Chapter 6

Inflammation and Chronic Kidney Disease: Current Approaches and Recent Advances

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Motto: *"All disease begins in the gut." (Hippocrates)*

Abstract

Despite being a "silent epidemic" disease, chronic kidney disease (CKD) is considered one of the major causes of mortality, together with its main complication, the cardiovascular disease, which contributes to the poor prognosis of these patients. Inflammation has been recognized as an essential part of CKD and is closely linked to cardiovascular complications. The identification of novel biomarkers using omics technologies is rapidly advancing and could improve the early detection in renal diseases. Omics approaches, including proteomics, could provide novel insights into disease mechanisms, identifying at the same time accurate inflammatory biomarker panels with an essential role in disease monitoring and follow-up. Recent advances highlight the gut microbiota as an important source of inflammation in kidney diseases. An increasing body of evidence reveals the cross talk between microbiota and host in CKD; in addition, gut dysbiosis may represent an underappreciated cause of inflammation and subsequently could lead to malnutrition, accelerated cardiovascular disease and CKD progression. This chapter discusses the relationship between inflammation and CKD and highlights the novel approaches regarding microbiota involvement in CKD pathology, as well as their potential to facilitate improving the quality of life.

Keywords: chronic kidney disease, inflammation, gut microbiota, omics

1. Introduction

Chronic kidney disease (CKD) is defined, according to KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney

Disease–Mineral and Bone Disorder (CKD-MBD), as "abnormalities of kidney structure or function, present for more than 3 months, with implications for health." CKD is classified based on pathological cause, glomerular filtration rate category (from G1, normal, to G5, kidney failure), and albuminuria category (from A1, <30 mg/g, to A3 > 300 mg/g) [1]. It will inexorably lead to end-stage renal disease, unless managed as to address treatment of the underlying condition, diagnosing and treating the pathologic manifestations and timely planning for long-term renal replacement therapy. A recent systematic review and meta-analysis of observational studies revealed that CKD has an estimated global prevalence between 11 and 13%, with the majority of cases in stage 3 [2]. The complexity of CKD pathogenesis is underlined by a plethora of risk factors: genetic and epigenetic age [3], low birth weight, socioeconomic status, obesity [1], smoking and/or hypoxia [4], and vascular factors, induced by atherosclerosis [5], hypertension [6], and diabetes mellitus [7]. Furthermore, the *complications* of this disease also impact beyond the kidney, with cardiovascular burden (such as coronary artery disease, congestive heart failure, arrhythmias, and sudden cardiac death) as a major mark [8]. CKD associates also with enhanced formation of atherosclerotic plaques [9]. Other complications include endocrine dysfunctions involving hormones that control calcium [10] and phosphate balance [11], vitamin D metabolism, and, consequently, bone mineralization defects [12]. Hemodialysis patients are further at risk for cardiovascular complications, such as vascular overload leading to arterial stiffness [13] or, apparently paradoxical, ischemia induced by repeated episodes of hypovolemic hypoperfusion during hemodialysis [9].

Inflammation has been recognized as an essential part of chronic kidney disease (CKD) since the late 1990s and is now considered a well-established risk factor for this pathology [14], as well as for other renal pathologies. In fact, inflammation is now considered a key player in different major pathologies such as cardiovascular disease [15], neurodegeneration [16], or cancer progression and survival [17]. Chronic systemic inflammation, sometimes referred to as low-grade chronic inflammation, is characterized by 2–3 fold increase of circulating inflammatory mediators (such as interleukins 1, 6 tumor necrosis factor, and their soluble receptors), slow developing, persistent and of multifactorial origin, sometimes difficult to identify [18]. Recent findings associate chronic systemic inflammation with alteration of gut microbiota, which is in permanent cross talk with the immune system. This cross talk is essential for maintenance of a tolerant immune response toward commensal flora and elimination of pathogens [19]. Intestinal dysbiosis is detrimental for health in ways overpassing the intestinal environment, from production of toxic metabolites, overconsumption of energy, and molecular mimicry of host proteins [20]. This chapter will present an up-to-date findings relating to chronic systemic inflammation and CKD, with emphasis on gut dysmicrobism involvement and whether intervention on gut microbiota could be proven beneficial for the outcome of this fatal disease.

