Prognostic Value of Proinflammatory Markers in Patients After Kidney Transplantation in Relation to the Presence of Diabetes

D. Cieniawski[a,*], P. Miarka[a], E. Ignacak[a], A. Bętkowska-Prokop[a], M. Waluś-Miarka[b], B. Idzior-Waluś[b], M. Kuźniewski[a], and W. Sułowicz[a]

[a]Department of Nephrology, Jagiellonian University Medical College, Krakow, Poland; and [b]Department of Metabolic Diseases, Jagiellonian University Medical College, Krakow, Poland

ABSTRACT

Background. Patients who are receiving immunosuppressive treatment after kidney transplantation are at greater risk of developing new-onset diabetes after transplantation (NODAT). New biochemical markers that may contribute to a better assessment of the prognosis of renal failure for patients diagnosed with diabetes mellitus (DM) are needed. The aim of this study was to assess selected proinflammatory markers in patients after kidney transplantation depending on the prevalence of DM and to evaluate the predictive value of these cytokines.

Methods. A total of 82 patients were divided into 3 groups after kidney transplantation and were included in the analysis: group I, no DM; group II, DM diagnosed before transplantation; and group III, NODAT. Selected marker levels (platelet-derived growth factor, transforming growth factor β_1, tumor necrosis factor receptor II [TNF-RII], and high-sensitivity interleukin-6 [IL-6 HS]) were assessed by using enzyme-linked immunosorbent assays. For summary endpoint, a return to dialysis treatment and/or death of the patient was adopted.

Results. Patients with NODAT were characterized by higher levels of IL-6 HS and body mass index. There were no statistically significant differences in the levels of other assessed markers among the 3 analyzed groups. The summary endpoint was observed in 16 cases (19.5%). Patients with summary endpoint during the observation time at baseline had higher levels of TNF-RII (7180 vs 4632 pg/mL; $P = .0002$) and IL-6 HS (4.58 vs 2.72 pg/mL; $P = .033$).

Conclusions. Levels of inflammatory markers in patients after kidney transplantation did not differ between groups with and without DM. In the study population, DM was not a significant risk factor for graft loss or death. Patients who experienced these complications at baseline were characterized by higher values of TNF-RII and IL-6 HS.

CHRONIC KIDNEY DISEASE (CKD) is a growing medical problem. CKD involves high costs associated with renal replacement therapy and is characterized by a high mortality rate among patients [1]. Diabetes mellitus (DM) is one of the leading causes of CKD [2] and is associated with lower graft function and survival after kidney transplantation (KTx) [3]. Currently, KTx is considered the best treatment option for patients with end-stage renal disease. However, these patients also have an increased risk of developing new-onset diabetes after transplantation (NODAT). This disorder is mostly associated with type of immunosuppressive drugs used, age, race, donor type, obesity, and family history of DM [4]. Recent studies have shown that elevated levels of inflammation and oxidative

*Address correspondence to Dominik Cieniawski, Department of Nephrology, Jagiellonian University Medical College, Kopernika 15-15c, 31-501 Krakow, Poland. E-mail: dominik.cieniawski@gmail.com

0041-1345/16
http://dx.doi.org/10.1016/j.transproceed.2016.03.008

stress markers are associated with higher cardiovascular mortality, especially in patients with CKD [5]. Pathogenesis of DM is also connected with elevated activation of inflammation markers (ie, high-sensitivity interleukin-6 [IL-6 HS], tumor necrosis factor receptor II [TNF-RII], platelet-derived growth factor [PDGF], transforming growth factor β_1 [TGF β_1], adiponectin, C-reactive protein) [6–8]. There is no precise information about the influence of DM on renal graft function and patient survival.

The objectives of the present study were to compare selected proinflammatory cytokine levels in patients after KTx depending on the presence of DM and to assess a possible predictive value of selected markers in patients after KTx.

PATIENTS AND METHODS

The studies were performed in 82 patients who had undergone KTx (52 male patients and 30 female patients). Before beginning the study, patients were divided into 3 groups depending on etiology of kidney failure and presence of DM: group I, glomerulonephritis as the cause of end-stage renal disease without DM (n = 35); group II, DM was the cause of renal failure (n = 19); and group III, NODAT (n = 28). In group II, fourteen patients (73.7%) used insulin, and 5 (26.3%) took oral antidiabetic drugs. In group III, five patients (17.9%) were treated with diet only, 9 (32.1%) with oral drugs, and 14 (50.0%) with insulin. The immunosuppressive regimen consisted of a calcineurin inhibitor in combination with mycophenolate mofetil, sodium mycophenolate, azathioprine, mammalian target of rapamycin inhibitors, and steroids. The protocol was approved by the ethics committee of Jagiellonian University Medical College. All subjects gave informed written consent.

