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RESEARCH ARTICLE

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Monocyte chemoattractant protein-1 predicts the development of diabetic nephropathy

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Abstract

Aim: Diabetic nephropathy (DN) is a devastating complication of diabetes mellitus (DM). Therefore, screening strategies in order to prevent its development and/or retard its progression are of paramount importance. We investigated if monocyte chemoattractant protein-1 (MCP-1) was associated with new onset micro-albuminuria-the earliest sign of the albuminuric phenotype of DN- in patients with type 2 DM and normoalbuminuria.

Methods: We measured MCP-1 in serum and urine samples from patients of the Randomized Olmesartan And Diabetes Microalbuminuria Prevention (ROADMAP) study and its Observational Follow-up (OFU) cohort. A case control design was used with inclusion of 172 patients who developed microalbuminuria (MA) and of 188 well matched controls who remained normoalbuminuric.

Results: The median duration of follow-up for the ROADMAP cohorts was 6.5 years, whereas the mean time until occurrence of MA was 53.2 months. In the multivariate analysis, serum and urine MCP-1 remained significant predictors of new onset MA. The risk for MA increased continuously with increasing serum and urine MCP-1 levels but reached statistical significance only in the highest quartiles. The risk associations were stronger with serum MCP-1.

Conclusions: MCP-1 is a marker and possibly a mediator of early diabetic nephropathy. Further prospective studies are necessary to test whether diabetic patients with elevated MCP-1 levels would benefit from specific therapeutic interventions.

KEYWORDS

chronic kidney disease, diabetes mellitus, diabetic nephropathy, MCP-1, microalbuminuria, ROADMAP

Hermann Haller is on behalf of the ROADMAP steering committee.

1 | INTRODUCTION

Diabetic nephropathy (DN) is one of the cardinal organ manifestations of diabetes mellitus, increasing substantially the risk for cardiovascular complications, chronic kidney disease (CKD) and mortality. Therefore, screening strategies in order to prevent its development and/or retard its progression are of paramount importance for both, the individual patient and the health care system.[1] Considering the inflammatory pathogenesis of DN, there is a great scientific interest to find respective representative biomarkers in serum and urine.[2,3] Furthermore, many attempts have been made to modulate these markers therapeutically, albeit the results have been inconsistent as yet.[2,4]

We read with interest the article 'Evaluation of Urinary Biomarkers of Proximal Tubular Injury, Inflammation, and Fibrosis in Patients With Albuminuric and Nonalbuminuric Diabetic Kidney Disease' by Phanish et al., published on 2 February 2021.[5] The authors demonstrated that MCP-1 levels are significantly associated with CKD progression in diabetic kidney disease regardless of the presence of microalbuminuria.

Monocyte chemoattractant protein-1 (MCP-1/CCL2) is a ligand of C-C motif chemokine receptor 2 (CCR-2) and one of the most known and best studied chemokines so far.[6] Cell culture experiments and genetic studies augmented our understanding on the molecular mechanisms of its action.[7,8] In the clinical setting, MCP-1 has been consistently found to contribute to the pathogenesis of nearly all stages and all phenotypes of chronic and diabetic kidney disease.[9–12] Recent studies investigating novel molecules with inhibitory properties on the MCP-1/MCP-1 (CCL2/CCR2) signalling axis have offered new insights and renewed the interest on this chemokine.[13–15]

Therefore, we sought to test if serum and urinary MCP-1 levels are associated with new-onset microalbuminuria—the earliest sign of the albuminuric phenotype of DN—in a cohort of 360 normoalbuminuric patients with type 2 diabetes mellitus from the **ROADMAP** (Randomized Olmesartan And Diabetes Microalbuminuria Prevention) study and its Observational Follow Up (**ROADMAP-OFU**) cohort, being at risk for development of DN.

2 | RESULTS

There were no statistically significant differences in baseline demographics and clinical characteristics between cases (n = 172) and matched controls (n = 188), except for cardiovascular disease, which was more common in patients with future microalbuminuria (Table 1). The median duration of follow-up for the ROADMAP cohorts was 6.5 years, whereas the mean time until occurrence of MA was 53 months.

