VERSITA
DOI: 10.2478/rrlm-2013-0045

Research article

The predictive value of serum intercellular adhesion molecule 1 for the progression of diabetic kidney disease in type 2 diabetic patients

Valoarea predictivă a moleculei de adeziune intercelulară ICAM 1 pentru progresia bolii renale la pacienții cu diabet zaharat tip 2

Alina Ramona Potra[1], Ina Maria Kacso[1*], Ioana Cosmina Bondor[2], Mirela Gherman-Căprioară[1]

1. University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj Napoca, Department of Nephrology
2. University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj Napoca, Department of Informatics and Biostatistics

Abstract

In type 2 diabetes, the progressive nature of diabetic kidney disease (DKD) induces high risk of morbidity and mortality. The aim of our study was to assess the predictive value of serum intercellular adhesion molecule 1 (ICAM 1) for the increasing of albuminuria in early stages of type 2 DKD. Consecutive type 2 diabetic patients with a one year followed up were included in this study. Outcome measurement for assessing the progression of diabetic kidney disease was the change in urinary albumin to creatinine ratio (ΔuACR). 93 type 2 diabetic patients were enrolled in the study, of which 58 were normoalbuminuric and 35 patients were albuminuric. Their mean urinary albumin excretion was in microalbuminuric stage and had a close to normal estimated glomerular filtration rate. ΔuACR disclosed a positive correlation to baseline serum ICAM 1 (p=0.003, r= 0.31) and serum creatinine (p=0.026, r=0.23). In multiple regression, ICAM-1 (p=0.002) was the main determinant of ΔuACR. The correlation was even stronger in albuminuric patients (p=0.0003, r=0.57). In our type 2 diabetic patients, the main predictor of increase in uACR over one year of follow-up is baseline ICAM -1 level, with a particular role in albuminuric patients. It seems that ICAM-1 might be useful non-invasive biomarker in predicting the progression of DKD.

Keyword: *Intercellular adhesion molecule 1, diabetic kidney disease, progression*

Rezumat

Obiectiv. La pacienții cu diabet zaharat de tip 2, natura progresivă a afectării renale reprezintă un risc crescut de mobiditate şi mortalitate. Scopul studiului nostru a fost acela de a evalua valoarea predictivă a moleculului de adeziune intercelulară (ICAM 1) pentru creşterea albuminuriei în stadiile timpurii ale afectării

[*]**Corresponding author:** Kacso Ina Maria, Spitalul Clinic de Urgenta Cluj, Clinica de Nefrologie Mihai Manasia, 400006 Cluj Napoca Romania. Phone: 0040 741277206, 0040 264 592202, 0040 264 592771/ 336, Fax: +40 264 592202, e-mail: inakacso@yahoo.com

renale la pacienții cu diabet zaharat de tip 2. Metodă. S-au inclus în studiu pacienți consecutivi cu diabet zaharat de tip 2, urmăriți prospectiv timp de 1 an. Progresia bolii renale a fost evaluată prin modificarea în timp a raportului albumină urinară pe creatinină urinară (ΔuACR). Rezultate. 93 de pacienți cu diabet zaharat tip 2 au fost incluşi în studiu, dintre aceştia 58 fiind normoalbuminurici, iar 35 albuminurici. Media excreției urinare de albumină a fost în stadiu microalbuminuric şi au avut a valoare a filtrării glomerulare aproape normală. ΔuACR a prezentat o corelație pozitivă cu nivelul seric inițial al ICAM 1 (p=0.003, r= 0.31) şi cu creatinina serică. În regresie multiplă, ICAM 1 a rămas singurul determinant al ΔuACR (p= 0.002). La pacienții albuminurici, ΔuACR a prezentat o corelație şi mai puternică cu nivelul seric inițial al ICAM 1 (p=0.0003, r=0.57). Concluzii. La pacienții noştri cu diabet zaharat tip 2, principalul predictor al creşterii albuminuriei pe parcusul unui an de urmărire a fost nivelul seric inițial al ICAM 1, în special la pacienții albuminurici. ICAM 1 ar putea fi un biomarker non-invaziv cu utilitate clinică în prezicerea progresiei albuminuriei la pacienții cu diabet zaharat tip 2.

