THE IMPACT OF DIABETES IN PROGRESS OF CHRONIC KIDNEY DISEASE

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Abstract: Diabetes is the most common cause of kidney failure, accounting for nearly 44 percent of new cases. Even when diabetes is controlled, the disease can lead to CKD and kidney failure. Most people with diabetes do not develop CKD that is severe enough to progress to kidney failure. Nearly 24 million people in the United States have diabetes, and nearly 180,000 people are living with kidney failure as a result of diabetes.[1]year in the United States, more than 100,000 people are diagnosed with kidney failure, a serious condition in which the kidneys fail to rid the body of wastes.[1] Kidney failure is the final stage of chronic kidney disease (CKD).People with kidney failure undergo either dialysis, an artificial blood-cleaning process, or transplantation to receive a healthy kidney from a donor. Most U.S. citizens who develop kidney failure are eligible for federally funded care. In 2005, care for patients with kidney failure cost the United States nearly $32 billion.Diabetes mellitus still remains a serious health problem with a high prevalence worldwide in developed and developing countries, and with major impact on increasing the level od cardiovascular mortality and morbidity (1,2,3) is counted as the fourth cause of mortality in developed countries (3). In the United States and in Western countries diabetes with diabetic nephropathy, is recognized as the leading cause of kidney disease and chronic kidney disease at terminal stage. A large number of epidemiological studies have shown that one third of patients with hemodialysis or kidney transplanted patients with diabetes mellitus are tip 2. (4,5). Purpose of the paper:The purpose of the paper was to verify and document the impact of hyperglycemia in the rate of progress of chronic renal failure, as well as the correlation between hyperglycemia with cardiovascular disease and premature atherosclerosis of uremic and Diabetes Mellitus patients treated with hemodialysis, compared with the control group of healthy individuals. Material and methods of work, the control group, and forms of treatment with dialysis:In this prospective cohort research (,, cross-section ") are included 200 examiners, of whom 100 were uremic and diabetes mellitus patients, while 100 were healthy individuals who served as a control group. From uremic and DM patients treated with HD-N^{O}=.100), 40 of them (were female with an average age 59.60±8.90 and 60 were male, with an average age: 58.40±9.60 year. Control group of healthy examiners (voluntary blood donors) also were 100 of whom: 45 were female with an average age of =57.90±10.00 and 55 men with an average age of 58.60 ± 11.00 years. Control group was similar to the group of sick patients by age, gender and national affiliation. From total number of patients (100) 60 were with Diabetes Mellitus Tip-1 (D.M. Tip1 –insuline dependent) while 40 were patients with Diabetes Mellitus Tip-II (D.M. tip 2 –tretated with oral hypoglycemics), table number 1. Both, patients and control group were analyzed within 12 months-once every three months, a total of 4 measurements, glycaemia profile, glycosylated hemoglobin (HbA1c) and lipid profile. Numerous studies have verified the impact of control of blood glucose and glycosilated hemoglobin (HbA1C) values in preventing micro/ macrovasculare and cardiovascular disease (7).

Index terms: ESRD, Diabetes Mellitus (DM),ESRD, blood glucose (Gl), the glycosylated hemoglobin (HbA1c), lipids profile.

1 INTRODUCTION

A number of studies have pointed to the beneficial effects of intensive management of blood glucose. In the Diabetes Control and Complications Trial supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), researchers found a 50 percent decrease in both development and progression of early diabetic kidney disease in participants who followed an intensive regimen for controlling blood glucose levels. The intensively managed patients had average blood glucose levels of 150 milligrams per deciliter-about 80 milligrams per deciliter lower than the levels observed in the conventionally managed patients. The United Kingdom Prospective Diabetes Study, conducted from 1976 to 1997, showed conclusively that, in people with improved blood glucose control, the risk of early kidney disease was reduced by a third. Additional studies conducted over the past decades have clearly established that any program resulting in sustained lowering of blood glucose levels will be beneficial to patients in the early stages of CKD.

When our bodies digest the protein we eat, the process creates waste products. In the kidneys, millions of tiny blood vessels (capillaries) with even tinier holes in them act as filters. As blood flows through the blood vessels, small molecules such as waste products squeeze through the holes. These waste products become part of the urine. Useful substances, such as protein and red blood cells, are too big to pass through the holes in the filter and stay in the blood.Diabetes can damage this system. High levels of blood sugar make the kidneys filter too much blood. All this extra work is hard on the filters.