2. Inflammation and its impact on CKD progression: an update

Persistent, low-grade inflammation is considered crucial component of CKD, having a huge contribution to the development of all-cause mortality related to renal disease. There has been an ascending growth of interest regarding the role of inflammation in CKD and end-stage renal

disease (ESRD), which shifts the perception of inflammation as no longer a new, but rather a traditional risk factor for CKD morbidity and mortality [14, 21]. A challenging theory regarding the direct effect of inflammation on the progression of both CKD and cardiovascular disease came out with the assumption of association between markers of inflammation, changes in GFR and nutrition habits in elderly individuals. It was found that the deterioration in renal function (alteration of GFR, urea and creatinine) was associated with an increasing number of markers of inflammation and thrombosis [22]. Regardless of a genetic background, CKD is a condition that accelerates premature aging through diverse mechanisms in the internal milieu, counting DNA damage, inflammation, low Klotho expression, redox perturbations, toxicity, and local signaling of growth factors [23]. It is generally known that there is a heterogeneous distribution of intrarenal vasculature in normal conditions, and only medulla is under hypoxic conditions. In order to bypass energy deprivation in the deficient pO_2 parts of the kidneys, an avalanche of mediators is involved to regulate the complex processes, including hormones, autocoids, and vasoactive substances: medullipin, prostaglandins, endothelins, nitric oxide, angiotensin II, kinins, and adenosine. A state of sustained inflammation could surely alter the microvascular feedback to its regulators and could activate the reaction of an array of tubular toxins, including reactive oxygen species (ROS), generating further renal failure [24]. The highly reactive ROS could alter different structures and functional pathways in cells, and, as a repercussion, a vicious circle arises, in which the inflammatory cells are stimulated by cell damage caused by ROS, giving birth to a state of oxidative stress. The common oxidant "imbalance" theory is remarkably completed with recent advances regarding the cross talk between oxidants and antioxidants; the reasoning for antioxidant therapies consists thus in repairing the imbalances in the redox environment of cells [25]. The old theory suggesting the oxidative stress as a "unifying concept of cardiovascular disease in uremia" [26] is continuously enriched, and novel molecules, belonging to the Paraoxonase family, are suggested as potential biomarkers. Paraoxonase-1 seems to have a protective effect against lipoprotein oxidation and its expression is decreased in CKD patients, being a marker for antioxidant status [27]. The development of specific redox proteomic techniques will facilitate the implementation of new preventive and therapeutic strategies to fight against atherosclerosis and other metabolic diseases [28].

In comparison with the well-established clinical markers, proteomic biomarkers could offer an accurate and earlier detection of renal pathology. Although the "breaking point" could be various in different patients, in some populations, the circulating creatinine levels fall into normal ranges despite loss of more than 50% of renal function, so supplementary biomarkers of renal function are desired. Recent studies conclude that a cross talk between inflammation, bone, vasculature, and renal function exists in CKD. In early stage 2 of CKD, an increased expression of a panel of proteomic biomarkers was observed, including IL-6, TNF-α, osteoprotegerin, osteocalcin, osteopontin, and FGF-23, which, at a first glance, highlights the hope of improving the management of patients with CKD starting with early stages, which is an area to focus research in the near future [29]. Another study evaluating the association between kidney function, albuminuria, and biomarkers of inflammation in a large cohort of CKD patients showed that plasma levels of IL-1β, IL-1RA, IL-6, TNF-α, hs-CRP, and fibrinogen were higher among participants with lower levels of estimated glomerular filtration rate (GFR). Moreover, inflammation score was higher among patients with lower estimated GFR and higher urine albumin to creatinine ratio (UACR). These results demonstrated that biomarkers of inflammation were

inversely associated with measures of kidney function and positively with albuminuria [30]. The erythrocyte sedimentation rate, a nonspecific measure of inflammation, has been shown to be predictive of end-stage renal disease in adolescents [31]. The level of pro-inflammatory cytokine IL-2 was elevated in hemodialysis patients with uremic pruritus (a common tormenting symptom among these patients) when compared to hemodialysis patient controls without pruritus [32]. The results obtained from several researches suggest that tumor necrosis factor-like weak inducer of apoptosis (TWEAK) plays an important role in kidney injury associated with inflammation and promotes acute and chronic kidney diseases [33]. There are several studies testing different nanoconjugates that could prevent TWEAK-induced cell death and inflammatory signaling in different cell types, including renal tubular cells [34]. The results obtained from a study investigating hemodialysis patients showed that the group of patients with a specific pattern of high pro-inflammatory cytokines (IL-1, IL-6, and TNF-α) had increased mortality when compared to patients with a pattern of high T-cell regulatory or anti-inflammatory parameters (IL-2, IL-4, IL-5, IL-12, CH50, and T-cell number) [35].

