Therapy of chronic renal insufficiency: from renal physiology to cardiovascular outcomes

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Chronic renal insufficiency and atherosclerosis are tightly connected clinical syndromes. Overall, renal function assessed by estimated glomerular filtration rate correlates with total and cardiovascular mortality in a graded fashion. In addition, microalbuminuria is a prognostic indicator for both progression of chronic renal insufficiency and adverse cardiovascular outcomes. Chronic renal insufficiency related neurohumoral stimulation, including the renin–angiotensin-aldosterone system and the sympathetic nervous system is focused on, therapeutic implications are provided. In addition, the role of systemic inflammation with respect to endothelial function, vascular calcification and metabolism is highlighted. This review aims to summarize recent research results concerning chronic renal insufficiency pathomechanisms relevant to cardiovascular disease.

Keywords: aldosterone, angiotensin II, atherosclerosis, calcification, chronic renal insufficiency, inflammation, sympathetic nervous system

Chronic renal insufficiency (CRI) and atherosclerosis are tightly connected clinical syndromes. Very recently, CRI has been recognized to be a risk factor for cardiovascular disease [1]. This is true for both end-stage renal disease (ESRD), necessitating kidney replacement therapies [2], as well as for predialysis CRI [3] where the number of prospective intervention studies with hard end points is very limited at the moment. Disparity exists regarding how best to deal with the diagnosis of mild-to-moderate CRI. On the one hand, there is the notion that CRI may serve as a noninvasive surrogate for prevalent atherosclerosis similar to fundoscopy for the diagnosis of arterial hypertension [4]. Conversely, the validity of current classifications of CRI and its implications thereof are seriously doubted aiming to differentiate between CRI as a disease, and age-related, rather benign declines of glomerular filtration rate (GFR) [5]. Mechanisms linking CRI to atherosclerosis clearly involve neurohumoral stimulation including both the renin–angiotensin-aldosterone system (RAAS) [6] and the sympathetic nervous system (SNS) [7]. Moreover, cytokine activation prompting systemic inflammation [8] as well as calcium–phosphorus disturbances [9] may directly affect arterial-wall biology, thereby advancing atherosclerosis. When CRI is being diagnosed by serial testing for plasma creatinine and urea, a means to stratify CRI severity is offered by the modified National Kidney Foundation classification [10] displayed in Table 1. There, an equation established by the Modification of Diet in Renal Disease (MDRD) study using serum creatinine, age, race, gender and, optionally, serum albumin and urea allows for the estimation of the glomerular filtration rate (GFR), without buying common errors associated with collecting urine over a 24-h period [108]. Thus, the estimated GFR has become a *conditio sine qua non*, an essential prerequisite, to determine what is commonly referred to as renal function. Moreover, both microalbuminuria (30–300 mg/l) and macroproteinuria (>301 mg/l), including the nephrotic syndrome with daily protein loss of more than 3500 mg/l, are fundamental variables for the determination of the degree of CRI as proteinuria has been shown to be an important indicator for the progression of the disease in both diabetic and nondiabetic patients [11,12].

Evidence derived from a large US-based healthcare-system database incorporating longitudinal data of kidney function from more than 1.1 million patients suggests that the degree of impaired GFR relates to prognosis in terms of total mortality [3]. In this case, the degree of CRI correlates, in a graded fashion, with total mortality (Table 1). Using CRI stage 2 as a reference group, odds ratios (ORs) for total mortality in CRI were 1.2 for stage 3a, 1.8 for stage 3b, 3.2 for stage 4 and 5.9 for stage 5 [3]. In this study, the risk for myocardial infarction (MI) increased, suggesting that cardiovascular mortality widely determined the excess total mortality. These results support previous longitudinal data derived from a variety of community based studies, suggesting that CRI is a risk factor for the composite of MI, stroke and total mortality [13]. Furthermore, atherosclerosis involving renal arteries has the potential to

Table 1. Modified classification of degree of CRI [10].

Chronic renal insufficiency	Estimated GFR
Stage I	≥90 ml/min/1.73 m²
Stage II	89–60 ml/min/1.73 m²
Stage III A	59–45 ml/min/1.73 m²
Stage III B	44–30 ml/min/1.73 m²
Stage IV	29–15 ml/min/1.73 m²
Stage V	<15 ml/min/1.73 m²

Based on estimated GFR using creatinine, sex, ethnicity, gender (4-variables equation), or, in addition, urea and albumine (6-variables equation, MDRD study [108]).
CRI: Chronic renal insufficiency; GFR: Glomerular filtration rate.

obstruct renal perfusion, thereby aggravating neurohumoral stimulation and arterial hypertension. CRI sequelae, including arterial hypertension [14] and volume overload [15], inflammation [16], anemia [17] and a possible arteriovenous fistula [18], may facilitate the occurrence of left-ventricular hypertrophy and diastolic cardiac dysfunction.

