfate and p-cresyl sulfate, 35 % had a cardiovascular event versus only 15 % of patients with a low concentration of the toxins. This leads to the conclusion that the uremic toxins that were derived from the gut, that were obtained from the subjects suffering from gut-derived uremic toxins, severely enhance the risk of cardiovascular diseases amongst patients with CKD. The following graph displays the uremic toxic level and the cardiovascular event level together with the cardiovascular event risk factor graph.

Heart attacks, strokes, and heart failures are cumulative episodes in patients with CKD with varying amounts of uremic toxins originating from cardiovascular sources, as seen in Fig. 2. Increased cardiovascular generated uremic toxins enhance cardiovascular event rates. People who have higher levels of indoxyl sulfate and p-cresyl sulfate are also more likely to experience cardiovascular events, which indicates that there is a connection between elevated levels of heart-related uremic toxins and myocardial incidents among patients with CKD.

This research supports the idea that gut uremic toxins are most likely contributing direct causation of CVD in CKD patients. CVD risk factors such as, but not limited to, reduced arterial elasticity, increasing levels of blood pressure as well as abnormal lipid profiles were significantly associated with both indoxyl and p-cresyl sulfate. Such toxins are likely to act on cardiac activity either by protective or destructive mechanisms by enhancing inflammation, oxidative stress, and endothelial dysfunction. Patients with CKD who have high levels of uremic toxins have an exponentially increased cardiovascular risk on top of the CKD complications. Other interventions like microbiome modulation and increasing the amount and/or quality or dialysis have a probability of reducing CV risk by targeting reducing uremic toxin accumulation. Subsequent research is justified to work out specific measures to address the problem and transform the situation of CKD patients with cardiovascular disease.

Table 1. Baseline characteristics of study participants

Parameter	Value
Total number of patients	150
Age (mean ± SD)	58.4 ± 12.3 years
Gender (male/female)	75/75
CKD stage distribution	Stage 2: 40 %, stage 3: 40 %, stage 4: 20 %
Comorbidities	Hypertension: 72 %, diabetes: 63 %
Average indoxyl sulfate	112.5 ± 28.6 ng/mL
Average p-cresyl sulfate	145.3 ± 34.7 ng/mL

Table 2. Correlation between uremic toxins and cardiovascular risk factors

Cardiovascular risk factor	Indoxyl sulfate (r)	p-cresyl sulfate (r)
Arterial stiffness	0.72	0.68
Systolic blood pressure	0.65	0.61
LDL cholesterol	0.53	0.56
HDL cholesterol	–0.43	–0.47
Atherosclerosis	0.61	0.63

Conclusions

Research on the gut-derived uremic toxins indoxyl sulfate and p-cresyl sulfate, which cause cardiovascular issues in CKD patients, is reported in this article. An increased risk of cardiovascular problems, such as hypertension and atherosclerosis, is linked to greater levels of these pollutants. Interventions targeting vascular inflammation, oxidative stress, and endothelial dysfunction — three key stages in the pathophysiology of cardiovascular disease — were preferred by the research. Considering that those who suffered the most severe cardiovascular problems were also the ones most exposed to these contaminants, it could be worthwhile. For individuals with CKD, lowering the uremic toxin burden is

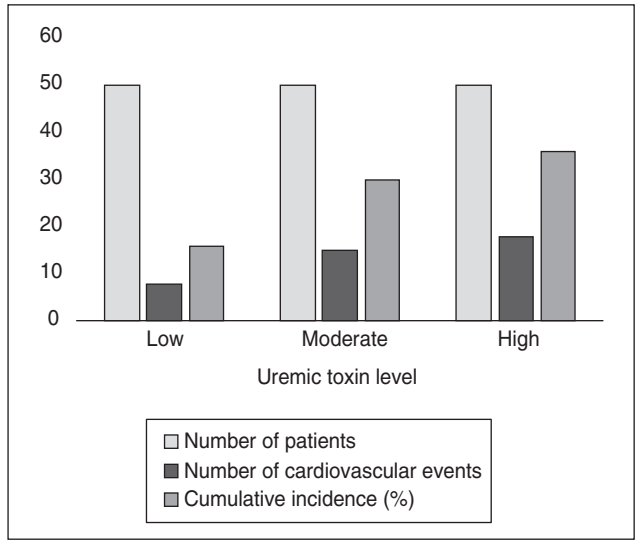

Figure 2. Cumulative incidence of cardiovascular events in CKD patients by uremic toxin levels

