CHRONIC KIDNEY DISEASE IN DIBETES

1. Doc.Dr.Nexhbedin Kahremani [2], 2. Prof.Dr.Sadi Bexheti [2], 3.Prof..Dr. Sci. Med. Lutfi Zylbeari[1,2,,], 4. Prof. Dr. Nasir Behxheti [2],5. Prof. Dr. Koco Cakalararovski

1. Private Special Hospital For Nefrology And Hemodialysis ,,Vita Medical Group"- Tetova, Macedonia
2. State University of Tetova, Medical Faculty, Tetova, Macedonia
3. Faculty of Medicine-Clinic for Nephrology- Skopje,R. Macedonia

Abstract: Kidney disease is a common finding in people with diabetes, with up to half of demonstrating signs of kidney damage in their lives(1,2,3). 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. Diabetes is counted as the fourth cause of mortality in developed countries. (4).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. (8,9).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 240 examiners, of whom 100 were uremic and diabetes mellitus patients, while 100 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), 45 of them (45%) were female with an average age 57.60±13.00 and 55 (55%) were male, with an average age: 58.50±10.50 year. Control group of healthy examiners (voluntary blood donors) also were 100 of whom: 45(45%) were female with an average age of 58.40±13.00 and 55 (55%) men with an average age of 57.60 ± 14.00 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 l 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).Kidney disease can be a particularly devastating complication, associated with substantial reduction in quality of life (13,14). A variety of forms of kidney disease can be seen in people with diabetes, including diabetic nephropathy, ischemic damage associated with vascular disease and hypertension, and other kidney diseases that are unrelated to diabetes (5,6).In this chapter, we will discuss the treatment and management of diabetes to slow the progression of CKD. Nephropatise basic diabetic manifestations is a progressive increase in proteinuria in people with diabetes with long duration with which leads finallycan lead to ESRD (10,11,12). Key risk factors for diabetic nephropathy include duration of diabetes, poor control glicemic, areterial hypertension, male gender, obesity and smoking.

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

1 INTRODUCTION

Chronic deficiency presents irreversible, progressive reduction of renal function and glomerular filtration. When glomerular filtration rate (GFR) decrease among 30-45 ml / min, while serum creatinine concentrations begin to rise above 280 µmol / l,ure>18mmol/l the progress of renal failure begins with increased faster with chronic renal failure is meant renal injury, when GFR is <90 ml / min, 1.73 m2 .CKD and which lasts more than 5 months. Diabetes today is extremely big socio-economic problem, due to material expenditures. As most frequent presenting increased risk factors leading to rapidly progressive renal damage are: arterial hypertension,, excessive loss of protein through the urine, MIA syndrome diabetic disorders, lipid disorders, etc.

1. Doc.Dr.Nexhbedin Kahremani- State University of Tetova, Medical Faculty, Tetova, Macedonia
2.Prof.Dr.Sadi Bexheti- State University of Tetova, Medical Faculty, Tetova, Macedonia
3.Prof..Dr. Sci. Med. Lutfi Zylbeari- State University of Tetova, Medical Faculty, Tetova, Macedonia

4. Prof. Dr. Nasir Behxheti- State University of Tetova, Medical Faculty, Tetova, Macedonia
5. Prof. Dr. Koco Cakalararovski- Faculty of Medicine-Clinic for Nephrology- Skopje,R. Macedonia

At the table number 1 are identified normal and pathological values of and albuminuria and proteinuria(**M-Males**,**F-Females**)

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

Patients with ESRD and Diabetes are required to adhere to the rules of the consumption of protein 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 transferin..

At the table number 2 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 kidney	FG exacerbated	FG stable	FG improved

The protein excess in urine may be reduced if we stick to following preferences : use of lower doses of ACE inhibitor, salt restriction, use of beta blockers, angiotensin II receptor antagonist (when values of K are <5.0 mmol/l), use of hypoli-pemic(statins, fibrat,-niacin, choolestipol, chole-styramine etc. normali-zation of glycemia. A good control of glycemia, when the level of HbA1c is < 7,0%, significa-ntly inhibits the progression of diabetic nephropathy . Uremic patients treated with HD, HbA1c values should behave < 8,0% (15,16,17). 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%, ampu-tation for 39% etc. Any reduction in glycosy-lated hemoglobin for 1%, is in high positive correlation with risk reduction for 21% of CVD, and 37% of microvascular complica-tions. 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(14) . 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 < 20-25 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 (16,17,18). 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.(21,22).

2. MATERIAL AND METHODES

In this prospective cohort research (,, cross-section ") are included 200 examiners, of whom 120 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 (No.100), 45 of them (45%) were female with an average age 57,60 ± 13.00 while 55 (55%) were male, with an average age: 58.50 ± 10.50 year. Control group of healthy examiners (voluntary blood donors) also were 100 of whom: 45(45%) were female with an average age of =58.00±13.20 and 55(55%) men with an average age identic of 57.60 ± 14.00 years. 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 analyze8d 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 (GI) 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 %. All analyzes provided by the study protocol, were defined at the Institute of Clinical Laboratory at the University Clinical Centre of Skopje.