The goal of this review is to summarize reno-cardiovascular disease mechanisms as they are pertinent to therapeutic considerations in CRI. Ultimately, it is hoped that this review will encourage clinicians to participate in clinical research to help bring about more specific therapies for the predialysis stage of CRI.

Chronic renal insufficiency: common principles

In CRI, uniform common final pathways usually present in the individual courses of disease. For example, the occurance of microalbuminuria may directly relate to endothelial injury known to be an early event both in renal disease and atherogenesis. Overt proteinuria affects tubulo-interstitial function. Both angiotensin II and aldosterone mediate a variety of adverse effects to renal function and to the cardiovascular system when tissue concentrations are elevated. Amongst others, angiotensin II activates membrane-bound NADPH oxidase known to be a source of superoxide anion , and facilitates cardiac and renal [19–21] fibrosis. Likewise, aldstosterone is implicated in left-ventricular hypertrophy, fibrosis and increased oxidative stress [22].

Endothelial injury

Microalbuminuria regularly occuring as an initial pathologic finding in renal disease may result from a combination of endothelial dysfunction and glomerular damage [23]. Proven mechanisms of causing microalbuminuria include arterial hypertension, diabetes mellitus and chronic inflammation [24]. Interventions that are able to improve endothelial function do have the potential to attenuate or reverse microalbuminuria [25,26]. Therefore, the notion exists that microalbuminuria predominantly represents a dysfunctional endothelium within the glomerular filter apparatus. From a therapeutic perspective, the inhibition of the RAAS using angiotensin-converting-enzyme (ACE) inhibition or angiotensin II-receptor-subtype-1 blockade (ARB) reduces microalbuminuria effectively [27–29]. However, only ACE inhibition translates into less mortality as shown in diabetic nephropathy [30]. This dramatic difference in outcome may be due to bradykininergic effects on endothelial function mediated by ACE inhibition; however, not by ARB. Bradykinin prompts the release of nitric oxide (NO) via activation of the constitutive, endothelial NO synthase, thereby lowering arteriolar tone and deactivating platelet function [31].

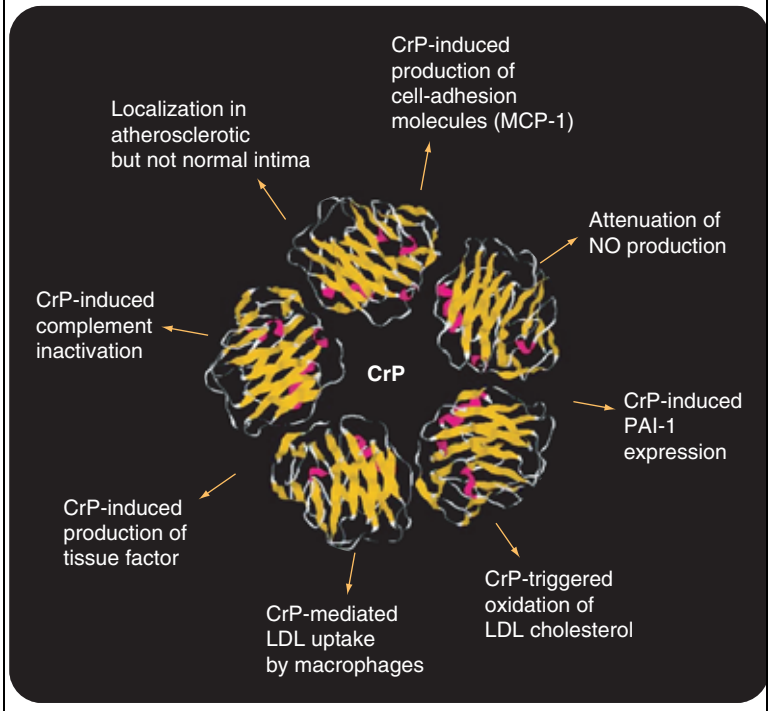
Hyperhomocysteinemia [32] as well as the endogenous inhibitor of endothelial NO synthase, asymmetric dimethylarginine [33], and overall inflammation [34] are candidate cardiovascular risk factors implicated in endothelial injury that is prevalent in both CRI and ESRD. For the latter, controversy still exists as to whether or not C-reactive protein (CrP) itself represents a cause of atherosclerosis, or an epiphenomenon of atherogenesis. Once CrP is elevated in CRI, evidence suggests it to be directly involved in impairing endothelial function and differentiation. In cell culture, the differentiation of endothelial progenitor cells was found to be attenuated by CrP, thereby limiting the vascular regenerative power [35,36]. In apolipoprotein-E-deficient

mice, CrP was found to promote atherosclerosis by a more intense complement activation, and by an increased expression of angiotensin II-receptor-subtype-1 receptor, vascular cell adhesion molecule-1 and collagen [37]. Figure 1 shows the actions of CrP relevant to atherogenesis.