Cuvinte cheie: *molecula de adeziune intercelulară ICAM 1, boala renală diabetică, progresie*

Received: 23rd April 2013; Accepted: 6th September 2013; Published: 9th December 2013.

Introduction

Diabetic kidney disease (DKD) is a serious complication of type 2 diabetes, being one of the major causes of end stage renal disease in most developed country. It is associated with increased morbidity, mortality and significant economic burden. Due to the high prevalence of type 2 diabetes worldwide, identification of new biomarkers in order to detect DKD in early stages (potentially reversible stages) has become a subject of high interest. Nowadays, researcher's attention turned to understanding the role of inflammation in the pathogenesis of diabetic nephropathy (1 - 3). Experimental studies have shown that leukocyte infiltration is present in all stages of diabetic nephropathy (4). It seems that ICAM-1 is essential for promoting macrophage infiltration into renal tissue, triggering inflammation (5). Consistent experimental and clinical studies suggested that ICAM 1 plays an important role in the pathogenesis of type 2 DKD.

We conducted a prospective study in order evaluate the role of serum ICAM 1 as a non-invasive biomarker for the progression of type 2 DKD. In this perspective, such biomarker may be an important tool in identifying patients with high-risk, allowing the initiation of early specific strategies to prevent long term renal complications.

Subjects and methods

In the study included type 2 diabetes referred to the Clinic of Nephrology *Mihai Manasia* Cluj for evaluation and who agreed to complete a prospective follow-up of 12 months. The diagnosis of type 2 diabetes was made in accordance to World Health Organization criteria. Patients with albumin to creatinine ratio more than 1 g/24hours were excluded. We also excluded from the study patients with inflammatory systemic disease or nondiabetic kidney disease.

A specific questionnaire was filled out, being recorded the duration since the diagnosis of diabetes was made, type of medication they used, presence or absence of diabetic retinopathy and any other associated acute/chronic disease. Blood pressure, weight, height, and waist circumference were measured. Routine laboratory analysis, glycated hemoglobin and C reactive protein (CRP) were assessed. Microalbuminuria and creatininuria were determined from urinary morning spot. Circulating levels of serum ICAM-1 were assessed by using ELISA (R&D Systems) method. Presence and stage of DKD was defined as mean of three urinary albumin-to-creatinine ratio (uACR) by using first morning urine specimen. We considered that patients were normoalbuminuric if uACR was less that 30 mg/g and albuminuric if uACR was equal or more that 30mg/g. Estimated glomerular filtra-

Table 1. General characteristics of the patients at baseline and after 1 year follow up

Characteristics (n=93)	Baseline values	After 1 year follow up	p
eGFR (ml/min)	77.16 (53.25- 100.20)	80.37(53.86-102.18)	**0.007**
SBP (mmHg)	140.00 (130.00-150.00)	130.00 (120.00-140.00)	**0.001**
DBP(mmHg)	80.00 (75.00-90.00)	80.00 (77.50-80.00)	**0.005**
BMI kg/m^2	31.35 ± 5.86	31.44 ± 6.15	0.50
Waist circumference (cm)	108.76 ± 12.66	109.16 ± 13.61	**0.001**
Total cholesterol (mg/dl)	186.19 ± 37.30	187.17 ± 44.08	0.80
HDL cholesterol (mg/dl)	45.03 ± 11.89	44.69 ± 11.24	0.59
Triglycerides (mg/dl)	153 (116.75-200)	142 (111.25-194.25)	0.51
LDL cholesterol (mg/dl)	105.67 ± 35.94	106.23 ± 41.39	0.87
Urinary ACR (mg/g)	17.67 (4.94 – 54.79)	27.77 (6.70- 95.91)	**0.00002**
Serum ICAM-1 (ng/ml)	218.00 (173.00- 270.00)	202.00 (163.00-263.00)	0.29
CRP (mg/dl)	0.30 (0.10-0.80)	0.31 (0.10-0.77)	1.00

