RISK FACTORS FOR DEVELOPMENT OF CARDIOVASCULAR COMPLICATIONS IN PATIENTS WITH CHRONIC RENAL DISEASE AND DIABETIC NEPHROPATHY

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Abstract

Introduction: Cardiovascular diseases are the most frequent causes of morbidity and mortality in patients with chronic renal disease. The aim of our paper is to evaluate the risk factors of cardiovascular complications in patients with various stages of chronic renal disease (CRD), with or without diabetes mellitus (DM).

Patients and methods: The study included 98 patients with different stages of the CRD, with creatinine clearance <60 ml/min/1,73m2, and laboratory parameters monitored: homocysteine, BNP, cholesterol, LDL, HDL, HbA1c, Body Mass Index (BMI). First group comprised 49 patients with DM, age 50-82 years, M 28/F 21. Second group comprised 49 patients without DM, age 35-80 years, M 18/F 31. The IMT (intima media thickness) was measured by B-mode ultrasonography, and all patients had echocardiography examination done by 2D Doppler ultrasonography.

Results: The IMT values in diabetic patients had statistically significant positive correlation with homocysteine values of r=0,9393, p<0,034, and cholesterol r=0,289, p<0,05, compared to non-diabetics. A significant negative correlation was found between the ejection fraction (EF) and BMI in both groups, more prominent in non-diabetics r=0,289, p<0,044 (diabetics r=0,162, p>0,05). 47,4% of diabetics had arteriosclerotic changes on carotid arteries, 8,5% had stenosis of ACC, and 22,0% had rhythm abnormalities on ECG.

A positive correlation between IMT and BMI was found in diabetics, but was not statistically significant r=0,111, p>0,05. In the diabetics group a significantly higher (p<0,05) values of BNP, HbA1c, proteinuria, BMI, and cholesterol were found, and significantly lowered EF (p<0,0001).

Conclusion: Risk factors for cardiovascular complications in patients with DM are various, and the most pronounced significance was found in the values of homocystein, BNP and cholesterol.

KEY WORDS: Diabetes mellitus, chronic renal disease, cardiovascular complications.

Introduction

Diabetic nephropathy is one of the most significant complications of diabetes mellitus and also the most frequent cause of end-stage renal insufficiency. The number of patients who end up on an active haemodialysis treatment increased by 20% in the last 10 years. Cardiovascular complications, induced by accelerating arteriosclerosis, comprise almost 50% of all morbidity and mortality causes in diabetics, and patients with renal insufficiency caused by diabetes have an increased risk of cardiovascular complications (1). It is well-known fact that the traditional risk factors for cardiovascular disease are: diabetes mellitus, anemia, microalbuminuria, proteinuria, azothemia, hyperlipidemia, obesity, smoking, physical inactivity, and non-traditional factors are: metabolic and hemodynamic disturbances. Combined impact of diabetes mellitus and a renal disorder increased the risk of cardiovascular (CV) complications and offer poorer prognosis for survival of these patients compared to general population. There are a number of hemodynamic and metabolic disorders in diabetic nephropathy, which disturb the structure and function of myocardium, and the progressive hypertrophy of the left ventricle (LVH) starts in the early stage of renal insufficiency with still normal secretory function. It starts with the lowering of the glomerular filtration rate (GFR), combined with arterial hypertension and anemia, which mark the future LVH.

Aim

The aim of the study was to evaluate the frequency of risk factors for cardiovascular disease in patients with various stages of renal disease, with or without diabetes mellitus.

