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CKJ REVIEW

A journey from microenvironment to macroenvironment: the role of metaflammation and epigenetic changes in cardiorenal disease

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ABSTRACT

Chronic non-communicable diseases have become a pandemic public problem in the 21st century, causing enormous burden on the economy, health and quality of life of societies. The role of a chronic inflammatory state in the pathogenesis of chronic disease has been more comprehensively recognized by recent findings. The new paradigm 'metaflammation' focuses on metabolism-induced (high fat or fructose-based diet or excessive calorie intake) chronic inflammation. There is a close correlation between the increased incidence of chronic kidney disease (CKD) and chronic heart failure with both increased inflammatory marker levels and western-type diet. In this review we describe the concept of metaflammation, its role in the development of CKD and chronic heart disease, the molecular and signalling pathways involved and the therapeutic consequences.

Keywords: cardiovascular disease, diet, epigenetics, kidney disease, Klotho, metaflammation, pentoxifylline

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INTRODUCTION

Excessive nutrient intake and chronic non-communicable metabolic diseases are prominent hallmarks of the 21st century. Noticeably, chronic heart failure (CHF) is one of the largest pandemic health problems, involving >26 million people worldwide [1]. Its incidence and prevalence are increasing in association with modern lifestyles. It is estimated that 8 million patients have CHF in the USA alone, and its prevalence is expected to increase by 46% by 2030. In 2012, its economic burden on the USA reached $31 billion and is expected to increase by 127% in 2012–30 [1]. Likewise, chronic kidney disease (CKD) represents another major public health problem imposing remarkable economic and social burdens globally. CKD also has indirect impacts on society by increasing the severity of morbidities, including cardiovascular disease (CVD), diabetes, hypertension, human immunodeficiency virus and malaria [2, 3]. Indeed, CKD is an independent risk factor for CVD morbidity and mortality [4–6]. Remarkably, the Global Burden of Disease 2015 study directly attributed 1.2 million deaths, 19 million disability-adjusted life years and 18 million years of life lost from CVD to CKD [3, 7]. The Global Burden of Disease study further detected 5–10 million annual deaths from CKD. Indeed, the worldwide prevalence of CKD is 3–18%, translating to 500 million patients [8]. In some countries, CKD was estimated to become the second leading cause of death after Alzheimer's disease by 2100 [9]. Knowledge of the aetiology and pathophysiology of CKD and CHF is required to tailor more efficient, targeted and individualized treatments [10].

In recent years, multiple studies have supported a pathogenic role of systemic chronic inflammatory conditions on many chronic diseases: inflammaging [11–15]. Inflammation is essential to protect the body against pathogens and also to promote healing, remodelling and renewal of tissues. However, the outcome of inflammatory activation depends on its duration and severity and whether it is appropriate for the nature and magnitude of the insult. During evolution, acute and adequate inflammatory responses provided a survival advantage and defense against pathogens. However, chronic, sterile and low-grade inflammation does not have a role in evolutionary development. The naturally protective inflammatory state can become an unfavourable condition that promotes further tissue injury in the long term [16, 17].

Recently a new paradigm called metaflammation (also termed metainflammation) has emerged and is suggested to play a role in various chronic diseases including CHF and CKD. In this review we first define metaflammation and then explore the role of metaflammation in the development and progression of CHF and CKD and the therapeutic implications.