Values are presented as mean ± SD for normally distributed variables and median (25^{th} -75^{th} percentiles) for the abnormally distributes ones. SD – standard deviation, eGFR– estimated glomerular filtration rate according to abbreviated Modification of Diet in Renal Disease formula, SBP- systolic blood pressure, DBP – diastolic blood pressure, BMI – body mass index, HDL- high density lipoprotein, LDL- low density lipoprotein, ACR- urinary albumin to creatinin ratio, ICAM-1 - intercellular adhesion molecule 1, CRP – C reactive protein

tion rate (eGFR) was determined using abbreviated Modification of Diet in Renal Disease (MDRD) formula (6). In order to evaluate the progression of DKD we assessed the increase in urinary albumin excretion over the one year followed up period (ΔuACR), by the difference between uACR at the end of the study and baseline value.

The present study was approved by the ethical committee of our university and all the patients have signed an informed consent to participate at the study.

Statistical analysis

Statistical analysis was performed SPSS 13.0 software system, StatView 7.0 and Microsoft Excel program. Data are expressed as mean ±standard deviation for normally distributed continuous variables or as median (25^{th}-75^{th} percentiles) for non-normally distributed variables.

Significant difference of two means for normally distributed continuous variables (according to Kolmogorov-Smirnov test) was assessed using t test; for non-normally distributed variables Mann-Whitney test was applied. Correlations using Pearson's correlation coefficient (r) are presented, followed by linear multivariate regression using stepwise and enter method. P values < 0.05 were considered statistical significant.

Results

Ninety-three type 2 diabetic patients (62.37% male, median age 64) completed this prospective observational study. Sixty-eight of these patients were previously included in another transversal study that we conducted, in which the inclusion and exclusion criteria were quite similar. The average duration of type 2 diabetes was 7 (5-14) years and the majority of this population was hypertensive, 77.41% being treated with blockers of the renin angiotensin system (angiotensin converting enzyme/ angiotensin II receptor blockers), 29.03% patients were treated with insulin, 43.01% were treated with oral antidiabetic agents, 18.27% received a combination between insulin/oral therapy and 9.67% were only on diet. Baseline characteristics of the patients and at one year follow up are presented in *Table 1*.

Table 2. Multiple regression for the whole cohort of type 2 diabetic patients

	Unstandardized Coefficients		Standardized Coefficients	p	95% Confidence Interval for B	
	B	Std Error	Beta		Lower Bound	Upper Bound
(Constant)	702.96	374.45		0.06	-1447.86	41.95
Serum ICAM 1	1.44	0.45	0.34	**0.002**	0.55	2.32
eGFR	-2.32	1.18	-0.20	0.05	-4.67	0.03
BMI	3.29	5.60	0.06	0.56	-7.84	14.42
Diabetes duration	-1.37	4.64	-0.03	0.77	-10.60	7.86
SBP	2.33	2.18	0.11	0.29	-2.01	6.67
Total cholesterol	-0.25	0.96	-0.03	0.80	-2.16	1.66
HDL cholesterol	5.22	3.07	0.19	0.09	-0.89	11.33
CRP	31.07	40.66	0.08	0.45	-49.81	111.94

Enter method - dependent variable ΔuACR - difference between urinary albumin to creatinine ratio at the end of the study and baseline value. ICAM -1 - intercellular adhesion molecule 1, eGFR– estimated glomerular filtration rate according to abbreviated Modification of Diet in Renal Disease formula, BMI – body mass index, SBP - systolic blood pressure, HDL- high density lipoprotein, CRP – C reactive protein

Table 3. Multiple regression for the whole cohort

	Unstandardized Coefficients		Standardized Coefficients	p	95% Confidence Interval for B	
	B	Std Error	Beta		Lower Bound	Upper Bound
(Constant)	-232.37	102.93	-2.26	0.03	-436.93	-27.81
Serum ICAM-1	1,34	0.43	0.31	**0.003**	0.48	2.19

Stepwise method- dependent variable ΔuACR - difference between urinary albumin to creatinine ratio at the end of the study and baseline value.

