Urinary Chemoattractant Protein 1: A New Biomarker of Renal Fibrosis

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Accumulation of fibrous tissue in the renal interstitium, often accompanied by atrophy of tubules, is a morphological phenomenon strongly associated with the development of reduced renal function in health as well as disease [1]. Progressive renal fibrosis can occur in many glomerular diseases but whether it is due to a self-sustaining process or depends on continuing glomerular (or tubule) injury is a matter of ongoing debate [2]. In addition, the precise nature of the relationship between progressive renal fibrosis and deterioration of renal function (e.g., glomerular filtration rate) remains obscure. Nevertheless, a non-invasive means of detecting and quantifying renal interstitial fibrosis (and tubular atrophy) would be quite attractive as it would open up new possibilities for study of the interactions of such fibrosis with renal functional disturbances in ways not dependent on serial renal biopsies – an impractical tool for longitudinal investigations.

Several such biomarkers, alone or in combination, using serum, urine or imaging have been investigated, such as collagen and its fragments [3], microRNA [4], transforming growth factor β [5], connective tissue factor [6], special modifications of renal ultrasound [7, 8], renin angiotensin system [9], metalloproteinases [10] and monocyte chemoattractant protein 1 (MCP-1) [11] to name a few. Studies of MCP-1 have been of special interest as this

chemokine seems to lie in the casual pathogenic pathway for the production of renal fibrosis. Tissue macrophages, monocytes and dendritic cells secrete MCP-1 and the production level is enhanced in various forms of inflammation [11, 12]. Type IV collagen (COLIV) is also of interest as it is a component of basement membranes (glomeruli and tubules) and may play a role in regulation of fibrosis [13].

In this issue of the *American Journal of Nephrology*, Wang et al. [14] present an intriguing and novel study of the utility of urinary MCP-1 (uMCP) and COLIV excretion and in predicting renal fibrosis, not in disease, but in healthy, normal living donors. Pre-implantation renal biopsies provided an opportunity to examine whether one or both of these urinary biomarkers could predict the presence and extent of naturally occurring renal fibrosis. After adjustment for the effects of age and gender, renal function and albumin excretion, higher uMCP but not urinary COLIV (uCOLIV) levels were associated with greater renal fibrosis (and tubular atrophy). MCP-1 or COLIV levels in spot urine collections were expressed in absolute terms or relative to urine creatinine in pg/mg of creatinine or $\mu\text{g}/\text{mg}$ of creatinine, respectively. Values of uMCP or uCOLIV were determined at one time period only, during the pre-transplant evaluation, and renal fi-

brosis and tubular atrophy was determined using a semi-quantitative score by pathologic analysis of the pre-implantation biopsy performed at the time of transplantation (at some variable time after the collection of the urine specimen). It is not clear if the pathologist was 'blinded' to the results of the urinary studies. A total of 634, mainly Caucasian, donors were studied between 2005 and 2011. Donors were approximately aged 23–67 years of age (mean $\pm$ 2 SD). The baseline measured GFR (mGFR) was 102 ± 18 ml/min/1.73 m² and albumin excretion was normal in all subject. About 15% had hypertension and 10–15% were obese or overweight. As previously reported [15], nephrosclerosis (focal and global glomerulosclerosis, interstitial fibrosis, tubular atrophy and arteriolonephrosclerosis) increased with age and about 4% of the biopsies revealed fibrosis in >5% of the interstitial area. The median levels of uMCP were 1.49 pg/mg creatinine with no fibrosis rising to 4.33 pg/mg creatinine with 10% fibrosis and this was correlated with an increase in albuminuria (but still within the normal range) but not with a change in mGFR. No association between uCOLIV and renal fibrosis were noted.

This study provides strong support for uMCP as a biomarker for renal fibrosis, with the additional value that MCP-1 lies with the pathogenic pathway for such fibrosis. Thus, the biomarker is not only 'diagnostic' but also might serve as a potential target for intervention. Several points concerning this novel investigation are worthy of comment: (1) the source of the uMCP is unknown. No serum levels of MCP-1 were measured. The correlation of uMCP with albuminuria could be due to enhanced glomerular permeability, increased filtered load, enhanced local production or impaired renal tubular reabsorption of normally filtered MCP-1 (MCP-1 is a monomeric protein of 13 kDa); (2) percutaneous renal

biopsies do not generally assess the degree of fibrosis in medulla compared to cortical zones, so the conclusions are limited to the phenomenon of renal cortical fibrosis; (3) an increase in adipose tissue can elevate serum MCP-1 levels and uMCP excretion [16]. The degree to which such adiposity contributed to the observed correlations is uncertain and further studies to explore the relationship of adiposity and naturally occurring renal fibrosis are warranted; (4) dietary sodium intake can influence inflammation and alter MCP-1 production and excretion [17]. No urinary sodium measurement was conducted, but the correlations of uMCP with renal fibrosis persisted after adjustment for albuminuria, suggesting that systemic 'micro-inflammation' was not a likely factor. The correlation of urinary albumin excretion and uMCP has been well documented previously, as noted by the authors.

While this well-done and novel study shows that increasing uMCP, but not uCOLIV, associates with renal fibrosis (and tubular atrophy) even after adjustment for age, gender, renal function and albuminuria in normal healthy living donors, any causal inferences must be tempered by the cross-sectional nature of the study design. Longitudinal studies will be required to see whether enhanced uMCP will reliably predict the later development of progressive renal fibrosis in disease states. Nevertheless, this study supports the notion that uMCP is a very promising biomarker for the non-invasive assessment of the degree of renal interstitial fibrosis, even in subjects with normal renal function.

Disclosure Statement

None.

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