After many years, they start to leak and useful protein is lost in the urine. Having small amounts of protein in the urine is called microalbuminuria.When kidney disease is diagnosed early, during microalbuminuria, several treatments may keep kidney disease from getting worse. Having larger amounts of protein in the urine is called macroalbuminuria. When kidney

disease is caught later during macroalbuminuria, end-stage renal disease, or ESRD, usually follows.In time, the stress of overwork causes the kidneys to lose their filtering ability. Waste products then start to build up in the blood. Finally, the kidneys fail. This failure, ESRD, is very serious.

Chronic deficiency presents irreversible, progressive reduction of renal function and glomerular filtration. When glomerular filtration rate (GFR) decrease among 30ml / min, while serum creatinine concentrations begin to rise above 240 μmol / l, the progress of renal failure begins with increased faster (6). With chronic renal failure is meant renal injury, when GFR is <90 ml / min, 1.73 m2 IRK and which lasts more than 3 months. Diabetes today is extremely big socioeconomic problem, due to material expenditures. As most frequent presenting increased risk factors leading to rapidly progressive renal damage are: high arterial pressure, excessive loss of protein through the urine, diabetic disorders, lipid disorders etc.

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For early detection of chronic renal injury first must be established criteria for early diagnosis of the basic disease, determining the stage of damage according to GFR, renal disease diagnostic screening, detection of manifestations and complications of renal lesions, detection of risky factors in the impact of progress of renal and cardiovascular damage. Kidney function can be checked by estimating how much blood the glomeruli filter in a minute. The calculation of eGFR is based on the amount of creatinine, a waste product, found in a blood sample. As the level of creatinine goes up, the eGFR goes down.Kidney disease is present when eGFR is less than 60 milliliters per minute.The American Diabetes Association (ADA) and the National Institutes of Health (NIH) recommend that eGFR be calculated from serum creatinine at least once a year in all people with diabetes.Urine albumin. Urine albumin is measured by comparing the amount of albumin to the amount of creatinine in a single urine sample. When the kidneys are healthy, the urine will contain large amounts of creatinine but almost no albumin. Even a small increase in the ratio of albumin to creatinine is a sign of kidney damage.Kidney disease is present when urine contains more than 30 milligrams of albumin per gram of creatinine, with or without decreased eGFR.The ADA and the NIH recommend annual assessment of urine albumin excretion to assess kidney damage in all people with type 2 diabetes and people who have had type 1 diabetes for 5 years or more

Under the proposal of K / DOQI and NKF (National Kidney Foundation), the levels of renal damage are determined according to GFR. (Table 1).

Phases	Description of renal damage	GFR* ml/min/1.73m^2
1	Mild renal impairment with normal filtering	≥ 90
2	The slight decrease in renal function	60-89
3	The average reduction in renal function	30-59
4	Severe damage in renal function	15-29
5	**Renal failure**	**< 15 (dialysis)**

*** GFR-Glomerul Filtration Rate**

At the table number 2 are identified normal and pathological values of proteinuria and albuminuria. (M=Males,F=Females)

Values	Proteinuria	Microalbuminuria
M=17-250 mg/L	**M > 250mg/L**	**M= < 17mg/L**
F < 25 mg/L	**F= 355mg/L**	**F= 25- 355 mg/L**

Patients with chronic kidney disease (CKD) and Diabetes are required to adhere to the rules of the consumption of protein (when the cleareance of the endogen creatin is below 50-40 ml/min/1.73m$^{2)}$, they should consume 0.6-0.8 g/Kg/PT/ per day or 30-35 kcal/kg. Clinical results from the study by MDRD (Modification of Diet in Renal Disease) has verified that if arterial pressure is on borders: 125/75 mmHg and consumptions of proteins is from 0,6–0,8 g/Kg /PT per day, significantly affects the inhibition and prevention of rapid progression of renal damage. As parameters for the determination

of nutritional status, should be taken: concetracion of albumin, concentration of serum transferrin and body mass index (BMI)

At the table number 3 we presented the definition of progress, remission and regression of chronic nephropathy manifested by proteinuria

Parameters	Progression	Remission	Regression
Proteinuria	>1.0 g/24 h	< 1.0 g/24 h	< 0.3 g/24 h
Levels of FG	FG diminished	FG stable	FG increased
The structure of the kidn	FG exacerbated	FG stable	FG improved

