

# OBSERVATIONAL STUDY REGARDING RISK FACTORS AND COMORBIDITIES FOR CHRONIC KIDNEY DISEASE IN DIABETES MELLITUS PATIENTS FROM BIHOR COUNTY

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## ABSTRACT

**Introduction.** Chronic kidney disease is a common comorbidity in diabetes mellitus type 2 patients because of presence of numerous risk factors such as obesity, hypertension, hyperglycemia and dyslipidemia.

**Material and methods.** Our retrospective, observational study included 300 patients with type 2 diabetes mellitus from Bihor County and had the purpose to establish a clinical profile and to determine the risk factors associated with this pathology. Results. The prevalence of CKD was 75.67%. Older age, worse glucose control, presence of diabetic polyneuropathy and diabetic retinopathy, higher weight, past history of cardiovascular events, the presence of metabolic syndrome and hyperuricemia were associated with the presence of CKD.

**Conclusion.** The clinical characteristics of type 2 diabetes mellitus patients with CKD is significantly worse compared with the population without CKD.

**Keywords:** diabetes mellitus, chronic kidney disease, risk factors for renal disease

## INTRODUCTION

Diabetes mellitus is a major cause of CKD because of the numerous negative effects of hyperglycemia and insulin resistance at the glomerular level such as increased oxidative stress, glycation of glomerular proteins, activation of pro-inflammatory pathways and osmotic stress (1). Patients with diabetes mellitus are often obese and have metabolic syndrome. Metabolic syndrome represents a clinical association between obesity, hypertension, hyperglycemia and dyslipidemia that significantly increase the risk of cardiovascular disease, type 2 diabetes, chronic kidney disease (CKD), and total mortality. It was been observed that the incidence of CKD and end-stage renal disease in recent years has paralleled the increasing prevalence of metabolic syndrome has sparked a great interest in the role of metabolic syndrome as

a novel risk factor for both cardiovascular disease and CKD (1).

The association between metabolic syndrome and CKD greatly increases the cardiovascular risk, data from one study demonstrated that the presence of CKD (defined as eGFR <60 ml/min/1.73 m<sup>2</sup>) and metabolic syndrome (defined by the NCEP-ATPIII) is associated with a 5.56-fold higher risk of cardiovascular events (2). There are multiple pathways that predispose a person with metabolic syndrome to develop CKD. Hypertension specific for metabolic syndrome increases the intraglomerular pressure with apparition of albuminuria, enhanced sodium reabsorption as an effect of insulin resistance determines the activation or renin-angiotensin-aldosterone system because of lower levels of sodium at the level of macula densa with increased tonus of efferent arteriole and increase of glomerular filtration pressure, dyslipi-

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demia specific in metabolic syndrome promotes inflammation, oxidative stress with podocyte injury and pro-inflammatory cytokine promote the processes of glomerular fibrosis (3,4).

### AIM

The purpose of our retrospective, observational study was to establish the clinical profile, frequency of CKD and to analyze some epidemiological and clinical risk factors for CKD in a cohort of diabetes mellitus patients from Bihor county regardless if they have type 1 or type 2 diabetes mellitus.

### MATERIAL AND METHOD

Our study included 300 patients, with diabetes mellitus type 2 or type 1, evaluated in one day hospitalization, in the diabetes mellitus ward of the Oradea County Clinical Emergency Hospital. The study was done between 01.01.2016 and 31.12.2018. This study is an observational retrospective one. Systematic sampling method was used for the selection of the patients, every tenth hospitalized patient was included in the study; data used for the research was obtained from the analysis of the medical records. The study was done with the agreement of the hospital's Ethics Committee nr.11379/07.05.2019.

The criteria used for inclusion were: patients with age over 18 years, patients with confirmed diabetes mellitus and complete data in medical record. Exclusion criteria: patients in whom we did not have the complete data needed for the study, patients under medication that may have influenced the results (glucocorticoids), patients with major acute infections (not to influence blood glucose levels).

The following variables were determined for each patient: height, weight, BMI; diabetes mellitus type and duration; presence of comorbidities (cardiovascular disease: hypertension, myocardial infarction, ischemic heart disease), dyslipidemia, hepatic steatosis, presence of micro/macrovascular complications (diabetic retinopathy, diabetic polyneuropathy, arteriopathy). The following biological test values were determined: blood glucose, glycosylated hemoglobin, liver tests, hemoglobin, current and previous creatinine, current and former GFR, uric acid, lipid profile (cholesterol, TGL, HDL, LDL-cholesterol, TGL/HDL-ratio), the presence of proteinuria and/or changes in the urinary sediment.

