The Most Common Complications and Prevalence of Diabetic Kidney Disease in Patients with Diabetes Mellitus: a Single Center Experience

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Background: It is generally accepted that the most serious complication of diabetes melitus is diabetic kidney disease. Diabetic kidney disease (DKD) is the leading cause of chronic and end-stage kidney disease and multiple complications including cardiovascular disease, infection, and death. **Objective:** The aim of our study was to detect the development and/or progression of the main complications related to diabetes, that are associated with the subsequent development of renal dysfunction. **Methods**: This prospective cohort study that included 97 participants with diabetes mellitus of both the genders mean age 58.3 ± 14.4 years, lasted for one year. Patients were divided into two groups: 74 with some form of chronic kidney disease (CKD) and 23 without CKD at baseline. CKD was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 and/or the presence of albuminuria. **Results:** We treated 97 diabetics, 50 males (51%) and 47 femles (49%). The mean diabetes duration was 10.5 years. Six (6.2%) patients were type 1 DM and 91 (93.8%) were type 2 DM. The group with eGFR <60 mL / min/1.73 m^2 showed a higher incidence of cardiovascular disease (p <0.001) dyslipidemia (p = 0.0016), mean C reactive protein (CRP) (p=0.002) mean duration of diabetes was longer (p = 0.003), higher serum creatinine (p <0.003). The prevalence of albuminuria (micro or macroalbuminuria) was high in patients with advanced CKD (86,5%). The progression rate to macroalbuminuria was 81% at the end of follow –up and 18.2 % of diabetic patients had progressed to microalbuminuria from normalbuminuria. There was no deterioration in renal function in the group of patients with eGFR >60 mL/min., at the end of the study. Worsening of CKD at the end of follow-up was observed in 14.5% of diabetics, all with eGFR <60 ml / min / 1.73 m2, of whom six (10.9%) required initiation of renal replacement therapy. **Conclusion** Among our subjects with diabetes, the overall prevalence of diabetic kidney disease did not change significantly, while the prevalence of albuminuria increased and the prevalence of decreased eGFR increased.

Keywords: Diabetes mellitus; Diabetic nephropathy; Chronic kidney disease; Albuminuria.

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1. BACKGROUND

Diabetes mellitus (DM) is a worldwide public health challenge. WHO estimated that there were around 422 million people living with diabetes and that there was a rising trend in the number of people living with DM by 2040, prevalence is projected to increase to 642 million, with disproportionate growth in low- to middle-income countries (1,2). The reasons for this increase are multiple and involve epidemiological and socio-economic aspect, such as lifestyle and genetic background (3). Moreover, these patients are drawn to the attention of nephrologists and diabetologists because of the severity of clinical complications which are related to metabolic disease. Among these people, type 2 diabetes (T2DM) accounts for over 90% of all persons with diabetes (4). It is generally accepted that the most serious complication of diabetes mellitus is diabetic nephropathy (diabetic kidney disease in the K/DOQI Guidelines) (5). The development of diabetic kidney disease occurs both in type 1 and type 2 diabetes with similar evolution over time for both types of diabetes. Diabetic kidney disease (DKD) is frequently associated with T2DM and the leading cause of chronic kidney

Caracteristics	Total No pts (%)	CKD (-) No pts(%)	CKD (+) No pts(%)	P value
Number	97 (100)	23 (23.6)	74 (76.4)	
Male	50 (51.0)	12 (52.0)	38 (51.3)	0.511
Age yr	58.3 ± 14.4	56.6 ± 15.1	59.9 ± 13.7	0.321
Diabetes duration yr	10.5 ± 6.7	8.5 ± 6.7	11.8 ± 6.9	0.003
BMI (kg/m2)	25.1 ± 3.6	24.5 ± 3.4	25.9 ±4.0	0.152
Hypertension	71 (73.2%)	15 (65.2)	56 (75.6)	0.068
CVD	23 (23.7)	6 (26.1)	17 (73.9)	<0.001
Dyslipidemia	33 (34)	6 (26.0)	27 (36.5)	0.016
HbA1c	7.8 ± 1.8	7.5 ± 1,7	8.0 ± 1.8	0.108
Creatinine umol/L	97.3 ± 26.5	79.6 ± 17.7	106.0 ± 26.5	<0.001
eGFR, mL/ min/1,73m2	64.7 ± 16,5	85 ± 10.2	46.1 ± 17.4	<0,001
Cholesterol mmol/L	4.9 ± 1.0	4.8 ± 0.9	4.9 ± 1.0	0.217
Trigliceride mmol/L	2.0 ± 1.2	1.7 ± 0.9	2.2 ± 1.4	0.0015
CRP mg/dL	0.89 ± 1,3	0.77 ± 1.23	1.19 ± 1.6	0.002
Normoalbuminuria	33 (34)	23 (100.0)	10 (13.5)	
Microalbuminuria	9 (9.3)	0	9 (12.2)	
Macroalbuminuria	55 (56.7)	0	55 (74.3)	

