Cardiovascular complications in patients with diabetic nephropathy receiving pharmacological versus renal replacement therapy

Irena Głowińska [1,2], Janusz Grochowski [1], Jolanta Małyszko [2]

[1] Dialysis Center, Maków Mazowiecki, Poland

[2] Department of Nephrology and Transplantology, Medical University, Białystok, Poland

Abstract: Introduction. Diabetic nephropathy is a significant complication of diabetes mellitus and one of the major causes of renal replacement therapy. Cardiovascular complications are predominant causes of death in these patients. **Objectives.** To evaluate the influence of hemodialysis on cardiovascular risk factors and on their frequency in diabetic nephropathy patients. **Patients and methods.** 4 groups of renal failure patients were studied. Group 1 consisted of 71 hemodialyzed patients with non-diabetic nephropathy. Group 2 consisted of 29 hemodialyzed patients with diabetic nephropathy. Group 3 consisted of 50 patients with renal failure in the predialysis period (glomerular filtration rate <60 ml/min). Group 4 consisted of 50 non-dialyzed patients with diabetic nephropathy in the pre-dialysis period. Complete blood count, blood gas, blood urea nitrogen, creatinine, glucose, lipidogram, electrolytes, parathormone, iron and dialysis adequacy (Kt/V) were assessed. Arterial blood pressure, resting ECG, echocardiography, body mass index, ankle–arm index, the prevalence of ischemic heart disease, myocardial infarction and chronic heart failure (NYHA classification) were also evaluated. **Results.** In hemodialyzed patients with diabetic nephropathy lower complete blood count, less severe calcium-phosphate disorders, higher triglycerides and lower high-density lipoproteins cholesterol, with more frequent obesity, ischemic heart disease and peripheral arterial obstructive disease were found. Myocardial hypertrophy, cardiac arrhythmias, contractility disturbances, myocardial infarction and chronic heart failure were more common in the hemodialyzed patients, regardless of the cause of the renal disease. **Conclusions.** The risk factor for cardiovascular complications is greater in patients with diabetic nephropathy. Hemodialysis increases the frequency of cardiovascular complications in these patients and adversely affects the outcomes.

Key words: arterial hypertension, chronic heart failure, coronary artery disease, diabetic nephropathy, peripheral arterial obstructive disease

INTRODUCTION

Diabetic nephropathy is one of the major complications of both type 1 and 2 diabetes mellitus; it is also at present one of the main causes of renal replacement therapy world-wide. The number of diabetic patients who are hemodialyzed has increased by 20% over the past 10 years, which is linked to both the wide availability of renal replacement therapy and ageing of society [1-4].

Cardiovascular complications induced by accelerated development of atherosclerosis constitute even up to 50% of all the causes of mortality in hemodialyzed diabetic patients. The longest number of cardiovascular complications are found in the youngest patients [5-8].

Patients with diabetes-induced renal failure are at risk of both diabetes-specific complications and those tied to renal failure and renal replacement therapy, such as proteinuria, fluid retention, anemia, hyperthyroidism, hyperhomocysteinemia, oxidation stress, chronic inflammatory state and coagulation disorders. Coexistence of renal failure, diabetes mellitus and cardiovascular diseases carries poorer prognosis and survival as compared to the general population [9,10]. Renal failure increases the risk of cardiovascular complications fivefold, whereas dialysis – twentyfold.

In patients with diabetic nephropathy there are a number hemodynamic and metabolic disturbances that affect the structure and function of the myocardium. Progressive left ventricular hypertrophy (LVH) starts at an early stage of renal failure even with the normal secretory function; it advances with the decrease in glomerular filtration rate (GFR), whereas the concomitant arterial hypertension and anemia determine further LVH [8,11-15].

Correspondence to:
Prof. Jolanta Małyszko, MD, PhD, Klinika Nefrologii i Transplantologii, Uniwersytet Medyczny, ul. Żurawia 14, 15-540 Białystok, Poland, phone: +48-85-74-09-464, fax: +48-85-74-34-586, e-mail: jolmal@poczta.onet.pl
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Table 1. Population data describing the analyzed groups

	Group 1	Group 2	Group 3	Group 4	p
Age	55.2 ±16.7	59.8 ±14.36	57.4 ±16.65	63.7 ±11.93	NS
Sex (%) W/M	31/69	48/52	42/58	48/52	NS 0.085 (1 vs. 2)
CKD duration	6.88 ±5.86	5.48 ±3.70	3.36 ±3.85	2.61 ±1.95	0.0003 (1 vs. 3) 0.0002 (2 vs. 4)
HD duration	3.92 ±4.21	2.81 ±2.51	–	–	NS
DM duration		17.7 ±4.64	–	18.4 ±7.51	NS
Cigarettes (%)	27	10	40	40	0.07 (1 vs. 2) 0.005 (2 vs. 4)
BMI	27.46 ±6.1	30.45 ±9.1	27.54 ±3.00	31.64 ±5.8	0.03 (3 vs. 4)

Values given as average ±standard deviation.