Materials and Methods

The study comprised 98 patients with different stages of chronic renal disease (CRD) with creatinine clearance (Clc) ≤ 60ml/min/1,73 m^2. The first group consisted of 49 patients with diabetes (DM), mean age 64,20±9,39 years. There were 28 (57,1 %) males and 21 (42%) females. 28 (47,4%) patients received the insulin therapy. All patients received antidiabetic, antihypertensive, antilipemic, diuretic and cardio protector medication. The second group consisted of 49 non-diabetic patients, mean age 63,67±10,36 years. There were 18 (36,7%) males and 31 (42,9%) females. The causes of CRD were: Chronic pyelonephritis – 18 patients (36,7%), chronic glomerulonephritis – 10 patients (20,4%), polycystic kidney disease – 10 patients (20,4%), uric arthritis – 3 patients (6,1%), nephroangiosclerosis – 2 patients (4,1%), obstructive nephropathy – 2 patients (4,1%), Renal cancer – 2 patients (4,1%), kidney agenesis – 1 patient (2%), amyloidosis – 1 patient (2%). All patients received anti hypertension medication, antilipemics, antianemics, diuretics and cardio protectors. The standard laboratory methods, used by the central laboratory at the Clinical Center, were used: Hb, Hct, Fe, ferritin, urinary proteins, creatinine clearance, total cholesterol, HDLC, LDLC, triglycerides, blood glucose, HbA1c, homocysteine, BNP. The values of systolic and diastolic pressures were measured, and also ECG, heart ultrasound, and Doppler of carotid arteries were obtained. The following statistical methods were used in data processing: number, percentage, arithmetic mean, standard deviation, standard error, range, Chi-square test ($\chi 2$), ANOVA (one-way analysis of variance) and Spear correlation coefficient ($p<0,05$).

Results

It can be seen in table 1 and on chart 1, respectively, that in diabetics group there were 42,9% (21) of females and 57,1% (28) of males. Mean age was 64,2±9,39 years. Chart 2. shows that in the non-diabetic group there were significantly more females 63,3% (31) than males 36,7% (18). Mean age was 63,67±10,36 years.