Metaflammation

PubMed first recorded use of the term metaflammation in 2008 [18]. More recently, it was defined as a chronic low-grade inflammatory state induced by alterations in metabolism [17]. The complex link between body nutrition status, metabolic pathways and immune signalling has been preserved, with roots back to *Drosophila*, as an evolutionary adaptation to starvation. For example, activation of innate immune system components such as tumour necrosis factor (TNF) and Toll-like receptors (TLRs) blocks insulin pathway signalling through c-Jun N-terminal kinase (JNK) and myeloid differentiation primary response gene (*MyD88*) pathways. This may be one of the multiple links between the inflammatory state and nutritional status [17]. As early as 1983, TNF-α secreted from macrophages was shown to induce insulin resistance in adipocytes, supporting a close link between inflammation and metabolic syndrome [19]. The presence of macrophage infiltration in obese mice adipose tissue further supported this hypothesis and became an important milestone to understand the pathophysiology of metabolic syndrome [17]. Free fatty acid exposure triggers polarization of adipose tissue macrophages to M1-type macrophages, which inhibit insulin function [17]. The transformation of resident adipose tissue quiescent macrophages to active macrophages initiates further recruitment of macrophages and secretion of inflammatory molecules, including monocyte chemoattractant protein-1, interleukin-6 (IL-6) and TNF [20]. Insulin resistance has been linked to immune system dysfunctions, including thymic atrophy, impaired number and function of regulatory T cells (Tregs), natural killer cells, and dendritic cells [21]. Additionally, in obese mice, adipose tissue regulatory B cells are decreased. These cells secrete IL-10 and transforming growth factor β1 (TGF-β1), which have anti-inflammatory properties [21]. These observations may have therapeutic consequences. As an example, induction or transfer of $CD4^+$ latency-associated peptide Tregs as immunotherapy decreased inflammation in adipose tissue, hepatosteatosis and pancreatic islet cell hyperplasia [22].

The role of endoplasmic reticulum (ER) dysfunction in metaflammation

The ER is a key organelle in the regulation of cellular and metabolic homeostasis. Maintenance of the proteome consistency is required for cell homoeostasis [23]. In the presence of misfolded proteins, the ER unfolded protein response is activated to decrease cellular stress via increasing proper protein folding, chaperone availability and misfolded protein clearance. ER stress induces nuclear factor kappa light chain enhancer of activated B cells (NF-κB) signalling that regulates the immune and inflammatory response system ranging from haematopoietic cell production to cytokine secretion. ER stress results in an excessive inflammatory response, and the ER has an essential role in lipid homoeostasis and regulation of insulin-induced signalling pathways [23, 24]. In this regard, obesity-induced ER stress impaired insulin signalling through serine phosphorylation of insulin receptor substrate 1 and overactivation of JNK via inositol requiring enzyme 1 [25]. An oral chemical chaperone (4-phenyl butyric acid or dimethylsulphoxide) reduced ER stress, decreased hepatosteatosis and improved insulin sensitivity [26].

Inflammasome and metaflammation

The inflammasome is composed of multimeric proteins that activate caspase-1 cleavage of pro-inflammatory cytokines IL-1β and IL-18 in the presence of danger-associated molecular patterns (DAMPs), infection, cellular/tissue damage or metabolic dysregulation, resulting in pro-inflammatory cell death (i.e. pyroptosis) [27]. Inflammasome and associated caspase and IL systems are key modulators of metabolism and adipocyte function. Caspase-1 is overexpressed during adipocyte differentiation. Mice deficient in caspase-1 or nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) (inflammasome component) had better insulin sensitivity and adipocyte oxidation/metabolism and mitochondrial function than wild-type mice [28]. Indeed, caspase-1 or inflammasome inhibitors have been proposed as novel treatments for metabolic syndrome [28].

High mobility group box 1 (HMGB1) is one component of chromatin that stabilizes nucleosomes and changes DNA configuration to facilitate transcription [29]. HMGB1 is released by necrotic cells and activates the inflammasome in macrophages by binding to receptors for advanced glycation end products (RAGEs) [29, 30]. In this regard, anti-HMGB1 antibodies reduced weight gain and liver inflammation, further supporting a role for inflammation in metabolic syndrome [30]. Indeed, HMGB1 is significantly elevated in CKD and correlates with glomerular filtration rate (GFR) as well as with markers of inflammation and malnutrition [31].

Epigenetics in metaflammation

Epigenetic changes [DNA methylation, post-translational histone modifications and microRNAs (miRNAs)] modulate gene expression and thus inflammatory and metabolic signalling [32]. Epigenetic changes may be responsible for 'metabolic memory', particularly in adipose tissue macrophages, which is one of the key elements driving low-grade chronic inflammation [20]. Epigenetic changes facilitate the expression or repression of certain genes both acutely and chronically. Since epigenetic modifications may be transferred to daughter cells, there is the potential to perpetuate changes in gene transcription. This may explain metabolic memory and long-term effects of acute tissue injury. As an example, both inflammatory mediators and albuminuria decrease kidney expression of the cardioprotective, anti-ageing and anti-inflammatory hormone through epigenetic changes that may be concerned with NF-κB [33, 34]. For example, kidney Klotho downregulation persists long after renal function has been recovered in acute kidney injury [33]. Indeed, Klotho suppression has been proposed as a key contributor to inflammaging in CKD [35] and epigenetic modulation of Klotho expression improves kidney injury [36]. Epigenetic regulators in response to inflammatory signals also regulate insulin resistance. Overexpression of the epigenomic co-repressor G protein pathway suppressor 2 in obese mice improves insulin resistance and reduces inflammation and macrophage recruitment in adipose tissue [20].