Table number 3. Distribution 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. 4: Presentation of patients by sex and age average

Gender	Number	The average age
Men	55 (55%)	58.50±10.50
Women	45 (45%)	57.60 ± 13.00

The average age of male patinets was: 58.50±10.50 while at females was: 57.60 ± 13.00 years, average age difference between the two sexes according to statistics, was not significant p=0.0005.,

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 p<0.0001. Comparative statistics of the para-meters of blood glucose and glycol-sylated hemoglobin between the two groups, was analyzed with test called studentov,,t", while for depen-dent and independent exam-ples, as well as non-parametric tests, we used Mann-Whitney-U test.

3 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.5. Presentation of the average values of the parameters analyzed to examine patients with DM type 1 - the Insulin-Dependent N^0 = 60) and DM type 2 (with oral hypoglycemic-N^0 = 40)

Parameters	Number	Average	Minimum	Maximum	± SD
Patients with Diabetes Mellitus, Type 1 (insulin-dependent N^0 =60)					
HbA1c %	60	8.50	6.2	13.50	6.40
Glycaemia	60	8.90	7.80	10.50	3.70
LT	60	7.40	2.50	9.20	2.70
TG	60	3.90	1.8	4.16	1.10
Cholesterol	60	5.80	1.50	6.80	1.42
HDL-ch	60	1.10	0.42	3.20	0.95
LDL-ch	60	4.90	1.80	5.90	0.98
Patients with type 2 D. Melltus tip 2 (oral hypoglycemic - N^0 = 40)					
Glycaemia	40	9.00	6.40	12. 60	5.60
HbA1c %	40	8.70	5.60	9.50	4.80
LT	40	7.50	5.30	10.80	4.90
TG	40	3.75	2.80	4.80	0.98
Cholesterol	40	5.40	1.80	6.70	2.30
HDL-ch	40	1.04	0.70	1.60	0.0
LDL-ch	405	4.80	3.80	5.70	0.90

Table number 6 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) N^0-60 at the beginning of the study

Parameters	Average values	± SD
Potassium (mmol/l)	4.60	0.80
Urea(mmol/l)	15.70	4.80
Creatinin(mmol/l)	320.0	30.00
Uric acid(µmol/l)	380.00	45.60
GFR (by Cocroft&Gault)	5.00 ml/min	6.80

Table number 7. 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)	5.2	0.90
Urea (mmol/l)	19.80	3.80
Creatinin (mmol/l)	380.00	13.50
Uric acid(µmol/l)	390.00	16.00
GFR (by Cocroft&Gault)	54.00 ml/min	5.10

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 2 (treated with oral hypoglycemic) N0 = 40 at the beginning of the study

Parameters	Average values	± SD
Potassium (mmol/l)	4.50	0.60
Urea (mmol/l)	14.80	3.20
Creatinin (mmol/l)	375.00	16.80
Uric acid (µmol/l)	380.00	29.20
GFR (by Cocroft&Gault)	56.00 ml/min	7.80

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 2 (treated with oral hypoglycemic) N0 = 40 after 12 months

Parameters	Average values	± SD
Potassium (mmol/l)	5.20	0.80
Urea (mmol/l)	16.00	2.80
Creatinin (mmol/l)	390.00	15.00
Uric acid (µmol/l)	420.00	17.00
GFR (by Cocroft&Gault)	50.00 ml/min	6.80

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 10. 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	0.48595	0.870230
HbA1c %	9365.000	0.48350	0.065240
LT	1240.000	-0.136579	0.800460
TG	679.400	-3.25700	0.001480
Cholesterol	1080.500	0.39670	0.801430
HDL-ch	1050.000	0.68810	0.607500
LDL-ch	1235.600	-0.08740	0.954520

The difference which was recorded between the average values of patients with DM type 1 and type 2 DM was nonsignificant, for p <0.005. Significant difference was recorded only at: TG (p =0.001480)