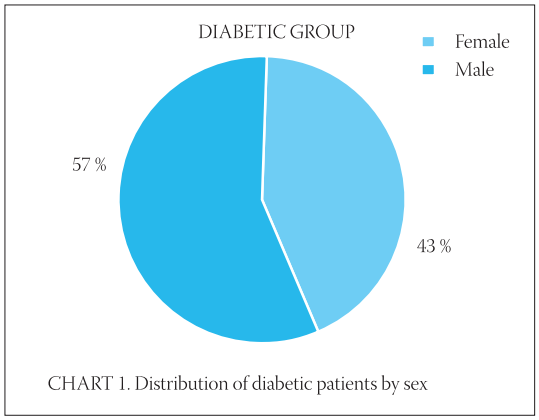

CHART 1. Distribution of diabetic patients by sex

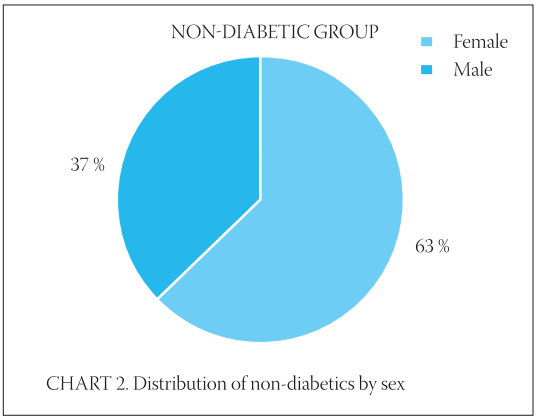

CHART 2. Distribution of non-diabetics by sex

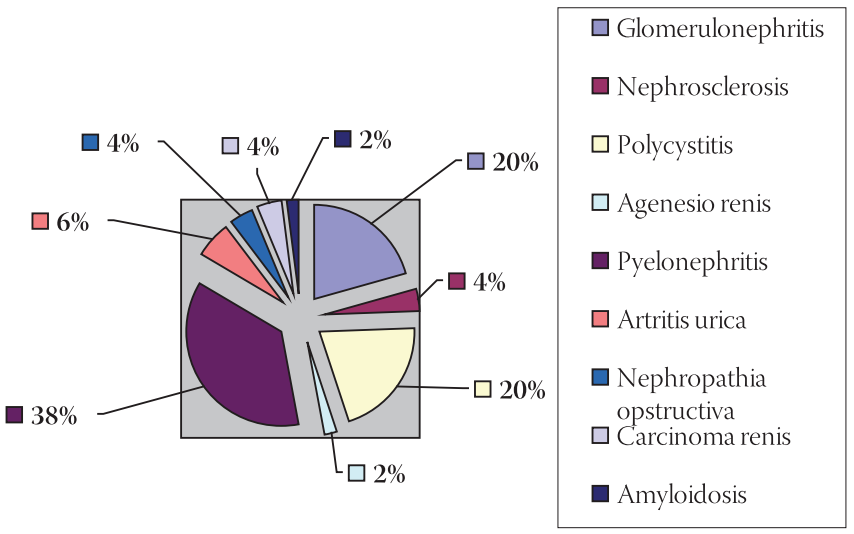

CHART 3. Causes of the CRD in non-diabetics

	Diabetics n=49	Non-diabetics n=49	Total n=98
Males	28 (57,1 %)	18 (36,7 %)	46 (46,9 %)
Females	21 (42,9 %)	31 (63,3 %)	52 (53,1 %)
Total	49 (50 %)	49 (50 %)	98 (100 %)

χ^2=4,097 p=0,043

TABLE 1. Distribution of patients by sex

Chart 3 shows the distribution of causes of CRD in non-diabetic group: chronic pyelonephritis – 18 patients (36,7%), polycystic kidney disease – 20,4% (10 patients), chronic glomerulonephritis – 20,4% (10 patients), renal cancer – 4,1% (2 patients), obstructive nephropathy – 4,1% (2 patients), uric arthritis – 6,1% (3 patients), kidney agenesis – 2% (1 patient), amyloidosis – 2% (1 patient). nephroangiosclerosis – 4,1% (2 patients). Table 2 shows that diabetics have significantly higher values (p<0,001) of BMI, urinary proteins, blood glucose, HbA1c, BNP and IMT, and significantly lower values of EF. Mean value of homocysteine in the groups were also increased, but ranges between minimal and maximal values were much higher in diabetics group. Correlation between IMT and LDLC in diabetics is statistically significant R0=0,064; p<0,05. In non-diabetics there was no significant correlation. (Chart 4)

There is a positive, statistically significant correlation between IMT and BNP in diabetics R0=0,0303; p<0,034. There was no significant correlation in non-diabetics. (Chart 5)

There is negative statistical correlation between EF and BMI in both groups, more pronounced in non-diabetics R0=0,289; p<0,044, than in diabetics R0=0,162; p>0,05. (Chart 6)

Parameter	Patient Group	Mean value		p value
BMI	Diabetics	32,9	±3,8	p <0,001
kg/m²	Non-diabetics	28,7	±2,1	
Creatinine	Diabetics	232,1	±151,4	n.s.
µmol/l	Non-diabetics	236,3	±132,1	
Urop	Diabetics	1,4	±1,7	p<0,001
gr/l	Non-diabetics	0,7	±1,1	
Creat. Clear.	Diabetics	37,2	±18,1	n.s.
ml/min.	Non-diabetics	36,8	±19,1	
Hb	Diabetics	125,9	±17,7	n.s.
gr/dl	Non-diabetics	127,6	±17,3	
Fe	Diabetics	12,3	±3,8	p<0,001
µg/ml	Non-diabetics	13,8	±4,8	
Chol	Diabetics	5,4	±1,4	n.s.
mmol/L	Non-diabetics	5,9	±1,7	
HDLC	Diabetics	1,1	±0,4	n.s.
mmol/L	Non-diabetics	1,1	±0,3	
LDLC	Diabetics	3,3	±1,2	n.s.
mmol/L	Non-diabetics	3,8	±1,7	
Trig	Diabetics	2,3	±1,2	n.s.
mmol/L	Non-diabetics	2,5	±1,4	
Blood glucose	Diabetics	9,1	±3,8	p<0,001
mmol/L	Non-diabetics	6	±0,8	
HbA1c	Diabetics	7,5	±1,3	p<0,001
(%)	Non-diabetics	6	±0,4	
Homocyst	Diabetics	22,1	±15,4	n.s.
umol/L	Non-diabetics	22,1	±8,1	
BNP	Diabetics	508	±851,0	p<0,001
pg/mL	Non-diabetics	227,5	±274,9	
BP systolic	Diabetics	154,2	±24,6	n.s.
mmHg	Non-diabetics	145,8	±23,4	
BP diastolic	Diabetics	90,4	±11,9	n.s.
mmHg	Non-diabetics	87,7	±9,4	
IMT	Diabetics	1,1	±0,3	p<0,001
mm	Non-diabetics	0,8	±0,2	
EF	Diabetics	46,2	±10,9	p<0,001
(%)	Non-diabetics	51,4	±11,2	