Inflammation and metabolic disorders interplay with genetic and epigenetic factors and have a key role in the development of chronic non-transmissible diseases (Figure 1). Below, we separately discuss these issues in cardiorenal disorders, including CHF and CKD.

The adenosine monophosphate–activated protein kinase (AMPK) pathway also plays an important role in the metabolism, inflammation and CHF–CKD cascade. Recent studies suggest that AMPK might act as an inflammatory repressor, and inhibition of AMPK increases inflammation, especially in obese humans [37]. In the same line, AMPK activation might suppress inflammation by inhibition of the NF-κB pathway and overexpression of AMPK inhibits the NF-κB pathway in endothelial cells [38]. Furthermore, adiponectin decreased angiotensin II–induced cardiac hypertrophy by decreasing NF-κB activity in rats, but this beneficial effect disappeared after AMPK inhibition [39]. Experimental studies showed that the cardioprotective effect of metformin requires AMPK activation [40, 41]. Last but not the least, the cardioprotective effect of statins might also be mediated at the molecular level by increasing AMPK and nitric oxide production in human umbilical vein endothelial cells and in mouse aortas and myocardium [42]. Thus the AMPK pathway may be another mediator of metabolism inflammation, CKD and CVD, and this issue needs further investigation.

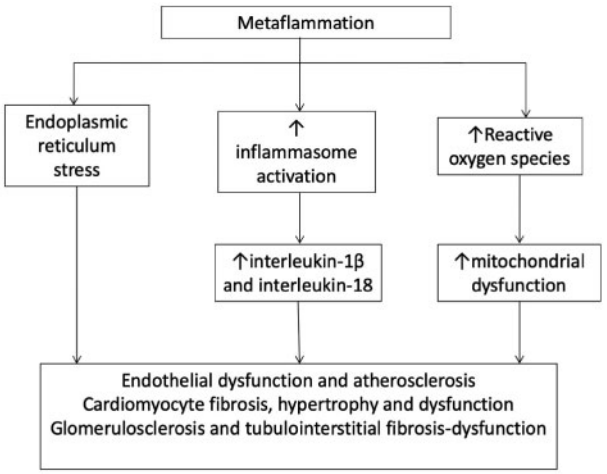

FIGURE 1: Postulated mechanisms between inflammation, insulin resistance, ER stress and systemic diseases.

Chronic heart disease

Recent evidence has shown a close relation between increased inflammatory markers and CHF [43–45]. There is an ongoing discussion of whether systemic inflammation plays a role in the pathogenesis of CHF, is a consequence of CHF, or both, contributing to a 'vicious cycle' of disease severity [46]. For example, the serum TNF level increases in the decompensation phase of CHF and is an independent prognostic factor for both cardiac and non-cardiac-related mortality in CHF [16, 47]. Additionally, TNF and IL-1β downregulate Ca^{+2}-related gene expression, including sarcoplasmic reticulum Ca^{+2} ATPase and Ca^{+2} release channels; impair the efficiency of gap junction mechanisms, leading to dysregulated electrical conduction and unsynchronized contraction and have a negative inotropic effect on myocytes, concluding with eccentric cardiomyocyte hypertrophy, myocardial fibrosis, ventricular dilation and ultimate CHF [47, 48]. Inflammation- or CKD-driven Klotho deficiency also contributes to cardiomyopathy, and recombinant α-Klotho prevents and retards uraemic cardiomyopathy [49].