Glomerular function & tubular–interstitial function

Once CRI stage 4 (an estimated GFR < 30 ml/min/1.73 m²) has been reached, CRI progressively deteriorates in a vicious cycle due to the limited number of functioning nephrons that are getting impaired by uremic toxins, albumin overload and sequelae of RAAS activation. In addition, the specific glomerular barrier function for serum proteins maintained by endothelial cells, glomerular cells as well as by the glomerular basement membrane may deteriorate. The resulting proteinuria, in turn, forecasts the development or worsening of chronic renal failure. Therefore, therapeutic goals in CRI include the reduction of an existing proteinuria.

Figure 1. C-reactive protein (CrP) actions on coagulation, endothelial function, complement system and cell-adhesion molecules.



CrP: C-reactive protein; LDL: Low-density lipoprotein; MCP-1: Monocyte chemoattractant protein-1; NO: Nitric oxide; PAI-1: Plasminogen activator inhibitor-1. Modified from [61].

Proteinuria directly affects renal tubular function in terms of tubular hypertrophy and interstitial fibrosis. Macroproteinuria activates type-2 transforming growth factor (TGF)-β [38], thereby inducing inflammation, tubular injury and interstitial fibrosis. Specific TGF-β antagonism attenuates this process and may represent a potential therapeutic option in CRI [39]. Moreover, in the case of the nephrotic syndrome, characterized by urinary protein losses of more than 3.5 g/l and reactive perturbation of protein synthesis, there is an increased risk of venous thrombosis and pulmonary embolism. Therefore, once serum albumin is less than 25 g/l, an anticoagulation is to be initiated [40]. In CRI with macroproteinuria, including the nephrotic syndrome, the contraction of the intravascular volume maximally activates the RAAS. Likewise, an impaired arginine vasopressin receptor function in the elderly as well as a disturbed urine-concentration ability in chronic hypercalcemia result in a decreased capacity to reabsorb free water. The resulting hypovolemic state activates the RAAS [41–43].

Renin–angiotensin–aldosterone system

RAAS activation inadvertently occurs in CRI due to derangements in volume homeostasis, SNS activation, or renotubular insensitivity to aldosterone with resulting electrolyte shifts. Therefore, RAAS modulation therapies represent a mainstay in the treatment of CRI. Both ACE inhibitors and ARB were found to be beneficial agents in diabetic and nondiabetic nephropathy [44–46]. In addition, preliminary evidence suggests aldosterone antagonism to be effective in reducing proteinuria in a model of CRI [47].

In nondiabetic CRI patients, a combined RAAS modulation therapy appears to be superior to either ARB- or ACE-inhibitor monotherapy [48]. An ARB monotherapy does not prevent angiotensin II increasing and exerting deleterious effects such as oxidative stress [19]. Likewise, ACE-inhibitor monotherapy does not control alternative pathways, such as the ability of chymase to generate angiotensin II. Even when a combined treatment of ARB and ACE inhibitors is being used in nondiabetic CRI, the end point of worsening the illness is still being reached by many patients, suggesting that escape mechanisms of aldosterone generation may exist in spite of a dual RAAS blockade [48]. Future research needs to identify the value of an antialdosterone blockade as an additional, renoprotective measure.

Hyperkalemia & aldosterone activation

An antialdosterone therapy represents a promising therapeutic options for CRI due to escape mechanisms yielding elevated tissue aldosterone concentrations in spite of ACE inhibitors or ARB treatment [49]. Aldosterone increases oxidative stress and inflammatory renal injury [50,51]. Independent from angiotensin II, aldosterone is directly activated by elevated serum concentrations of potassium. Thus, uremic hyperkalemia also evokes aldosterone generation that, in turn, cannot correct the hyperkalemia as soon as the renotubular system failed. In this case, symptomatic treatment and/or kidney replacement therapy initiation is required.

Generally in CRI, a careful dose titration of eplerenone or spironolactone and therapy monitoring are mandatory because of the known risk of hyperkalemia. Also, other drugs increasing serum potassium, such as ACE inhibitors and ARB, need to be used with great caution, especially in combined application. With respect to antialdosterone treatment, more outcome studies are needed to evaluate the merits and perils in CRI. However, epleronone, a specific mineralocorticoid receptor antagonist, is not allowed in CRI with a GFR of less than 50 ml per minute per 1.73 m² because of the risk of hyperkalemia. For the same reason, antialdosterone treatment has to be avoided in Type II diabetes [22].