Availability of omics multiplex technology offered the opportunity of shifting the analysis of single individual marker toward assessing cytokine panels [36]. It was described an inflammatory panel, consisting of pro-inflammatory cytokines IL-1, IL-6, and TNF-α with anti-inflammatory ones IL-2, IL-4, IL-5, IL-12, CH50, as well, with a significant impact on CKD patients' survival [35]. Recently, significant attention has been granted to the potential role of adipokines in CKD, such as pro-inflammatory leptin, apelin, omentin, visfatin, resistin, and anti-inflammatory adiponectin. Based on the data from the National Health and Nutrition Examination Survey (NHANES), it was shown that CKD is correlated with increased leptin levels [37]. Moreover, adiponectin expression in ESRD patients was also significantly increased compared to healthy individuals [14].

Atherosclerosis is now considered a chronic inflammatory disease and, in turn, cardiovascular disease is a major complication of CKD. Thus, a vicious circle is created between inflammation and CKD. Atherosclerosis is accelerated in CKD by complex mechanisms involving a cross talk between lymphocyte T helper type 1 and subendothelial macrophages as antigen presenting cells. The triggers of this cellular response are alteration of lipid metabolism and subendothelial deposit of plasma lipoproteins. Locally recruited lymphocytes react to autoantigens from the apolipoprotein B100 protein of LDL, generating an inflammatory response [38]. Within the predialysis CKD patients, the prevalence of inflammation is increasing and represents a critical indicator of patient health and future outcome. In ESRD, the process of hemodialysis itself may contribute to the pro-inflammatory state, and different types of dialysis membrane could determine an inflammatory response. However, hemodialysis does not represent the only source of inflammation, since the predialysis CKD patients already manifest a certain inflammatory state [39]. A persistent inflammatory state in CKD is not only linked to cardiovascular complications but is also one of the key players in the development of malnutrition/protein-energy wasting, having as consequence the malnutrition-inflammation-cachexia syndrome in CKD/ESRD patients. It was also described, in a cohort of dialysis patients, that circulating levels of IL-1 and IL-6 could suppress the PTH secretion, which, in turn, may reflect the malnutrition-inflammation-cachexia syndrome, rather than the low bone turnover disease [40]. The pathophysiology of inflammation could be different with regard to different racial, ethnic, or genetic features. Recent studies specify that dietary habits

could add a peculiar signature to the gut microbiota composition, and intestinal dysbiosis itself could thus interfere with the inflammatory mechanisms in CKD population.

In summary, persistent low-grade inflammation has been recognized as an important component of CKD scenario, playing major roles in the pathophysiology of the disease, with a major imprint on its complications. Nevertheless, further investigations are necessary to decipher the role of inflammation in CKD population, particularly in the early stages.

3. The role of inflammation in the development of cardiovascular diseases in CKD

Cardiovascular disease represents one of the main determinants of CKD's poor prognosis, since early stages of CKD are significantly correlated with increased risk of subsequent coronary heart disease [41]. In agreement with several clinical studies, approximately 50% of patients with CKD have a rising mortality due to the cardiovascular complications, such as advanced calcific arterial and valvular disease; however, the mechanisms that involves the accelerated calcification in CKD continue to be questionable, thus no specific therapies have emerged to target the disease prevention [42].

The current CKD guidelines are recommending the screening for vascular calcification (VC), for the reason that VC represents a cardiovascular risk factor, and it is correlated with an increased morbidity and mortality in CKD group, culminating in CKD stage 5. Vascular calcification is now considered an active process that involves many proteins, as possible candidate markers [43]. In CKD individuals, several studies have highlighted various circulating biomarkers that could play important roles in extra-skeletal calcification and mineral metabolism alterations, which are considered characteristics of CKD-mineral bone disorder (CKD-MBD) [44]. As a result, these findings have revealed that CKD-MBD comprises laboratory and bone abnormalities and vascular calcification and has deleterious consequences on clinical outcomes; however, these processes are interconnected and they have to be studied in association with cardiovascular diseases [1].

