

The Complement System in Hemodialysis Patients: Getting to the Heart of the Matter

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Cardiovascular disease is by far the leading cause of death in patients with end-stage renal disease (ESRD), comprising more than half of all known causes of death [1]. Arteriosclerosis, characterized by medial calcification and sclerosis, and atherosclerosis, characterized by lipid plaque formation, are 2 distinct processes that play a major role in the etiology of cardiovascular disease in ESRD. It is incompletely understood which factors drive the accelerated arteriosclerosis and atherosclerosis observed in advanced chronic kidney disease.

Arteriosclerosis is characterized by progressive calcification of the arterial tunica media. Vascular calcification is already abundantly present in adolescent patients with ESRD [2], and it is therefore not surprising that cardiovascular disease is the main cause of death even in children and young adults with ESRD [3]. The development and progression of vascular calcifications, and subsequent dismal clinical outcomes [4], is accompanied by profound deregulations in calcium/phosphate metabolism in many ESRD patients. Consequently, the involvement of serum phosphate and its regulating hormone fibroblast growth factor 23 (FGF23) as potential risk factors for adverse cardiovascular outcomes in ESRD has been extensively studied over the past decade [5, 6]. These studies have consistently demonstrated associations be-

tween high levels of serum phosphate and FGF23 and cardiovascular morbidity and mortality. Yet, so far, no intervention has been shown to simultaneously restore calcium/phosphate metabolism and improve cardiovascular prognosis. Furthermore, although it is plausible to assume that deregulated calcium/phosphate metabolism contributes to media calcification, its potential role in atherosclerotic plaque formation is less clearly defined. In atherosclerosis additional processes, including the activation of pro-inflammatory pathways, may instead play a more prominent role.

The complement system is an important component of innate immunity that primarily functions as a host defense against pathogenic infections. Uncontrolled activation of the complement system can result in renal and systemic diseases including atypical hemolytic uremic syndrome (aHUS) [7] and membranoproliferative glomerulonephritis [8]. Furthermore, deregulations in the complement system have also been linked with endothelial dysfunction, atherosclerosis, and impaired coagulation [9]. Of interest, several studies in non-renal patients have shown associations between complement components and cardiovascular disease. Particularly a higher circulating level of C3, which plays a central role in the activation of the complement pathway (fig. 1), has been

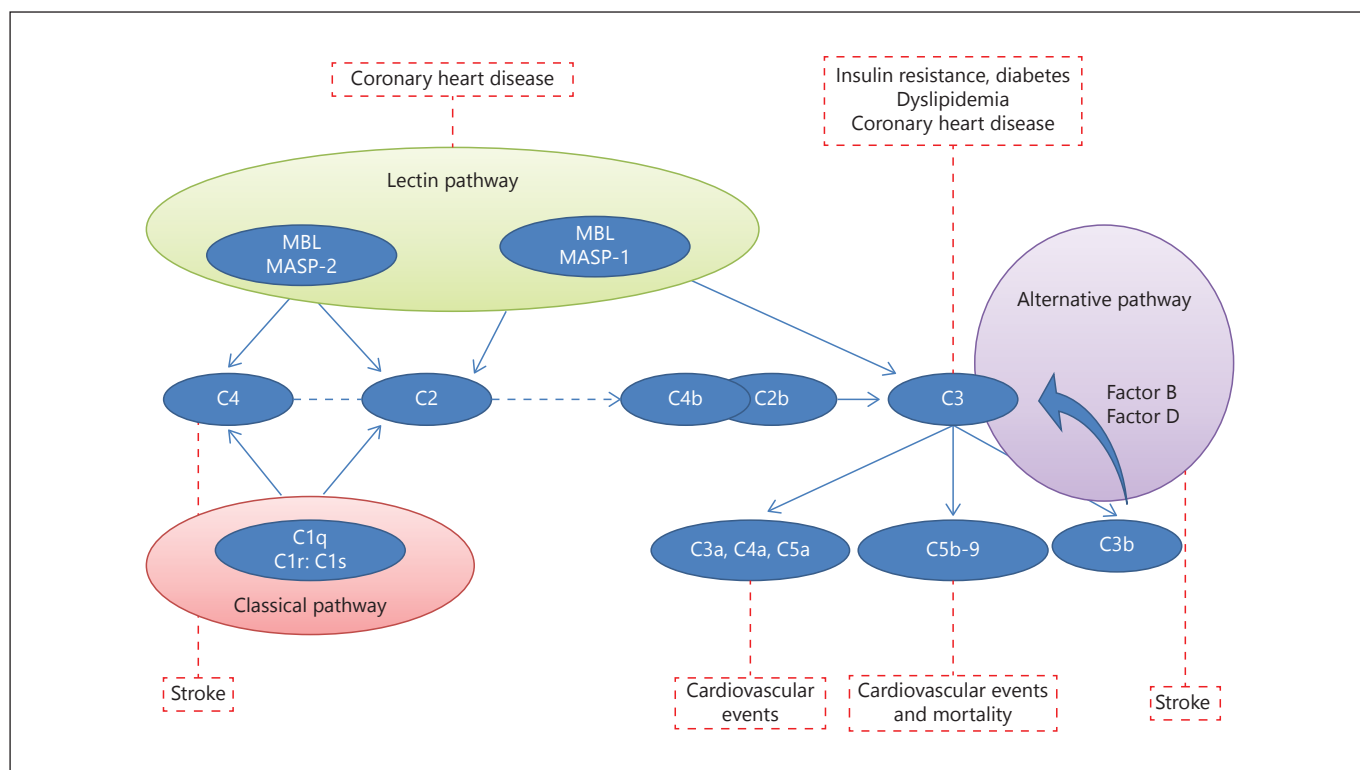


Fig. 1. The complement system and cardiovascular risk. Overview of the main components of the complement system, and its associations with cardiovascular disease and its risk factors. The complement system consists of the classical pathway, the lectin pathway, and the alternative pathway, all of which converge on the C3-mediated generation of C5b-9, the MAC, C3a-5a, and C3b.