Metabolic syndrome has been defined according to IDF criteria (5) as the presence of 3 of the

following conditions: systolic blood pressure  $\geq 130$  mmHg or diastolic blood pressure  $\geq 85$  mmHg or treatment for hypertension, hypertriglyceridemia  $\geq 150$  mg/dl or lipid-lowering treatment, increased fasting blood glucose above 100 mg/dl or antidiabetic treatment, HDL-cholesterol below 40 mg/dl in men and below 50 mg/dl in women or, for those with BMI  $> 30$  kg/m<sup>2</sup> central obesity can be affirmed, even if abdominal circumference was not measured.

Blood pressure values, according to the ESC/ESH 2018 Guide for the management of hypertension were defined as: normal systolic blood pressure  $< 130$  mmHg, diastolic blood pressure  $< 85$  mmHg, normal-high blood pressure SBP between 130 and 139 mmHg, diastolic blood pressure between 85 and 89 mmHg, target values for those with hypertension and treatment: below 140/90 mmHg (6).

Serum uric acid was considered elevated if it had values above 6 mg/dl in women, respectively 7 mg/dl in men. In the analysis performed, we included the patients with hyperuricemia who have values above these thresholds but also those who have normal serum uric acid values, but have hyperuricemia treatment (regardless of the type of medication). A value of HbA1c  $< 7\%$  was considered as very good glycemic control, a value of HbA1c between 7 and 8% was considered as good glycemic control, a value of HbA1c between 8.1 and 9% was considered as average glucose control while a HbA1c  $> 9\%$  was considered as uncontrolled diabetes mellitus.

CKD was defined according to the guidelines (7) by: reduction of glomerular filtration rate (RFG) below 60 mL/min/1.73 m<sup>2</sup>, with a minimum duration of 3 months or renal impairment lasting more than 3 months. Renal impairment can be diagnosed in the absence of knowledge of the etiology and consists of structural or functional abnormalities of the kidney reflected by: anomalies of urine examinations (proteinuria, albuminuria, hematuria, and leukocytosis); abnormalities of blood tests (nitrogen retention, dyselectrolytemia, metabolic acidosis); abnormalities of renal imaging investigations; pathological lesions of the kidneys at renal biopsy.

Statistical analysis was done using the SPSS 26.0 version, values were tested whether they have continuous distribution using Kolmogorov-Smirnov test. Chi-squared test was used for comparing frequencies and Student test was used for comparing mean values, a value of  $p < 0.05$  was considered statically significant.

## RESULTS

The general characteristics of the patients and the incidence of CKD according to stage are illustrated in Table 1 and Table 2.

**TABLE 1.** Characteristics of the included patients

Parameter	No	%
<b>Sex</b>		
Women	143	47.67
Men	157	52.33
<b>Age</b>		
<30 years	6	2
31-40 years	7	2.33
41-50 years	25	8.33
51-60 years	91	30.33
61-70 years	115	38.33
>70 years	56	18.67
<b>Living environment</b>		
Rural	98	32.67
Urban	202	67.33
<b>HbA1c</b>		
< 7%	105	35
7.1-8%	59	19.67
8.1-9%	55	18.33
>9%	81	27
<b>Diabetes complications</b>		
With complications	214	71.33
Diabetic polyneuropathy	200	66.67
Diabetic retinopathy	96	32
<b>Comorbidities</b>		
With associated pathology	287	95.67
Cardiovascular disease	277	92.33
Hypertension	263	87.67
Ischemic heart disease	233	77.67
Heart failure	113	37.67
Peripheral artery disease	80	26.67
Hepatic steatosis	205	68.33
COPD	71	23.67
Prostate adenoma	44	14.67
Hypothyroidism	80	26.67

**TABLE 2.** Prevalence of CKD in the included group

CKD	No	%
CKD	227	75.67
Stage 1	16	7.05
Stage 2	103	45.37
Stage 3	90	39.65
Stage 4	17	7.49
Stage 5	1	0.44

The differences between the two groups of diabetes mellitus patients, with and without CKD are illustrated in Table 3 and Table 4.

Both in the group with CKD and in the one without CKD, men predominated (50.66% vs 57.53%,  $p = 0.308$ ), the ratio men/women being

1:1, respectively 1.4:1. In the group with CKD the age of the patients was between 29 and 84 years, and in the group without CKD the age of the patients was between 16 and 83 years. The mean age was 63.84 years in the group with CKD, significantly higher than in the group without CKD (54.93 years,  $p < 0.001$ ). Both in the group with CKD and in the one without CKD, the patients from the urban environment predominated (67.84% vs 65.75%,  $p = 0.741$ ), the urban/rural ratio being 2.1:1, respectively 1.9:1.

