

“Inflammasome” Activity in Dialysis Patients: The Need to Go beyond Membrane Separation Mechanisms

Mario Cozzolino^a Paola Ciceri^a Claudio Ronco^b

^aDivision of Nephrology and Dialysis, ASST Santi Paolo e Carlo, Department of Health Sciences, University of Milan, Milan, Italy; ^bInternational Renal Research Institute of Vicenza (IRRV), Vicenza, Italy

Keywords

Inflammation · Dialysis · Uremic toxins

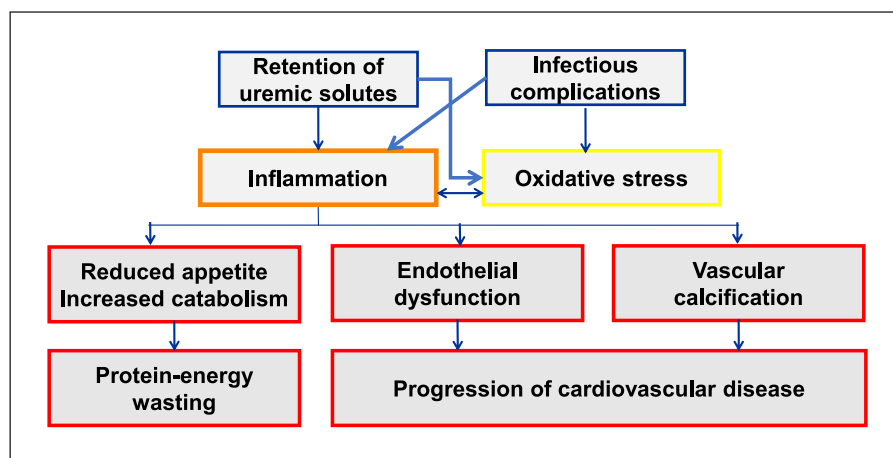
In dialysis population, cardiovascular disease represents the major risk factor for mortality [1]. Since advanced chronic kidney disease frequently results from hypertension and diabetes mellitus, the increased cardiovascular disease risk in these patients has been assumed to be the result of these underlying diseases. Nevertheless, it has been elucidated how renal failure represents per se a cardiovascular risk factor independently of both hypertension and diabetes mellitus [2, 3].

In the last decade, there have been significant improvements in the management of cardiovascular disease in the general population, but it is not known if these interventions result in similar benefits for dialysis patients. In addition, differences in the types, distribution, mortality, and pathophysiology of cardiovascular disease in dialysis patients suggest that generalization of data from patients without kidney disease should be extrapolated with caution. Cardiovascular risk factors among dialysis patients can be divided into those that are nonspecific to kidney disease and those that are specific to renal failure [1].

There is higher prevalence of many traditional factors for cardiovascular risk (age, male gender, hypertension, diabetes, dyslipidemia, and physical inactivity). Furthermore, dialysis patients have disease-related risk factors such as anemia, hyperhomocysteinemia, chronic kidney disease-mineral bone disorder, oxidative stress, malnutrition, and chronic inflammation [4]. There is evidence that uremic factors may be implicated in the pathogenesis of cardiovascular disease in dialysis patients, since cardiovascular survival improves after kidney transplantation even in high-risk patients [5, 6]. Between disease-related cardiovascular risk factors, chronic inflammation represents a major one, which may be detected by high levels of proinflammatory cytokines (Fig. 1).

Recently, research focalizes not only on inflammation but more specifically on inflammasome. The inflammasomes are innate immune system receptors and sensors that induce inflammation in response to infections derived from host proteins. Recent developments have greatly enhanced our understanding of the molecular mechanisms by which different inflammasomes are activated [7]. Additionally, increasing evidence in animal models, supported by data in humans, strongly implicates an involvement of the inflammasome in the initiation

Fig. 1. Inflammation is a significant factor leading to progression of cardiovascular morbidity and mortality in dialysis patients.



and/or progression of diseases with a high impact on public health, such as cardiovascular disease. Interestingly, recent studies pointing toward new therapeutics that target inflammasome activity in inflammatory diseases have been reported. In this direction, one question is: “*How to control inflammasome activity in dialysis patients?*”

One feature of chronic inflammation is high levels of circulating proinflammatory cytokines, which are produced mostly by aberrantly activated monocytes [8]. The molecular mechanism of cytokine dysregulation is still not fully understood, but emerging evidence suggests the involvement of inflammasome activity. Several factors are involved in these mechanisms: (1) exogenous factors (dialysis treatment, central venous catheter, intestinal bacteria); (2) cellular factors (oxidative stress, cell senescence, endothelial reticulum stress); (3) tissue factors (hypoxia, fluid overload, sodium overload); (4) uremic toxins (calcium phosphate, indoxyl sulfate, advanced glycation end products).

Several lines of evidence suggest that classic dialysis techniques are fairly inefficient in removing these molecules, and therefore, new blood purification strategies have been developed to improve removal of such factors [9]. Advances in our understanding of uremic retention solutes as well as improvements in dialysis membranes, sorbents, and techniques (such as expanded hemodialysis or hemoperfusion) could offer the opportunity to ameliorate clinical symptoms and outcomes, facilitate personalized and targeted dialysis treatment, and improve quality of life, morbidity, and mortality, reducing inflammasome activity [10]. Thus, we can implement various strategies to combat chronic inflammation in dialysis patients. First, we should plan interventions aiming at decreasing

the production of inflammatory cytokines, such as lifestyle interventions (balanced diet with low inflammatory potential, physical exercise, smoking cessation, reduction of periodontal disease). Second, we can plan systematic use of drugs with potential anti-inflammatory and antioxidant effects (renin-angiotensin II-aldosterone system inhibitors, statins, sevelamer, cholecalciferol, vitamin E). Third, we can apply strategies to increase removal of inflammatory molecules by advanced dialysis techniques (on-line hemodiafiltration) or modified and functionalized dialysis membranes (expanded hemodialysis). Fourth, we can take advantage of adsorption as a further mechanism of blood purification. Interestingly, new sorbents with high biocompatibility have been developed to allow direct contact of blood patients with the adsorption bed. Adsorption allows efficient removal of medium and high molecular weight molecules, including protein-bound uremic toxins, such as indoxyl sulfate and p-cresyl sulfate, relieving symptoms in dialysis patients [11, 12].