Cardiovascular calcification represents though an exceptional marker of chronic inflammatory status in CKD, strongly correlated with morbidity and mortality. Curiously, CKD accelerates the atherosclerosis evolution and it has been showed that CKD produces increasing vascular inflammation and calcification. Recent advances highlighted the potential involvement of matrix vesicles (secreted by macrophages), as key molecules in the alternative processes independent of osteogenic differentiation [45]. Deciphering the association between these mechanisms and signaling pathways could bring novel insights into the mechanistics of calcification and could possibly move forward to new therapeutic strategies aiming at cardiovascular disease in CKD [46]. These findings are in concordance with the genetics, and it was shown that 40–50% of coronary calcification cases could be linked to genetic predisposition, considering that several loci were linked to coronary arterial calcification [47]. The involvement of single polymorphisms located at 9p21 locus near the cyclin genes was proposed as a genetic mechanism of this pathology; the concerned genes could be generally associated with cellular senescence and inflammation, although the accurate causative DNA sequences continue to be uncertain [48]. Recent evidence

suggests that the overlap between CKD and cardiovascular disease is due, on one hand, to the dynamic cross talk between these organs, resulting in cardio-renal syndrome, increasingly recognized [49] and, on the other hand, it could be linked to the common etiologies of these major diseases (hypertension and diabetes mellitus). It has also been investigated as a possible common disorder of the kidneys and heart whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ; nevertheless, a complete picture of the mechanisms implicated in these processes is still missing [49]. The highly reactive oxygen species (ROS) present the potential of disrupting different structural and functional pathways in cells. Therefore, the inflammatory cells are activated by cell damage produced by ROS; thus, a vicious circle of chronic disturbance is constantly perpetuated. The oxidant imbalance theory comprises several important pathways and cell metabolism also has been under the surveillance of the cross talk between oxidants and antioxidants. The role of oxidative stress in the pathogenesis of CKD relies though on the hypothesis that antioxidant therapies could target and reconstruct the disturbances in the redox environment of cells [50]. Different therapeutic strategies have been considered to decrease oxidative stress (OS) in models of CKD and cardiovascular disease, proposing a low oxidant intake in different dietary approaches. Oxidative stress and inflammation increase with aging, and these conditions are related to kidney failure in its early stages, as well. There are evidences that a diet supplemented with oxidants could produce increased serum levels of OS and inflammatory mediators in both normal aging and in CKD. It is mentioned that dietary intervention could offer novel therapeutic strategies by reducing OS and inflammation in patients with CKD and in aging population with decreased kidney function [51].

Due to the circulating nature of many inflammatory mediators (cytokines and immune cells), it is tempting to hypothesize that the immune system could have crucial roles in organ interactions and could mediate the reciprocal dysfunction that is experienced in cardio-renal syndromes.

4. Omics technologies and clinical relevance of proteomic biomarkers in renal diseases: rolling proteomics into clinics

Over the last decade, there has been an increasing progression of omics approaches, accompanied by remarkable improvement of methodologies and analytical instruments, based on the concept that a thorough characterization of a complex system, providing novel perceptions into functional pathways and regulatory networks, could be deciphered in frame of these omics. In the light of recent advances in bioinformatics and biostatistics on state-of-the-art platforms, the access of scientists in correlating the experimentally observed data regarding the fundamental biochemical and pathological mechanisms was facilitated [52, 53]. Proteomic biomarkers in kidney disease may represent, along with classical markers serum creatinine and urinary albumin, valuable tools in clinical diagnosis due to their accurate potential for clinical implementation. Moreover, proteomic biomarkers could also be useful in characterizing the most suitable therapeutic targets in a given patient or disease setting [54].

The huge step forward was accomplished by coupling liquid chromatography with mass spectrometry, enabling untargeted protein identification. Additionally, capillary electrophoresis had

also an accelerated development in the last years, being able to rapidly separate analytes in a highly reproducible manner [55]. Also, matrix-assisted laser desorption/ionization (MALDI) platform has moved the boundaries above, being able to assess tissue specimens with high resolution in order to discriminate individual cells. This approach can provide detailed information related to CKD and the potential to detect specific biomarkers. Recent evidence suggests that MALDI could generate molecular signatures of primary and secondary kidney injury, with one particular signal, identified as serine/threonine-protein kinase MRCK gamma, being overexpressed in the glomeruli of primary membranous nephropathy (MN). These findings could be potential future targets for the further stratification of these patients [56]. Other studies emphasize the role of omics technologies, including MALDI to generate molecular signatures capable to distinguish between normal kidney and pathological kidney, with specific signals representing potential indicators of CKD development [57]. Kidney and Urinary Pathway Knowledge Base (KUPKB) represents an open source to explore multi-omics data and to generate new *in silico* theories using a novel approach based on semantic web technologies [58]. Moreover, CKDdb represents the most comprehensive molecular information resource in characterizing CKD-related experiments and model systems, potentially useful in the design of disease models, thus avoiding the challenges related with handling and integration of heterogeneous enormous data [59].