ΔuACR disclosed a positive correlation to baseline serum ICAM 1 (p=0.003, r= 0.31), this correlation can be observed in *Figure 1*. ΔuACR disclosed also a positive correlation to serum creatinine at baseline (p=0.026, r=0.23) and at the end of the study (p=0.00004, r=0.41).

The only baseline parameter that correlated with ΔGFR was glycaemia (p= 0.047, r=0.22).

In multiple regression, using enter method and ΔuACR as the dependent variable, ICAM 1 was the main predictor of ΔuACR (*Table 2*).

In multiple regressions using stepwise method, using all studied parameters as independent variables, the only predictor of ΔuACR was serum ICAM 1 (*Table 3*).

Based on their baseline uACR, 58 patients were normoalbuminuric, and 35 patients had their baseline uACR on albuminuric range. The characteristics of patients according to baseline uACR are depicted in *Table 4*. In normoalbuminuric patients, ΔuACR did not show the same positive correlation to baseline serum ICAM 1 that we observed on the whole group of patients, but even disclosed a negative correlation (p= 0.046, r= - 0.26), it can be observed in *Figure 2*. In albuminuric patients ΔuACR disclosed a strong positive correlation to baseline serum ICAM-1 (p=0.0003, r=0.57), as depicted in *Fig-*

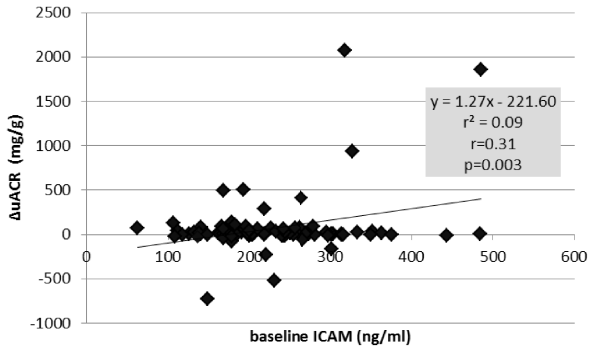

Figure 1. Correlation between baseline serum ICAM1 levels and ΔuACR in the whole groupe of type 2 diabetic patients

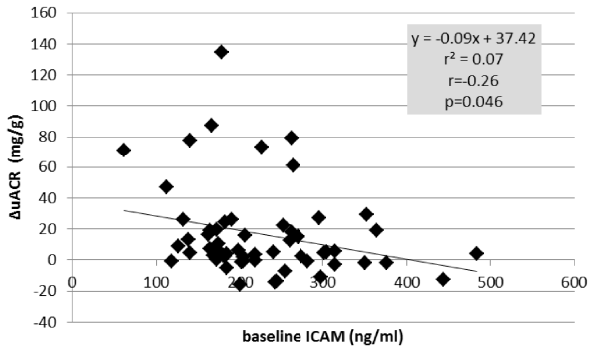

Figure 2. Correlation between baseline serum ICAM 1 levels and ΔuACR in normoalbuminuric patients

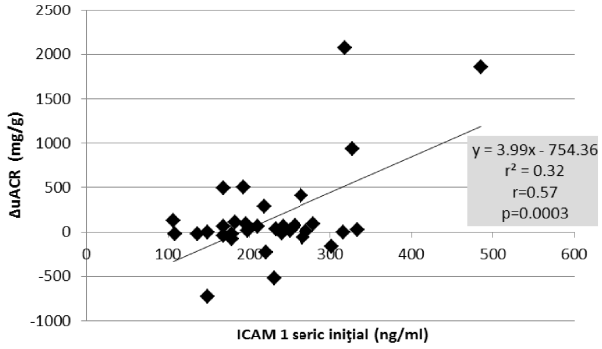

Figure 3. Correlation between baseline serum ICAM1 levels and ΔuACR in albuminuric patients

Legend: ICAM - intercellular adhesion molecule 1; ΔuACR - difference between baseline urinary albumin-to-creatinine ratio and at the end of the study

ure 3. No other baseline parameter correlated to ΔuACR. If we divided patients according to medication there was no difference between groups as far as concerns the serum levels of ICAM, nor the progression of albuminuria.