Abbreviations: BMI – body mass index, DM – diabetes mellitus, HD – hemodialysis, CKD – chronic kidney disease, NS – not significant

The aim of the study was to evaluate risk factors of cardiovascular diseases as well as the effect of hemodialysis (HD) on the frequency of these diseases in patients with diabetic nephropathy. In addition, the frequency of cardiovascular complications were analyzed.

PATIENTS AND METHODS

4 groups of patients with renal failure treated in the Dialysis Centre and the Outpatient Clinic of Nephrology (the Danish Red Cross SP ZOZ ZZ in Maków Mazowiecki) in the years of 2000–2004 were studied (Table 1). The study was retrospective. The patients' medical records and dialysis protocols were analyzed. The study was approved by the Bioethical Committee of the Regional Medical Chamber in Warsaw.

Group 1 included 71 hemodialyzed patients (22 women and 49 men) from 18–82 years old. The patients had been hemodialyzed 3 times a week for 0.5–23 years (the median of 3.92 years). 66 patients (93%) were dialyzed through the arterio-venous shunt, and the others through the Perm-Cath intravenous catheter. The causes of renal failure were: glomerulonephritis (n=32), polycystic kidneys (n=9), chronic pyelonephritis (n=5), arterial hypertension (n=5), systemic vasculitis (n=2), drug-induced renal damage (n=2), cancer (n=3), interstitial nephritis (n=1), amyloidosis (n=1), Alport syndrome (n=1), uric acid diathesis (n=1), rheumatoid arthritis (n=1), vesico-ureteral reflux (n=1), renal artery stenosis (n=1), injury (n=1) and tuberculosis (n=1). In 4 cases the cause of end-stage renal failure was unknown. 19 patients (27%) were cigarette smokers.

Group 2 was composed of 29 patients (15 women and 14 men) with nephropathy induced by type 2 (n=26) and type 1 diabetes mellitus (n=3) at the age of 28–78 years, who were treated with hemodialysis. They had been hemodialyzed 3 times a week for 0.5–12 years (a median of 2.8 years). 27 patients (94%) were dialyzed through the arterio-venous shunt, whereas the other subjects – through the Perm-Cath intravenous catheter. They had been treated for diabetes mellitus for 12–26 years (a median of 17.7 years). They all received subcutaneous insulin. 3 individuals (10%) were cigarette smokers.

Group 3 was composed of 50 patients (21 women and 29 men) with pre-dialysis chronic renal disease (GFR <60 ml/min) from 20–84 years old. The duration of renal failure from the time of diagnosis was 0.5–18 years (a median of 3.3 years). The causes of renal failure were: glomerulonephritis (n=11), chronic pyelonephritis (n=4), arterial hypertension (n=8), amyloidosis (n=4), injury (n=1), congenital defects of the urinary system (n=1), nephronophtisis (n=1), polycystic kidneys (n=1), obstructive nephropathy (n=3), systemic lupus erythematosus (n=2), neoplasm (n=2), infection-induced renal damage (n=1), urinary lithiasis (n=2), glycol intoxication (n=1), ankylosing spondilitis (n=1) and hemolytic uremic syndrome (n=1). In 6 cases the cause of end-stage renal failure was unknown. 20 subjects (40%) were cigarette smokers.

Group 4 was composed of 50 patients (24 women and 26 men) with pre-dialysis nephropathy induced by type 2 (n=45) and type 1 (n=5) diabetes mellitus from 36–82 years old. They had been treated for diabetes mellitus for 3–33 years (a median of 18.4 years) The duration of renal failure since the moment of diagnosis was 0.5–10 years (a median of 2.6 years). 20 patients (40%) were cigarette smokers. All the patients received subcutaneous insulin.

In the groups studied the following variables were determined using standard laboratory methods carried out in the hospital laboratory: complete blood count, blood urea nitrogen, creatinine prior to hemodialysis as well as in the pre-dialysis period, glucose, total cholesterol, triglycerides, low-density lipoproteins (LDL), hihg-density lipopro-