Associations with cardiovascular disease and/or risk factors are indicated in dotted lines, and smaller font sizes reflect weak evidence (limited studies and/or sample size). MASP = Mannose-binding-lectin-associated serine proteases; MBL = mannose-binding lectin.

linked with insulin resistance and incident diabetes [10, 11], disturbed lipid metabolism [12], and incident and prevalent coronary heart disease [13, 14]. Besides C3, higher circulating levels of mannose-binding lectin have also been associated with incident coronary artery disease [15], whereas factor D (also known as adipsin) and C4 have been linked with the development of stroke [16, 17]. More downstream, the role of C5b-9, comprising the membrane attack complex (MAC), has been implicated in atherosclerotic plaque formation in preclinical studies [18], and its soluble form has been associated with all-cause mortality and major cardiovascular events in patients with myocardial infarction [19]. Similarly, the downstream component C5a has been associated with cardiovascular disease in patients with advanced atherosclerosis [20]. Although these data come from a limited number of studies performed in generally small cohorts, and reported data have not always been consistent [9], these findings do warrant further investigation of the role

of the complement system in patients with advanced chronic kidney disease.

In this issue of *Nephron*, Lines et al. [21] link activation of the complement system with an increased risk of cardiovascular events in hemodialysis patients. The authors performed a post-hoc analysis of a clinical trial in which 260 hemodialysis patients were randomized to dialysis with a vitamin E-coated dialysis membrane or a non-vitamin E-coated equivalent. The type of dialysis membrane did not modify mortality at one year after initiation of the trial, nor did this affect circulating levels of the complement components C3, factor D, factor H, or soluble C5b-9. However, when assessing complement components measured at baseline, the authors found that a higher baseline C3 level was associated with a higher risk of subsequent cardiovascular events. Given the relatively small sample size and limited number of patients developing a cardiovascular event ($n = 33$), the authors could not adjust for potential confounders. Thus, this pioneer-

ing study should be followed up by larger and more extensively adjusted analyses in order to substantiate this observation. Interestingly, when additionally studying the relationship between C5b-9 and cardiovascular events, the authors found that both a high and a low level of C5b-9 was associated with a higher cardiovascular risk in hemodialysis patients. Further studies are needed to understand the implications of this observation, which can at least partly be reconciled with previous data [19].

Which mechanisms could connect complement activation and the increased risk of cardiovascular disease in hemodialysis patients? First, complement activation may induce a pro-inflammatory state in the vascular wall, promoting atherosclerotic plaque formation and destabilization. Second, cardiovascular fat serves as a source of C3, and hence C3 could be merely a marker of prevalent atherosclerosis [22]. This further supports the need for analyses adjusted for markers and/or risk factors of prevalent atherosclerosis such as obesity, diabetes and hypertension. A third possibility, also raised by Lines et al. [21], is that complement activation could well be induced by dialysis treatment in itself, for instance, due to the use of bioincompatible materials including the dialysis membrane [23]. It is well established that hemodialysis in itself inflicts cardiovascular stress, which could be mediated by hemodynamic effects [24], but also by a pro-inflammatory profile of patients prone to experience hemodialysis-induced cardiac stress [25]. This pro-inflammatory state may, in turn, be related to dialysis (membrane)-induced complement activation in this category of patients. Unfortunately, the vitamin E-coated membranes used in the active treatment arm of the trial reported by Lines et al. [21] affected neither complement activation (although the effect on more specific markers such as C3d could not be assessed in this study) nor clinical outcomes [21]. On the other hand, the authors also observed declining C3 levels over time in both study arms (p-trend <0.0001), which would render a main role for hemodialysis treatment as a cause of complement activation less likely.

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Should the complement system be considered a novel therapeutic target to improve cardiovascular outcomes in hemodialysis patients? The therapeutic potential of interventions targeting the complement system to modify cardiovascular risk in diabetic patients was recently highlighted by the identification of a novel peptide that abolished C3-induced prolongation of fibrin clot lysis, by interfering with the interaction between C3 and fibrinogen [26]. This peptide could provide a novel therapy targeting thrombosis in patients with diabetes. The complement C5 inhibitor eculizumab has shown beneficial effects not only in patients with aHUS, but also in some (but not all) patients with dense-deposit disease [27]. Importantly, a recent study also showed reduction of inflammation, endothelial damage and thrombosis by eculizumab in patients with aHUS [28], but whether such effects could also be observed in ESRD patients without hemolytic uremic syndrome is unclear. Given the high costs of eculizumab, its potential application to reduce the excessive cardiovascular risk in the hemodialysis population seems currently one bridge too far. Meanwhile, it may be worthwhile to further document the relationship between complement components and cardiovascular outcomes in well-adjusted analyses in larger cohorts, and to study the cardiovascular protective effects of interventions targeting complement activation, including eculizumab, in selected patient groups.

Disclosure Statement

The author has no conflicts of interest to declare.

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