In most patients with CKD, the duration of diabetes was over 6 years (73.57%), and in those without CKD it was between 1 and 10 years (65.76%). The mean duration was significantly longer in patients with CKD than in those without CKD (10.21 years vs. 6.00 years,  $p < 0.001$ ). Good and very good metabolic control was determined in 50.66% of patients with CKD and in 67.13% of those without CKD, the average value of HbA1c being significantly higher in the group with CKD than in those without CKD (8.15% vs. 7.71,  $p = 0.019$ ).

In the group with CKD the prevalence of complications was significantly higher than in the group without CKD (74.45% vs 61.64%,  $p = 0.036$ ). The difference is significant both in the case of polyneuropathy (70.04% vs 56.16%,  $p = 0.029$ ) and in the case of retinopathy (36.56% vs 17.81%,  $p = 0.003$ ). Oral antidiabetic monotherapy was administered to 35.68% of patients with CKD, a significantly lower percentage than in patients without CKD (67.12%,  $p < 0.001$ ), whereas insulin was administered significantly higher to patients with CKD than in those without (40.09% vs 19.18%,  $p = 0.001$ ).

The combination of oral antidiabetic drug and insulin was significantly lower in patients with CKD than in those without CKD (24.03% vs 13.70%,  $p = 0.058$ ). In patients with CKD, the prevalence of obesity was significantly higher than in patients without CKD (79.30% vs 57.53%,  $p < 0.001$ ), the mean BMI being also significantly higher in patients with CKD (33.27 kg/m<sup>2</sup> vs. 30.93 kg/m<sup>2</sup>,  $p < 0.001$ ). The prevalence of associated diseases was significantly higher in patients with CKD than in those without CKD (98.24% vs 87.67%,  $p < 0.001$ ). With the exception of COPD, prostate adenoma and hypothyroidism, where the prevalence was non significantly higher in patients with CKD ( $p > 0.05$ ), the prevalence of other asso-

ciated diseases was significantly higher in the group with CKD.

The major cardiovascular events in the antecedents were registered in a significantly higher percentage in the group with CKD (14.98% vs 4.11%,

$p = 0.014$ ). Both the prevalence of metabolic syndrome and hyperuricemia was significantly higher in patients with CKD than those without (81.50% vs. 67.12%,  $p = 0.010$ , respectively 49.78% vs. 34.25%,  $p = 0.021$ ).

**TABLE 3.** Epidemiological clinical characteristics, comorbidities and pharmacological treatment according to presence or absence of CKD

Parameter	CKD (n = 227)		Without CKD (n = 73)		p-value
	No.	%	No.	%	
<b>Sex</b>					
Women	112	49.34	31	42.47	0.30
Men	115	50.66	42	57.53	
<b>Age</b>					
<30 years	1	0.44	5	6.85	< 0.01
31-40 years	3	1.32	4	5.48	
41-50 years	15	6.61	10	13.7	
51-60 years	61	26.87	30	41.1	
61-70 years	96	42.29	19	26.03	
>70 years	51	22.47	5	6.85	
<b>Living environment</b>					
Rural	73	32.16	25	34.25	0.74
Urban	154	67.84	48	65.75	
<b>Diabetes duration</b>					
< 1 year	12	5.29	11	15.07	< 0.01
1-5 years	48	21.15	23	31.51	
6-10 years	50	22.03	25	34.25	
>10 years	117	51.54	14	19.18	
<b>HbA1c</b>					
< 7%	74	32.6	31	42.47	0.01
7.1-8%	41	18.06	18	24.66	
8.1-9%	47	20.7	8	10.96	
>9%	65	28.63	16	21.92	
<b>Complications</b>					
With complications	169	74.45	45	61.64	
Diabetic polyneuropathy	159	70.04	41	56.16	0.02
Diabetic retinopathy	83	36.56	13	17.81	0.03
<b>Diabetes treatment</b>					
Oral antidiabetics	81	35.68	49	67.12	< 0.01
Insulin	91	40.09	14	19.18	< 0.01
Oral antidiabetics + insulin	55	24.23	10	13.7	0.05
<b>Weight status</b>					
Normal weight	12	5.29	9	12.33	<0.01
Overweight	35	15.42	22	30.14	
Obesity	180	79.3	42	57.53	
Obesity gr.1	106	46.7	24	32.88	
Obesity gr.2	50	22.03	14	19.18	
Obesity gr.3	24	10.57	4	5.48	
<b>Major cardiovascular events</b>					
Acute coronary syndrome	15	6.61	0	0	0.01
Stroke	15	6.61	3	4.11	
Acute coronary syndrome + stroke	4	1.76	0	0	
Total	34	14.98	3	4.11	