Table 2. Differences in the laboratory test results between the patient groups

Parameter	Group 1	Group 2	Group 3	Group 4
HbA_{1c} (%)	–	6.66 ±1.4	–	7.17 ±0.1
Hemoglobin (g/dl)	10.15 ±1.4	10.04 ±1.1	11.47 ±2.4	11.56 ±3.2
Hematocrit (%)	29.63 ±3.9	29.71 ±3.6	34.45 ±7.2	32.99 ±4.8
Erythrocytes ($\times 10^6/\mu l$)	3.22 ±0.5	3.29 ±0.4	3.82 ±0.8	3.87 ±0.5
Total protein (g/dl)	6.53 ±0.7	6.61 ±0.6	6.16 ±0.9	6.53 ±0.7
Albumins (g/dl)	3.91 ±0.7	3.81 ±0.5	4.13 ±0.3	4.61 ±0.5
Urea before HD (mg/dl)	151.9 ±36.9	133.6 ±30.3	95.5 ±51.3	80.3 ±38.8
Urea after HD (mg/dl)	55.83 ±20.8	52.35 ±15.3	–	–
Creatinine before HD (mg/dl)	9.53 ±2.5	9.4 ±15.2	2.93 ±1.6	2.18 ±1.1
Creatinine after HD (mg/l)	4.19 ±1.4	3.15 ±0.9	–	–
K^+ before HD (mEq/l)	5.63 ±0.7	5.23 ±0.6	4.47 ±0.4	4.57 ±0.5
K^+ after HD (mEq/l)	4.16 ±0.4	4.19 ±0.4	–	–
Iron (μg/ml)	68.12 ± 63.2	56.54 ±38.1	63.00 ±23.8	53.46 ±19.7
Ferritine (mg/dl)	782.6 ±373.6	687.9 ±364.9	234.3 ±360.8	174.5 ±240.4
Calcium (mmol/l)	2.38 ±0.4	2.30 ±0.3	2.26 ±0.2	2.25 ±0.3
Phosphor (mmol/l)	1.79 ±0.5	1.51 ±0.4	1.48 ±0.5	1.44 ±0.4
PTH (pg/ml)	324.1 ±377.3	168.9 ±168.6	–	–
Total cholesterol (mg/dl)	172.6 ±38.1	169.2 ±41.7	191.2 ±49.5	192.1 ±64.6
HDL cholesterol (mg/dl)	48.97 ±16.3	46.56 ±19.3	56.92 ±17.6	45.51 ±13.3
LDL cholesterol (mg/dl)	93.83 ±29.5	86.38 ±28.7	105.62 ±40.2	115.18 ±49.1
TG (mg/dl)	150.7 ±88.9	162.7 ±107.3	125.7 ±60.9	151.3 ±79.7
Kt/v	1.29 ±0.2	1.27 ±0.2	–	–

HbA_{1c} – glycated hemoglobin, HDL – high-density lipoprotein, LDL – low-density lipoprotein, PTH – parathormone, TG – triglycerides, others – see Table 1

teins (HDL), potassium, calcium, phosphates, parathormone, iron and ferritin.

Arterial blood pressure was also subject to evaluation (taken after hemodialysis). It was taken using a manual spring sphigmomanometer. In patients without arterio-venous shunt, blood pressure was taken on the arm with higher blood pressure values at the initial visit. The cuff size was selected according to the patient's arm perimeter. Measurements were taken three times in the sitting position. The first one was taken 10 minutes after the patient's rest, and the following two measurements were made with 2-minute intervals. In hemodialyzed patients the mean value of 3 consecutive measurements during hemodialysis protocols was taken into consideration, whereas in pre-dialysis patients – that of 3 consecutive visits. Arterial hypertension was diagnosed at the value of >140/90 mmHg.

Resting ECG was performed in all the patients using an AsCARD 3 device. Tracing from 12 standard leads was recorded with a chart speed of 50 mm/s. In hemodialyzed patients ECG was performed after HD. In the analysis of the ECG tracing, particular attention was paid to the presence of a scar following myocardial infarction, or silent myocardial ischemia, arrhythmia (atrial fibrillation) and left ventricular hypertrophy using the Sokolow-Lyon index.

A transthoracic echocardiographic examination was carried out using a TS 1000 exd device by the Echoson company, with a 3.5 MHz sector transducer, in M-mode and 2D, applying standard procedures. The following were evaluated:

- end diastolic thickness of the ventricular septum
- end diastolic thickness of the posterior wall of the left ventricle
- left ventricular ejection fraction
- aortic valve surface area
- mitral valve surface area.

In addition, calcification of the aortic and mitral valves were evaluated. The left ventricular myocardium contractility was subject to qualitative analysis. In hemodialyzed patients the examination was performed between the times of HDs.

Obesity was diagnosed as body mass index (BMI) >25 kg/m^2.

The ankle–arm index was measured using a Sonomed Doppler ultrasound flow detector (Sonomed, Warsaw) with

Table 3. Medications used in all the study groups

	Group 1 (%)	Group 2 (%)	Group 3 (%)	Group 4 (%)
ACEI	21	31	58	92
β-adrenolytic	89	69	62	84
Calcium channel blocker	11	27	14	14
Diuretic	55	59	70	70
α-blocker	13	0	14	4

ACEI – angiotensin-converting enzyme inhibitors

a 5 MHz transducer. Peripheral arterial obstructive disease was diagnosed at an ankle–arm index value of <0.9.

The frequency of ischemic heart disease, myocardial infarction and chronic heart failure (according to the NYHA classification) was established based on the history and abnormal results of the above-mentioned examinations.

Statistical analysis

An analysis of the distribution of variables was made using the Shapiro-Wilk test. In order to compare the measurements of many groups single-factor analysis of variance was applied (ANOVA). In the case of statistically significant differences the Tukey test was used for the post hoc analysis. For the comparison of variables with normal distribution in only 2 groups, statistical hypotheses were checked using the t-Student test for independent variables. For variables with a distribution other than normal, we used the U Mann-Whitney test.

Variables in the nominal (qualitative) scale were compared using the χ^2 Pearson test with Yates' correction, or the Fisher test for an expected number of less than 5.

Zero hypotheses were rejected at p <0.05. The results were presented as the arithmetical mean of ±SD (standard deviation). The calculations were made using the STATISTICA 6.0 software (StatSoft Inc., USA).