The emerging knowledge generated by the application of omics (genomics, proteomics, and metabolomics) in major diseases, including CKD, could provide new insights into the pathophysiology of the disease by identifying novel biomarkers that could improve, in real time, the early diagnostics, monitoring, and prognostics; thus, omics will provide a major impact in the field of personalized medicine [60].

5. Gut microbiota as a source of inflammation in CKD: a bidirectional relationship

Accumulating evidence over the recent years has highlighted that chronic inflammation represents a nontraditional risk factor in CKD population and was revealed that gastrointestinal tract is a major player in systemic inflammation occurring in CKD [61]. The gut microbiota preserves the symbiotic relationship with the host in normal conditions and is essential for regulation of local and systemic immunity [62], although its imbalance has latterly been related with several diseases [63]. Alteration in the functions or signaling pathways of the commensal flora contributes to the pathogenesis of diverse diseases, including chronic inflammation and renal disorders, as well; gut bacterial DNA fragments have been detected in the blood of both predialysis CKD and chronic hemodialysis patients [64]. The decisive role of the biochemical milieu in shaping the gut microbiota, in terms of structure, composition, and function, which could promote a proinflammatory activity, was also described and it could simultaneously restrict the beneficial effects offered by a balanced microbiota. Such conditions could lead to an altered status, targeting inflammation, uremic toxicity, and other complications inside the CKD patients [65]. The interactions are bidirectional: on the one hand, uremia negatively interferes with the microbiota, altering the composition and metabolism and, on the other hand, the microbiota dysbiosis releases compounds that are normally excreted by the kidneys

but could be considered as potential uremic toxins, both conditions further leading to a toxin avalanche exposure, due to the disruption of the epithelial barrier with an increased intestinal permeability, often referred to as "leaky gut," a condition that has been reported in CKD [66].

Uremia status seems to impair the intestinal barrier function and promotes inflammation throughout the gastrointestinal tract. A prospective, observational study reported the baseline concentration of indoxyl sulfate, a uremic toxin that could have a predictive power in CKD progression [67]. Other uremic toxins, p-cresol sulfate and trimethylamine N-oxide (TMAO), were assessed in relation to kidney function (estimated GFR), and the results conclude that the elevated expression was associated to an increased risk for all-cause mortality in ESRD patients. [68]. Uremia represents a condition that accompanies kidney failure and CKD. Uremic toxins originated in, or inserted into, the body via the intestine, such as glycation metabolites, phenols, indoles, all may play important roles in CKD pathophysiology. Consequently, it is biologically plausible, but not well accepted, that a crucial player in the toxic scenario of the CKD resides in the gut microbiota [69].

Deciphering the role of gut microbiota in CKD progression needs a complex comprehension regarding its composition, function, and homeostasis within each individual. As expected, the gut microbiota composition shows great variations, representing a unique signature with each individual harboring, consisting mainly of Gram-negative Bacteroidetes and the Gram-positive low-GC Firmicutes [68]. Gut dysbiosis in CKD was correlated with an increase in pathogenic flora compared to symbiotic flora, which, along with enhanced intestinal permeability, increases absorption of endotoxins with harmful consequences in the organism. The gut-derived uremic toxins, along with an expanded permeability of the intestinal barrier, have been correlated with an increased inflammatory state and oxidative stress, which are constant features of advanced CKD, with a major impact on its complications [65]. The dysbiotic intestinal microflora could be correlated to the intestinal wall edema and ischemia, as well as to a defective colonic epithelial barrier [65]. Recent evidences suggested that several circulating metabolites derived from gut microbiota metabolism could be related to systemic immunoinflammatory response and kidney damage. It has been shown that short-chain fatty acids (SCFAs), which are metabolites essentially derived from dietary fiber fermentation in the gut, are significant players in modulation of immunity, blood pressure, glucose, and lipid metabolism. In addition, SCFAs also "modulate different cell signal transduction processes via G-protein–coupled receptors and act as epigenetic regulators by the inhibition of histone deacetylase and as potential mediators involved in the autophagy pathway." Though controversial, the SCFAs may be regarded as potential therapeutic targets and seem to represent the link between kidney damage and inflammatory response [70]. Gut inflammation is prevalent in CKD and is subsequently involved in systemic inflammation by disruption in the epithelial tight junction, leading to endotoxin and bacterial translocation; this state is associated with a defective Nrf2 pathway. On the basis that Nrf2 represents a protein that regulates the expression of antioxidant proteins that protect against oxidative damage triggered by injury and inflammation, oral administration of Nrf2 activator (study conducted on rats) has reestablished the epithelial tight junction protein expression, alleviating arterial hypertension and rehabilitating the markers of kidney function [71].