Patients with new-onset microalbuminuria had significantly higher baseline levels of serum and urine MCP-1 (Table 1). In the multivariate analysis (adjusted for age, sex, body mass index, smoking status, mean arterial pressure, estimated glomerular filtration rate [eGFR], glycated haemoglobin, low density lipoprotein, urine albumin-creatinine-ratio, cardiovascular diseases, duration of diabetes and duration of follow-up until new-onset MA) serum and urine MCP-1 remained both significant predictors of new-onset microalbuminuria (Table 2). If patients were stratified according to the quartile of their MCP-1 levels at baseline, the associations remained robust. The risk for microalbuminuria increased continuously with increasing MCP-1 levels, but reached statistical significance only in the highest quartiles (Table 2, Figure 1A,B, Figure S1A and Figure S1B). Patients with higher MCP-1 levels had a two- to threefold higher risk for albuminuric DN development. This was the case for MCP-1 levels in serum and urine specimens as well. The risk associations were generally stronger with serum MCP-1 (Table 2).

3 | DISCUSSION

Currently, blood urea nitrogen, serum creatinine, formulas to eGFR, proteinuria and albuminuria are measures used to assess the presence and progress ofDN.[16] However, these measures are imprecise, do not correspond to renal tissue injury and are relatively insensitive to detect minor alterations in renal function. Therefore, a need of more appropriate biomarkers is present, especially at early stages of diabetic kidney disease.

Here, we examined serum samples and clinical follow-up data of normoalbuminuric type 2 diabetic patients participating in ROADMAP, an international randomized placebo-controlled trial focussing exclusively on the prevention of MA.[17] Particularly, in that study the anti-inflammatory effects of the angiotensin II type 1 receptor blocker Olmesartan were assessed. Peculiar emphasis was given to the identification and appropriate management of blood pressure and other modifiable cardiometabolic risk factors for DN, such as obesity, dyslipidaemia, HbA_{1c} and blood glucose. Despite the multifactorial intervention, the clinical manifestation of DN was not prevented however delayed, since MA developed in a significant proportion of study participants.[2]

Although urine albumin-to-creatinine ratio is the most significant predictor and a major contributing risk factor for DN, it does not capture all cases.[18] Therefore, it may be possible that other more specific markers, reflecting underlying—foremost inflammatory—diseases, are better surrogates to determine the risk of developing DN and to assess the efficacy of interventions aiming to prevent its onset or retard its progression.

We addressed the inflammation hypothesis in the pathogenesis of DN by investigating if the mediator of inflammation MCP-1 is dysregulated before its overt clinical manifestation.[3]

We found that MCP-1 levels in serum and urine were altered several months before the clinical onset of DN. In this regard, MCP-1 seems to be a strong and independent determinant, since the risk associations increased incrementally with its baseline concentrations and were concordant in serum and urine.

MCP-1 is a potent chemokine, playing a key role in monocyte recruitment of the tubulointerstitium in DN.[6] Its neutralization by means of the L-RNA aptamer Emapticap restored glomerular

TABLE 1 Baseline characteristics and follow-up data of patients with and without future microalbuminuria

