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ORIGINAL INVESTIGATION

Patients with type 2 diabetes mellitus and diabetic nephropathy have higher risk for foot ulceration

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Abstract

Background and Aims: The primary aim of this study was to analyze the association between renal parameters and the risk for the presence of diabetic foot by using the International Working Group on the Diabetic Foot (IWGDF) classification in patients with type 2 diabetes mellitus (T2DM).
Subjects and Methods: We conducted a prospective, cross-sectional study, which included 107 consecutive hospitalized patients with T2DM, aged 35–65 years, over the 6-month period. Patients were examined and tested for diabetic foot and classified according to the IWGDF into four groups. The presence of kidney disease was assessed based on clinical practice guideline for diabetes and chronic kidney disease and classified into grades [1–5] based on the estimated glomerular filtration rate (eGFR) calculated with Cockcroft-Gault and modification of diet in renal disease formula. The patterns of proteinuria were assessed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis.
Results: Only 4 (3.7%) patients were classified into risk 0 group, 65 (60.7) into risk group 1, 22 (20.6%) into risk group 2 and 16 (15.0%) of patients were classified into risk group 3. Patients in risk group 2 and 3 had significantly higher serum creatinine level, lower eGFR, higher proportion of grade 4 renal insufficiency, type 4 proteinuria and higher rate of proliferative diabetic retinopathy. Serum creatinine showed the highest predictive accuracy in detecting patients at high risk for diabetic foot (area under the curve 0.769, 95% confidence interval 0.674–0.864) (Figure 2). Serum creatinine >143 μmol/L had a 95% specificity and serum creatinine >67 μmol/L had 95% specificity.
Conclusion: Patients with T2DM at high risk for diabetic foot syndrome have significantly impaired renal function, without the significant differences in other anthropometric and metabolic parameters. Simple serum creatinine measurement may be useful for detecting high-risk patients.

Key words: Diabetic foot; risk; International Working Group on the Diabetic Foot; renal insufficiency; diabetic nephropathy

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic disease with the increasing prevalence worldwide. It is estimated that 422 million people had T2DM in 2015. The total number of patients with T2DM will increase to 650 million in 2035. The global prevalence of T2DM is 8.8%, which is similar to the prevalence of T2DM in Macedonia is estimated to 10.3%, which is similar to global prevalence [1]. There are many factors that may increase the risk of developing diabetes such as increased age, urbanization, sedentary lifestyle, and poor eating habits. Microvascular and macrovascular complications are leading cause of morbidity and mortality. Diabetic foot syndrome is a complex of heterogeneous disorders composed both from macrovascular (peripheral artery disease) and microvascular components (distal symmetric polyneuropathy) but also with foot deformities. Approximately, 25% of patients will eventually develop diabetic foot and 30% will develop diabetic nephropathy [2]. Vice-versa, diabetes is the most common cause of ulcerations and non-traumatic amputations. The risk of death after amputation increases up to 70%, and more than 50% will die within the first 5 years after amputation. Metabolic control of diabetes is crucial to prevent or delay the appearance of diabetic foot syndrome and all other complications. Intervention in modifying risk factors such as glucose regulation, blood pressure regulation, lipid control, smoking cessation, and lifestyle changes should also be attributed. Diabetic nephropathy is the leading cause of end-stage renal disease in the world. The presence of diabetic nephropathy is associated with increased risk of having other complications such as diabetic retinopathy, diabetic neuropathy and diabetic foot syndrome [3]. On the other hand, patients that have retinopathy, hypertension, hyperlipoproteinemia and hyperuricemia, have more rapid progression of diabetic kidney disease [4]. The association between moderate to severe renal insufficiency and the development of diabetic foot is well known [5,6]. Moreover, it is well known that patients with chronic kidney disease on dialysis have 10 times higher risk for foot amputation compared with T2DM patients in general. This may be due to the fact that uremia worsens diabetic polyneuropathy in people with diabetes by reducing the nerve conductivity [7]. Chronic kidney disease is also associated with increased prevalence of peripheral artery disease, which also strongly contributes to the development of diabetic foot syndrome [8,9].