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In conclusion, accumulating evidence recognizes that dietary fiber may reverse gut dysbiosis and abolish microinflammation, being in agreement with epidemiological evidence suggesting correlations between higher dietary fiber intake, better kidney function, and lower inflammation, at least in the general population. Many researchers accept that supporting intestinal health and restoring the integrity of the gut wall will represent one of the most important goals in improving the quality of life within CKD individuals.

6. Restoring microbiota balance: the exploration of novel therapeutic avenues in renal diseases

Intestinal inflammation and gut microbiota dysbiosis, as well, are now recognized as important contributors in chronic inflammation and other CKD complications, thus explaining the gut-therapeutic novel avenues taken into consideration in designing CKD interventions [61] .

The microbiota can be considered as a recently discovered "organ," being involved in many pathological axes, in relation with almost every organ, including kidneys; there are different metabolites derived from microbiota dysbiosis engaged in distinct physiology pathways linking to renal dysfunction [72]. The bidirectional relationship between gut microbiota and CKD is noted in many studies, and the effect of CKD on gut structure, leading further to dysbiosis (**Figure 1**) is also mentioned. The abundance of specific bacterial groups are dominated by Bacteroides, Prevotella, or Ruminococcus in normal individual gut microbiota [73], and these enterotypes are markedly correlated with long-term diets, especially the proteins and

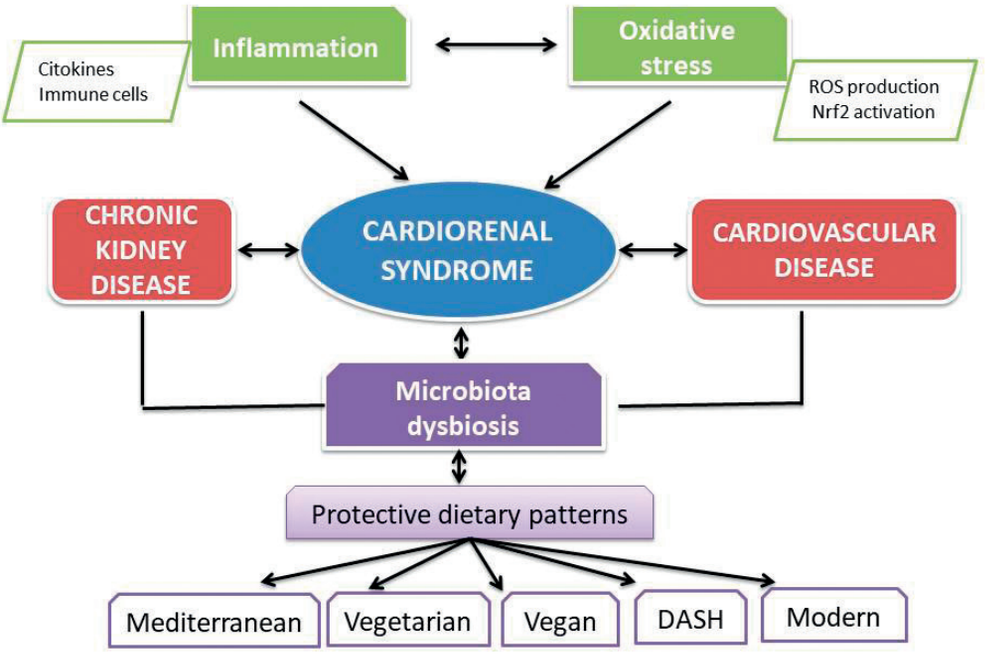

Figure 1. The crosstalk between CKD and inflammation in correlation with microbiota dysbiosis modulation.

animal-fat level (Bacteroides) versus carbohydrates (Prevotella) [74]. On the other side, the gut microbiota in CKD patients is altered, particularly with a decreased amount of Lactobacillaceae and Prevotellaceae families, and with an increased amount (more than 100 times higher) of Enterobacteria and Enterococci, species that are normally found in lower concentrations in healthy individuals [65]. The "supplementary organ" has also an important contribution to digestion, using two different catabolic pathways: saccharolytic (fermentation), with a high prevalence of Bifidobacteria and Lactobacilli, having short-chain fatty acids as end products, and the second, proteolytic (putrefaction) pathway, involving some species within Clostridium, Bacteroides, Enterobacterium, Bifidobacterium, and Lactobacillus [75] that leads to short or branched-chain fatty acids and other cometabolites, considered as microbial uremic toxins [76]. Another controversial mechanism linked to microbial dysbiosis in CKD patients involves the elevated gastrointestinal urea secretion, leading to important amounts of ammonia, which, in turn, contribute to the disturbance in the commensal bacteria [77]; therefore, targeting the gut microbiota composition could represent a promising approach in CKD monitoring and follow-up. Hence, it is considered that a balanced microbiota is mainly saccharolytic and therefore diet itself owns a beneficial role in modulating the gut microbiota composition [78].