The protein excess in urine may be reduced if we stick to following preferences : salt restriction, use of lower doses of ACE inhibitor, use of beta blockers, angiotensin II receptor antagonist (when values of K are < 5.0 mmol/l), use of statins, normalization of glycemia. A good control of glycemia, when the level of HbA1c is < 7,0%, significantly inhibits the progression of diabetic nephropathy . Uremic patients treated with HD, HbA1c values should behave < 8,0%. A prospective study on diabetes has verified that intensive treatment of diabetes and normalization of elevated blood glucose values, has reduced for 16 -21% risk of acute myocardial infarction, from peripheral vascular diseases has been reduced for 35%, amputation for 39% etc. Any reduction in glycosylated hemoglobin for 1%, is in high positive correlation with risk reduction for 21% of CVD, and 37% of microvascular complications. Therefore, the control of glycemia and HbA1c, should be the primary obligation in the early detection of diabetic nephropathy. Past years was dominating the perception that patients with type 2 diabetes with nephropathy and proteinuria had relatively good prognosis compared with patients with type 1 diabetes, however contemporary studies in recent years have verified that are equally at risk from CKD the two groups of patients with diabetes (9). Although kidney metabolism of insulin plays a small role for endogenous insulin mostly metabolized and degraded by the liver, exogenous insulin (at patients in isulin) primarily is eliminated by the kidneys, causing proteinuria with effects of diabetic nephropathy . In patients with renal failure levels of insulin, proinsulin and C-peptides are grown..(10).Renal clearance of C-peptide is larger compared to that of insulin, therefore examination of the concentration of C-peptide as a first warning on the secretion of insulin, is necessary at patients with diabetes. During the early stage of renal failure the insulin cleareance form kidneys is weakened, because of renal hipoperfusion (blood flow in kidneys is reduced), and as e result of beginning of decline of renal function, with what we have consequently reducing insulin extraction from body tissue. This phenomenon compensate the fall of insulin filtration up to that stage when GFR is < 20 ml /min, after which purification of insulin is reduced even further and as a result of increased half-life of insulin, and general requirements for insulin even more are reduced . There are experimental studies in animals showing that chronic renal failure significantly affects the prevention and suppression of extra renal metabolism of insulin eg in skeletal muscles and liver. Therefore happens that diabetic patients (insulin dependent) manifest decline in demand for insulin (insulin dose reduction) due to suppression of insulin metabolism. Some patients with CKD treated with HD often manifests symptoms of hypoglycemia because of the prolonged half-life of insulin in circulation and reduced elimination, while in normal circumstances renal tubes capacity to absorb insulin filter is large(14).

2. MATERIAL AND METHODES

In this prospective cohort research (,, cross-section '') are included 0examiners, of whom 100 were uremic and diabetes mellitus patients, while 120 were healthy individuals who served as a control group. Blood taken for examination inserted into the vial with a few drops heparin (5ccm serum) were sent for analysis at the Institute of Clinical Laboratory in Skopje. From uremic and DM patients treated with HD (No.100), 40 of them were female an 60 were male, with an average age: 59.50 ± 10.50 year. From total number of patients (100) 60 were with Diabetes Mellitus Tip-1 (D.M. Tip1 –insuline dependent) while 40 were patients with Diabetes Mellitus Tip-II (D.M. tip 2 –tretated with oral hypoglycemics), table number 1. Both, patients and control group were analyzedd within 12 months – once every three months, a total of 4 measurements, glycaemia profile, glycosylated hemoglobin (HbA1c) and lipid profile. Methods of determining the concentrations of lipids, glycaemia (Gl) and HbA1c are presented below. Reference value for glycaemia and HbA1c were taken according to the criteria proposed by the World Health Organization (WHO)- for glycaemia = 3.5-6.5 mmol/l and HbA1c % = 4.4% -6.6 %.