Variables	Total (n = 360)	Microalbuminuria (n = 172)	Normoalbuminuria (n = 188)	p
Demographic characteristics				
Age				
Median—years (min–max)	58 (33-75)	58 (39-75)	57 (33-75)	0.343
<55 years—no. (%)	118 (32.8)	57 (33.1)	61 (32.5)	
≥55 years—no. (%)	242 (67.2)	115 (66.9)	127 (67.5)	
Male sex—no. (%)	176 (48.9)	86 (50.0)	90 (47.9)	0.687
Tobacco smoking—no. (%)				
Non-smoker	226 (62.8)	108 (62.8)	118 (62.8)	0.913
Current-smoker	59 (16.4)	29 (16.9)	30 (16.0)	
Former-smoker	75 (20.8)	35 (20.3)	40 (21.3)	
Physical examination				
Body-mass index—kg/m^2	31.3 ± 4.7	31.2 ± 4.9	31.3 ± 4.5	0.585
Blood pressure—mmHg				
Systolic	137.0 ± 15.4	137.7 ± 15.9	136.5 ± 15.0	0.665
Diastolic	80.7 ± 8.7	80.4 ± 8.9	80.9 ± 8.6	0.412
Mean arterial pressure	99.4 ± 10.0	99.4 ± 10.4	99.4 ± 9.7	0.769
Laboratory values				
Estimated GFR—ml/min/1.73 m^2	86.4 ± 16.3	85.9 ± 15.6	86.9 ± 16.9	0.656
HbA_{1c}—%	7.8 ± 1.5	7.9 ± 1.6	7.8 ± 1.5	0.811
LDL cholesterol—mmol/l	3.1 ± 1.0	3.0 ± 1.0	3.1 ± 1.0	0.621
UACR—mg/g	8.2 ± 7.5	9.0 ± 7.9	7.5 ± 7.1	0.075
Medical history				
Cardiovascular diseases—no. (%)	44 (12.2)	28 (16.3)	16 (8.5)	**0.025**
Duration of diabetes—months	76.5 ± 71.9	80.8 ± 72.6	72.6 ± 71.2	0.143
Biomarkers				
MCP-1 serum—pg/ml	392.5 ± 130.2	407.9 ± 120.3	378.3 ± 132.9	**0.004**
MCP-1 urine—pg/ml	440.4 ± 1020.7	528.7 ± 1404.8	360.1 ± 432.9	**0.048**
Ratio MCP-1/Creatinine urine—pg/mg creatinine	171.3 ± 146.3	183.4 ± 159.4	160.3 ± 132.7	**0.034**
Mean time until first detection of microalbuminuria—months	-	53.2 ± 15.2	-	-

Note: Data are presented as mean ± standard deviation or median (min-max) for continuous variables and n (%) for categoric values. Cardiovascular disease was defined as history of coronary heart disease, myocardial infarction, stroke or transient ischaemic attack, or peripheral vascular disease. Significant values are shown in 'bold'.

Abbreviations: eGFR, glomerular filtration rate (calculated with the use of the abbreviated Modification of Diet in Renal Disease formula); g, gram; HbA_{1c}, glycated haemoglobin; kg/m^2, body weight divided by the square of the body height; l, litre; LDL, low density lipoprotein; MCP-1, monocyte chemoattractant protein-1; mg, milligram; ml, millilitre; mmHg, millimetre of mercury; mmol, millimole; pg, picogram; UACR, urine albumin-to-creatinine ratio.

endothelial glycocalyx functions and reduced tissue inflammation in diabetic mice.[14] In an exploratory phase IIa clinical trial performed with a cohort of diabetic patients with albuminuria and preserved renal function, Emapticap lowered the urine albumin-to-creatinine ratio significantly in the intervention arm compared to baseline. However, the difference in comparison to the placebo group did not reach significance. The drug specific adverse events were negligible and the albuminuria lowering effects persisted long after its discontinuation.[13] Another study using a selective inhibitor of the CCR2, CCX140-B, showed better efficacy in a in a diabetic population with similar characteristics, although the albuminuria response was here inversely correlated with the on-treatment MCP-1 levels.[15] Baricitinib, a JAK 1/2 inhibitor, reduced the urine albumin-to-creatinine ratio and MCP-1 levels in patients with advanced DN.[19] All three

TABLE 2 Associations of kidney tubule injury marker MCP-1, categorized by quartiles, with new onset of microalbuminuria in ROADMAP and ROADMAP-OFU (defined by a UACR of more than 35 mg/g in women or more than 25 mg/g in men)

Biomarkers			Events (*n*)	Incidence rate (cases per 1000 person-years)	OR (95% CI)	Adjusted OR (95% CI)
Serum MCP-1	Linear model	Per twofold higher biomarker concentration	165	93.7	1.002 (1.000 to 1.003)[a]	1.003 (1.001 to 1.005)[a]
	Quartiles	1	32	74.5	1.000 (reference)	1.000 (reference)
		2	40	90.2	1.463 (0.798 to 2.682)	1.981 (0.973 to 3.08)
		3	45	100.1	1.842 (1.005 to 3.374)[a]	3.166 (1.539 to 6.512)[a]
		4	48	108.0	2.115 (1.153 to 3.881)[a]	3.239 (1.570 to 6.683)[a]
Urine MCP-1/ Creatinine	Linear model	Per twofold higher biomarker concentration	142	93.4	1.001 (0.999 to 1.003)	1.002 (1.000 to 1.004)[a]
	Quartiles	1	29	75.8	1.001 (reference)	1.000 (reference)
		2	31	81.5	1.093 (0.568 to 2.105)	0.954 (0.441 to 2.062)
		3	39	98.2	1.681 (0.877 to 3.221)	1.798 (0.817 to 3.956)
		4	43	119.2	2.152 (1.116 to 4.150)[a]	2.574 (1.186 to 5.587)[a]