Key mechanisms to preserve the gut microbiota balance are considered to include special diets, such as Mediterranean diet, (detailed in **Table 1**) enriched in nondigestible carbohydrates, subject to fermentation by gut microbiota, with low quantities of proteins or fats [75]. It was also revealed that dietary content and their metabolites, such as advanced glycated end products (AGEs), types of uremic toxin resulted in the glycation process, could be closely linked to CKD. Promising therapeutic targets based on nutrition approaches include uremic toxin absorbents and inhibitors of AGEs or the receptor for AGEs. Also specific types of amino acids (d-serine) or fatty acids (palmitate) have been indicated to be related with CKD progression, but they are preliminary results and further studies are needed to confirm their efficacy [79]. It is worth mentioning that dietary interventions could increase the quality of life in CKD patients, though their certain effects on mortality, cardiovascular events, and ESRD remain unclear [80]. The significance of a proper diet was settled in large retrospective cohort studies, which evidenced that the mortality occurrence in predialysis patients that were under dietitian surveillance decreased 19% compared with the patients not under any dietary treat. The conclusion that emerged is that a nutritional care in early stages of CKD could have a better prognosis on survival; however, randomized clinical trials are needed to prove this hypothesis [81].

Another area of potential beneficent therapies in CKD patients relies on the administration of prebiotics and probiotics, and the combination of both therapies into "synbiotic" preparations [81].

Probiotics are defined as "live microorganisms that when administered in adequate amounts confer a health benefit on the host" [82]. Probiotics consist of living bacteria, which can reshape gut microbiota, with impact on the inflammatory status, and are mainly represented by Bifidobacteria species, Lactobacilli, and Streptococci. A study on mice revealed that treatment with Lactobacillus acidophilus could have the potential to attenuate the development of atherosclerotic lesions in mice by reducing the oxidative stress and the inflammatory response [83]. However, the optimal dose of the bacteria essential to obtain an impeccable engraftment

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Dietary type	Diet summary	Effects on CKD	References
Mediterranean diet	Carbohydrates, basically unrefined grains, fruits and vegetables, nuts, olive oil, fish, and a moderate consumption of red wine, dairy products, and red meats	PROTECTIVE: potentially restoring microbiota balance, ameliorating CKD conditions, slow down disease progression.	[78, 91, 92]
Vegetarian diet	Fruits and vegetables, olive oil	ADDITIONAL BENEFITS: reduce the burden of uremic toxins; attention must be paid to serum potassium levels.	[93, 94]
Vegan diet	Fruits and vegetables, olive oil	POSITIVE: the addition of inulin modulates microbiota metabolism and the high fiber intake of vegan diet may have favorable effects on intestinal microbiota.	[93]
DASH diet	Consistent with a dietary approach to hypertension	PROTECTIVE: decreased risk of rapid eGFR decline.	[95, 96]
Modern dietary pattern	High intake of fruit, soy milk, egg, milk, and deep-fried products	PROTECTIVE: inversely associated with CKD.	[97]
Western diet	Excessively rich in protein and low in fruit and vegetables, grains, and fibers	DETRIMENTAL: increased risk of rapid eGFR decline.	[96]
Southern diet	Fried foods, organ meats, sweetened beverages Rice, pork, and vegetables, and low intake of wheat	DETRIMENTAL: independently associated with mortality in persons with CKD.	[98] [97]
Modern dietary pattern, with increased cadmium intake	High intake of fruit, soy milk, egg, milk, and deep-fried products, with cadmium contamination in parts of the food supply	DETRIMENTAL: directly associated with CKD.	[97]
DGA diet	Diet based on Dietary Guidelines for Americans (DGA)	DETRIMENTAL: rapid kidney function decline.	[99]
DAL diet	Diet enriched in dietary acid load	DETRIMENTAL: increased risk of ESRD and mortality.	[100–103]

Table 1. Different dietary patterns assessed in association with CKD.

and the suspicion whether these bacteria will resist in the uremic habitat remain questionable [84]. A multinational trial involving patients with CKD stage 3 and 4 has described that half year treatment with proprietary formulation of *S. thermophilus*, *L. acidophilus*, and *B. longum* over has induced a significant decline in urea nitrogen circulating levels and has also enhanced the quality of life scores in these patients. It still remains unclear whether the described interventions may alter the integrity of gut tight junction barrier; thus, more studies are needed to enlarge the knowledge in this area [85].