Table number 4. Presentation of diabetes patients under therapy

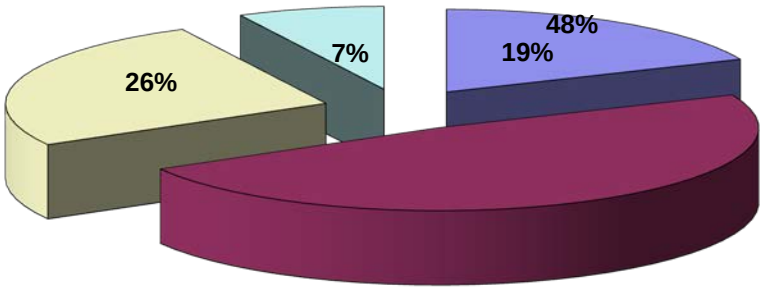
Tot. pacients	D.M Tip 1 (insulin-dependent)	D.M Tip 2 (oral hypoglicemic)
N°=100	60	40

Table number 5: Distribution of patients according to national affiliation

Gender	Macedonians (45%)		Albanian (55%)	
	Number	%	Number	%
Men	25	25.0	35	30.0
Women	20	20.0	20	25.0

Table number 6: Distribution of patients according BMIx: male=55 and female = 45

BMIx	Women	Men
Poor feeding	10	20
Normal feed	22	30
More feed	8	9
Obesity instance II-a	5	6



Graph. Number1

From the total number of examinated patients – 100 (100%) by BMIx, with the highest percentage of 48.0% were patients that belong to the group that were normal feeded, than follows the group of patients fed highly with 26 %, then the group fed poor 19.0%, and finally the group with second-degree obesity -a(II-a) with 10%, under the table and graph number 9. The difference between patients according to statistics is not significant with p<0.0005, and shows that this is homogeneous groups of patients.

Statistical processing of material examined: Values obtained of blood glucose, HbA1c% and lipids (Total chol., TG, HDL-ch, LDL-ch) and control group are presented with average values and standard deviation X +/_ SD. We tested the association between obtained variables, with linear regression analysis (y=Bx+A) where it was estimated the correlation coefficient ,,r" with statistical value for ,,p" less than 1%, p<0.0001. Comparative statistics of the parameters of blood glucose and glycosylated hemoglobin between the two groups, was analyzed with test called Studentov ,,t" test. Statistically significant differences between the group of patients and control group for obtained values of the examined parameters, were analyzed with the test so-called,,Anonova Two-Factor" with statistical value for ,, p " less than 5%, respectively <0.0005.

GAIEND RESULTS:

Results (glycaemia, HbA1c, lipids,-tot.chol.,TG, HDL, LDL) obtained from patients group and control group are presented in tabular form. From these tables we can observe that at the two gruops of patients (DM Type-1 and DM Type- 2), are verified high concentrations of lipids and HbA1c with significant statistical differences for *p<0.0001*, compared with control group. Between obtained values of patients (DM Type-1 and DM Type- 2), was not noticed any significant difference, facts that are consistent with many other studies. Lipid parameters presented a significant increase of the concentrations of: LDL-ch and TG, while low concentrations of HDL-ch at two group of patients with IRKT and DM, compared with the results from the control group. Values obtained the total cholesterol (TCH) from the group of patients with DM and IRKT, compared with control group did not show any statistical significance.

Table nr.7. Presentation of the average values of the parameters analyzed to examine patients with DM type 1 - the Insulin-Dependent N^0 = 75) and DM type 2 (with oral hypoglycemic-N^0 = 45)

Parameters	Number	Average	Minimum	Maximum	± SD
Patients with Diabetes Mellitus, Type 1 (insulin-dependent N^0 =60)					
HbA1c %	60	9.8	6.00	13.50	6.30
Glycaemia	60	10.60	7.50	11.20	3.70
LT	60	7.50	2.40	12.80	2.90
TG	60	3.80	1.0	4.00	1.30
Cholesterol	60	6.80	1.40	6.70	1.60
HDL-ch	60	1.00	0.48	3.705	0.90
LDL-ch	60	4.90	1.80	5.90	0.80
Patients with type 2 D. Melltus tip 2 (oral hypoglycemic - N^0 = 40)					
Glycaemia	40	7.60	4.80	9.00	3.10
HbA1c %	40	8.70	5.80	8.70	3.90
LT	40	7.60	5.0	10.80	1.60
TG	40	3.90	2.60	4.70	0.80
Cholesterol	40	5.60	1.50	6.40	1.80
HDL-ch	40	1.04	0.70	2.20	0.75
LDL-ch	40	4.90	2.40	5.60	0.85

Table number 8. The average values of the analyzed paramaters for urea, creatinin and uric acid (serume values) and GFR defined under formula from Cocroft&Gault in ml / min in examined patients with DM Type 1 (insuline dependent) N0 = 75 at the beginning of the study