TNF-like weak inducer of apoptosis (TWEAK) is a member of the TNF cytokine superfamily that activates the Fn14 receptor and activates both the canonical (as TNF) and the non-canonical (unlike TNF) pathways of NF-κB [50, 51]. In addition to decreasing Klotho through epigenetic mechanisms, TWEAK directly promotes cardiac dysfunction and failure through downregulation of the mitochondrial biogenesis regulator PGC1α, an action of TWEAK that also contributes to CKD [52, 53], and increases vascular calcification [54]. In keeping with this, higher serum TWEAK levels are associated with the severity of coronary artery disease, particularly in CKD Stages 2 and 3 patients [55], and predict mortality in haemodialysis patients [56]. Liver TWEAK signalling is differentially activated by palm oil in association with insulin resistance [57] and in response to a high-fat diet, and it contributes to liver steatosis, fibrosis and inflammation and insulin resistance [58].

In addition to IL-1β and TNF superfamily cytokines [59], IL-6 also contributes to CHF. Thus it decreases myocardial contractility and promotes cardiac hypertrophy and fibrosis leading to diastolic dysfunction by signalling through Gp130 to activate Janus kinase/signal transducer and activator of transcription 3 [47, 60]. IL-6 is the cytokine that best correlates with adverse cardiovascular outcomes in CKD [61]. However, C-reactive

protein (CRP) is the marker of systemic inflammation most commonly used in clinical practice, and it associates with diabetes mellitus, atherosclerosis and CHF. A direct role of CRP on CV injury has been suggested [62]. CHF and inflammation may be further linked through endothelial dysfunction and haemodynamic dysregulation via improper endothelial activation and increased vascular stiffness [14, 16, 63–65]. Inflammation-induced vascular permeability may cause fluid extravasation and further amplify cardiac dysfunction [16]. Additionally, venous congestion due to CHF may trigger more pro-inflammatory cytokine release, increase endotoxin absorption from the gut and promote kidney dysfunction that, in turn, further promotes inflammation and increased gut permeability [66, 67]. CHF is also associated with an altered gut microbiota that correlates with systemic inflammation in CHF [46, 68, 69].

Alteration of gut microbiota is another factor linking metabolic disorders, inflammation and chronic diseases such as CKD and CHF. Vaziri *et al.* [70] showed that the microbial composition of the gut is highly different in end-stage renal disease (ESRD) patients compared with healthy subjects. Due to changes like diet and colonic transit time in CKD patients, microbial metabolism moves towards a predominantly proteolytic fermentation. The percentage of bacterial families possessing urease, uricase and indole- and *p*-cresol-forming enzymes increase, whereas the percentage of bacterial families possessing butyrate-forming enzymes decreases in CKD patients. This increase of protein fermentation occurs at the expense of carbohydrate fermentation and disrupted epithelial barrier. This suggests that altered microbial composition and metabolism may have a role in the dysfunctional epithelial barrier, which is associated with bacterial translocation and endotoxinaemia, increases in systemic inflammation and the risk for CVD [71]. This altered dysfunction of the intestinal barrier in CKD. This pathophysiologic process is now considered one of the mechanisms explaining high cardiovascular burden in CKD patients.

With time, the vicious cycle between inflammation and CHF becomes more and more prominent and eventually it may be unbreakable [16]. Both TLRs and RAGEs are elemental pattern recognition receptors for detection of DAMPs, such as HMGB1 and others. The metabolic syndrome–associated chronic inflammatory state induces activation of TLR- and NF-κB-associated inflammatory responses on cardiac myocytes, contributing to insulin resistance, inflammation and further cardiomyocyte injury [46].

Metaflammation also contributes to endothelial dysfunction, vascular calcification and atherosclerosis [72]. Dyslipidaemia originating from metabolic syndrome [including decreased levels of high-density lipoprotein and increased levels of triglycerides, total cholesterol and low-density lipoprotein (LDL)] is an independent risk factor for adverse cardiovascular outcomes [73, 74]. Atherogenic adipokines are also released by adipose tissue [72].

Metaflammation is also associated with mitochondrial dysfunction, decreasing energy availability and increasing mitochondrial reactive oxygen species (ROS) production [75]. Indeed, energy metabolism is thought to be a key driver of diabetic cardiomyopathy, and it has been proposed that an improved fuel profile is a key contributor to the improved outcomes of patients on sodium-glucose co-transporter 2 inhibitors [76].