Cardiovascular consequences of chronic renal insufficiency

Anemia & left-ventricular hypertrophy

Anemia due to erythropoietin deficiency as indicated by low retikulocytes is a common finding in CRI. When untreated, a high-output condition of chronic heart failure ensues. This, in turn, is a cause of left-ventricular hypertrophy known to be associated with an increased risk for cardiac sudden death [52,53]. Therefore, a correction of anemia using erythropoietin analogues is mandatory because it has the potential to reverse left-ventricular hypertrophy in ESRD [54]. Then, according to ferritin serum levels, an exogenous iron supplementation may be considered. However, exceeding the normal range of ferritin serum levels may translate into elevated oxidative stress because iron catalyses the formation of reactive oxygen species [55,56]. Hence, iron overload has to be avoided.

In cases of erythropoietin-resistant anemia, other causes of anemia should also be identified. As inflammation is a common finding in CRI, an anemia due to infection may be considered. In the case of infection, iron supplementation has to be avoided.

Inflammation

As CRI progresses, the occurance of systemic inflammation becomes an issue [57] either due to immunologic phenomena depending on the renal disease, as a result of complicated urinary-tract infections, or as consequence of pro-inflammatory hormone actions. In ESRD, both an elevated interleukin (IL)-6 [58] and CrP serum concentration [59] were shown to be predictive for mortality similar to the general population where large, prospective studies proved CrP to be a cardiovascular risk factor [34] over the full range of CrP concentrations [60]. Renal and extrarenal sources of either low-grade or overt systemic inflammation need to be considered, including chronic, uremic gastritis, metabolic syndrome, atherosclerosis, or in the case of ESRD, venous-access infections, catheters, the hemodialysis procedure itself or the failed native kidneys. Of course, other concomitant inflammatory disease such as bronchitis or skeletal disorders, or habits such as smoking, may add up to the state of overall systemic inflammation.

Vascular calcification: intima- versus media-based atherosclerosis

CRI patients are recognized as being at high risk for atherosclerosis including coronary heart disease [61]. Elevated homocysteine, increased systemic inflammation, duration of uremia, dyslipidemia, elevated calcium–phosphorous (Ca × P), as well as a low serum level of fetuin-A, appear to be risk factors for the vascular calcification process in CRI [62].

Besides the classic, intima-based atherosclerosis evident as atherosclerotic plaques, there is a type of media sclerosis very common in CRI, especially in ESRD patients. Intima-based atherosclerosis primarily affects the large conduit arteries and classic cardiovascular risk factors seem to be attributable. In contrast, arterial-media sclerosis is a nonobstructive type of vascular calcification. In this case, the duration of hemodialysis and an elevated Ca × P possibly caused by calcium-based phosphate binders, vitamin D or hyperparathyrhoidism, are risk factors. The presence of arterial-media sclerosis implies a poor prognosis [63]. Uremic arteriolopathy or calciphylaxis cutis is a special type of arterial-media sclerosis defined by intimal proliferation, fibrosis and calcification of small arteries, arterioles or capillaries predominantly of the skin [64,65]. Almost exclusively, uremic arteriolopathy occurs in ESRD; however, cases have also been described in nondialysis CRI [66] as well as

in primary hyperparathyroidism, inflammatory bowel disease or cancer [65]. Although the risk factors for uremic arteriolopathy are essentially the same as for arterial-media sclerosis, a deficiency of fetuin-A, a vitamin K-dependent matrix protein inhibiting ectopic calcification, appears to be relevant [67]. Overall prognosis of uremic arteriolopathy is poor, especially when skin ulcerations occur [68].

Sympathetic nervous system activation: risk of cardiac sudden death

CRI is a state of SNS overactivation due to uremia and signals arising from the failing kidneys that even remain prevalent once kidney-replacement therapy (dialysis or renal transplant) has corrected the uremic state [69]. In addition, oxidative stress related to exogeneous iron application and internal sources such as angiotensin II-stimulated NADPH oxidase may sustain SNS activation via a blunted sympathoinhibitory baroreflex or direct CNS effects [70]. Therefore, antisympathetic strategies need to be implemented in the medical control of blood pressure. In an animal model, both β-adrenergic, and a combination of α- and β-adrenergic blockade appear to convey renoprotection [71,72]. Conversely, the ARB, losartan, and the ACE inhibitor, enalapril, have been proven to lower SNS tone in CRI [73], The mechanism of which may be twofold. First, at the site of the afferent limb of reflex mechanisms arising from the failing or failed native kidneys and second, in the brain by attenuation of oxidative stress [74] as angiotensin II-induced superoxide anion derived from NADPH oxidase accounts, in part, for SNS activation [19]. Likewise, aldosterone-induced oxidative stress will be attenuated by mineralocorticoid receptor antagonists, thereby normalizing SNS tone. In ESRD, the SNS system activation (plasma norepinephrine levels) may determine prognosis very much like in chronic heart failure [7,75]. Other measures to reduce oxidative stress include the use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors or statins known to deactivate NADPH oxidase via less isoprenylation of a critical subunit [76]. Statins do also have the potential to correct a SNS overactivation, as shown in a model of SNS overactivity in chronic heart failure [77,78].