Parameters	Average values	± SD
Potassium (mmol/l)	4.50	0.70
Urea(mmol/l)	14.70	2.80
Creatinin(mmol/l)	325.00	42.00
Uric acid(µmol/l)	386.00	48.60
GFR (by Cocroft&Gault)	58.00 ml/min	5.80

Table number 9. The average values of the analyzed paramaters for urea, creatinin and uric acid (serume values) and GFR defined under formula from Cocroft&Gault in ml / min in examined patients with DM Type 1 (insuline dependent) N0 =60 after 12 months

Parameters	Average values	± SD
Potassium (mmol/l)	5.40	0.80
Urea (mmol/l)	18.50	2.60
Creatinin (mmol/l)	390.60	12.50
Uric acid(µmol/l)	450.00	28.00
GFR (by Cocroft&Gault)	52.00 ml/min	5.90

Table number10. The average values of the analyzed paramaters for urea, creatinin and uric acid (serume values) and GFR defined under formula from Cocroft&Gault in ml / min in examined patients with DM Type 2 (treated with oral hypoglycemic) N0 = 60 at the beginning of the study

Parameters	Average values	± SD
Potassium (mmol/l)	4.80	0.90
Urea (mmol/l)	14.60	3.4
Creatinin (mmol/l)	370.00	16.00
Uric acid (µmol/l)	380.00	29.60
GFR (by Cocroft&Gault)	60 ml/min	6.50

Table number 11. The average values of the analyzed paramaters for urea, creatinin and uric acid (serume values) and GFR defined under formula from Cocroft&Gault in ml / min in examined patients with DM Type 2 (treated with oral hypoglycemic) N0 = 40 after 12 months

Parameters	Average values	± SD
Potassium (mmol/l)	5.40	0.60
Urea (mmol/l)	15.00	2.80
Creatinin (mmol/l)	390.00	14.50
Uric acid (µmol/l)	410.00	15.60
GFR (by Cocroft&Gault)	50.00 ml/min	6.20

In the tables we can notice that between the parameters of the two groups of patients with DM (Insulin dependent patients and patients that are treated with oral hypoglycemic) there is no significant difference, except a slight increase of urea, kreatinin, uric acid and a mild decration of gromerular filtration (but on a significant decration) that shows the stabilization of diabetes takes place, and the rate of the renal insufficiency will slow down.

Table number 12. Presentation of the Mann-Whitney U-test for the difference of the analyzed parameters values at patients with DM type 1 and DM type 2.

Parameters	U	Z	*p-level*
Glicemi	6750.000	0.47595	0.850240
HbA1c %	8365.000	0.48350	0.006540
LT	1140.000	-0.126579	0.900480
TG	658.400	-3.25700	0.001240
Cholesterol	1086.500	0.37690	0.701420
HDL-ch	1076.800	0.56810	0.607800
LDL-ch	1147.600	-0.09840	0.964540

The difference which was recorded between the average values of patients with DM type 1 and type 2 DM was nonsignificant, for p <0.0005. Significant difference was recorded only at: TG (p = 0.001240)

DISCUSSION:

Diabetic nephropathy, classically defined by the presence of proteinuria occurs in significant percent of patients with type 1 which formerly called insulin-dependent and type 2 which formerly called non-insulin-dependent diabetes mellitus (DM). It also can occur in the patients with secondary forms of DM for example after pancreatitis or pancreatectomy if the duration of DM is longs-enough and level of glycemia high enough to result diabetic complications

Approximately 20% to 30% of patients with type 1 DM will have microalbuminuria after a mean duration of diabetes of 15 years and less than half of these patients will progress to macroalbuminuria which also called overt nephropathy After overt nephropathy development, the substantial number of patients will progress to end-stage renal disease (ESRD) with reported rates of 4% to 17% at 20 years and approximately 16% at 30 years from time of initial diagnosis of DM