Epigenetic modifications and CHF

Differentiating healthy cardiomyocytes during development and failing or stressed cardiomyocytes share epigenetic modification patterns [77]. During CHF, epigenetic modifications regulate the expression of transcription factors, angiogenic factors and natriuretic factors, among others [77–79]. Since there is an association of increased DNA methylation levels with pathological hypertrophy and impaired contractility in failing cardiomyocytes, inhibition of DNA methylation has been proposed as a treatment option for CHF since it has the potential to reverse pathologic norepinephrine and Ca^{+2}-induced cardiac fibrosis [79]. DNA methylation inhibitors are already in clinical use for malignancy [32].

Histone post-translational modifications have also been associated with metabolic syndrome, inflammation and heart disease. Of >50 known histone post-translational modifications, acetylation and methylation are the best characterized. Histone acetylation modulates gene expression associated with cardiomyocyte function, inflammation and fibrosis [79]. Sirtuins are histone/protein deacetylases that regulate mitochondrial function and cell survival. Specifically, SIRT1 and SIRT3 protect cardiomyocytes from stress [80]. Histone deacetylase inhibitors decrease cardiac fibrosis and hypertrophy and improved myofilament Ca^{+2} sensitivity [81]. Trimethylation of histone H3 on lysine 4 or lysine 9 were markedly different between normal hearts and heart failure both in experimental animals and in humans [82]. However, the potential therapeutic consequences of this observation remain unexplored.

Altered messenger RNA expression also contributes to heart failure. As an example, miR-208a, which is released into the circulation during heart injury, is associated with the expression of the α- myosin heavy chain and is a regulator of cardiac hypertrophy and conduction [83]. miR-208a is required for normal cardiac function [84], but when overexpressed, it induced hypertrophy and arrhythmia [84]. In this regard, targeting miR-208a by anti-miR protected Dahl hypertensive rats from hypertension-induced heart failure [85]. Interestingly, miR-208a targets mediator complex subunit 13 (MED13), one of components of the mediator complex that regulates fatty acid, cholesterol, lipid and cellular energy homoeostasis, increasing energy expenditure [79, 86]. Cardiac-specific overexpression of MED13 or pharmacologic inhibition of miR-208a (leading to MED13 upregulation) in mice conferred resistance to high-fat diet-induced obesity and showed an improvement in systemic insulin sensitivity and glucose tolerance [86]. In summary, these studies demonstrated a close relationship between the epigenetic regulation of cardiac function and metabolic diseases and a potential of miR208-α inhibition in the treatment of cardiac and chronic metabolic diseases. Upregulation of miR-23, miR24 and miR-195 was also associated with cardiac hypertrophy and ischaemic cardiomyopathy through the MAPK signalling pathway [79, 87, 88]. The number and types of heart failure-related miRNA or other epigenetic changes are rapidly increasing and may provide novel therapeutic targets for CHF.

CKD. The role of chronic inflammation on the pathogenesis of CKD and its complications is widely recognized [12, 89–91]. CKD is a cause of low-grade chronic inflammation and chronic inflammation decreases kidney Klotho expression and increases oxidative stress, adhesion molecules, aberrant matrix composition and fibrosis of renal tissue, leading to progressive renal dysfunction [92].

Oxidative stress may have a role in the progression of kidney disease independent from the aetiology. The formation of ROS occurs both in the renal cortex and medulla. Increased ROS has various effects, such as microinflammation, which is frequently seen in CKD [93, 94]. Oxidative stress has been considered the link between inflammation and CVD in CKD [95]. Oxidative stress is closely related to endothelial dysfunction and endothelial dysfunction, in turn, is closely related to arterial

hypertension, arteriosclerosis and heart failure [96]. Undoubtedly, the most elaborated role of oxidative stress is acknowledged in diabetic nephropathy (DN). This issue is very important since DN is the most common form of CKD. Especially in DN, mitochondrial dysfunction has been well demonstrated [97] and antioxidant supplementation was beneficial in DN [98, 99].

Patients with metabolic syndrome have an increased frequency of renal vascular sclerosis, tubulointerstitial fibrosis and tubular atrophy [100, 101]. Despite the strong association of metaflammation and metabolic syndrome with CKD, further studies are needed to elucidate the exact pathogenesis and potential novel therapeutic implications. Several questions remain to be clarified: Does CKD *per se* originate from metaflammation? Does chronic inflammation accelerate a pre-existent CKD? Does CKD worsen already existing metaflammation? Is this a vicious cycle—and at what stage of CKD can it be arrested?