Note: **Adjusted for:** age, sex, body mass index, smoking status, mean arterial pressure, eGFR, glycated haemoglobin (HbA_{1c}), low density lipoprotein, urine albumin-to-creatinine ratio, cardiovascular diseases, duration of diabetes, duration of follow-up (until MA or last visit).

Abbreviations: eGFR, estimated glomerular filtration rate; MCP-1, monocyte chemoattractant protein-1.

[a]Represents significant results with $p < 0.05$.

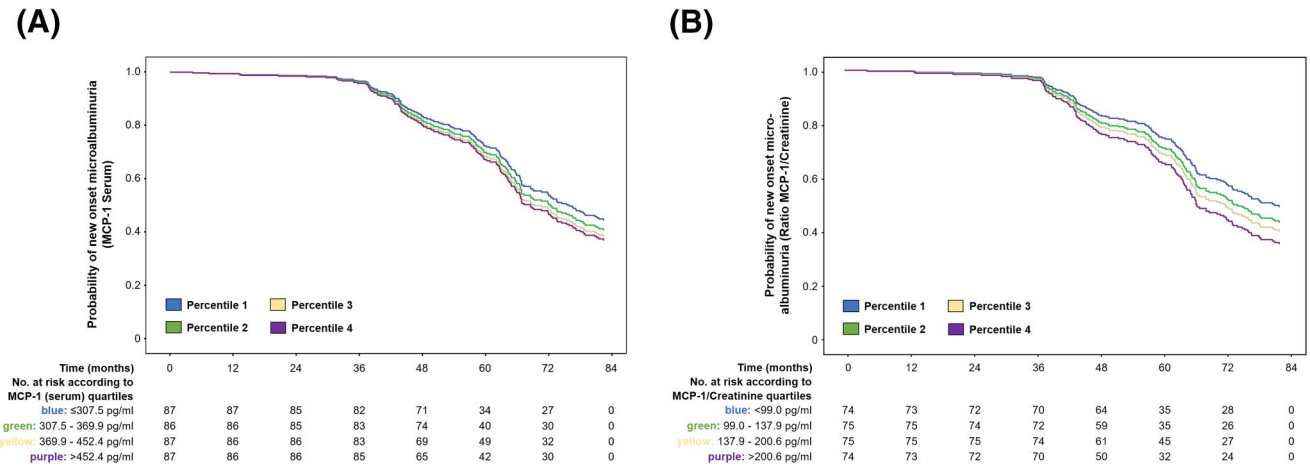

FIGURE 1 (A) Cox regression plot for new-onset microalbuminuria according to the quartiles of serum monocyte chemoattractant protein-1 (MCP-1) at baseline adjusted for age, sex, body mass index, smoking status, mean arterial pressure, estimated glomerular filtration rate (eGFR), glycated haemoglobin (HbA_{1c}), low density lipoprotein, urine albumin-to-creatinine ratio, cardiovascular disease, duration of diabetes, duration of follow-up (until development of MA or last visit). (B) Cox regression plot for new-onset microalbuminuria according to the quartiles of urine MCP-1/Creatinine at baseline adjusted for age, sex, body mass index, smoking status, mean arterial pressure, eGFR, glycated haemoglobin (HbA_{1c}), low density lipoprotein, urine albumin-to-creatinine ratio, cardiovascular disease, duration of diabetes, duration of follow-up (until development of MA or last visit)

clinical trials were designed to test for intervention within the MCP-1 pathway in addition to best standard of care, for example, maximal renin angiotensin blockade.