ESRD and diabetes are characterized by high risk of micro and makrovasculare disease, therefore are necessary numerous studies to detect new factors of cardiovascular risk, particularly those complications that are closely related to microvascular disease, as a result of unregulated diabetes. Among the risk factors that in recent years have been given special attention are higher concentration of lipoproteins and hyperglycemia There are documented facts that a large number of patients with DM and ESRD are potential candidate of a large number of diseases: cardiovascular, unstable angina pectoris, ischemic heart disease, acute myocardial infarction, left ventricular hypertrophy, congestive heart weakening , brain stroke macrovascular complication, peripheral vascular diseases diabetic vascular complications, diabetic retinopathy etc. All the above mentioned diseases are frequent and the main causes of morbidity and mortality of uremic and diabetic patients treated with HD (15-21) therefore the American Association of Diabetes always suggests the maintenance and regulation of normal values of glycemia. Irregular checks and bad control of glycemia, are calculated as a indipedent risky factors rapid progression in ESRD (regardless of the type of diabetes). The exact mechanism of insulin resistance of diabetic patients with ESRD is unclear, although some experts in their clinical studies have verified that during uraemia glucose production and glucose absorption from liver are normal, however skeletal muscles are the principal place of insulin resistance, while the oxidation of glucose is relatively normal. (22). Other factors that contribute to insulin resistance at uremic patients with diabetes are: accumulation of uremic toxins (proinflammatory cytokines, Interleucin,, MIA syndrome , secondary hyperparathyroidism , increase of PTH, renal anaemia metabolic acidosis , iron deficiency, intravenously supplementation therapy with calcitriol (1,25-dihydroxyvitamin D) (23,24). A number of studies have verified that supplementation and correction of renal anemia with Eritropoetin significantly increase the sensitivity of insuline increase secretion of insulin and decrease blood glucose level (25,26).The need for insulin in patients with DM and ESRD showa a biphasic requirement. At the beginning control (where GFR> 50 mL / min) and balance of glycemia is deteriorating due to insulin resistance. Therefore to achieve normalization of glucose are needed higher doses of insulin. With advanced kidney failure and reduction of GFR <50 ml / min, insulin needs are smaller, and for normalization of glycemia are needed lower doses of insulin, even in some extreme cases may be necessary to stop with insulin. The need for insulin is also reduced due to reduced calorie intake of uremic patients with diabetes. The measurement of HbA1c should be the most accurate method to assess glycemic control at patients with diabetes and ESRD, and uremic patients treated with HD (27-33). Management of diabetic patients with advanced kidney disease, involves the use of low protein diet and limited sugary foods. In patients with type 1 diabetes (insulin therapy) food and insulin should be taken at certain time, and also attention should be paid to body weight, physical activity etc. Therefore, patients with diabetes and chronic renal failure should be advised to consume food with a limited amount of protein and to compensate the losses of calories from carbohydrates. Quality dietary control of these patients calls for close collaboration between experts in the field of diabetology, nephrology and dietology. This group of patients should avoid oral hypoglycemic, because of risk from hypoglycemia, with the exception of Glipizide or repaglinide. It is proven and documented that there is a high correlation between renal damage (micro / makroalbuminurise and proteinurise) and high values of glycaemia and HbA1c, with the rapid pace of progress of esrd, associated with diabetic nephro-pathy, and retinopathy.. A large number of studies on the role and effect of diabetes, have verified that patients with diabetes have pace and higher frequency of chronic renal damage progression. During blood laboratory examinations of patients with DM (regardless of the type of diabetes) is always present hypertrigly-ceridemia and high values of C-Reactive Protein (PCR), that also shows the presence of a silent inflammation in patients with diabetes mellitus (DM) and chronic renal failure. Monitoring of hyperglycemia and HbA1c (within three months), should be basic postulate and one of the primary measures in pursuit of the pace of IRK and diabetic nephropathy. A large number of epidemiological studies have verified that with regulation and control of hyperglycemia, significantly is reduced the incidence rate of renal disease, therefore the American Association for Diabetes annually provides recommendations on control and regulation of hypergly-cemia and elevated HbA1c values of patients with ESRD and Diabetes Mellitus, which recommendations signify-cantly slows down the pace of progress of the IRK and the risk of CVD. In recent years the