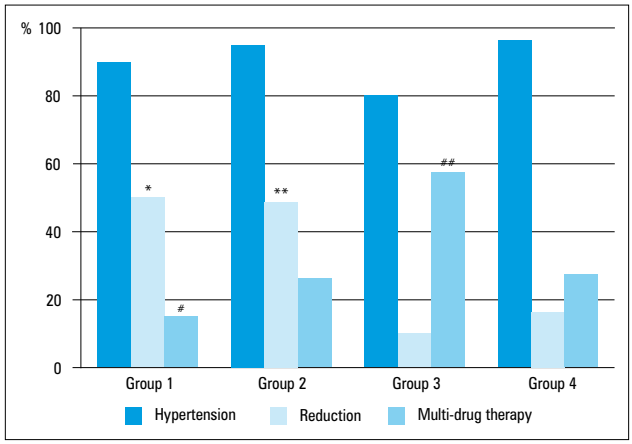

Fig. 1. Frequency of hypertension. * p <0.05 in comparison with group 3, ** p <0.05 in comparison with group 4, # p <0.05 in comparison with group 2 and 3, ## p <0.05 in comparison with group 4

RESULTS

Population data and differences in the frequency of classical risk factors of cardiovascular complications in the groups studied are presented in Table 1. In the groups studied no differences in age and sex were found. The majority of the cigarette smokers were pre-dialysis patients. Obesity more often occurred in patients with diabetes; however, it was only statistically significant between groups 3 and 4. The differences in laboratory investigation results between the groups studied, including risk factors of cardiovascular complications specific for the population with chronic renal disease, were presented in Table 2. With respect to the pharmacological treatment, the intergroup differences were reffered to hipotensive therapy (Table 3).

Arterial hypertension in the groups studied was 89% in group 1, 93% in group 2, 80% in group 3 and 96% in group 4. No difference between the groups was observed (Figure 1).

A <130/80 mmHg reduction in blood pressure in the groups studied was achieved in: group 1 – in 49%; group 2 – in 48%; group 3 – in 10%; and group 4 – in 16% of the patients. Lower blood pressure values were shown in group 1 compared to group 3, and group 2 vs. group 4. No significant differences were observed between groups 1 and 2, or groups 3 and 4.

In order to achieve a blood pressure of <130/80 mmHg multi-drug therapy was required in: group 1 – 15%; group 2 – 27%; group 3 – 58%; and group 4 – 28% of patients. Multi-drug therapy was significantly less frequently used in group 1 patients than in groups 2 and 3, as well as in group 4 compared to group 3. There was no difference between groups 2 and 4.

The prevalence of left ventricular hypertrophy in the groups studied, assessed on the basis on ECG, was: 58% in group 1, 44% in group 2, 26% in group 3 and 28% in group 4. Left ventricular hypertrophy was more often found in group 1 than in group 3, and in group 2 than in group 4. There were no differences between groups 1 and 2, or groups 3 and 4. Atrial fibrillation in the groups studied was detected

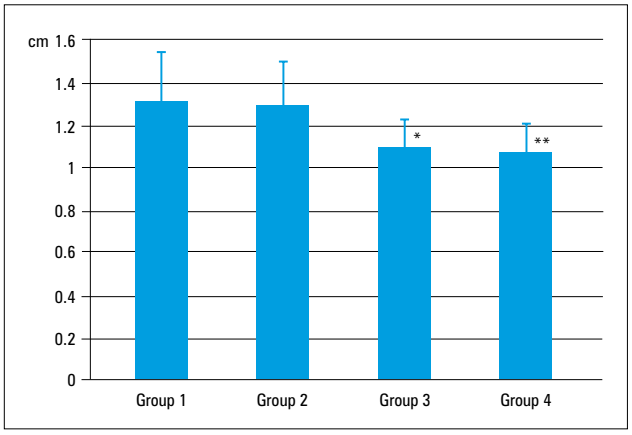

Fig. 2. Thickness of the left ventricle muscle (septum) calculated in centimetres on echocardiography. * p <0.05 in comparison with group 1, ** p <0.05 in comparison with group 2

in: 24% in group 1, 7% in group 2, 2% in group 3 and 10% in group 4. Cardiac arrhythmias were more frequently diagnosed in group 1 than in groups 2 and 3, and less frequently in group 3 than in group 4. No difference was found between groups 2 and 4.

The thickness of the left ventricular myocardium (septum), evaluated on the basis of echocardiography, was significantly larger in group 1 than in group 3 and in group 2 than in group 4 (Figure 2).

Cardiac contractility disorders more frequently occurred in group 1 than in group 3, and in group 2 than in group 4. No differences were observed between groups 1 and 2 and between groups 3 and 4 (Figure 3).

Dysfunction of the mitral valve on echocardiography was more frequently observed in group 1 (30%) than in group 2 (11%), and in group 1 than in group 3 (5%). No differences in the frequency of the aortic valve defect were found.

Coronary artery disease less frequently occurred in group 1 than in group 2, and in group 3 than in group 4 (Figure 4). There were no differences between groups 1 and 3 and between groups 2 and 4.

