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Higher Serum Levels of Stromelisyn 2 (MMP10) but not Matrilysin (MMP7) in Patients with End-Stage Chronic Kidney Disease on Chroniodialysis

Tsvetelina Velikova[1], Toni Velikov[2] & Georgi Mihailov[3]

[1]Clinical Immunology, University hospital Lozenetz, Kozyak 1 str., 1407 Sofia, Bulgaria

[2]Department of Emergency edicine, University Hospital – Tsaritsa Joanna, Byalo more 8 str, 1527 Sofia, Bulgaria

[3]Clinic of Chemodialysis, University Hospital – Tsaritsa Joanna – ISUL, Byalo more 8 str, 1527 Sofia, Bulgaria

Correspondence: Corresponding author: Tsvetelina V. Velikova, MD, PhD Clinical Immunology, University Hospital Lozenetz, Kozyak 1 str., 1407 Sofia, Bulgaria, Mobile: 00359883306049, E-mail: tsvelikova@medfac.mu-sofia.bg

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Abstract

Matrix metalloproteinases (MMPs) are endopeptidases with proteolytic activity against components of extracellular matrix, such as collagen and elastin, which are involved in many biological and pathophysiological processes in humans. There is some evidence for MMPs` role in nephrogenesis, renal damage, and remodeling, such as MMP-7 (matrilysin) and MMP-10 (stromelysin). However, the implication of MMPs in the pathogenetic renal changes in patients with chronic kidney disease (CKD) is poorly understood. Therefore, we aimed to measure the serum levels of circulating MMP-7 and MMP-10 in patients at different stages of chronic kidney disease and to analyze the impact of MMP-7 and MMP-10 on the renal disease burden of these patients. In our study, we have evaluated 80 persons – 20 with CKD (II – IV stage), 20 with end-stage CKD on chronic hemodialysis, and 40 age and sex-matched control subjects: 20 with isolated arterial hypertension and 20 healthy persons. The serum samples were tested for MMP-7 and MMP-10 by performing enzyme immunoassay method. Serum levels of both investigated MMPs were most increased in end-stage CKD patients on hemodialysis. The concentration of MMP10 was significantly higher in CKD patients on chroniodialysis than healthy persons ($p < 0.001$), and patients with isolated arterial hypertension ($p < 0.001$) and patients at different stages of CKD ($p = 0.037$). To conclude, it is possible that the increased levels of MMP-10 could be associated with poor prognosis and eventually need for dialysis treatment at earlier stages. We hypothesize that CKD is associated with alterations of MMPs and that may be related to the severity of atherosclerosis in this clinical setting.

Keywords: Chronic Kidney Disease, Matrix Metalloproteinases, MMP-7, Matrilysin, MMP-10, Stromelysin 2, Chroniodialysis, End-Stage Kidney Disease.

1. Introduction

Matrix metalloproteinases (MMPs) are a group of zinc-containing and zinc-dependent endopeptidases which possess the capacity to cleave components of extracellular matrix, mostly type IV collagen and elastin.[1,2] There have been identified 28 different MMPs in humans.[3,4] MMPs are secreted in a non-active form which requires activation to develop proteolytic activity. Several MMPs are involved in a range of physiological processes, such as embryogenesis, normal tissue remodeling, wound healing and angiogenesis.[5] In healthy tissue, the activity of MMPs is ordinarily low, but the increased expression and activity are observed mainly due to loss of the control mechanisms. Specific MMPs are described to play a role in some pathological processes such as inflammation, tissue ulceration, cancer, bone turnover, nephritis, and fibrosis.[6,7] Cleaving mostly the type IV collagen - the main component of vessels and basement membrane, MMPs were thought to be involved in the induction, progression, and repair of renal disease.[2] The expression of MMPs in the kidney is complex, species dependent but their localization has not been thoroughly characterized.[4] Some studies revealed recently that MMP-7 (matrilysin) is expressed in human renal tubular disease and mouse models of acute renal tubular injury and fibrosis[8] whereas MMP-10 (stromelysin 2) is associated with atherosclerotic changes, particularly in patients with chronic kidney disease (CKD).[9] However, the roles of MMPs in the pathogenetic changes in the kidney at CKD are poorly understood, partly because there are a limited number of investigations regarding the MMPs in the kidney and their role in nephrogenesis, renal damage and renal remodeling[1]. Therefore, we aimed to measure the serum levels of circulating MMP-7 and MMP-10 in a cohort of Bulgarian patients at different stages of CKD and analyzed the impact of MMPs in the renal disease burden of these patients.