incidence of ESRD as a result of unregulated diabetes and diabetic nephropathy not only in the US and Europe, but also in the Balkans, has an increase of 33% -40%, which arises from the the failure to treat the diabetes. Therefore recent years nephrologists always suggest and propose that the measurement and monitoring of blood glucose, HbA1c, arterial pressure and lipid control, to be one of the manda-tory measures for doctors at primary and second-dary practice which evidently will reduce the rapid pace of diabetes. Since the initial stages of diabetes appearance (DM) there are also disorders of lipid (dyslipidaemia), therefore early examination of these disorders in patients with DM (Type-1 and Type-2) can significantly affect the prevention and slowdown of the early appearance of renal injury. Patients with diabetes mellitus are a higher risk for early atherosclerosis compared with healthy population, as well as its consequences on the cardiovascular system. According to contemporary thoughts diabetes is a multi-factorial disease etiology, and its main characteristic is hyperglycemia accompanied by metabolic disorders of sugars, fats, and proteins, which are manifested by disturbances in the secretion of insulin, insulin resistance, or by interaction all the aforementioned mechanisms. As the underlying factors of appearance of cardiovascular and cerebrovascular disease, and early atherosclerosis in patients with DM, disorders or metabolism of lipids have an important role. Genetic factors that influence the development of cardiovascular and cerebrovascular diseases, and atherosclerotic processes, are disruption of reverse transport of HDL-cholesterol, cumbersome expression of B-receptors compared with E-receptors, reduced conversion of VLDL to IDL and LDL-ch (34-37).ApoB-$_{100}$ provides the absorption of cholesterol from hepatic and extrahepatic tissue by binding to receptors B/E enabling the extraction of triglycerides from the liver. Increased concentrations of ApoB-$_{100}$ except in patients with Diabetes Mellitus (DM) are also recorded in other diseases as hyperproteinemia: Type II-A, II-B, Type-IV, Type-V, the period of pregnancy, nephrotic syndrome, hiperapo-ß lipoproteinemia, hepatic duct obstruction, smoking, use of diuretic, excessive use of ß-inhibitor therapy with corticosteroids, therapy with ciclosporin (CSA) and in patients with chronic renal failure Small lipoprotein-A (Lp/a/) antigen (Apolipoprotein/a/; Apo/a/) is synthesized in the liver and in intracellular way via disulfide links is connected with ApoB-$_{100}$. Lp(a) for the first time discovered Berger in 1963 (44) and is assumed that is a variation of LDL-cholesterol (LDL-ch) and quantitative marker for the risk of atheromatous [Lp(a)-atheromathosis]. Lp(a) reacting with fibrinolysis by enforcing thrombogenesis and formation of atherosclerotic plaque. Lp(a) in plasma circulates together with ApoB-$_{100}$ as the protein basis of lipoproteins (Lp) rich with esterified cholesterol. Lipoprotein(a) can be calculated as the reactant in the acute phase of injury. A large number of studies have documented that between CVD and high value HgbA1c there is a high positive correlation with IRKT patients and Der mellitus (38-40).Numerous epidemiological studies and the American Association for diabetes (AAD) have verified and documented that the regulation and regular check of glycemia decreases the risk of cardiovascular disease (CVD) and their complications wich reduces the mortality rate in uremic patients treated with HD. Concentration of glycated hemoglobin (HgbA1c) (which represents the average value of glycemia within three months) is calculated as the gold standard in the assessment of the risk of CVD in patients with ESRD treated DM and HD(41,42). American Association for diabetes (AAD) always calls and suggests examination of glycated hemoglobin in order to behave adequate treatment decisions and treatment of diabetes in patients with ESRD in order to reduced the complications of diabetic nephropathy [R=60], and slow the pace of progress of the ESRD (50). This happens by the lack of consensus on HgBA1C testing of patients with ESRD and diabetes type 1 and type 2 that in the initial stages of the disease, especially in those patients who are treated with EPO therapy prior to treatment with HD. In the pace of disease progression in patients with diabetes and ESRD affect many factors: the pharmacodynamic effects uremic acid, the procedures dialysis itself, influence of insulin pharma-cokinetics on carbohydrate metabolism and oral hypoglycemics, oxidative stress, lipidic peroxi-dasis, MIA syndrome, HTA, hypertriglyceridemia, shortened erythrocyte life, renal anemia etc. ESRD and DM patients, due to the appearance of anemia in the initial stages should be treated with Eritropoetin (rHuEpo) because eritropoetina increases the percentage of reticulocyte and stimulates the production of new red blood cells (43). Some authors have verified a high correlation between high concentrations of ApoB-100 and Lp (a), and proteinuria in patients with diabetes mellitus. The above phenomena are justified by the fact that proteinuria results with increased protein synthesis in the liver, which increased synthesis, stimulates more the synthesis of apoproteins with origin from liver, and in particulary increases the concentration of apoliporoteins (a), a constituent of lipoproteins (a). A number of authors have verified early atherosclerosis in patients with DM-Tip1 and those with DM-Tip2 measured with the the scale of the occlusion of peripheral arteries, which is in high correlation with high concentrations of Lp (a). Results obtained from lipid profile showed a high disorder for both groups of exami-ned patients (those with Type 1 DM and those with DM-Tip.2), which is consistent with all studies about disorders of lipid profile at patients with diabetes. A significant number of patients with DM compared with control groups of healthy individuals present high concentrations of ApoB-100, HbA1c% and Lp (a). This high correlation many authors correlate with the first symptoms of kidney damage from diabetes (the presence of macro- and micro- proteinuria) at those patients. A number of approxi-mately 40% of patients with diabetes and esrd a year before starting treat-ment with HD, have not check the value of HbA1c. According to recent reports from the Association of American nephrologists have there are evidences for increased use of insulin and oral hypoglycemic, which tells us about aggressive access in the treatment of patients with ESRD and diabetes. In the presentation of cardiovas-cular diseases and mortality rates at uremic and diabetic patients treated with HD, in addition to increased sugar level, also affect many other factors such as: disorder of lipid metabolism, hyperapolipoproteinemia, pharmacodynamic effects of uremia, uremic toxins, hemodialysis as medical procedure, effects of insulin, disorders of carbohy-drate metabolism, disorders of coagulation factors, arterial hypertension, smoking, secondary hyperparathyroidism, hyperhomocysteinemia, thrombotic factors, Oxidative stress etc.There are documented facts that the number and the life of erithrocytes at patients with ESRD are reduced, so is expected the decrease of concetration of HbA1c. Eritropoetin therapy of uremic patients with diabetes treated with hemodialysis, is proved that increases the percentage of new red blood cells in circulation, with the smallest exposure of glycemia during the process of glycolysis. HbA1c measurement is required every three months, but there are a group of patients with large discrepancy of values of glycaemia, so measurements of HbA1c at that group of patients should be more frequent. (44,45).Chronic hyperglycemia combined with dyslipidemia and hiperapolipoproteinemi even further increase the risk of morbidity and mortality from cardiovascular disease in uremic patients with diabetes treated with chronic hemodialysis terminals. Many studies were done about primary causes of ESRD in developed countries. In the past decades, several