The prevalence of myocardial infarction in the groups studied was: 15% in group 1, 31% in group 2, 6% in group 3 and 13% in group 4. Myocardial infarction occured more frequently in group 1 than in group 3, and in group 2 than in group 4. No differences were observed between groups 1 and 2 and between groups 3 and 4.

Cardiac failure was more prevalent in group 1 than in group 3, and much less in group 3 than in group 4 (Figure 5). No differences were found between groups 1 and 2 and between groups 2 and 4.

Peripheral arterial obstructive disease of the lower extremities less frequently occurred in group 1 than in group 2, whereas more frequently in group 2 than in group 4 (Figure 6). The comparison of the above-mentioned parameter in groups 3 and 4 showed the value of p close to the level of statistical significance (p=0.08).

DISCUSSION

A retrospective analysis showed that in patients with diabetic nephropathy there was more risk factors for cardiovascular complications and they ran a worse course than in patients with non-diabetic nephropathy, although the number of classic risk factors is similar in both groups.

Over half of the patients had anemia prior to renal replacement therapy. This occurred in each of the groups studied. Lower values of complete blood count were found in hemodialyzed patients in comparison with pre-dialysis patients, despite the fact that all hemodialyzed people receive erythropoietin (erythropoietin α or β), as well as intravenous iron. The parameters of iron metabolism, i.e. iron and ferritin, were within reference ranges. The mean values of complete blood count in the groups studied were lower than the normal ones. The patients in the pre-dialysis period were administered erythropoietin [16].

In the group of hemodialyzed patients, higher calcium and phosphates, as well as calcium-phosphate product beyond the reference value, were found in patients with non-diabetic nephropathy. No differences were shown in the pre-dialysis population, which may suggest that the duration of nephropathy and the therapy applied including renal replacement therapy worsen the disturbances in the calcium-phosphate balance. In the hemodialyzed patients, parathyroid hormone (PTH) concentrations in non-diabetic patients were found to be higher than in the diabetic ones, which was most likely because hyperglycemia and insulin deficit inhibit PTH secretion. Similar results were presented by Gupta et al. [17]. In the hemodialyzed patients calcium-phosphate disorders were treated with calcium carbonate and active vitamin D_3 (alphacalcidol); the synthesis of the latter as well as the response of target tissues to it were markedly inpaired [18]. In the patients studied higher triglycerides and lower HDL cholesterol were found in diabetic patients, both in those treated with

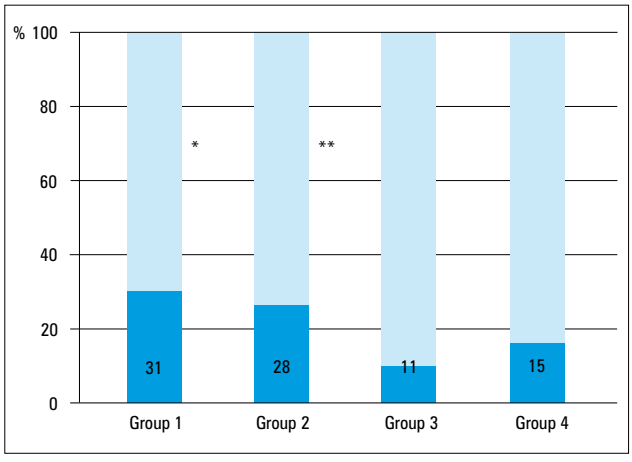

Fig. 3. Contractility disturbances cardiac on echocardiography. * p <0.05 in comparison with group 3, ** p <0.05 in comparison with group 4

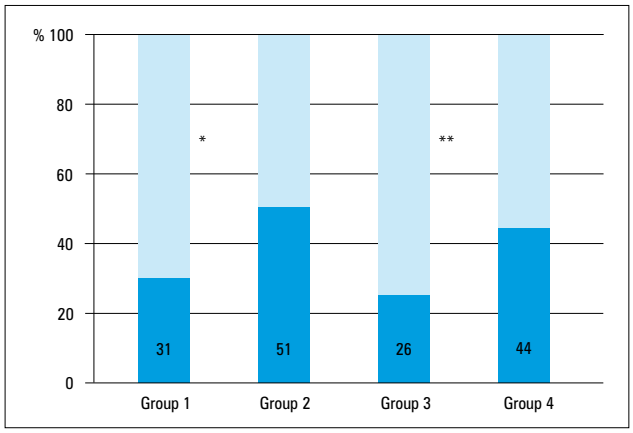

Fig. 4. Prevalence of coronary heart disease. * p <0.05 in comparison with group 2, ** p <0.05 in comparison with group 4

hemodialysis and those in the pre-dialysis period. The lipid disorders particularly occurred patients with type 2 diabetes mellitus; the disorders were accompanied by obesity, assessed using BMI, which can be encountered much more frequently in this population of patients. Similar results were obtained by Howard et al. as well as Laakso et al. [19,20]. No such differences in LDL and total cholesterol were found. It should be noted, however, that even though the absolute values of the LDL cholesterol fraction are not elevated, it has been shown in many papers that the risk of atherogenesis in this group of patients is higher due to the predominance of small dense LDL particles (subclass B LDL), which are atherogenic. HDL cholesterol is a proportional, whereas total cholesterol is, paradoxically, an inversely proportional predictive factor of cardiovascular events. Despite the results of the 4D study (Die Deutsche Diabetes Dialyse), the use of statins in patients with end-stage renal failure produced no benefits [21].