2. Material and methods

2.1Subjects

We enrolled 80 persons in our study – 20 with CKD (II – IV stage) and 20 with end-stage CKD on chronic hemodialysis at mean age 57 ± 16 years (34.7% females), and 40 control subjects - 20 with isolated arterial hypertension and 20 healthy persons, all age, and sex-matched. The patients in each group were included after previously considerate inclusion criteria. All patients were informed about the purpose of the experiment and had signed written confirmed consent approved by the Ethic Committee of the Medical University of Sofia and the Ethic Committee of University Hospital "Tsaritsa Joanna – ISUL," Sofia.

2.2 Chroniodialysis regimen

The chronic dialysis for patients with end-stage CKD was performed three times a week. The serum samples were obtained after the dialysis cycle and stored at -80°C prior ELISA testing.

Enzyme immunoassays

The serum levels of MMP-7 and MMP-10 were measured by ELISA (MMP7 Human ELISA kit, MMP10 Human ELISA kit, Abcam, UK). We strictly followed the manufacturer's instructions.

Statistical methods

The row data were statistically evaluated by parametric and non-parametric tests using Software package for statistical analysis (SPSS®), IBM 2009, version 19 (2010) and Excel (2010). Differences were considered significant when the p-value was less than 0.05.

3. Results

The mean serum levels of MMP-7 and -10 in all investigated groups are displayed in Table 1.

Table 1. Mean serum levels of matrix metalloproteinases-7 and 10 in the different study groups

	MMP-7, ng/ml	**MMP-10, ng/ml**
Healthy persons	44.01	617.83
Patients with arterial hypertension	73.08	832.37
Patients with CKD	41.04	871.72
Patients with end-stage CKD on chroniodialysis	69.44	2452.35

We found approximately 1.5-fold higher mean serum level of MMP-7 among patients with isolated arterial hypertension and CKD patients on dialysis than those on stages I–III CKD and then healthy persons (Figure 1).

CKD patients on chroniodialysis exhibited significantly much higher concentration of MMP-10 than healthy persons ($p < 0.001$), than patients with isolated arterial hypertension ($p < 0.001$) and patients at different stages of CKD ($p = 0.037$) (Figure 2).