However, it remains elusive whether we can predict the risk of diabetic foot syndrome by assessing chronic renal insufficiency.

The primary aim of this study was to analyze the association between renal parameters and the risk for the presence of diabetic foot by using the International Working Group on the Diabetic Foot (IWGDF) classification. The secondary aim was to assess the impact of other metabolic parameters on the risk for diabetic foot syndrome.

2. Patients and Methods

2.1. Study protocol

This study was prospective, cross-sectional study, performed at the university Clinic of endocrinology in Skopje, Macedonia. A total of 107 consecutive hospitalized patients with T2DM patients over the 6-month period were included in the study. Fasting plasma glucose, glycated hemoglobin (HbA1c), serum urea, creatinine, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, triglycerides, thrombocytes, albumins in 24-h urine collection along with the sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) were measured in all patients. Body weight and height, blood pressure, history of tobacco use, history of diabetic retinopathy, and duration of diabetes were recorded.

Detailed examination of each patient was carried out, to identify lower-extremity complications and risk factors, such as history of lower extremity ulcerations and amputation, peripheral sensory neuropathy, peripheral vascular disease, foot deformities, limited joint mobility, and abnormal foot pressures. Neuropathy was evaluated with a 10 g Semmes-Weinstein monofilament. Peripheral artery disease was defined as a nonpalpable dorsalis pedis or posterior tibial arterial pulse and ankle brachial index in either foot <0.80. We defined deformity as any contracture that could not be fully corrected manually. Foot ulcers were defined as full-thickness wounds involving the foot or ankle. Infection was defined by criteria consistent with the International Working Group and Infectious Diseases Society of America guidelines.

Risk stratification for the presence of diabetic foot was performed according to the IWGDF. Patients were categorized into four groups: 0 - no peripheral neuropathy; (1) peripheral neuropathy present; (2) peripheral neuropathy with peripheral artery disease and/or a foot deformity; (3) peripheral neuropathy and a history of foot ulcer or lower-extremity amputation.

Calculation of estimated glomerular filtration rate (eGFR) based on both Cockroft-Gault formula and modification of diet in renal disease (MDRD) formula were used for stratification of chronic renal insufficiency. According to the Clinical Practice Guideline for Diabetes and chronic kidney disease (KDOQI) chronic renal insufficiency was classified into 5 categories: Stage 1 ≥ 90 mL/min/1.73 m^2; Stage 2 60-89 mL/min/1.73 m^2; Stage 3 30-59 mL/min/1.73 m^2; Stage 4 15-29 mL/min/1.73 m^2; Stage 5 <15 mL/min/1.73 m^2. The pattern of proteinuria was assessed by SDS-PAGE and classified into following types: 0 - Normal excretion of urinary albumines normal excretion with discrete selective glomerular proteins; 1 - incipient nonselective glomerular proteinuria; 2 - nonselective glomerular proteinuria; 3 - incomplete tubular proteinuria; 4 - complete mixed proteinuria. Albuminuria was classified as microalbuminuria (albumins 30-300 mg/L) and macroalbuminuria (albumins >300 mg/L).

2.2. Statistical analyses

Continuous variables were compared with Kruskal–Wallis one-way analysis of variance and expressed as mean with standard deviations. Categorical variables were compared with Chi-square test with Yates correction. Spearman correlation was performed to analyze the association between the variables. Receiver operating characteristic (ROC) analysis was performed to establish optimal cutoff values for continuous variables and to calculate sensitivity and specificity. ROC analysis was performed only for variables with significant Spearman correlation coefficients. Statistical analyses were performed in SPSS version 20.0. $P < 0.05$ was considered statistically significant.

3. Results

Patients had a mean age of 59.1 ± 5.9 years; 50.5% were male and 49.5% were female. They had a mean duration of diabetes of 12.9 ± 6.2 years, mean glycated hemoglobin of 9.5 ± 1.9%, and a mean body mass index of 28 kg/m^2.

Only 4 (3.7%) patients were classified into risk 0 group, 65 (60.7) into risk group 1, 22 (20.6%) into risk group 2 and 16 (15.0%) of patients were classified into risk group 3. For further analyses, risk group 0 and 1 were merged into group 1.