forms of glomerulonephritis (GN) were the most common initiating cause of ESRD in these countries. However because of more aggressive treatment of GN and possibly because of rapid increase in the prevalence of obesity and diabetes, it is well established that diabetic nephropathy is now the leading cause and or probably with hypertensive nephropathy are the most common causes of ESRD in developed countries. For example according to the result of United States renal data system, diabetes is the most common cause of ESRD, accounting for approximately 45% of cases.

5CONCLUSION:

For conclusion we can say that the knowledge of mechanisms, etiopathogenesiss, function and abnormalities on polymorphism and the negative impact of hyperglycemia and dyslipidemia are among the indipendent and risky factors of CVD and premature atherosclerosis, in patients with terminal chronic renal failure (ESRD) and diabetes. Treatment and normalization of their values at the initial stages of the disease is of big importance, and can significantly affect the prevention and can prevent premature progression rate of ESRD and atherosclerotic processes in coronary, cerebral and peripheral arteries. Uremic and diabetic patients treated with HD (regardless of the type of diabetes) are at high risk of early atherosclerosis appearance. Hyperglycemia and dyslipidemia are among the most dangerous factors of progress of ESRD. Therefore, improvement, balancing and regular control of diabetes and lipid, are the first step in preventing the pace of progress and the incidence of ESRD, early atherosclerosis and cardiovascular disease. Are needed to further studies on the occurrence of CVD in uremic patients with diabetes treated with HD, in order to propose appropriate attitudes on the control of blood glucose and HbA1c Diabetic kidney disease occurs in the significant percentage of patients with type 1 and type 2 DM. Although the prevalence of progressive renal disease generally lower estimated in type 2 diabetes, however, recent data suggest that the renal risk is currently equivalent and the time to ESRD from the onset of proteinuria were similar in the two types of diabetes. It is well established that diabetic nephropathy particularly type 2 and hypertensive nephropathy are the leading cause of ESRD in developed and developing countries reflects the catastrophic sequelae of these two silent killers.based on the facts, at the early stages of the disease.

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