In addition to oxidative stress, carotid atherosclerosis may also blunt the afferent limb of the sympathoinhibitory baroreflex, leading to a propensity of SNS overactivation. As a consequence this overactivation, the risk of sustained ventricular tachycardia and sudden cardiac death increases [79].

Therapeutic implications

Generally, once the specific treatments of primary, immunologic or secondary causes of CRI such as urinary tract obstructions, renal artery stenosis, complicated urinary tract infections, or long-standing hyperglycemia, have been initiated, additional renoprotective measures should be considered as soon as the estimated GFR has been found to be declined. Concomitant medications that potentially treat renal function, including a variety of nephrotoxic drugs such as over-the-counter pain-relief medications, cyclo-oxygenase (COX)-2 inhibitors, nephrotoxic antibiotics or lithium-containing drugs, should, if possible, be withdrawn. Once CRI reaches Stage IV, the patient should be referred to a nephrologist on a regular basis. Renoprotective strategies are detailed below.

Antihypertensives: blood pressure versus cardiorenal protection

A vigorous blood-pressure control is a mainstay in the treatment of CRI, as arterial hypertension is literally always present once CRI has been diagnosed. To prevent end-organ damages, including a further deterioration of renal function itself, normotension is a primary treatment goal in CRI. Antihypertensive strategies; however, do not equally yield cardiovascular protection, even when lowering blood pressure effectively. To resolve this dilemma, both antihypertensive and additional, pleiotropic drug effects need to be considered.

In diabetic nephropathy, both ACE inhibitors [27] and ARBs [28,29] were shown to reduce microalbuminuria, a predictor of cardiovascular disease and mortality [80], due to pleiotropic effects independent of blood pressure lowering. In addition, losartan [29] and irbesartan [28] slowed down CRI worsening, yet they were not shown to affect overall mortality. Conversely, as the CRI subgroup analysis of the Heart Outcomes Prevention Evaluation (HOPE) revealed, ACE inhibition (ramipril) conveys a 20% risk reduction (RR) of the primary composite outcome, including mortality in the CRI study population [6]. This overall RR is similar to the 22% seen in the non-CRI, cardiovascular high-risk study population and is not completely explained by blood pressure

lowering alone [81]. In a head-to-head trial, the ACE inhibitor, enalapril, and the ARB, telmisartan, were equally effective in attenuating the fall of GFR in CRI over a 5-year period [82]. However, larger end-point studies directly comparing ARBs with ACE inhibitors are lacking in Type II diabetes [30]. More recently, in diabetic nephropathy related to Type-1 diabetics, a small randomized, cross-over trial provided evidence that 300 mg irbesartan per oral, on top of an ACE inhibitor, represents a safe intervention yielding a 25% reduction of albuminuria [83]. In diabetic nephropathy with preserved GFR, small pilot studies testing combination treatments of ARB and ACE inhibitors found a significant reduction in albuminuria irrespective of blood-pressure change [84,44]. However, until more data becomes available for CRI of diabetic cause, a dual RAAS inhibition is discouraged.

In nondiabetic CRI, the combined use of ACE inhibitors and ARB was shown to be superior to either monotherapy [48]. In this case, other blood-pressure effects exerted by angiotensin II appear to be relevant because the combined treatment of ACE inhibitor and ARB did not yield a better blood-pressure control, but slowed down the progression to ESRD [85]. In addition, antialdosterone therapy appears to be a therapeutic option in mild CRI presenting with severe hypokalemia as a consequence of RAAS activation. Secondary causes of hyperaldosteronism, such as prescribed or surreptious use of diuretics, need to be excluded, GFR needs to be higher than 50 ml/min/1.73 m². Likewise for ARB and ACE inhibitors, an antialdosterone therapy beneficially affects microalbuminuria [86]. In hypertensive patients with normal kidney function, the combination of an antialdosterone therapy with a proven dose of an ACE inhibitor was found to be superior to either monotherapy in reversing left-ventricular hypertrophy [87]. The latter may represent a rationale for a wider use of antialdosterone therapy in mild CRI because left-ventricular hypertrophy, a common finding in CRI patients, gives reason to diastolic cardiac dysfunction and relates to an elevated risk for sudden cardiac death [52,33].