Anthropometric parameters and blood samples were collected in the morning during the routine ambulatory control visit. Assessment of levels of the inflammatory markers was made by using immunoenzymatic methods (Diaclone [SAS Besancon, Besançon, France] for IL-6 HS and TGF β1; Quantikine [R&D Systems Inc, Minneapolis, Minn, United States] for PDGF and TNF RII) at the beginning of the study in 2010. The samples were collected when patients were in stable condition with no active infection, inflammatory process (C-reactive protein level <10 mg/L), or rejection. The follow-up period covered 4 years. A return to dialysis treatment and/or death of the patient was adopted as the summary endpoint.

Data for variables were prospectively collected during follow-up from clinical records. All statistical analyses were performed by using commercially available software (Statistica version 10.0 [StatSoft, Tulsa, Okla, United States]). The Mann-Whitney rank sum *U* test, Student *t* test, analysis of variance, and analysis of variance Kruskal-Wallis tests were used in the statistical analysis. Results were considered to be significant at $P < .05$.

RESULTS

Table 1 presents a description of the study groups and biochemical results. Patients with NODAT had significantly higher levels of IL-6 HS and body mass index than the other patients. Compared with the group without DM, patients with NODAT also had higher PDGF levels and a lower estimated glomerular filtration rate. The fasting glucose level in patients without DM was significantly lower than in the other 2 groups. There were no differences observed in other biochemical and clinical parameters. In addition, compared with patients with DM (groups II and III together) vs group I, there were no statistically significant between-group differences in level of proinflammatory markers (median PDGF, 484.35 vs 313.50 [$P = .119$]; TGF β_1, 19.20 vs 19.20 ng/mL [$P = .983$]; TNF-RII, 4717.00 vs 4725.00 pg/mL [$P = .458$]; IL-6 HS, 2.49 vs 2.59 pg/mL [$P = .405$]). Table 2 presents the basic clinical and biochemical data of patients with and without DM.

Table 1. Clinical and Biochemical Data of the Group Without Diabetes (Group I), With DM Before Transplantation (Group II), and With DM Diagnosed After Transplantation (Group III)

Variable	Group I (n = 35)	Group II (n = 19)	Group III (n = 28)	*P*		
				Group I vs Group II	Group I vs Group III	Group II vs Group III
Age, y	47.42 ± 12.80	49.90 ± 11.97	56.50 ± 11.07	.492*	*.006*†	.102†
Age at transplantation, y	40.43 ± 12.89	43.00 ± 12.28	49.32 ± 10.47	.538†	*.005**	.104†
Time after transplantation, mo	84.54 ± 36.23	84.95 ± 32.48	91.96 ± 64.87	.968*	.567*	.666*
BMI, kg/m^2	26.04 ± 4.53	26.29 ± 3.67	29.78 ± 4.79	.842*	*.003**	*.013**
Weight, kg	76.13 ± 15.76	74.04 ± 13.81	82.16 ± 13.28	.629*	.112*	*.049**
Height, m	1.71 ± 0.09	1.67 ± 0.08	1.67 ± 0.09	.185*	.108*	.862*
Creatinine, μmol/L	114.71 ± 30.05	122.03 ± 46.17	125.92 ± 45.87	.978†	.248*	.673†
eGFR, MDRD, mL/min	62.80 ± 18.76	54.46 ± 19.34	54.26 ± 28.52	.163*	*.032*†	.509†
SBP, mm Hg	140.14 ± 17.17	144.47 ± 21.00	146.61 ± 27.18	.360†	.571†	.836†
PDGF, pg/mL	829.50 ± 683.63	839.74 ± 792.12	550.48 ± 635.88	.963†	*.017*†	.055†
TGF β_1, ng/mL	34.02 ± 37.35	39.71 ± 34.30	21.64 ± 21.85	.296†	.427†	.051†
TNF-RII, pg/mL	4719.32 ± 1289.10	4717.60 ± 1328.80	5827.90 ± 2591.80	.718†	.156†	.161†
IL-6 HS, pg/mL	2.92 ± 2.29	2.46 ± 1.50	3.64 ± 1.96	.228†	*.026*†	*.014*†
Fasting glucose, mmol/L	4.97 ± 0.52	6.99 ± 3.11	6.86 ± 2.03	*.003*†	*<.001*†	.610†
Glycosuria, no. (%)	0	5/26.3	1/3.6	–	–	–

Values are given as means ± standard deviations unless otherwise indicated.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; PDGF, platelet-derived growth factor; SBP, systolic blood pressure; TGF β_1, transforming growth factor β_1; TNF-RII, tumor necrosis factor receptor II; IL-6 HS, high-sensitivity interleukin-6.

*Student *t* test.

†Mann-Whitney rank sum *U* test.