Discussion

In this study were included patients with type 2 diabetes without advanced kidney disease, in order to assess the predictive role of serum ICAM-1 for the progression of diabetic kidney disease in early stages. Progression of DKD was assessed by increasing in uACR over the followed up period. uACR worsen and showed significant difference between baseline and the end of the study, but it was still in microalbuminuric range. Even if the increase in uACR was small in magnitude, this may have significant clinical importance due to the fact that albuminuria is known to be an independent and significant risk for cardiovascular morbidity and all-cause mortality (7, 8).

After one year follow up, we observed an increase in eGFR. This may be due to the fact that in this study were included mostly patients with incipient kidney disease and we might assist to hyperfiltration which specific to early diabetic kidney disease. This is why we could not asses the progression of diabetic kidney disease by ΔeGFR. Moreover, most of our patients were with incipient diabetic kidney disease, mostly in microalbuminuric stage, so the one year follow up period was not enough in order to quantify the progression of diabetic kidney disease by eGFR. In our patients, as expected, we found that patients with higher level of serum creatinine showed a more important aggravation of albuminuria.

In our cohort serum ICAM 1 positively correlated with ΔuACR. Moreover, baseline serum ICAM 1 level was the only predictor of ΔuACR. We hypothesize that ICAM-1 plays an important role in the inflam-

Table 4. Comparison between normoalbuminuric and albuminuric patients at baseline and after 1 year follow up

Parameter	Evaluation moment	Normoalbuminuric patients (n=58)	Albuminuric patients (n=35)	p
eGFR(ml/min)	Baseline	80.67 (61.10-100.20)	55.86 (43.97-87.91)	**0.002**
	One year follow-up	87.59 (65.01-110.77)	62.21 (45.03-96.89)	**0.01**
BMI (kg/m2)	Baseline	31.65±5.42	30.85±6.57	0.26
	One year follow-up	31.85±5.79	30.76±6.75	0.19
SBP (mmHg)	Baseline	130.00 (120.00-142.50)	140.00(140.00-160.00)	**0.05**
	One year follow-up	130.00 (120.00-140.00)	140.00 (125.00-150.00)	0.07
DBP (mmHg)	Baseline	80.00 (75.00-90.00)	85.00 (80.00-90.00)	0.70
	One year follow-up	80.00 (80.00-80.00)	80.00 (70.00-85.00)	0.91
Total cholesterol (mg/dl)	Baseline	184.43±37.67	189.11±37.03	0.56
	One year follow-up	183.36±44.05	193.49±44.03	0.29
HDL cholesterol (mg/dl)	Baseline	44.69±12.65	45.61±10.68	0.72
	One year follow-up	44.72±11.22	44.66±11.44	0.98
Triglycerides (mg/dl)	Baseline	153.00 (111.50-201.00)	153 (126.00-200.00)	0.37
	One year follow-up	133.00 (108.00-195.50)	164.00 (131.00- 293.00)	0.34
CRP (mg/dl)	Baseline	0.30 (0.10-0.80)	0.20 (0.10- 0.80)	0.77
	One year follow-up	0.31 (0.15- 0.85)	0.20 (0.10- 0.65)	0.50
Serum ICAM 1(ng/ml)	Baseline	206.00 (174.00- 270.00)	198.00 (168.00-242.00)	0.69
	One year follow-up	200.00 (162.50-248.00)	202.00 (162.00- 304.00)	0.87
uACR (mg/g)	Baseline	8.73 (2.33- 17.34)	179.14 (49.58- 456.92)	**<0.0001**
	One year follow-up	17.07 (4.72-32.65)	164.35 (35.77- 583.68)	**<0.0001**
ΔuACR(mg/g)		6.15 (0.99- 20.86)	26.91 (-26.34 -111.84)	0.27

Values are presented as mean ± SD for normally distributed variables and median (25^{th} -75^{th} percentiles) for the abnormally distributes ones.