Table 1. Baseline characteristics of the study population according to the presence chronic kidney disease at baseline. Values are presented as number (%) or mean ± standard deviation. Legend: CKD, chronic kidney disease; BMI, body mass index; HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease;

disease and end-stage renal disease. The glomeruli become deposited with abnormal proteins, leading to inflammation and scarring. Diabetic nephropathy leads to progressive deterioration in kidney function. Albumin extraction of 30-300 mg /24 hours (microalbuminuria) is the first detectable sign of renal injury associated with diabetes. Diabetic nephropathy was defined as persistent albuminuria > 300 mg/24 h, retinopathy, and no history of other renal disease. Chronic kidney disease (CKD) in the setting of diabetes or diabetic kidney disease (DKD), manifests clinically as albuminuria, reduced glomerular filtration rate (GFR), or both (4).

2. OBJECTIVE

The aim of our study was to detect the development and/or progression of the main complications related to diabetes, that are associated with the subsequent development of renal dysfunction. The secondary goal was to establish clinical and laboratorial parameters most associated with the presence of diabetic kidney disease in this population.

3. METHODS

This prospective cohort study that included 97 participants with diabetes mellitus of both the genders mean age 58.3 ± 14.4 years, was conducted at Clinic of Nephrology, Clinical Centre, Sarajevo, Bosnia and Herzegovina, during period of 1year (01.02.2020- 01.2.2021). Participants who were aged 18 years or older, with diabetes mellitus, defined as use of glucose-lowering medications (insulin or oral hypoglycemic medications), hemoglobin A1c of 6.5% or greater, or both, were included in the present analyses and had available data for medication use, hemoglobin A1c, serum creatinine concentration, and urine albumin and creatinine concentrations. Patients were divided into two groups regarding the presence or absence

Caracteristics	Baseline (No)	The end of follow-up (No)
Normoalbuminuria	33	27
Microalbuminuria	9	10
Macroalbuminuria	55	60
Total	97	97

Table 2.Transitions for albuminuria categories from baseline to the end of follow-up in diabetic patients

of CKD at baseline. We excluded subjects who had known inherited kidney diseases, cancer, or acute renal failure caused by other circumstances (drug use, contrast media, and so on). The data included gender, age, comorbid medical conditions, history of hypertension and cardiovascular disease (CVD), body mass index (BMI), daily urinary output, total cholesterol, triglycerides, C-reactive protein (CRP). Hypertension was defined as a systolic blood pressure above 140 mmHg or diastolic blood pressure above 90mmHg and/or need for antihypertensive medication. Cardiovascular disease was defined as a history of coronary, cerebrovascular and/or peripheral artery disease, and/or of congestive heart failure. Body mass index (BMI) was calculated using the following formula: BMI=weight (kg)/height (m^2). The blood samples were collected in the morning before the first meal and after 12 hours of fasting. Glycosylated hemoglobin (HbA1c) was analyzed using high-performance liquid chromatography. Serum creatinine concentrations were measured by a kinetic rate Jaffe method. CKD staging was done according to the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines of National Kidney Foundation (5). Stages of CKD were defined as follows: stage 1 (estimated glomerular filtration rate eGFR ≥90 mL/min/1.73 m^2); stage 2 (eGFR 60 to 89 mL/min/1.73 m^2); stage 3 (eGFR 30 to 59 mL/min/1.73 m^2); stage 4 (eGFR 15 to 29 mL/min/1.73 m^2); and stage 5

(eGFR <15 mL/min/1.73 m^2). The GFR was estimated using MDRD equation. MDRD equation: GFR= 32788 x Scr $^{-1.154}$ x age $^{-0.203}$ x constant. CKD was defined as eGFR <60 mL/min/1.73 m2 and/or the presence of albuminuria. Albuminuria was defined by the urinary albumin as microalbuminuria (30 to 300 mg/24h) or macroalbuminuria (>300 mg/24h). Any DKD was defined as albuminuria, reduced GFR, or both. The renal outcome was worsening nephropathy, defined as the initiation of renal replacement therapy, progression to macroalbuminuria, or worsening of CKD stage at the end of follow-up than at baseline.