An independent risk factor for cardiovascular complications in patients with renal disease and dialyzed patients is arterial hypertension, which increases the progression of renal disease [22-24]. In the previous studies arterial hypertension was found in over 80% of patients in both groups. It should also be noted that in high-risk patients with arterial hypertension it is usually necessary to use 2 or more hipotensive drugs in order to achieve blood pressure values of <130/80 mmHg (which was presented in the 2007 ESH/ESC guidelines for the treatment of arterial hypertension) [25]. The above conclusion was confirmed in the current analysis. Among the pre-dialysis patients BP values of <130/80 mmHg were obtained in 10% of patients with diabetic nephropathy and in 16% of patients with non-diabetic nephropathy. Multi-drug therapy was necessary in 58% of patients with diabetic nephropathy and 28% of patients with another type of nephropathy. Since in the development of hypertension a substantial role is played by water and salt retention, along with the decrease of GFR, the control of arterial blood pressure in dialyzed patients should involve an appropriate assessment of fluid balance and an attempt to achieve the "dry body weight". Hypotensive drugs play a secondary role in dialyzed patients. In the hemodialyzed patients studied, a reduction in blood pressure to a value of 130/80 mmHg was achieved in about 50% of patients. Multi-drug therapy was necessary in 27% of patients with diabetic nephropathy and in 15% of patients hemodialyzed for other reasons.

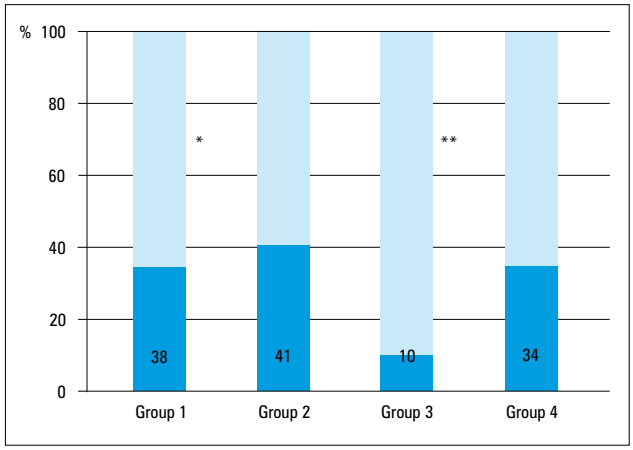

Fig. 5. Prevalence of chronic heart failure. * p <0.05 in comparison with group 3, ** p <0.05 in comparison with group 4

The evaluation of cardiovascular complications in the study groups was based on echocardiographic results, resting ECG and the ankle–arm index. Almost 75% of patients starting hemodialysis had left ventricular hypertrophy, whereas 15% had systolic dysfunction. Analysing the results of resting ECG and echocardiography in the group treated with dialysis and the pre-dialysis group one observes that myocardial hypertrophy occurs much more frequently in dialyzed patients than in those treated pharmacologically. This is caused by the fact that hemodialyzed patients are at a higher risk of accelerated myocardial hypertrophy. The risk factors are: increased water and salt retention, the dialysis shunt, particularly with high flow, which is an additional burden for the circulatory system, and increased anemia. No statistically significant differences were found between subjects with diabetes and those without diabetes. One should note, however, that patients with diabetic nephropathy were treated for a shorter period, had more frequent medical examinations (follow-up in the outpatient clinic in the pre-dialysis period) and compliance checks.

In the studied groups the mitral valve dysfunction was most frequently found in the group of dialyzed patients with non-diabetic nephropathy; no statistically significant differences were found between the groups concerning the aortic valve dysfunction. The increased frequency of valvar defects in dialyzed patients is associated with more frequent disorders of calcium-phosphate metabolism as well as a longer duration of dialysis therapy [26,27]. This causes the progressive calcification of valvar annuli and cusps, particularly in the aortic valve (in approx. 55% of patients) and the mitral valve (approx. 40%), which additionally increases the risk of death among those patients [28,29].

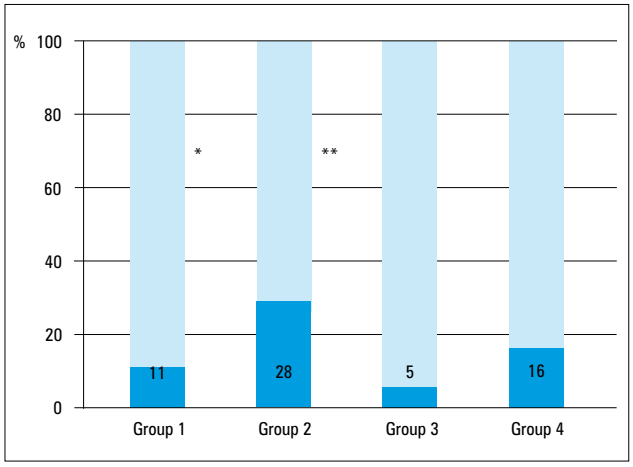

Fig. 6. Frequency of thromboangitis obliterans of the lower extremities. * p <0.05 in comparison with group 2, ** p <0.05 in comparison with group 4

In the present work, the prevalence of cardiac arrhythmias were also subject to analysis. Cardiac arrhythmias are more frequent in dialyzed patients than in those treated pharmacologically, which probably results from more common electrolyte disorders such as hypo- and hyperpotassemia, mainly associated with nutritional errors, but also with damaged structure and impaired function of the myocardium. Among patients with diabetic nephropathy, fluctuations of glycemia, both hypo- and hyperglycemia, as well as insulin itself and concomitant cardiac ischemic disease and diabetic nephropathy are all conducive to cardiac arrhythmias.