There were no significant differences in age, gender, duration of diabetes, smoking status, HbA1c, BMI, systolic blood pressure, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, thrombocyte count, proteinuria, albuminuria nor blood nitrogen between the groups. However, patients in risk group 2 and 3 had significantly higher serum creatinine level, lower eGFR and higher proportion of grade 4 renal insufficiency. Moreover, patients in the risk group 3 had higher rate of SDS-PAGE type 4 proteinuria and higher rate of proliferative diabetic retinopathy (Table 1). eGFR was significantly higher when calculated by Cockroft-Gault then MDRD formula (78.0 ± 24.1 vs. 70.6 ± 23.2, $P < 0.05$).

We found positive correlation between the risk score and the grade of nephropathy (Spearman rho = 0.360, $P < 0.001$). Moreover, we found significant association between blood nitrogen (Spearman rho = 0.354, $P < 0,001$), creatinine (Spearman rho = 0.448, $P < 0.001$), eGFR (Cockroft-Gold) (Spearman rho = −0.369; $P < 0,001$), MDRD (Spearman rho = −0.434), and significant difference in SDS-PAGE pattern ($\chi^2 = 17.0$; $P = 0.002$).

When we pooled patients from risk group 2 and 3 and compared them with risk group 1, similar association was observed. Higher proportion of patients was at higher risk for diabetic foot as the grade of renal insufficiency increased (Figure 1a). Interestingly, fewer patients with grade 5 renal insufficiency were at high risk for diabetic foot, when compared with grade 4 renal insufficiency. On the other hand, the proportion of patients at high risk increased with pattern of proteinuria according to SDS-PAGE (Figure 1b).

To evaluate the predictive capacity of renal parameters, we performed a ROC analysis. Serum creatinine showed the highest predictive accuracy in detecting patients at high risk for diabetic foot (area under the curve 0.769, 95% confidence interval 0.674-0.864) (Figure 2). Serum

Table 1. Characteristics of the study population divided based on IWGDF risk score. Continuous variables are expressed as mean (first column) and standard deviation (second column); categorical variables are expressed as number (first column) and percentage within each group (second column)

	Risk score 0 and 1 (N=69)		Risk score 2 (N=22)		Risk score 3 (N=16)	
Age (years)	58.3	6.1	61.4	4.9	59.7	5.3
Male gender n (%)	32	46.4	13	59.1	9	56.2
Smoking status n (%)						
Current smokers	16	23.2	5	22.7	2	12.5
Non-smokers	47	68.1	16	72.7	12	75.0
Ex-smokers	6	8.7	1	4.5	2	12.5
Diabetic retinopathy n (%)						
Without	31	44.9	13	59.1	7	43.8
Nonproliferative	7	10.1	2	9.1	5	31.2
Proliferative	3	4.3	2	9.1	4	25.0A
Duration of diabetes (years)	11.8	5.4	13.6	7.0	15.7	7.7
HbA1c (%)	9.37	1.86	9.98	1.67	9.63	2.11
BMI (kg/m^2)	27.9	2.9	28.3	4.0	28.3	4.1
Systolic blood pressure (mmHg)	137.0	17.7	136.6	22.6	132.2	10.9
Total cholesterol (mmol/L)	5.0	1.5	5.0	1.7	5.1	1.4
Triglycerides (mmol/L)	2.4	1.9	2.4	1.3	2.3	1.1
LDL cholesterol (mmol/L)	2.9	1.2	2.9	1.6	3.1	1.2
HDL cholesterol (mmol/L)	1.1	0.4	1.2	0.6	1.1	0.3
Thrombocytes (×10^9)	266.1	118.4	237.3	92.9	277.1	87.6
24 h proteinuria (g/L)	29.4	168.7	91.7	293.7	125.5	341.0
Albuminuria						
Grade 1	17	24.6	3	13.6	1	6.2
Grade 2	45	65.2	18	81.8	12	75.0
Grade 3	7	10.1	1	4.5	3	18.8
Urea (mmol/L)	6.2	2.7	8.1	5.0	8.3	2.7
Creatinine (μmol/L)	87.0^{B,C}	32.7	124.0	59.6	117.9	42.5
eGFR C&G (ml/min)	85.0^{B,C}	21.6	64.7	24.9	66.3	21.9
eGFR MDRD (ml/min)	77.3^{B,C}	20.9	58.0	23.7	59.2	21.5
Renal insufficiency n (%)						
Grade 1	4	5.8	0	0.0	0	0.0