Inflammation-affecting therapies

Recent evidence from two large studies points to the fact that CrP released from the liver upon proinflammatory cytokine stimulation, including IL-6, increases the incidence of cardiovascular events [34,60]. Hence, in addition to existing classic cardiovascular risk factors such as dyslipidemia, arterial hypertension and diabetes mellitus that may be present, elevated levels of CrP may indicate and actively participate in atherosclerosis prevalent both in CRI and endstage renal disease. Therefore, CrP measurements should be included in routine cardiovascular risk assessments in CRI, ESRD and renal allograft bearers. Once elevated, a possible source of infection needs to be ruled out. In cases of systemic inflammation with no identifiable source of infection, a symptomatic therapy with statins [88] and/or a combination of ezetimibe–statin may be employed to lower CrP values. Currently, the hydrophilic statin, rosuvastatin, is being tested in a randomized fashion in a large trial with patients having systemic inflammation and low LDL cholesterol to test the anti-inflammatory statin property for patient outcome [61]. Even in hemodialysis patients, statin therapy effectively lowers CrP serum concentrations [89]. In addition, lifestyle modifications including physical exercise [90], aspirin medication [91] and an adequate amount of sleep [92] potenitally made possible via the so-called vagal-inflammatory reflex [93,94], represent interventions to lower CrP. A number of treatment options are still under investigation, such as the use of the TNF-α antagonist, infliximab [95].

Calcium phosphate metabolism-affecting therapies

From a clinical perspective, three modifiable conditions emerge from the pathophysiologic scenario detailed above. First, any elevation of Ca × P (exceeding 4.5 mmol²/l²) needs to be addressed either by the therapeutic use of calcium-free phosphate binders, by discontinuation of vitamin D-containing drugs, or by correction of a prevalent state of hyperparathyroidism, either by surgery or the use of calcium-mimetic drugs. Second, anti-inflammation-guided therapies in a broad sense may affect fetuin-A expression. Third and finally, coumadin use in chronic renal insufficiency may adversely affect fetuin-A expression, thereby fascilitating cardiovascular calcification.

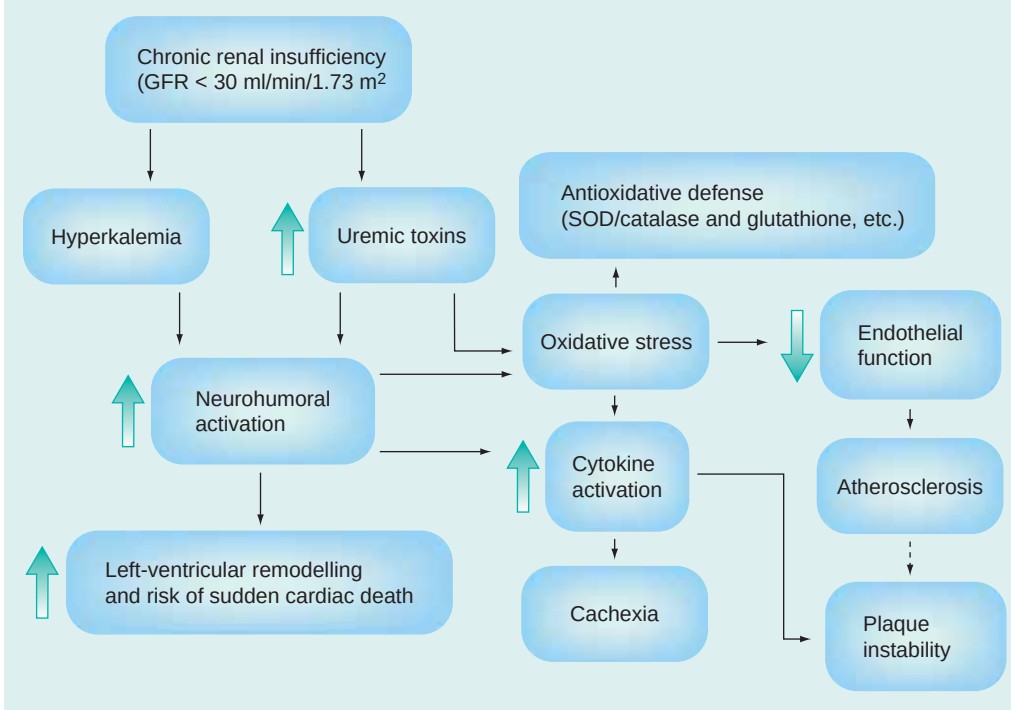
Metabolism

In CRI, especially in ESRD, the nutritional state deteriorates. For aclong time, until now, this observation was reduced to a food-intake problem,