The observations regarding oxidative stress, CKD and CVD are not confined in the context of diabetes and metabolic disorders. The role of oxidative stress–related CVD is also evident in other types of CKD. For example, a recent review by Andries *et al.* [102] clearly demonstrated that excessive oxidative stress is closely associated with endothelial dysfunction and hypertension, even in the early stages of autosomal dominant polycystic kidney disease. Endothelial nitric oxide synthase uncoupling due to increased asymmetric dimethylarginine and mitochondrial dysfunction are postulated mechanisms linking oxidative stress and CVD in autosomal dominant polycystic kidney disease.

Among the drivers of tissue injury in the CKD metainflammatory environment, recent data have focused on the NLRP3 inflammasome, which contributes to western diet and fructose-induced renal inflammation, renal cholesterol accumulation and hyperuricaemia, as evidenced by protection in Nlrp3 knockout mice [103, 104]. Tubular cell lipotoxicity induced by continuous exposure to LDL cholesterol and long-term overnutrition was characterized by intralysosomal lipid accumulation, lysosomal dysfunction, oxidative stress and tubular dysfunction leading to NLRP3 inflammasome activation that inhibited the sirtuin-1/LKB1/AMPK pathway to dampened lipid breakdown, leading to a vicious cycle of further phospholipid accumulation, oxidative stress and mitochondrial damage [105]. In this regard, in a transcriptomic study of a large cohort ($n = 95$) of normal and fibrotic human kidney tubules, inflammation and metabolism were the top dysregulated pathways in the diseased kidneys. Specifically, tubulointerstitial fibrosis samples had lower expression of key enzymes and regulators of fatty acid oxidation and higher intracellular lipid deposition. Indeed, fatty acid oxidation is the key energy source in tubular cells and inhibition of fatty acid oxidation in tubule epithelial cells caused ATP depletion, cell death, dedifferentiation and intracellular lipid deposition [106].

The Chronic Renal Insufficiency Cohort (CRIC) study established the link between impaired renal function [lower estimated glomerular filtration rate (eGFR)] or kidney injury (higher albuminuria) and levels of inflammatory markers, including IL-1β, IL-6, TNF, CRP and fibrinogen [92]. There is evidence for all of them being more than markers of risk by contributing to the pathogenesis of CKD progression and cardiovascular complications [11]. CRP may have deleterious effects on renal blood flow through the NF-κB pathway in endothelial cells leading to endothelial dysfunction and triggering vasoconstriction through recruitment of angiotensin-II and endothelin 1, and decreasing nitric oxide synthesis [107]. Higher CRP and TNF levels were independently associated with accelerated renal function loss [108] as well as with decreased survival in haemodialysis patients [109, 110]. Fibrinogen may increase blood viscosity and decrease microvascular flow as well as being a mitogen for renal fibroblasts [52].

Further evidence for altered lipid metabolism in CKD progression and vascular injury is derived from the pleiotropic actions of statins, which, beyond LDL reduction, can interfer with intracellular prenylation processes, displaying anti-inflammatory and anti-fibrotic properties [111–113]. Thus, in CKD patients, atorvastatin decreased levels of inflammatory marker (CRP, IL-1β and TNF) and improved cardiovascular function independent of its impact on lipid profile in CKD [114].

Epigenetics and CKD

In recent years, evidence has emerged on the role and importance of epigenetic modifiers on both embryonic kidney development and acute kidney injury and CKD [115]. Abnormalities in DNA methylation, histone modifications and miRNA have been described and shown to contribute to CKD progression. Genome-wide studies (GWASs) observed prominent differences in DNA methylation of CpG sites between DN and healthy subjects [116]. Demethylation of genes for methylenetetrahydrofolate reductase and connective tissue growth factor was a predisposing factor for the development of DN [116]. Indeed, the differentially methylated regions were associated with profibrotic genes [116]. Also, hyperglycaemia and oxidant stress increase the expression of the histone methyl transferase 'SET7' that facilitates the transcription of profibrotic genes in DN [117]. Furthermore, changes in methylation patterns of mitochondria-associated genes (peptidase, mitochondrial β subunit; translation elongation factor, mitochondrial; AU RNA binding methylglutaconyl-CoA hydratase) are seen in DN, suggesting the connection between mitochondrial dysfunction and DN [117].