eGFR– estimated glomerular filtration rate according to abbreviated Modification of Diet in Renal Disease formula, BMI – body mass index SBP- systolic blood pressure, DBP – diastolic blood pressure, HDL- high density lipoprotein, LDL- low density lipoprotein, CRP – C reactive protein , ICAM-1 - intercellular adhesion molecule 1, uACR- urinary albumin to creatinin ratio, ΔuACR - difference between urinary albumin to creatinine ratio at the end of the study and baseline value

mation, activation of endothelial cells and kidney injury, which is expressed as increased uACR in the early stages of diabetic kidney disease.

ICAM 1 is an endothelial transmembrane protein which mediates cell to cell interaction, facilitates T lymphocytes activation and leukocyte endothelial transmigration into the renal tissue, its primary receptor being leukocyte adhesion protein-1 (LFA-1). In diabetic milieu and upon cytokine stimulation, ICAM 1 gene expression on the surface of endothelium cells is up-regulated. ICAM 1 protein binding activity with LFA-1 is increased and more lymphocytes from blood are transferred into glomeruli and interstitium (9), triggering in-

flammation (5). All this together promotes glomerular injury, proteinuria, mesangial proliferation (10), fibroblast proliferation and interstitial fibrosis (11). Moreover, experimental studies have shown that in diabetic nephropathy glomerular ICAM 1 expression is increased and is directly associated to kidney injury and increased urinary albumin excretion (12, 13), ICAM 1 deficient mice having reduced renal damage (14, 15). In patients with chronic kidney disease, levels of plasma ICAM 1 levels are positively correlated to urinary albumin excretion (16). In type 1 diabetes, well design transversal and prospective clinical studies, sustain the fact that ICAM 1 is a key factor in the development and progression of diabetic nephropathy (17, 18). As far as concerns type 2 diabetic patients, it is known that they express higher serum ICAM 1 levels compared to controls.

As we mentioned above, sixty-eight patients from our study were included in a previous transversal study that we conducted (19). The strong correlation found between serum ICAM 1 and albuminuria in that study, in accord to other reports in the literature (20), triggered the present prospective follow-up study aiming to assess the predictive role of serum ICAM 1 for the progression of diabetic kidney disease.

In the present study, the correlation between baseline serum ICAM 1 levels was even stronger in albuminuric patients. As far as concerns the normoalbuminuric subgroup of patients, Δ uACR did not show the same correlation but even disclosed a negative correlation. It seems that serum ICAM 1 level cannot predict the patients who will develop the diabetic kidney disease, but might have an important role in predicting the progression of diabetic kidney disease in albuminuric patients.

Some studies have reported that angiotensine II blockade reduce inflammation, including serum ICAM 1 (21). However, the differences between patients which were treated or not with blockers of the renin angiotensin system were not significant. In a previous study we found that angiotensin converting enzyme inhibitors treatment and better glycemic control are associated with lower levels of sICAM-1 in diabetic hemodialysis-treated patients with cardiovascular disease (22).

One limitation of this study is the relatively small number of patients. Larger prospective studies are needed to sustain the role of serum ICAM 1 as a noninvasive biomarker for the progression of diabetic kidney disease.

Acknowledgements

This study was founded by the Grant of Universty of Medicine and Pharmacy „Iuliu Hatieganu" Cluj-Napoca, No. 27020/32/15.11.2011, Romania

Abbreviations

DKD - diabetic kidney disease
ICAM 1 -intercellular adhesion molecule 1
ΔuACR- difference between urinary albumin to creatinine ratio at the end of the study and baseline value
uACR - urinary albumin to creatinine ratio
BMI - body mass index
HbA1C - glycated hemoglobin
CRP - C reactive protein
eGFR - *Glomerular filtration rate estimated by* abbreviated Modification of Diet in Renal Disease formula
MDRD - abbreviated Modification of Diet in Renal Disease
ΔeGFR - difference between *glomerular filtration rate* at the end of the study and baseline value
LFA-1 - leukocyte adhesion protein-1

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