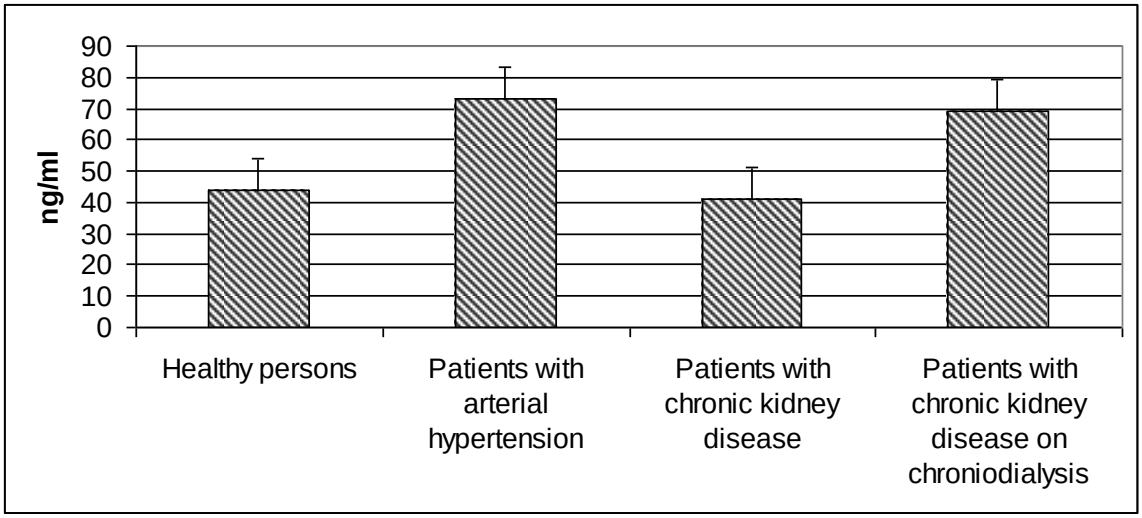

Figure 1. Differences in serum levels of matrix metalloproteinases 7 in the study groups

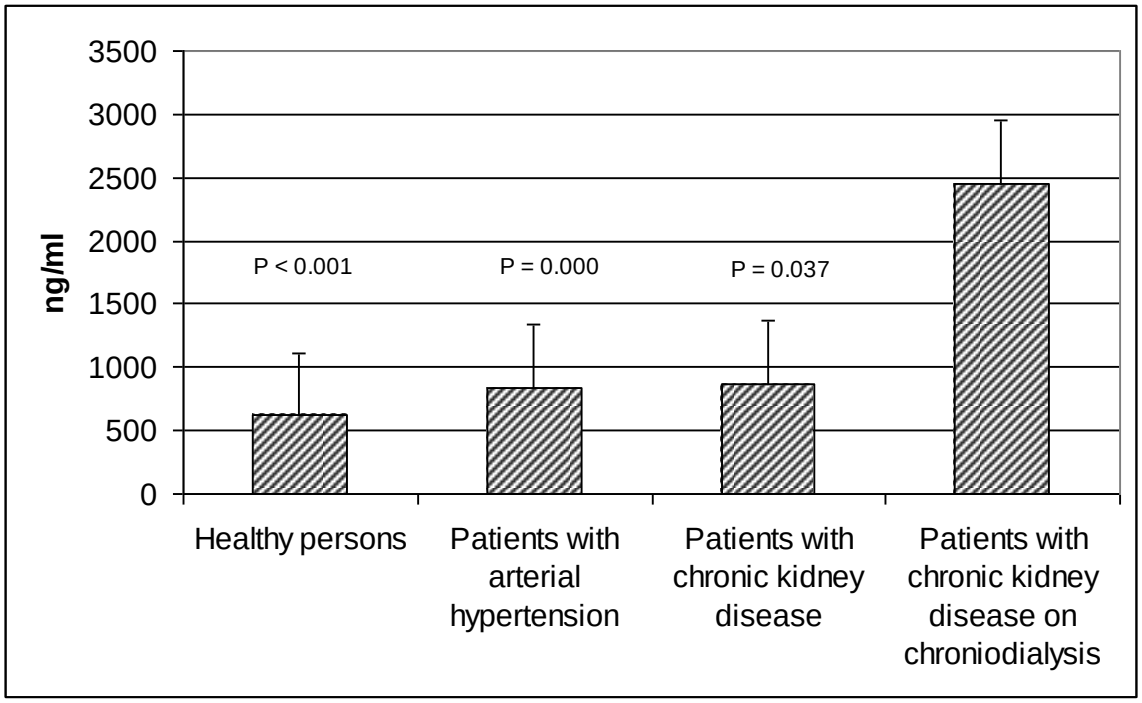

Figure 2. Differences in serum levels of matrix metalloproteinases 10 in the study groups

Detected serum levels of MMP-10 were higher compared to the levels of MMP-7 (Table 1). The correlation between two parameters did not reach significance (p = 0.081).

4. Discussion

Among different MMPs, we have paid particular attention to two of them - MMP-7 and MMP-10 which are thought to be involved in CKD pathogenesis.