(*Contd...*)

Table 1. (*Continued*)

	Risk score 0 and 1 (N=69)		Risk score 2 (N=22)		Risk score 3 (N=16)	
Grade 2	52	75.4	11	50.0	8	50.0
Grade 3	7	10.1	4	18.2	3	18.8
Grade 4	2	2.9[B,C]	5	22.7	3	18.8
Grade 5	4	5.8	2	9.1	2	12.5
SDS-PAGE n (%)						
0	20	29.0	1	4.5	1	6.2
1	23	33.3	9	40.9	2	12.5
2	14	20.3	5	22.7	4	25.0
3	7	10.1	4	18.2	2	12.5
4	5	7.2	3	13.6	7	43.8A

[A]Significant difference when compared with risk group 1; [B,C]Significant difference when compared with risk group 2 and 3. IWGDF-International Working Group on the Diabetic Foot, HbA1c-Glycated hemoglobin, BMI-Body mass index, LDL-Low-density lipoprotein, HDL-High-density lipoprotein, eGFR-Estimated glomerular filtration rate, MDRD-Modification of diet in renal disease, SDS-PAGE-Sodium dodecyl sulfate polyacrylamide gel electrophoresis

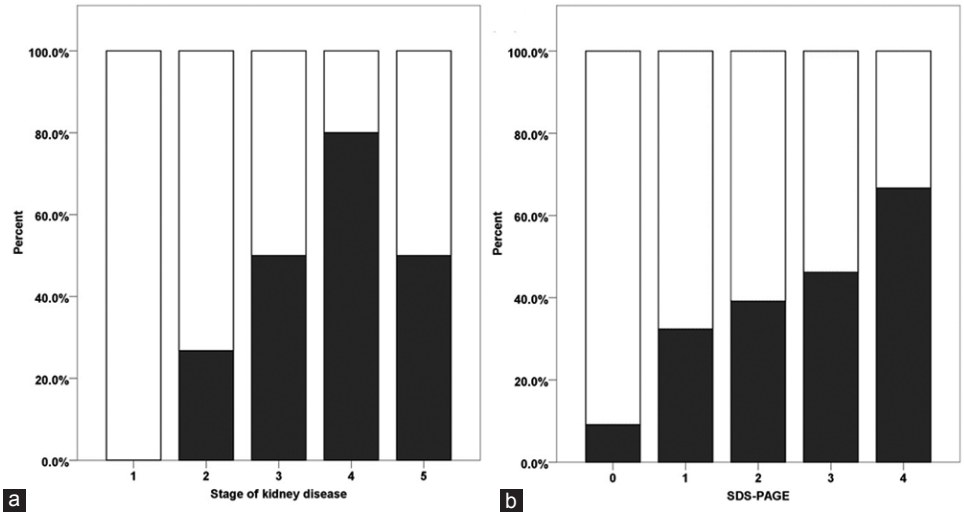

Figure 1. Proportion of patients at high risk for development of diabetic foot (black bars) in patients with certain stage of renal insufficiency (a), and with certain pattern of proteinuria determined by sodium dodecyl sulfate polyacrylamide gel electrophoresis (b)

creatinine >143 μmol/L had a 95% specificity and serum creatinine >67 μmol/L had 95% specificity. This means that patients with creatinine >143 μmol/L have high risk for diabetic foot with 95% certainty.

4. Discussion

Our study showed that patients with T2DM at high risk for diabetic foot syndrome have significantly impaired renal function, without the significant differences in other anthropometric and metabolic parameters. Moreover, simple serum creatinine measurement showed very good accuracy in detecting high-risk patients.