Ledo *et al.* [118] investigated novel genes in the vicinity of CKD-associated single nucleotide polymorphisms (SNPs). They showed a strong correlation between SNPs (FAM47E, PLXDC1, ACSM2A/B, ACSM5 and MAGI2) and candidates for CKD development [118]. In another study, Xu *et al.* [119] identified three genes (*NAT8B*, *CASP9* and *MUC1*) that have a causal effect on eGFR [119]. Parsa *et al.* [120] performed a GWAS in the CRIC study participants. CKD progression defined as change in eGFR over time among 1331 blacks and 1476 whites with CKD status. They identified 12 SNPs among black patients and 6 SNPs among white patients. Among blacks without diabetes, rs653747 in LINC00923 was associated with ESRD. In contrast, rs931891 in LINC00923 associated with an eGFR decrease in white patients without diabetes.

Histone deacetylase inhibitors reduced inflammation, fibrosis and expression of α-smooth muscle actin, collagen I, fibronectin, TGF-β1 and NF-κB [117]. In addition to the well-known acetylation and methylation of histones, a role for histone crotonylation in nephroprotection was recently described [121]. Crotonate is a short-chain fatty acid produced by the gut microbiota [122]. Finally, various miRNAs have been implicated in the pathogenesis of DN, including miRNA-25, miRNA-23b, miRNA-21, miRNA-29a, miRNA-146a and others [123].

Role of mitochondrial dysfunction in CKD

Mitochondria have major regulatory functions in energy, Ca^{+2} and iron homoeostasis, inflammation, cell death pathways and oxidative stress and mitochondrial dysfunction and have received attention as a potential therapeutic target in kidney disease [124]. In particular, proximal tubular epithelial cells have high energy requirements and oxygen consumption to support

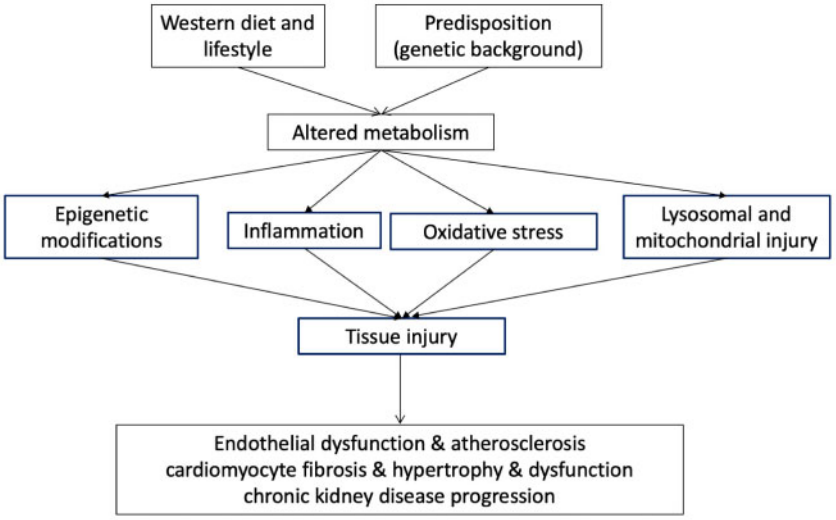

FIGURE 2: The interaction of the macroenvironment (in this case, western diet and lifestyle) and genetic predisposition determines the magnitude and type of metabolic alterations, which in turn drives a change in the microenvironment through epigenetic modifications, oxidative stress, mitochondrial and lysosomal dysfunction and an inflammatory response, leading to progressive tissue injury. Several positive feedback loops form vicious circles that increase the severity of tissue injury and dysfunction, leading to cardiac and kidney disease progression. All contributing factors and pathways may be subject to therapeutic manipulation.

molecule secretion and reabsorption. Metabolic syndrome and diet may disrupt this balance. As an example, even transient postprandial hyperglycaemia may increase the glucose load in proximal tubules and increase oxygen and energy requirements to reabsorb filtered glucose, which through coupling to sodium reabsorption also contributes to CHF [125]. Moreover, hyperglycaemia can directly induce mitochondrial oxidative stress, contributing to endothelial and tubular dysfunction, podocyte injury and activation of apoptosis [126, 127]. DM-induced mitochondrial DNA oxidative stress causes endothelial dysfunction and podocyte loss via endothelin 1/endothelin 1 receptor type A signalling [126]. Treatment with the mitochondrial-targeted potent antioxidant mitoTEMPO improved endothelial injury, albuminuria and glomerular sclerosis [126]. Additional mitochondrial protective strategies are undergoing clinical trials in kidney and CVD [124].