TABLE 2. Laboratory values by the groups

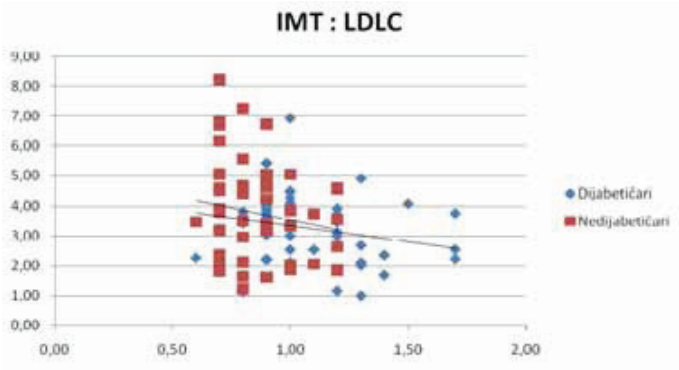

CHART 4. Graphical presentation of correlation between IMT and LDLC by the groups

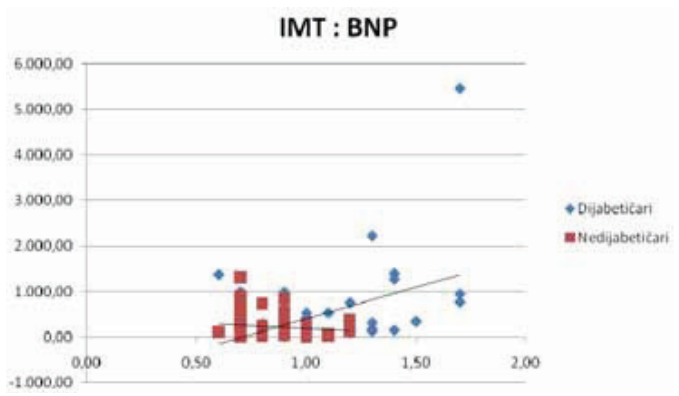

CHART 5. Graphical presentation of correlation between IMT and LDLC by the groups

Table 3. shows that in the diabetic group there was more patients with hypertension 36,7% (18 patients), myocardiopathy 28,6% (14 patients), healed myocardial infarction 24,5% (12 patients), implanted electro stimulator 8,2% (4 patients), and rhythm disorders 22% (13 patients). Equal number of patients in both groups had angina pectoris 14,3% (7 patients) and performed aortic-coronary by-passes 18,4% (9 patients). Two patients from the second group (non-diabetics) had aortic aneurism surgery. Table 4. shows that in diabetic group there was a larger number of patients with atherosclerotic changes

	Diabetics n=49	Non-diabetics n=49	Total n=98
HTA	18 (36,7%)	14 (28,6%)	32(32,7%)
Pacemaker	4(8,2%)	2 (2,1%)	6(6,1%)
Myocardiopathy	14 (28,6%)	3(6,1%)	17(18,5%)
Aortic-coronary by-pass	9(18,4%)	9(18,4%)	18(18,4%)
AMI	12(24,5%)	6(12,2%)	18(18,4%)
Angina pectoris	7(14,3%)	7(14,3%)	14(14,3%)
Op. Aortic aneurism	0(0%)	2(4,1%)	2(2%)
Rhythm abnormalities on ECG	13(22%)	10(16,9%)	23(38,9%)

TABLE 3. Distribution of heart diseases in the two groups, diabetics and non-diabetics

	Diabetics n=49	Non-diabetics n=49	Total n=98
Arteriosclerotic changes in carotids	28(47,40%)	6(10,20%)	34(57,60%)
Stenosis of one of the ACCs 40%-70%	5(8,50%)	3(5,00%)	8(13,50%)
Rhythm abnormalities on ECG	13(22,00%)	10(16,90%)	23(38,90%)