We suppose that inflammatory conditions related to diabetes mellitus and its associated risk factors increase circulating MCP-1 levels, which thereafter triggers bone marrow progenitor cells to differentiate into monocytes. In a further step, activated monocytes may transmigrate from the circulation into kidney tissue. This initially generated monocyte 'niche' has the propensity to release MCP-1 locally. A chemokine gradient is thereby formed with subsequent recruitment of more monocytes into the kidney and perpetuation of the inflammatory response until the development of the overt clinical phenotype of DN with subsequent release of paracrine acting MCP-1.[6]

Our findings are in line with results from the Action to Control Cardiovascular Disease (ACCORD) Trial, where the effect of intensive risk factor control on nephropathy was investigated. Here, the urinary MCP-1 to creatinine ratio strongly associated with subsequent eGFR decline in patients with microalbuminuria and preserved renal function at baseline. Similar to our study, there was a graded risk association between quartile of baseline urinary MCP-1 levels and outcome.[11] Our findings complement those of the ACCORD Trial, and of a similar analysis in cohorts of patients from the Joslin Diabetes Center and underline the importance of MCP-1 as a major pathogenic risk contributor of DN across its entire continuum, from subclinical to early overt clinical injury and subsequent disease progression.[12] The main findings of the above mentioned interventional and landmark clinical studies and of our subanalysis are summarized in Table S1.

In the multivariate analysis, models combining clinical and usual laboratory parameters with serum or urine MCP-1 demonstrated ROC AUCs of 0.768 (95%CI: 0.719–0.816) and 0.782 (95%CI: 0.731–0.833), respectively. Furthermore, the correlation analysis demonstrated a weak correlation between the urine albumin-to-creatinine ratio and serum and urine MCP-1 levels at baseline ($r = 0.041$, $p = 0.450$; $r = 0.004$, $p = 0.945$, respectively), suggesting divergence of albuminuric and inflammatory pathways in diabetic kidney disease. Even more, these results suggest a role for more than one inflammatory cytokine in progression of diabetic CKD and are consistent with studies demonstrating the role of inflammation in diabetic kidney disease.[2,20]

Strengths of our analysis are the focus on the albuminuric phenotype of DN, the use of a considerable number of cases and matched controls to test the hypothesis, the quantification of both, serum and urine MCP-1 levels and the long follow-up time of over 6 years. Our study has some limitations. We collected only one baseline random urine sample, and it is likely that repeated measurements and calculations of trends in biomarker levels would improve our ability to predict progression. Another limitation is the lack of kidney biopsy specimens to substantiate the kidney tissue damage and correlate these with laboratory findings.

4 | CONCLUSION

Inflammation has evolved as a key factor in the development and progression of diabetic kidney disease. The development of therapeutic interventions therefore focus on the modulation of inflammatory processes.

In this study of non-albuminuric diabetic patients with single measurements of urinary biomarkers at baseline, the clinical utility of serum and urinary MCP-1 levels as predictors of the albuminuric phenotype of DN was evaluated. We found that serum and urinary MCP1 levels are elevated in early DN, and these are likely to be markers and mediators of renal disease in diabetes at early stages, suggesting a role in onset and progression of diabetic kidney disease.

Further prospective studies are necessary to test whether diabetic patients with elevated MCP-1 levels will benefit from specific therapeutic interventions.

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CONFLICT OF INTEREST

The authors declare that they have no competing interest.

ETHICAL APPROVAL

The ROADMAP trial was a phase 3b study at 262 collaborating centres in 19 European countries. The ethics committee at each participating centre approved the study, and written informed consent was obtained from each patient. The trial was conducted in accordance with local laws and the internationally established principles for Good Clinical Practice which have their origin in the Declaration of Helsinki. One hundred and forty centres from 18 countries out of the original 262 ROADMAP centres from 19 countries participated actively in the ROADMAP-OFU trial. The ROADMAP-OFU study was reported and approved by the applicable ethics committees or competent authorities for each participating site according to the national requirements and the internationally established principles for Good Clinical Practice which have their origin in the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

Florian G. Scurt performed statistical analysis, reviewed and edited the manuscript. Jan Menne and Christos Chatzikyrkou conceived and designed the study. Christos Chatzikyrkou wrote the manuscript. Hermann Haller was the principal investigator of ROADMAP. Sabine Brandt, Anja Bernhardt and Peter R. Mertens reviewed and edited the manuscript.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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SUPPORTING INFORMATION

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