and was known as malnutrition. However, the evidence is lacking that nutritional efforts can successfully correct this obvious catabolic metabolism. In chronic heart failure, unintended weight loss of more than 7.5% of body weight within 6 months is called cardiac cachexia [96,61]. Although different etiologies, muscle wasting, i.e. a loss of lean body weight is a common observation in ESRD, too. However, body weight changes may be obscured by edema. Moreover, in chronic heart failure [97] as well as in end-stage renal failure [98], there is a puzzling observation called `cholesterol paradox´ meaning that a low cholesterol serum concentration relates to a poor prognosis. The explanation might be that, in both syndromes, the catabolic state extents to the liver synthesis of lipoproteins; this kind of catabolism relates to a higher mortality rate both in CRI [98] as well as in chronic heart failure [99]. Hypothetically, as outlined in Figure 2, neurohumoral stimulation and systemic inflammation may propagate this catabolic state of metabolism.

The phenotype of malnutrition often associates with the laboratory finding of inflammation and evidence for atherosclerosis, especially in ESRD. Thus, the term 'Malnutrition–Inflammation–Atherosclerosis (MIA) syndrome' was coined [100]. The causes of MIA remain unclear, however, inflammation appears to play a key role for muscle wasting, and inflammation may contribute to the process of atherosclerosis in renal disease as well. Although no specific treatment other than high-caloric diet is available at the moment, the use of the `subjective global assessment´, a short questionnaire and evaluation form, is recommended to identify patients at risk for a catabolic metabolism as early as possible [101]. Besides muscle wasting, a low serum albumin is often found depending on the prevalent state of inflammation, because albumine is inversely regulated to acute-phase proteins. Once the physical appearance of cachexia has been reached, the estimated GFR based on serum creatinine values may turn out

Figure 2. Uremic toxins and possible uremic hyperkalemia increase neurohumoral stimulation including the RAAS and the SNS resulting in arterial hypertension, left ventricular remodelling and increased arrhythmogenic potential.



On the cellular level, both and uremic toxins increase oxidative stress leading to cytokine activation once antioxidative defenses are saturated. Sequelae of cytokine-induced inflammation are plaque disrupture and cachexia including hypoalbuminemia and muscle wasting.
GFR: Glomerular filtration rate; RAAS: Renin–angiotensin–aldosterone system; SNS: Sympathetic nervous system; SOD: Superoxide dismutase.

falsely high. To assess muscle wasting, upper-leg and upper-arm circumferences may prove useful. Taken together, the term malnutrition standing for a catabolic state or cachexia seen in renal disease appears to be overly simplistic. Uremic toxins may mediate anorexia, while a variety of metabolic processes including protein-synthesis perturbations ultimately favour catabolism [102]

Cardiovascular outcomes: renal disease as a comorbidity

The existing body of evidence indicates that the diagnosis of CRI equal or greater than stage III predicts increased cardiovascular risk for the first [3] or the second MI [103]. Therefore, when CRI is present, therapeutic strategies should extent to an overall reduction of cardiovascular risk factors. In CRI, the degree of both albuminuria and GFR may serve as a guide for the imminent cardiovascular risk due to CRI.

Besides atherosclerosis, CRI adversely affects prognosis especially when it comes as a concomitant disease of other syndromes known to elicit neurohumoral activation such as chronic heart failure [104]. As Table 2 indicates, CRI and chronic heart failure share a surprising large common ground of disease mechanisms. In CRI, neurohumoral pathways including the SNS and RAAS are known causes of arterial hypertension; the same mechanisms specify a state of neurohumoral stimulation prevalent in CHF [75]. So it is conceivable that neurohumoral stimulation adds up in CRI patients suffering from chronic heart failure with compromised systolic function. In addition, there appears to be a wide propensity of CRI patients to diastolic cardiac dysfunction as well. Left-ventricular hypertrophy found in 60% of ESRD patients constrains diastolic cardiac function and, thus, translates into an overall increased risk of cardiac sudden death [52].

The use of the ARB losartan as RAAS modulation resulted in a significant reduction of hospitalizations due to heart-failure worsening, yet did not affect mortality [29]. Likewise, ARB treatment using irbesartan was shown to be associated with a lower incidence of chronic heart failure when used in CRI [28]. However, only RAAS modulation via ACE inhibition conveys a mortality benefit for CRI [6] very much similar to the chronic heart-failure condition [105] where ACE inhibitors are a first-line medication.