Prebiotics, specialized plant fibers that promote the growth of healthy bacteria in the gut, have also an important role in preventing CKD progression [84]. The candidate prebiotics comprise inulin, fructo-oligosaccharides, galacto-oligosaccharides, soya-oligosaccharides, xylo-oligosaccharides, and pyrodextrins and have potential in promoting the growth of Bifidobacteria and *Lactobacilli* species [86]. Recent evidence indicates that prebiotic oligofructose-enriched inulin (p-inulin) improves metabolic function, reduces inflammation, and mediates also weight loss [79]. Other prebiotic studies have described the role of supplements containing fructo-oligosaccharides (FOS) and/or inulin and their potential role in modulating the gut microbiota [75]. Prebiotic supplementation with FOS was correlated with a decline in proteolytic metabolites; thus, potential prebiotics such as AXOS could significantly imbalance the protein/carbohydrate fermentation ratio, resulting in alterations in the profile of fermentation metabolites, but the modifications related to microbiota composition remain ambiguous [87, 88].

Synbiotics represent the dual approach of combining a probiotic with a prebiotic and were the subject of several studies. The Synbiotics Easing Renal Failure by Improving Gut Microbiology (SYNERGY) Study was a single-center, double-blind, placebo-controlled, randomized crossover trial that tested the effects of synbiotics in CKD patients with moderate to severe stages [89]. In this study, preliminary results highlighted that administration of synbiotic therapy did result in appreciable decreasing in circulating levels of nephrovascular uremic toxins, being accompanied by a significant modulation of the stool microbiome (especially with enhancement of Bifidobacterium and deficiency of Ruminococcaceae) in CKD patients, not under antibiotics prescription [89]. The gut microbiota alteration in CKD produces the release of indoxyl sulfate and p-cresyl sulfate, which represent key uremic nephrovascular toxins. Emerging evidence reveals that gut microbiota modulation through diet supplementation with pre- and/probiotics could have an important role in inhibiting the generation of key nephrovascular toxins [90].

Considering the potential of all these preparations in shifting the uremic toxin expression and also in delaying the CKD progression, the exploration of these novel therapeutic avenues could provide vital insights into this inoffensive nutritional therapy.

7. Conclusions and future endeavors

Persistent, low-grade inflammation has been recently accepted as a potential hallmark of CKD, playing an essential role in its pathophysiology and being involved as well in the cardiovascular complications and all-cause poor prognosis in these patients. There has been an ascending growth of interest regarding the role of inflammation in CKD and end-stage renal disease, which shifts the perception of inflammation as no longer a new, but rather a traditional risk factor for CKD morbidity and mortality.

The increasing evidence regarding the tight cross talk between inflammation and kidney function became pathophysiologically relevant in patients with CKD, due to the development of proteomics, genomics, and other omics, and the advancements in state-of-the-art technologies for identification of novel biomarkers in renal diseases. The complex mechanisms in CKD development and progression would require not a single marker, but assessment of a panel of

biomarkers in order to enhance all types of alterations that characterize such a complex and insidious disease.

A variety of novel interventions have been recently proposed to target inflammation in CKD, and it seems that, in the near future, the conventional biomarkers could be proficiently improved, or even replaced with novel ones; however, confirmation of their efficacy, sensitivity, and specificity will definitely require randomized controlled and adequately interventional clinical trials.

Growing evidence indicates that gut microbiota can be considered as a recently discovered "organ," being involved in different pathological axes, in relation with almost every organ, including kidneys. Recent advances indicate that gut dysbiosis confers unexpected health risks. The gut-kidney axis has imposed itself in the renal diseases scenario as a novel therapeutic avenue with great potential in the forthcoming future. Emerging evidences highlight the possible correlation between dysbiosis and a wide range of diseases. The gut microbiota imbalance represents though the plausible missing link between nutrition and health, focusing on CKD. Alterations in gut microbiota and a myriad of host responses have been involved in CKD prognosis, high risk of cardiovascular complications, uremic toxicity, and inflammation. There is a vicious circle in CKD, in which, on one hand, toxic gut microbiota metabolites are the major circulating uremic toxins and, on the other hand, their aggregation deteriorates gut dysbiosis and promotes CKD progression.

This novel promising field of research could lead, in the near future, to the design of remarkably personalized nutritional procedures, in order to design the most convenient dietary strategy for each individual.

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