Future perspectives. The increasing evidence of an impact of diet-induced chronic inflammatory state on the initiation of chronic diseases has led to the design of clinical trials targeting inflammation in CKD and CVD (Figure 2). These range from open-label investigator-initiated trials of non-expensive drugs to large pharma-sponsored trials. As examples, pentoxifylline has anti-inflammatory actions and in DN it decreased albuminuria, preserved GFR, decreased circulating and urinary TNF and preserved Klotho levels in the circulation and in urine, in line with a Klotho-preserving action in cells exposed to inflammatory mediators of albumin [34, 128]. In another example, low-dose aspirin increased the anti-inflammatory lipid 15-epi-lipoxin A4 in CKD patients and decreased coronary and renal events [129]. In this regard, several anti-inflammatory drugs are undergoing clinical evaluation in DN [130]. On the other side of the spectrum, biological agents targeting specific cytokines have been proposed for nephro and cardiovascular protection [59]. The most striking demonstration of the feasibility and efficacy of this approach was the Canakinumab Anti-inflammatory Thrombosis Outcomes Study in patients with previous myocardial infarction and evidence of systemic inflammation [131]. Targeting IL-1β with canakinumab reduced non-fatal myocardial infarction, non-fatal stroke and cardiovascular death [131]. Additional approaches include the use of low-dose immunosuppressive agents. In experimental animals, mycophenolate mofetil reduced renal inflammation, oxidative stress, endothelial dysfunction and hypertension [132, 133]. Although mycophenolate mofetil is used in clinical practice to treat autoimmune diseases, including primary glomerulonephritis, vasculitis and lupus nephritis, as well as kidney transplant recipients, its potential use as a non-specific anti-inflammatory agent in non-immune CKD has not yet been tested. Another non-specific immunosuppressant, low-dose methotrexate, has been tested for cardiovascular protection. However, among patients with stable atherosclerosis, low-dose methotrexate did not reduce IL-1β, IL-6 or CRP or cardiovascular events [134]. Antioxidant treatments to reduce mitochondrial oxidative stress are another potential treatment option [124]. Lastly, epigenetic modulation is coming of age. Modulators of DNA methylation and post-translational histone modifications are already in clinical use, mainly in the oncology context [32]. Additionally, inhibitors of bromodomain and extraterminal proteins, which are readers of epigenetic clues, have been successfully used in experimental kidney injury and early clinical trials for CVD and CKD have been promising [135]. RNA interference approaches, either small-interfering RNAs or miRNA inhibitors (anti-miRs) or mimics have been tested clinically [136]. Patisiran is an RNA inhibitor that improved multiple clinical manifestations of hereditary transthyretin amyloidosis, a disease characterized by neurological cardiac and kidney manifestations, and was approved by regulatory authorities in the summer of 2018 [137]. While this is a very specific condition, these studies validate the feasibility of the approach. In any case, renal safety should be monitored in routine clinical practice, given the kidney safety signals from miravirsen, an anti-miR-122 for hepatitis C virus infection [138]. Finally, dietary modification or the use of prebiotic or probiotic approaches is another possibility [139].

CONCLUSION

Chronic inflammation induced by excessive nutrient intake and metabolic syndrome has reached epidemic proportions in the

21st century and is contributing to the increased prevalence and mortality from CVD and CKD.

Metainflammation is defined as a chronic low-grade inflammatory state induced by alterations in metabolism and is linked to CKD and CHF. Recent advances have identified key mediators and pathways that link altered metabolism and chronic inflammation with target organ injury. These include mitochondrial dysfunction, oxidative stress, genetic and epigenetic changes and altered gut microbiota. These recent findings have led to the design of novel therapeutic strategies, some of which have proved successful in Phase 3 clinical trials. A more detailed understanding of the cellular and molecular pathways involved will increase the array of therapeutic tools that may stem the current negative trend in mortality from CKD and CHF.

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AUTHORS' CONTRIBUTIONS

M.K., A.Y., B.A. and A.S. are involved in writing the manuscript. P.S., A.W., A.O. and M.K contributed to preparation and editing of the manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

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