In the case of nondiabetic CRI as well as in chronic heart failure, a combination treatment of ARB and ACE inhibitors yields an improved prognosis compared to either monotherapy [48,106]. In severe chronic heart failure; however, a RAAS modulation using an ACE inhibitor is extended by a mineralocorticoid-receptor blockade due to its proven effectiveness of lowering total mortality [107]. Whether or not to implement a triple RAAS blockade consisting of ACE inhibitor, ARB and antialdosterone treatment is currently subject to debate for the chronic heart-failure condition [106]. In CRI, antialdosterone treatment is not yet recommended for GFR of less than 50 ml/min/1.73 m² because of the risk of hyperkalemia.

Table 2. Signs, laboratory findings and mechanisms as prevalent in CRI or chronic heart failure.

	Chronic renal insufficiency	Chronic heart failure
SNS activation	+	+
RAAS activation	+	+
Peripheral edema	+	+
Pulmonary congestion	(+)	+
Interstitial pulmonary edema	+	(+)
Anemia	+	(+)
Inflammation	+	-
Cholesterol paradox	+	+
Hypoalbuminemia	+	(+)

+ Indicates present; (+) Indicates present to a leesre extent; -Indicates not present. Although incomplete, this summary suggests the presence of common neurohumoral pathways both in CRI and chronic heart failure leading to similar metabolic consequences including cachexia as shown by the `cholesterol paradox´, such as prognostic adverse outcome in patients with low LDL-cholesterol concentrations or hypoalbuminemia as an indicator of a catabolic metabolism when urinary losses are excluded.

CRI: Chronic renal insufficiency; LDL: Low-density lipid; RAAS: Renin–angiotensin–aldosterone system; SNS: Sympathetic nervous system.

Expert opinion & outlook

In mild CRI, a more comprehensive RAAS manipulation, including an aldosterone blockade, may attenuate disease progression as well as cardiovascular and renal sequelae of RAAS activation, including aldosterone-induced oxidative stress, fibrosis and apoptosis. In addition, strategies to attenuate inflammation need to be identified in CRI. Whatever the origins of the immunologic cascades, attenuating a state of systemic inflammation may become a realistic therapeutic goal within the near future. In this case, HMG coenzyme-A inhibitors (statins) appear

promising as they mediate pleiotropic, anti-inflammatory actions in addition to the known lipid-modifying effects. More specific, chemokine-receptor antagonism may have the potential to directly address renal cascades of inflammation. Likewise, TNF-a and TGF-b antagonism appear to be promising therapeutic options to attenuate inflammation-related disease progression.

In conclusion, interventions to decelerate the process of atherosclerosis in CRI and ESRD are desperately awaited. However, further research is needed to identify the atherogenesis in CRI, the underlying reasons for premature vascular calcification evident as arterial media sclerosis or intima-based atherosclerosis. For the immediate future, factors responsible for an increased Ca × P, including hyperparathyroidism and pro-calcification pathways on the level of vascular smooth muscle cells and matrix proteins, need to be addressed to lower the atherosclerosis disease burden in CRI.

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Highlights

- Evidence level A: Staging chronic renal insufficiency (CRI) severity according to the estimated glomerular filtraion rate (GFR) derived from the Modification of Diet in Renal Disease (MDRD) equation [108] directly translates into cardiovascular risk.
- Evidence level A: In CRI due to diabetic nephropathy, monotherapy with a proven dose of an angiotensin-converting enzyme (ACE) inhibitor is a lifesaving, and therefore recommended, first-line renin–angiotensin–aldosterone system (RAAS) modulation therapy [6].
- Evidence level A: In CRI of nondiabetic etiology, a combination therapy with a proven dose of an ACE inhibitor and an angiotensin II-receptor-subtype-1 blockade (ARB) should be established for prognostic reasons [48].
- Evidence level B: A Ca × P exceeding 4.5 mmol²/l² requires action, such as the application of phosphate binders, calcium-mimetic drugs, or correction of a prevalent hyperparathyroidism.
- Evidence level B: As a therapeutic goal, the degree of existing proteinuria should be reduced as much as possible [109].
- Evidence level C: In mild CRI (GFR > 50 ml/min/1.73 m²) and arterial hypertension (World Health Organization [WHO]-Stage 2), a combination therapy of a proven dose of ACE inhibitor with a low-dose specific mineralocorticoid receptor is recommended to reverse left-ventricular hypertrophy.
- Evidence level C: A prevalent state of systemic inflammation indicating an elevated cardiovascular risk should be addressed in CRI and end-stage renal disease (ESRD) by appropriate lifestyle modifications as well as the use of statins or low-dose aspirin.
- Evidence level C: Catabolic metabolism predominantly in ESRD is an important predictor of mortality. Underlying conditions such as uremia need to be corrected more effectively, a hypercaloric diet is recommended.

Evidence level A: Unequivocally supported by prospective, randomized studies; Evidence level B: Based on clinical and retrospective studies or on advice of expert panels; Evidence level C: Based on clinical studies.

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