In the diagnostic evaluation of cardiac ischemic disease, resting ECG and the echocardiographic evaluation of contractility were taken into consideration. On analysing the prevalence of contractility disorders in the studied groups, it was shown based on echocardiography, similarly to Goodman et al. [30], that there were much more frequent contractility disorders in the dialyzed patients than in those in the pre-dialysis period, as well as in the patients with diabetic nephropathy treated pharmacologically than in the non-diabetic patients. Chronic coronary artery disease occurs much more commonly in patients with diabetes mellitus even prior to renal replacement therapy irrelevant of the degree of renal damage [31]. In patients with renal failure it has an asymptomatic course approx. 10 times more frequently than in the general population, whereas in patients with diabetic nephropathy it is almost always asymptomatic. The prevalence of heart ischaemic disease in the studied group was greater among patients with diabetic nephropathy compared with the patients with non-diabetic nephropathy, both in those treated with hemodialysis and those treated pharmacologically (which was also shown by Herzog et al. [32]). On the other hand, no difference was shown between the groups with chronic renal disease without diabetes, which confirms the fact, the diabetes itself is a strong and independent risk factor of heart ischemic disease [33].

It is worth noting that myocardial infarction is more common in hemodialyzed patients than in those treated pharmacologically, both in the group with diabetic nephropathy and in the group with any nephropathy other than diabetic. No difference was found in the prevalence of myocardial infarction. The risk of death for myocardial infarction in patients with diabetes and silent ischemia is higher by 20% than in people with symptomatic ischemia, which is probably associated with a delay in the appropriate treatment; however, uremia and concomitant diseases, as well as delayed implementation of dialysis therapy and the dialysis itself in patients without diabetes clearly increase the risk of myocardial infarction.

Heart failure is much more common in hemodialyzed patients than in those treated pharmacologically, and in patients with diabetic nephropathy in the pre-dialysis period than in non-diabetic subjects. As Hillege et al. noted, with the progression of renal failure there is also a deterioration of congestive heart insufficiency [34]. In diabetic patients, the major factors that contribute further to heart failure include: cardiac microangiopathy, neuropathy of the cardiac autonomous nervous system and disturbed metabolism and fatty degeneration of the myocardium developing in uncontrolled diabetes mellitus (HbA_{1c} levels in persons in the pre-dialysis period are higher than those in dialyzed subjects). Ischemic changes of the lower extremities were evidently more common in diabetic patients, particularly in those treated with dialysis, which confirms marked effect of diabetes mellitus and end-stage of renal failure on the acceleration of atherogenesis. Atherosclerotic vascular disease of the lower extremities occur in 25% of diabetics, with an almost similar prevalence in both sexes; lesions occur at an earlier age and progress more rapidly [35].

A limitation of this study might be the relatively small groups of patients representing a single dialysis center. The observation is being continued in order to prospectively assess the course of the disease and the complications in patients treated pharmacologically and with hemodialysis.

The study results lead to the conclusion that risk factors of cardiovascular complications are more frequent in patients with diabetic nephropathy than in those without diabetes. It was also noted that hemodialysis increases the prevalence of cardiovascular complications in those patients and worsens their course, which may partly result from the stage of the disease. In end-stage renal failure, dialysis is the therapy of choice due to the pancity of organs for transplantation. Pharmacological therapy used at initial stages of renal failure effectively slows the progression of the disease.

REFERENCES

1. Amann K, Wiest G, Klaus G. The role of parathyroid hormone in the genesis of interstitial cell activation in uraemia. J Am Soc Nephrol. 1994; 4: 1814-1819.
2. de Zeeuw D. Albuminuria: a target for treatment of type 2 diabetic nephropathy. Semin Nephrol. 2007; 27: 172-181.