MMP-7 levels were increased in the group of dialysis patients when compared with the other CKD group and healthy persons (Figure 1). Some studies on animal models of experimental renal tubular injury showed that MMP-7 was expressed in response to injury in the distal nephron. Moreover, Surendran et al. found a correlation between MMP-7 expression in human kidney diseases and chronic renal tubular damage due to fibrosis where mRNA level of matrilysin was increased as renal fibrosis progressed.[8] On that basis, we can speculate that the increased level of MMP-7 may point out the development of fibrosis and could be a potential biomarker for fibrotic complications in CKD. These hypotheses are based on the presumption that serum levels of MMP-7 represent its protein expression

in the injured kidneys. However, it is well known that in some circumstances the systemic protein levels do not mirror the local production of specific proteins.

The lack of MMP-7 expression in healthy kidneys in humans and mice[8] is in consistent with our findings for a lower level of MMP-7 in the control group of healthy persons. Similarly, MMP-7 concentrations were higher in patients from the control group with isolated arterial hypertension than in the healthy persons. However, these observations also did not reach statistical significance.

The concentration of MMP-10 was significantly higher in the dialysis CKD patients group than in the other three groups (Figure 2). A cross-sectional study of Belal et al.[9] with 40 patients of CKD showed that serum level of MMP-10 measured by ELISA was at mean concentration of 601 ± 132.12 pg/dl in the control group whereas the mean level in patients on dialysis group was 2306.45 ± 335.247 pg/dl, results which are similar to our findings. They observed the mean level of MMP-10 in patients at earlier stages of CKD 1857.45 ± 387.1 pg/dl which is about 2-times higher than our group of CKD patients at II-IV stages.[9] The difference between all three groups has been statistically significant ($p<0.001$) whereas in our study the highest level of MMP-10 was measured in CKD on chroniodialysis, and the levels in control groups and a group of early stages of CKD patients were similar. Belal et al.[9] also found that atherosclerosis defined by the carotid intima-media thickness was severe in a group on dialysis as well as a significant positive correlation between MMP-10 and carotid intima-media thickness in all groups. Coll et al. also showed that among the patients with CKD at different stages atherosclerosis comorbidity correlated with MMP-10 levels.[10] It is well accepted that the underlying cardiovascular disease in patients with even early-staged CKD is one of the causes for increased mortality in these patients than in the general population.[11] MMP-10 has alternative properties – on the one hand, it can contribute to the pathogenesis of atherosclerosis by promoting migration and proliferation of vascular smooth muscle cells into the vessel wall's intima which leads to plaque formation.[12] On the other hand, however, MMP-10 contributes also to plaque volume diminishing through degradation of extracellular matrix in the intima.[13] This explains the reduced fibrous content in atherosclerotic plaques.[10] Some studies have shown that chronic conditions such as CKD often underlie very severe arterial disease which represents a high risk in patients with CKD with primary importance both for public health and for clinical reasons.[14] Moreover, atherosclerosis is 10-20 times more often in patients with CKD, especially in end-stage renal disease.[14] This is in consistent with our findings for the highest level of MMP-10 in CKD patients on chroniodialysis. Coll et al. also showed that serum levels of MMP-10 were associated with the severity of atherosclerosis in patients with CKD.[10] It is suggested that at early stages MMPs are involved in breakdown of the glomerular basal membrane, whereas at later stages, they contribute to extracellular matrix removing which is associated with scarring and fibrosis.[3] This model could explain the relationship between MMPs and proteinuria in many pathological conditions in spite that the role of MMPs in atherosclerosis and proteinuria in kidney disease progression is not yet completely elucidated.[3] Other studies have also shown that expression and secretion of MMP-10 by human endothelial cells could be induced by different inflammatory and prothrombotic stimuli.[14-16] Zoccali et al. have considered MMPs as markers for angiogenesis before the onset of proteinuria and markers for progression of CKD at late stages[14].

5. Conclusion

What causes these results we can only speculate, but it is possible that the increased levels of MMP-10 could be associated with poor prognosis and eventually need for dialysis treatment at earlier stages. We hypothesize that CKD is associated with alterations of MMPs and that may be related to the severity of atherosclerosis in this clinical setting. Furthermore, the role of MMPs in renal diseases, proteinuria and atherosclerosis may lead to the development of new therapeutic approaches for future perspectives.

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Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest

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