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As clinicians, we often feel disarmed in front of the relentless decline of renal function in patients with diabetes despite optimal medical treatment. In the last decade, inflammation and ways to target it have become probably the most promising therapeutic approach to tackle diabetic nephropathy (DN).

Research studies in experimental animal model of diabetes have implicated the innate immunity as an important pathogenic mechanism driving the development and progression of DN [1]. The innate immunity is a non-specific defence mechanism characterized by up-regulation of monocyte chemoattractant protein-1 (MCP-1) paralleled by an increase in macrophage infiltration in the glomeruli and tubular interstitium.

MCP-1 is an inflammatory cytokine that binds to its receptor CCR2, expressed mainly on monocytes and macrophages. The chronic activation of the MCP-1/CCR2 system, driven by the metabolic and haemodynamic perturbations seen in diabetes, is an important player in the pathogenesis of diabetic chronic microvascular complications and, specifically in the kidney, drives renal inflammation (macrophage tissue infiltration), fibrosis and ultimately loss of renal function.

In this issue of NDT, Fufaa et al. describe, for the first time, in patients with type-1 diabetes without any clinical evidence of DN, an association between urinary MCP-1 concentrations and early renal lesions.

This work is a post hoc analysis of the renin–angiotensin system study (RASS) [2] where two renal biopsies were performed 5 years apart in patients with type-1 diabetes. The authors found a significant association between urinary MCP-1 at baseline and changes in renal structural parameters (specifically increased interstitial volume) at 5 years, an observation present only in women. No association was observed between urinary MCP-1 and early glomerular lesions.

The authors highlight the potential differences between sex and disease progression, and because of the study design (post hoc analysis), the absent potential association between urinary MCP-1 and the observed initial/mild glomerular lesions could relate to an insufficient statistical power of the study.

These data reinforce, in humans, the role of innate immunity in the very early stages of DN. Along with the observations of Fufaa et al., others have described, in patients with type-2 diabetes with chronic kidney disease, a significant association between elevated urinary MCP-1 levels and advanced tubulointerstitial lesions and macrophage infiltration, an occurrence mainly observed in patients with macroproteinuria (>3.5 g/day) [3].
Studies in humans have linked renal MCP-1 and kidney interstitial inflammation with albuminuria [4], and renin angiotensin aldosterone system (RAAS) inhibition is paralleled by suppression of renal MCP-1 and positive renal outcome [5].

Studies have investigated the −2518 A/G single-nucleotide polymorphism in the distal regulatory region of the MCP-1 gene believed to regulate MCP-1 expression. The presence of the −2518-A/A allele has been associated with DN in patients with type-1 diabetes [6], although data remain conflicting [1].

Targeting MCP-1, or its receptor CCR2, has been shown to reduce albuminuria and glomerular lesions in experimental animal models of DN [7, 8]. This concept has recently been translated in humans and, phase II, randomized, controlled, clinical trials are currently investigating the safety, tolerability and renoprotective effects of inhibition of the MPC-1/CCR2 receptor system.

Different CCR2 antagonists have been developed and are currently being tested in clinical trials: CCX140-B (Clinical Trials.gov Identifier—CTG: NCT01447147), PF-04634817 (CTG: NCT01752985). Direct inhibitors of MCP-1 have also been developed, one of these NOX-E36 (CTG: NCT01547897), a novel mirror-image RNA oligonucleotide scaffold that, by binding to target molecules, results in their inhibition [9].

Specifically both the CCR2 antagonist CCX140-B (Chemo-centrx, press release, MOUNTAIN VIEW, Calif., 12 December 2014, http://ir.chemocentryx.com/releasesdetail.cfm?ReleaseID=887402) and NOX-E36 (ASN Renal Week 2014, FR-OR120, https://www.asn-online.org/abstracts/) have shown a positive preliminary anti-albuminuric renoprotective effect on top of RAAS inhibition, and future studies will investigate further the safety and efficacy of these compounds as renoprotective agents in patients with DN.

Inhibition of innate immunity by targeting the MCP-1/CCR2 system seems a promising therapeutic target and in the next few years we will hopefully be in a position to gain some benefit for patients with diabetes and DN.

The research on innate immunity has been expanding and has been focusing on the different ‘macrophage phenotypes’ that can be observed at the tissue level. Macrophages can retain an M1 or M2 phenotypic polarization that represents two very distinct opposing activities of macrophages [10]; it is important to remember that many intermediate phenotypes are likely to exist, and more understanding is needed in this respect [11].

The M1 macrophage phenotype has been attributed mainly with cytotoxic functions while the M2 phenotype role resides mainly in fibrosis and tissue-remodelling/repair functions [12].

Classical M1 activation is stimulated by Toll-like receptor ligands and interferon-γ, while the alternative M2 activation is stimulated by interleukin-4 and 13; these states, respectively, mirror the Th1 (activation of macrophages and cell-mediated immunity and phagocyte-dependent responses) and Th2 (strong antibody production, inhibition of macrophage functions, phagocyte-independent responses) polarization that is observed in T-cells [13].

Chronic diseases, of which diabetic chronic vascular complications are an example, do not display classical ‘foreign’ antigens for adaptive immune responses (humoral immunity, and cell-mediated immunity). Chronic diseases are, instead, associated with M1- or M2-type responses (innate immunity) that, because of the chronic insult (germ-free), become a disease mechanism and/or its cause.

Studies in an experimental animal model of diabetes have suggested that an early polarization towards M1 (classically activated) instead of M2 (mediating renal tissue fibrosis/repair) phenotype could be implicated in the pathophysiology of the early phase of diabetic kidney disease [14, 15]. At later stage of disease, a shift towards a chronic activation of M2 phenotypes is believed to drive those cellular mechanisms driving glomerulosclerosis, tubular interstitial fibrosis and secondary organ failure [16].

Novel strategies have considered favouring a shift from M2 to M1 in the macrophage phenotype, as shown for RAAS inhibitors, that appears to be an attracting therapeutic target in the advanced stages of DN [16].

Some indications suggest that MCP-1 favours a shift towards an M2 macrophage phenotype [13, 17]; certainly more understanding of macrophage phenotype polarization is required in different disease settings, and future work might open new potential therapeutic avenues to pursue.

In conclusion, the residual risk or renal disease progression in patients with DN is still extremely high despite current optimal treatment; innate immunity, MCP-1 and macrophage tissue infiltration seem very promising targets for future treatment of DN on top of standard of care with RAAS inhibition. More clinical studies are required before these novel therapeutic approaches are fully validated in humans, but we remain positive in the continuous effort to beat kidney disease in diabetes.

CONFLICT OF INTEREST STATEMENT

None declared.


REFERENCES


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