Statistical analysis

The collected data were statistically processed, using the descriptive and statistical methods, with SPSS version 16.0, Med Calc and Microsoft Office Excel 2007 SP2. Data for continuous variables is presented as mean ± standard deviation, and categorical factors are reported as percentages. The significance of differences in measurements among groups was tested using the independent sample t-test, paired t-test, or Mann-Whitney U test for continuous measures. All P-levels were two-tailed, and statistical significance was defined if p <0.05.

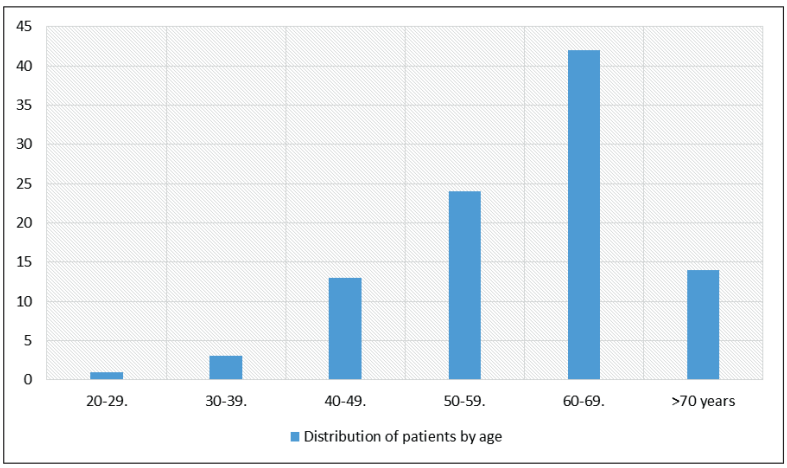

Figure 1. Distribution of patients by age

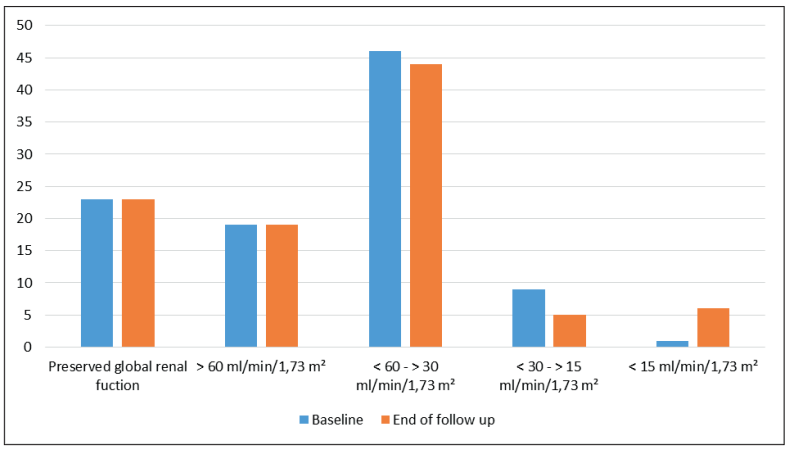

Figure 2. Comparasion of GF from baseline to end of follow up

4. RESULTS

In the study period of 1 year, we treated 97 diabetics, 50 males (51%) and 47 females (49%). The mean age was 58.3 ± 14.4 years and mean diabetes duration was 10.5 ± 6.7 years. Six (6.2%) patients were type 1 DM and 91 (93.8%) were type 2 DM. Fifty-six (57.7%) of the ninety-seven patients were older than sixty years (Figure 1).

The baseline clinical characteristics of all the study subjects are shown in Table 1.

Among the 97 patients with DM, 76 patients (76,4%) had CKD at baseline. The average duration of diabetes was longer in patients with CKD (p=0.003), they were older than those without CKD, and more frequent history of hypertension. The group with eGFR <60 mL/min/1.73 m^2 showed a higher incidence of cardiovascular disease (p<0.001), dyslipidemia (p=0.0016), average values C reactive protein (CRP) (p=0.002), higher serum creatinine (p<0.003) and the mean eGFR levels differed significantly between the no CKD and severe CKD group. In this study the prevalence of CVD in patients with CKD was 73.9%. Among the traditional CV risk factors were overweight (measured as a BMI>25kg/m2; average BMI was 25.1±3.6kg/ m2). Mean HbA1c and BMI did not differ significantly in both groups. The prevalence of albuminuria (micro or macroalbuminuria) was high in patients with chronic kidney disease, 86.5%. Only 13.5% of patients with CKD had normoalbuminuria. There was no deterioration in renal function in patients with GFR >60 by the end of the study.