the simplest intervention to implement. To develop a novel approach to treating cardiovascular illnesses, additional study is required. As far as my profession is concerned, there is no known way to reduce the cardiovascular stress associated with chronic kidney disease. Predisposed CKD patients with a tendency to cardiovascular difficulties have the highest chance of improving outcomes and quality of life once the uremic toxin burden is reduced.

Recommendations

The function of gut-derived toxins must be assessed in extensive, multicenter clinical trials encompassing various CKD populations. To improve the reliability of clinical translation, consistent techniques for measuring toxins are essential. Microbiome modification, nutritional interventions, and tailored dialysis all seem potential for lowering the clinical burden of CKD. Toxin monitoring and cardiovascular risk assessment should be integrated into clinical decision-support and patient-centered care.

Ethical approval

The Institutional Ethics Committee of each participating center had to provide their permission before the study could begin. Their anonymity was preserved throughout the study in accordance with ethical standards and legislation. This study examines the specific aspect of the Declaration of Helsinki that guarantees participant privacy for their well-being. Current KDIGO (2022) and ESC (2023) guidelines emphasize cardiovascular risk management in CKD primarily through blood pressure control, lipid lowering, and dialysis optimization. However, they do not yet incorporate toxin-targeted interventions. The findings of this study suggest that future iterations of these guidelines could benefit from including microbiome-focused or toxin-reducing strategies, as they may offer additional protection against cardiovascular complications.

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Уремічні токсини кишкового походження та їх роль у розвитку серцево-судинних подій при хронічній хворобі нирок

Резюме. Хронічна хвороба нирок (ХХН) є тривалим та прогресуючим станом. Її розвиток зумовлений накопиченням у сироватці крові багатьох уремічних токсинів, частина з яких продукується кишковою мікрофлорою. Було показано, що два уремічні токсини, індоксилсульфат та р-крезилсульфат, погіршують перебіг серцево-судинних захворювань і прискорюють прогресування ХХН. З часом ці токсини ушкоджують серце, викликаючи набряк судин, оксидативний стрес та дисфункцію або повну втрату функції ендотелію. Зв'язок між уремічними токсинами, що виробляються в шлунково-кишковому тракті, і серцево-судинними подіями в пацієнтів із ХХН залишається недостатньо вивченим, особливо в контексті перспективних нових біомаркерів, які можуть сприяти ранній діагностиці серцево-судинних подій і своєчасному початку лікування. Метою було проведення систематичного огляду та аналізу факторів ризику серцево-судинних захворювань, пов'язаних зі специфічними уремічними токсинами кишкового походження, з особливим акцентом на артеріальний тиск, атеросклероз та жорсткість артерій в осіб із ХХН. Дослідження також спрямоване на уточнення ролі цих токсинів у клінічних подіях та патобіології серцево-судинних розладів при хронічних захворюваннях нирок. Крім того, розглянуто стратегії лікування, спрямовані на модифікацію певних факторів шляхом впливу на мікробіом для збереження позитивних клінічних результатів, а також втручання, що інгібують вироблення кишкових уремічних токсинів з метою усунення або пом'якшення їх негативного впливу. Контроль уремічних токсинів кишкового походження може сприяти зміні серцево-судинного профілю та зниженню ризику ХХН, що зрештою поліпшить клінічні результати та якість життя пацієнтів.

Ключові слова: хронічна хвороба нирок; уремічні токсини; кишкова мікробіота; серцево-судинні захворювання; індоксилсульфат; р-крезилсульфат; серцево-судинні фактори ризику