χ^2=8,490 p=0,2044

TABLE 4. Changes in Common Carotid Artery (ACC) by the groups

	Diabetics n=49	Non-diabetics n=49	t	p
Age	64,20±9,39	63,67±10,36	0,1	n.s.
BMI (kg/m^2)	32,94±3,83	28,73±2,08	45,5	p<0,0001
Hb (g/l)	125,89±17,71	127,63±17,26	0,2	n.s.
Systolic (mmHg)	154,18±24,61	145,81±23,43	3,0	n.s.
Diastolic (mmHg)	90,41±11,89	87,65±9,41	1,6	n.s.
LvldD (mm)	5,89±0,47	5,45±0,59	16,6	p<0,0001
LAD (mm)	4,28±0,49	4,00±0,52	7,0	p<0,009
EF (%)	46,18±10,88	51,45±11,25	5,5	p<0,021
LVPwd (mm)	1,42±0,15	1,16±0,21	49,1	p<0,0001
lVSd (mm)	1,46±0,21	1,24±0,23	22,1	p<0,0001
LV mass index (g/m^2)	726,98±165,44	534,02±151,45	36,3	p<0,0001

TABLE 5. Mean values of ventricular walls and the septum thickness

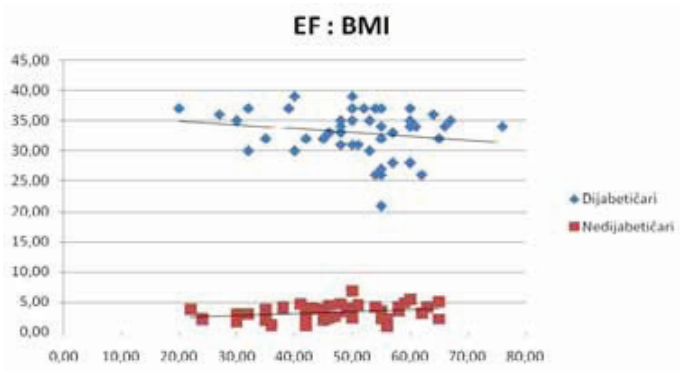

CHART 6. Correlation between EF and BMI by the groups

on carotid arteries 47,40% (28 patients), and ACC-ACI 40-70% stenosis had 8,5% (5 patients) diabetics. It can be seen in table 5 that the thickness of all measured ventricular walls in diastole LA, LV, posterior wall and the septum was significantly higher in diabetics, while the ejection fraction (EF) was lower. The LV mass index was significantly higher in the diabetics group.

Discussion

Cardiovascular diseases (CVD) are the most frequent complications of type 2 diabetes and in more than 60% of diabetics constitute the cause of death (1, 3, 7, 9). Our study shows that patients with diabetic nephropathy had more risk factors, both traditional and non-traditional, for the development of cardiovascular complications compared with non-diabetic patients. Increased body weight was more frequent in diabetics group, which is confirmed by significantly higher BMI values. The obesity is directly to blame for the occurrence of insulin resistance. The higher BMI further induces metabolic disturbances of lipids and blood glucose levels, which combined with hypertension, directly jeopardize the architecture and function of the heart muscle, and contribute to the development of arteriosclerosis (13, 14, 15). We have stressed that obesity and unregulated glycemia are directly reflected on lipid metabolism disorder, which further causes the development of arteriosclerosis and changes in peripheral and blood vessels of the heart. The diabetic group had higher mean values of HDLC cholesterol, while LDLC and total cholesterol were a bit higher in the non-diabetic group, which is consistent with the data from the literature (8, 18). Comparing the mean cholesterol values by the groups with carotid artery intima-media thickness (IMT), we have found statistically significant positive correlation between the IMT and LDLC cholesterol $R_0=0,289$; $p<0,05$, in the diabetics group. Mean values of Hct and Fe in diabetics group were somewhat lower; a significant anemia syndrome has not been found in neither studied group, probably because a large number of patients were receiving substitution therapy of erythropoietin and iron supplements, as suggested in some studies (6). Metabolic disorders in diabetics associated with increased body weight induce not only systemic, but also glomerular hypertension (although there are accounts of hypertension as an independent risk factor for cardiovascular occurrence), which affect the occurrence of microalbuminuria, proteinuria, and also represents a significant cardiovascular risk (9, 13, 14, 15, 16, 19, 21). We have found higher mean values of systolic and diastolic arterial pressures in the diabetics group, and significantly higher mean value of proteinuria, which other authors also suggest (1, 2, 21). Evaluation of cardiovascular risks in the studied groups was based on ECG and echocardiography findings. Risk factors inducing the development of future disorders in the heart are microangiopathies of coronary blood vessels, neuropathies of the heart nervous system, metabolic disorders and fatty degeneration of the myocardium (2, 7, 8). All of these changes occur as a consequence of high blood glucose and HbA1C levels in unregulated diabetes (1, 3, 7, 19). There were significantly higher mean values of blood glucose and HbA1C in our study, and a higher number of diabetics with left ventricular hypertrophy (22%) and heart rhythm abnormalities (1, 3). Also, a higher number of diabetics had implanted electro stimulator (8,2%), and higher number of patients had healed myocardial infarction (24,5%,), compared to non-diabetics. The number of patients with angina pectoris and performed aortic-coronary by-passes was equal in both groups. It is known that hyper-homocysteinemia, identified as a possible cause of cardiovascular disease,