**TABLE 4.** Prevalence of comorbidities according to CKD presence

Associated diseases	CKD (no=227)		Without CKD (no=73)		p
	No.	%	No.	%	
<b>With associated diseases</b>	<b>223</b>	<b>98.24</b>	<b>64</b>	<b>87.67</b>	<b>&lt;0.001</b>
<b>Cardiovascular disease</b>	<b>218</b>	<b>96.04</b>	<b>59</b>	<b>80.82</b>	<b>&lt;0.001</b>
<b>Hypertension</b>	<b>206</b>	<b>90.75</b>	<b>57</b>	<b>78.08</b>	<b>&lt;0.001</b>
<b>Ischemic heart disease</b>	<b>189</b>	<b>83.26</b>	<b>44</b>	<b>60.27</b>	<b>&lt;0.001</b>
<b>Heart failure</b>	<b>98</b>	<b>43.17</b>	<b>15</b>	<b>20.55</b>	<b>&lt;0.001</b>
<b>Peripheral artery disease</b>	<b>67</b>	<b>29.52</b>	<b>13</b>	<b>17.81</b>	<b>0.049</b>
<b>Hepatic steatosis</b>	<b>168</b>	<b>74.01</b>	<b>37</b>	<b>50.68</b>	<b>&lt;0.001</b>
<b>COPD</b>	<b>56</b>	<b>24.67</b>	<b>15</b>	<b>20.55</b>	<b>0.472</b>
<b>Prostate adenoma</b>	<b>36</b>	<b>15.86</b>	<b>8</b>	<b>10.96</b>	<b>0.304</b>
<b>Hypothyroidism</b>	<b>62</b>	<b>27.31</b>	<b>18</b>	<b>24.66</b>	<b>0.657</b>
<b>Metabolic syndrome</b>	<b>185</b>	<b>81.5</b>	<b>49</b>	<b>67.12</b>	<b>0.01</b>
<b>Hyperuricemia</b>	<b>113</b>	<b>49.78</b>	<b>25</b>	<b>34.25</b>	<b>0.02</b>

## DISCUSSIONS

In a study performed on 27,029 type 2 diabetes mellitus patients the factors that were predictors of CKD were age (the prevalence increased with increasing age), sex (male gender was identified as a risk factor), body-mass index (increased body-mass index was associated with increased CKD), triglycerides (increased values associated with increased prevalence) and LDL-cholesterol (8). In our study sex did not have any influence on CKD prevalence, while age and body-mass index were significantly associated with it. Metabolic syndrome as demonstrated by other studies represents an independent predictor of CKD in diabetes mellitus patients (9). The prevalence of cardiovascular disease was significantly higher in our group of CKD patients compared with patients without CKD, as demonstrated by data in literature (10). Patients with retinopathy and polyneuropathy are associated with CKD, as data from literature demonstrates retinopathy is a significant predictor not only for CKD presence but also for CKD progression (11). The same was true for diabetic neuropathy (12), which demonstrated that generally patients with CKD have a significant number of diabetic complications both microvascular and macrovascular. None of the included patients were on SGLT-2 or GLP-1 agonist therapy, this is particularly importance since these drugs decrease cardiovascular risk and offer renal protection, they reduce the risk of a diabetes mellitus patients for glomerular rate filtration decline and progression towards end stage kidney disease (13). It is also significantly that worse glycemic control is associated with CKD, there is no surprise regarding the

physio-pathological link between the two but the fact that only 35% of the included patients have a good glycemic control, a fact confirmed by numerous studies (14). Therapeutical education, use of modern types of insulin, adherence to therapeutic protocols and frequent monitorization of patients are mandatory for improving glucose control (14).

These data illustrate the importance of CKD screening in diabetes mellitus patients that have already at least one microvascular complication. Also, our study demonstrates the importance of interdisciplinary medical evaluation of diabetes mellitus patents with CKD given their higher prevalence of comorbidities, especially the cardiovascular ones.

## CONCLUSIONS

The prevalence of associated diseases was significantly higher in patients with CKD than in those without CKD and the major cardiovascular events in the antecedents were significantly higher in the group with CKD. Both the prevalence of MS and hyperuricemia was significantly higher in patients with CKD than in those without. Given the complex pathology that affects individuals with diabetes mellitus and CKD, physicians should pay attention and not forget about the importance of interdisciplinary in evaluation of these patients. Given the impact of glycemic control and obesity on CKD prevalence, novel therapies such as GLP-1 agonists or SGLT-2 inhibitors can be used as early pharmacologic agents for reducing weight, improving glucose control and offering cardiovascular protection.

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