Our study population had a mean age of 59 ± 5 years, while age >60 years is associated with increased risk of chronic complications [10]. On the other hand, only duration of diabetes is an independent risk factor for microvascular

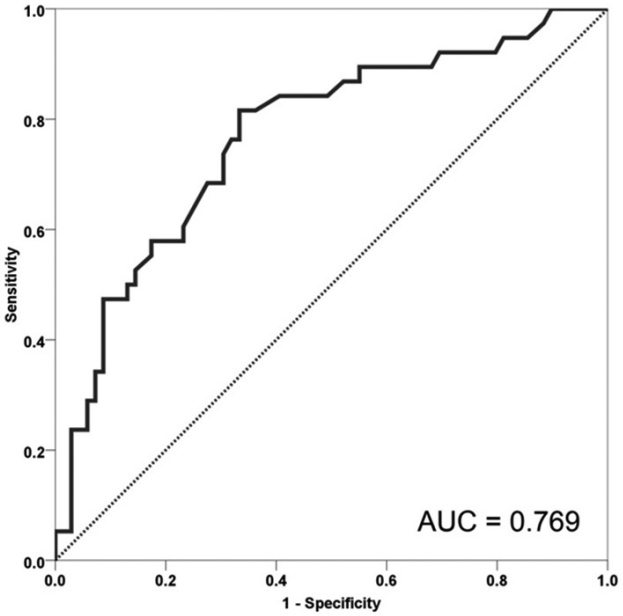

Figure 2. Receiver operating curve showing the predictive accuracy of serum creatinine in detecting patients at high risk for development of diabetic foot

complications. In our study, a mean duration of diabetes was 12 ± 6 years, which is optimal duration for the increased prevalence of both microvascular and macrovascular complications. In our study, high-risk patients did have longer duration of diabetes but it did not reach statistical significance. Interestingly, HbA1c was similar in all groups, showing overall poor glycemic control. HbA1c is also one of the independent risk factors for complications and mortality. The decrease of HbA1c by 1% is associated with the reduction of microvascular complications by 34% and macrovascular complications by 14%. Patients with very high HbA1c gain more benefit by greater reduction of HbA1c, but even minimal reduction in HbA1c is important for prevention of chronic complications [11]. The new recommendations from American Diabetes Association recommend that blood pressure should be <140/90 mmHg [12]. High systolic blood pressure (>140 mmHg) was observed in 42.7% of our patients. Randomized control trials have proven the benefit from keeping the blood pressure <140/90 mmHg for prevention of cardiovascular incidents but also for prevention of chronic kidney disease [13]. Although one could expect the direct association between blood pressure and diabetic foot syndrome, this was not observed in our study. The only significant difference between patients at high and low risk for diabetic foot syndrome in our study was lower eGFR and the presence of complete mixed proteinuria in patients at high risk. Calculation of eGFR proved to be effective in assessing renal function in patients with T2DM although significant differences may occur based on the formula used for it's calculation. This was also observed in our study. This may be explained by the fact that our patients had relatively high BMI, which has a direct impact on eGFR calculated with Cockroft-Gault formula. Interestingly, serum creatinine showed the strongest correlation with the risk of diabetic foot syndrome and was superior to eGFR in predicting high-risk patients. Microalbuminuria was present in 70.8% of our patients, while macroalbuminuria was present in 9.4%. The decrease of renal function and progression of chronic kidney disease is associated with the progression of microalbuminuria to macroalbuminuria [14]. We did not find a direct correlation between albuminuria and the risk for developing diabetic foot syndrome.

5. Conclusions

Patients with T2DM at high risk for diabetic foot syndrome have significantly impaired renal function, without the significant differences in other anthropomethric and metabolic parameters.

Simple serum creatinine measurement may be useful for detecting high-risk patients. Serum creatinine >143 μmol/L had a 95% specificity and serum creatinine >67 μmol/L had 95% specificity in detecting patients at high risk for the development of diabetic foot syndrome.

Future validation studies are needed to make this observation useful in everyday clinical practice.

Author Contributions

IA gave the idea for the article, wrote the paper, participated in drafting the article and gave her final approval. IM, IN, and NB participated in data acquisition, drafting of the article and gave their final approval. IB performed statistical analyses and gave their final approval. SJM and TM critically revised the manuscript, gave suggestions regarding data analysis and presentation and gave their final approval.

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