causes arteriosclerosis (12), and increased heart mass (13), and represents a significant risk factor of cardiovascular morbidity and mortality (13). We have found increased mean values of homocysteine in both groups, but the range between the lowest and the highest values was more significant in diabetics group (4). Significant arteriosclerotic changes were found in carotid arteries in 47,4% of patients, and 40-70% stenosis in one of the ACC in 8,5% of patients in diabetics group. As a newer marker that can be used for identification of cardiovascular complications is BNP (Brain Natriuretic Peptide), which is synthesized as a pre-pro BNP, mostly in myocardium of the ventricles, and whose value depends on heart contractility and load-pressure in the heart (overload). Increased serum values of the BNP is seen in patients with dysfunction of the left ventricle, correlates with the increase of pulmonary capillary pressure, with the increase in the end-diastolic pressure in the left ventricle, and ejection fraction in patients with systolic dysfunction (3, 5, 16, 17, 20, 21). A significantly higher value of BNP was found in patients with diabetic nephropathy. A significantly lower ejection fraction was found by echocardiography in diabetics group, and negative correlation between EF and BMI (R0=0,162; p<0,05). We also found a significantly higher LV mass index in diabetics group as a sign of hypertrophy of the left ventricle (20, 21).

Conclusion

Significantly higher values of BMI, urinary proteins, blood glucose, HbA1C, BNP and IMT were found in the diabetics compared to the non-diabetics group, and significantly lower values of ejection fraction (EF).

There is a significant positive correlation between IMT and BNP and IMT and LDLC in diabetics group, and negative correlation between EF and BMI.

A higher number of patients with increased systolic and diastolic pressures, healed myocardial infarction, rhythm abnormalities, implanted electro stimulators, and arteriosclerosis of the ACC were found in the diabetics group.

Our study showed that metabolic disorders in diabetic nephropathy, caused by an uncontrolled increase of blood glucose and HbA1C and other laboratory parameters, led to more frequent cardiovascular complications in the diabetics group, and that the regulation of their values was of strategic significance in the treatment of nephropathy. The results of the study are to a large extent limited by the fact that the patients in both groups were treated by reference therapies respectively.

List of Abbreviations

IMT	intima-media thickness
LDLC	low density lipoprotein cholesterol
HDLC	high density lipoprotein cholesterol
trig	triglyceride
BNP	Brain Natriuretic Peptide
EF	ejection fraction
BMI	body mass index
ACC-ACI	common carotid artery- internal carotid artery
CVD	cardiovascular diseases
AMI	acute myocardial infarction
BP - HTA	blood pressure - arterial hypertension
LVH	left ventricle hypertrophy
ECG	electrocardiograph
Hb	haemoglobine
Hct	hematocrit
Fe	iron
HbA1c	haemoglobine A1c
GFR	glomerular filtration rate
CRD	chronic renal disease
DM	diabetes mellitus

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