3. Ritz E. Diabetic nephropathy. Saudi J Kidney Dis Transpl. 2006; 17: 481-490.
4. Schram MT, Chaturvedi N, Schalkwijk CG. Vascular risk factors and markers of endothelial function as determinants of inflammatory markers in type 1 diabetes – The EURODIAB Prospective Complications Study. Diab Care. 2003; 26: 2165-2173.
5. Mitsnefes MM, Daniels SR, Schwartz SM. Severe left ventricular hypertrophy in pediatric dialysis: prevalence and predictors. Pediatr Nephrol. 2000; 14: 898-902.
6. Reis SE, Olson MB, Fried L. Mild renal insufficiency is associated with angiographic coronary disease in women. Circulation. 2002; 105: 2826-2827.
7. Johnstone LM, Jones CL, Grigg LE. Left ventricular abnormalities in children, adolescents and young adults with renal disease. Kidney Int. 1996; 50: 998-1006.
8. Levin A, Singer J, Thompson CR. Prevalent left ventricular hypertrophy in the predialysis population:identifying opportunities for intervention. Am J Kidney Dis. 1996; 27: 347-354.
9. Ritz E. Heart and kidney: fatal twins. Am J Med. 2006; 119 (Suppl. 1): S31-39.
10. Schiliaci G, Reboldi G, Verdecchia P. High normal serum creatinine concentration is a predictor of cardiovascular risk in essential hypertension. Arch Intern Med. 2001; 161: 886-891.
11. Mallamaci F, Zoccali C, Parlongo S. Troponin is related to left ventricular mass and predicts all-couse and cardiovascular mortality in hemodialysis patients. Am J Kidney Dis. 2002; 40: 68-75.
12. Blacher J, Demuth K, Guerin AP. Association between plasma homocysteine concentrations and cardiac hypertrophy in end-stage renal disease. J Nephrol. 1998; 12: 248-255.
13. Zoccali C, Mallamaci F, Benedetto F. Cardiac natriuretic peptides are related to left ventricular mass and function and predict mortality in hemodialysis patients. J Am Soc Nephrol. 2001; 12: 1508-1515.
14. Zoccali C, Mallamaci F, Maas R. Left ventricular hypertrophy, cardiac remodelling and asymetric dimethylarginine (ADMA) in hemodialysis patients. Kidney Int. 2002; 62: 339-345.
15. Demuth K, Blacher J, Guerin AP. Endothellin and cardiovascular remodelling in end--stage renal disease. Nephrol Dial Transpl. 1998; 13: 375-383.
16. Ritz E. Anemia and diabetic nephropathy. Curr Diab Rep. 2006; 6: 469-472.
17. Gupta A, Kallenbach LR, Zasuwa G. Race is a major determinant of secondary hyperparathyroidism in uremic patients. J Am Soc Nephrol. 2000; 11: 330-334.
18. Schoming M, Ritz E. Management of disturbed calcium metabolism in uraemic patients: 1. Use of vitamin D metabolites. Nephrol Dial Transpl. 2000; 15 (suppl. 5): 18.
19. Howard BV, Magee MF. Diabetes and cardiovascular disease. Curr Atheroscler Rep. 2000; 2: 476-481.
20. Laakso M. Cardiovascular disease in type 2 diabetes: challenge for treatment and prevention. J Intern Med. 2001; 249: 225-235.
21. Ritz E, Wanner C. Lipid changes and statins in chronic renal insufficiency. J Am Soc Nephrol. 2006; 17 (Suppl 3): S226-230.
22. Levin A, Thompson CR, Ethier J. Left ventricular mass index increase in early renal disease:impact of decline in hemoglobin. Am J Kidney Dis. 1999; 34: 125-134.
23. Marchais SJ, Guerin AP, Pannier B. Wave reflections and cardiac hypertrophy in chronic uremia: role of arterial wave reflections. Hypertension. 1193; 22: 876-883.
24. Guerin AP, Pannier B, Marchais SJ. Arterial remodeling and cardiovascular function in end-stage renal disease. Adv Nephrol. 1998; 27: 105-109.
25. Mancia G, de Backer G, Dominiczak A. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2007; 25: 1105-1187.
26. Zapolski T, Wysokiński A, Janicka L. Sztywność aorty oraz zwapnienia zastawek serca u chorych z przewlekłą niewydolnością nerek. Pol Arch Med Wewn. 2008; 118: 111-118.
27. Ribeiro S, Ramos A, Brandao A. Cardiac valve calcification in haemodialysis patients:role of calcium-phosphate metabolizm. Nephrol Dial Transpl. 1998; 13: 2037-2040.
28. Mazzaferro S, Coen G, Bandini S. Role of ageing, chronic renal failure and dialysis in the calcification of the mitral annulus. Nephrol Dial Transpl. 1993; 8: 335-340.
29. London GM, Pannier B, Marchais SJ. Calcification of the aortic valve in the dialyzed patients. J Am Soc Nephrol. 2000; 11: 778-783.
30. Goodman WG, Salusky IB. Non-invasive assessments of cardiovascular disease in patients with renal failure. Curr Opin Nephrol Hypertens. 2001; 10: 365-369.
31. Levin A, Djurdjev O, Barrett B. Cardiovascular disease in patients with chronic kidney disease: getting to the heart of the matter. Am J Kid Dis. 2001; 38: 1398-1407.
32. Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. New Engl J Med. 1998; 339: 799-805.
33. Foley RN, Parfrey PS. Cardiac disease in the diabetic dialysis patient. Nephrol Dial Transplant. 1998; 13: 1112-1113.
34. Hillege HL, Girbes AR, de Kam PJ. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation. 2000; 102: 203-210.
35. Veres A, Akbari CM, Primavera J. Endothelial dysfunction and the expression of endothelial nitric oxide synthase in diabetic neuropathy, vascular disease and foot ulceration. Diabetes. 1998; 47: 457-463.