Worsening of the stage of chronic renal disease at the end of follow–up occurred in 14.5% of diabetics, all with eGFR <60ml/min/1.73 m2. Initiation of renal replacement therapy was initiated in six patients (10.9%).

The rate of progression to macroalbuminuria was 81% (60/74) at the end of follow-up, and 18.2% (6/33) of patients with diabetes switched to microalbuminuria from normal albuminuria (Table 2).

5. DISCUSSION

Diabetic kidney disease is the leading cause of chronic and end-stage kidney disease in the world, leading to multiple complications including end-stage renal disease, cardiovascular disease, infection, and death (6). In present study, the prevalence of CKD was 76,4 %. In general, the rate of progression to CKD is slow, although there is a high prevalence of CKD in elderly patients (7, 8). This study included many older diabetics 57.8% (56/97 pts >60 years) who had diabetes for more than 10 years. Aging, T2DM, duration of diabetes ≥10 years are strong risk factors for deterioration of renal function. Risk factors for diabetic kidney disease can be classified as susceptibility factors (e.g., age, gender, race /ethnicity, and family history), initiation factors (e.g., hyperglycemia, and AKI), and pro-

gression factors (e.g., hypertension, dietary factors, and obesity) (4). The two most prominent identified risk factors are hyperglycemia and hypertension. Hypertension was found in 73.2% (71/97) of our diabetics. Hypertension is highly prevalent in patients with CKD and strongly correlated with left ventricular hypertrophy (LVH) and changes in cardiac structure tend to progress during CKD (9). Our study showed a high prevalence of cardiovascular disease in our population with CKD (73.9%). Chronic kidney disease patients present with a CV disease death rate that is 5 to 25 times higher than that seen in the general population (10). Poor glycemic control is an independent predictor of progression to the development of proteinuria (albuminuria) and / or end stage renal disease (ESRD) (11). Patients with early-stage DM1 or DM2 have shown that intensive blood glucose control early in the course of the disease shows a long-term beneficial effect on the risk of developing DKD (12, 13).

In patients with DM1, intensive glucose control intervention aimed at hemoglobin A1C (HbA1C) levels <7% reduced the nine-year risk of developing microalbuminuria and macroalbuminuria by 34% and 56%, respectively, compared to standard care (14). In our study, the prevalence of albuminuria was 86% (64/74) in patients with advanced CKD. Only 13.5% of patients with CKD had normoalbuminuria. It is generally believed that microalbuminuria serves as a marker for persons who may develop diabetic nephropathy and probably reflects its earliest manifestation (15). In patients with type 2 diabetes, one large study showed that subjects with macroalbuminuria had a higher rate of eGFR decline than subjects with microalbuminuria or normal albumin secretion, but this was not shown in another smaller study (16). A third study in a mixed group of subjects with type 1 and type 2 diabetes showed that subjects without albuminuria had a lower risk of worsening GFR than subjects with albuminuria (18).

Our study was done during the coronavirus pandemic. Hospital systems were rapidly collapsing in many countries, including Bosnia and Herzegovina, due to the large number of patients arriving at the same time without adequate treatment. The rapid collapse of the hospital health care system led patients to search for help from their family doctor. Patients returned to primary care due to all health problems, which certainly had a significant impact on the development and / or progression of major complications associated with diabetes, chronic and end-stage renal disease, and multiple complications, including cardiovascular disease, infection, and death, especially in persons over 65 years of age, who are a very risk group for COVID-19 infection (19-21). The importance of proper nutrition in controlling diabetes is well known. It has been proven that the active ingredients of food can strengthen or weaken the immune system (immunomodulation or immunosuppression). Organic balanced food adapted to each person (personal diet) is the first condition for creating an adequate natural defense system (22-24) .

6. CONCLUSION

Among our subjects with diabetes, the prevalence of albuminuria increased and the prevalence of decreased eGFR also increased. We are sure that lockdown, stress, limited physical activity, inadequate diet, during the coronavirus pandemic, have contributed to the development and worsening of complications of diabetic disease.

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