Finally, new targeted anti-inflammatory drugs are under research investigation: N-acetylcysteine, pentoxifylline, bardoxolone, and anticytokine drugs (tocilizumab, canakinumab, anakinra, etanercept). Anticytokine therapies have revolutionized the treatment of chronic inflammatory diseases, particularly autoimmune diseases during the last decades. Tumor necrosis factor (TNF)- α antagonists are available with indications in the fields of cardiology, rheumatology, dermatology, and gastroenterology. Other therapeutic approaches have been introduced in the last 10 years, e.g., the blockade of interleukins (IL-1, IL-6, and IL-12/23). The advantages of cytokine blockers are their rapid onset of action with high response rates and a tolerable safety profile [13, 14].

From the abovementioned spectrum of possibilities, we may hypothesize and we sincerely hope that, in the future, pharmacological and removal (extracorporeal) therapies might be combined. The final scope will be to achieve a lower level of inflammation in dialysis patients and, therefore, a better quality of life and survival in the long term. The development of further anticytokine drugs controlling inflammasome activity in dialysis patients is, therefore, required.

Conflict of Interest Statement

M. Cozzolino reports receiving research funding from Abbvie, Baxter, Keryx, and Shire; reports receiving honoraria from Abbvie, Amgen, Baxter, Shire, and Vifor-Fresenius; reports serving as a scientific advisor or member of and reports being part of speakers

bureau for Abbvie, Amgen, Keryx, Shire, and Vifor. P. Ciceri has no conflicts of interest. C. Ronco, in the last 3 years, has been consultant, medical advisor, or part of the speaker bureau receiving fees from the following companies: Asahi Medical, Aferetica, Baxter, B.Braun, Biomerieux, Bioparto, Cytosorbents, ESTOR, Fresenius Medical Care, GE Healthcare, Jafron, Kaneka, Medica, Medtronic- Bellco, Nipro, Spectral, and Toray.

Funding Sources

No funding to declare.

Author Contributions

Mario Cozzolino, Paola Ciceri, and Claudio Ronco wrote this editorial.

References

- 1 Cozzolino M, Mangano M, Stucchi A, Ciceri P, Conte F, Galassi A. Cardiovascular disease in dialysis patients. *Nephrol Dial Transplant*. 2018 Oct 1;33(Suppl_3):iii28–34.
- 2 Fox CS, Matsushita K, Woodward M, Bilo HJG, Chalmers J, Heerspink HJL, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet*. 2012;380(9854):1662–73.
- 3 Mahmoodi BK, Matsushita K, Woodward M, Blankestijn PJ, Cirillo M, Ohkubo T, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: a meta-analysis. *Lancet*. 2012;380(9854):1649–61.
- 4 Cozzolino M, Galassi A, Pivari F, Ciceri P, Conte F. The cardiovascular burden in end-stage renal disease. *Contrib Nephrol*. 2017; 191:44–57.
- 5 Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJL, Mann JF, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet*. 2013;382(9889):339–52.
- 6 Herzog CA, Asinger RW, Berger AK, Charytan DM, Diez J, Hart RG, et al. Cardiovascular disease in chronic kidney disease. A clinical update from kidney disease: improving global outcomes (KDIGO). *Kidney Int*. 2011;80(6): 572–86.
- 7 Aranda-Rivera AK, Srivastava A, Cruz-Gregorio A, Pedraza-Chaverri J, Mulay SR, Scholze A. Involvement of inflammasome components in kidney disease. *Antioxidants*. 2022 Jan 27;11(2):246.
- 8 Wang Y, Gao L. Inflammation and cardiovascular disease associated with hemodialysis for end-stage renal disease. *Front Pharmacol*. 2022 Feb 10;13:800950.
- 9 Cozzolino M, Ronco C. Medium cutt-off membranes: incremental or quantum leap innovation in haemodialysis? *Blood Purif*. 2021; 50(4–5):449–52.
- 10 Rosner MH, Reis T, Husain-Syed F, Vanholder R, Hutchison C, Stenvinkel P, et al. Classification of uremic toxins and their role in kidney failure. *Clin J Am Soc Nephrol*. 2021 Jul 7;16(12):1918–28.
- 11 Clark WR, Gao D, Lorenzin A, Ronco C. Membranes and sorbents. *Contrib Nephrol*. 2018;194:70–9.
- 12 Ronco C, Bellomo R. Hemoperfusion: technical aspects and state of the art. *Crit Care*. 2022 May 12;26:135.
- 13 Ridker PM, MacFadyen JG, Glynn RJ, Koenig W, Libby P, Everett BM, et al. Inhibition of interleukin-1 β by canakinumab and cardiovascular outcomes in patients with chronic kidney disease. *J Am Coll Cardiol*. 2018; 71(21):2405–14.
- 14 Cherney DZI, Lytvyn Y, McCullough PA. Cardiovascular risk reduction in patients with chronic kidney disease: potential for targeting inflammation with canakinumab. *J Am Coll Cardiol*. 2018;71(21):2415–8.