4 DISCUSSION

Among the risk factors that in recent years have been given special attention, are higher concentration of lipoproteins and hypergly-cemia.ESRD and diabetes are characte-rized by high risk of micro and macrovasculare disease, therefore are necessary numerous studies to detect new factors of cardiovascular risk, parti-cularly those complications that are closely related to microvascular disease, as a result of unregu-lated diabetes. 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 myocar-dial infarction, left ventricular hypertrophy, macrovascular complca-tion, peripheral vascular diseases, diabetic vas-cular 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. therefore the American Association of Diabetes always suggests the maintenance and regulation of normal values of glycemia. Patients with chronic renal failure have disturbed metabolism of glucose and insulin sensititvity. The basic mechanisms of disruption of glucose metabolism at diabetic patients with ESRD are not well known, but it is assumed that in this mechanism are involved and influencing: increase of gluconeo-genesis in liver, reduced hepatal and skeletal absorption of glucose from muscles helped by an impairment of intracellular metabolism of glucose , due to the reduced oxidation of glucose in carbon dioxide and water , or as a consequence of the reduced synthesis of glucagon. 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 ect.(21-27). A number of studies have verified that supplementation and correction of renal anemia with Eritropoetin significantly increase the sensitivity of insulin, increase secretion of insulin and decrease blood glucose level(,27,28,29,30). 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(28-33) . The need for insulin is also reduced due to reduced calorie intake of uremic patients with diabetes. (31,32). 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 34-37) .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. (38,39,40). 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, signifi-cantly 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 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 at higher risk for early atherosclerosis compared with healthy population, as well as its consequences on the cardiovascular system. According to contem-porary thoughts diabetes is a multifactorial disease etiology, and its main characteristic is hyperglycemia accompanied by metabolic disor-ders 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 atheros-clerosis in patients with DM, disorders on meta-bolism of lipids have an important role. Genetic factors that influence the development of cardio-vascular and cerebrovascular diseases, and atherosclerotic processes, are: disruption of reverse transport of HDL-cholesterol, cumberso-me expression of B-receptors compared with E-receptors, reduced conversion of VLDL to IDL and LDL-ch ((41-44). A large number of studies have documented that between CVD and high value HgbA1c there is a high positive correlation with IRKT patients and D. mellitus (45-48).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 . 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 and slow the pace of progress of the ESRD (49-52). In the pace of disease progression in patients with diabetes and ESRD affect many factors: the pharmacodynamic effects uremic acid, the perocedures dialysis itself, influence of insulin pharmacokinetics on carbohydrate metabolism and -oral hypoglycemics, oxidative stress, lipidic peroxi-dasis,MIA syndrome, arterial hyperten-sion, dyslipidemia, hypertrigly-ceride-mia, shorte-ned erythrocyte life, renal anemia etc. ESRD and DM patients, due to the appearance of anemia in the initial stages should be treated with eritro-poetin (rHuEpo) because eritropo-etina increases the percentage of reticulocyte and stimulates the production of new red blood cells. A number of authors have verified early athero-sclerosis 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 concen-trations of lipids. 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). 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, hyperapolipo-proteinemia, pharmacodynamic effe-cts of uremia, uremic toxins, hemodialysis as medical proce-dure, effects of insulin, disorders of carbo-hydrate metabolism, disorders of coag-ulation factors, arterial hypertension, smoking, secondary hyper-parathyroidism, hyperhomocyste-inemia, thrombo-tic factors, oxidative stress etc. There are docu-mented facts that the number and the life of erithrocytes at patients with ESRD are reduced, so is expected the decrease of concetration of HbA1c. Chronic hyperglycemia combined with dyslipidemia i even further increase the risk of morbidity and mortality from cardiovascular disease in uremic patients with diabetes treated HD.

5 CONCLUSION:

For conclusion we can say that the 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. 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. Uremic and diabetic patients treated with HD (regardless of the type of diabetes) are at high risk of early atherosclerosis appearance. Hyperglycemia and dyslipi-demia are among the most dangerous factors of progress of ESRD. Therefore, improvement 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 CVD.

Literature

1. prevalence of stages of diabetic nephropathy defined by urinary albumin/creatinine ratio J Am Soc Nephrol 7 1996 930 937

2. K. Reenders E. de Nobel H.J. van den Hoogen Diabetes and its long-term complications in general practice: a survey in a well-defined population Fam Pract 10 1993 169 172
3. M.R. Weir Albuminuria predicting outcome in diabetes: incidence of microalbuminuria in Asia-Pacific Rim Kidney Int 66 2004 S38S39
4. Grundy SM, Howard B, Smith SJr, Eckel R, Redberg R, Bonow RO. Prevention Conference VI: Diabetes and Cardiovascular Disease: executive summary: conference proceeding for healthcare professionals from a special writing group of the American Heart Association . Circulation. 2002; 105:2231–2239.
5. 5. Locatelli F, Del Vecchio L, Pozzoni P. Clinical benefits of slowingthe progression of renal failure. Kidney Int Suppl 2005; (99):S152–6.
6. 6. Manske CL. Hyperglycemia and intensive glycemic control indiabetic patients with chronic renal disease. Am J Kidney Dis1998; 32(5 Suppl 3): S157–71.
7. G. Mazzucco T. Bertani M. Fortunato Different patterns of renal damage in type 2 diabetes mellitus: a multicentric study on 393 biopsies Am J Kidney Dis 39 2002 713 720

8. V. Gambara G. Mecca G. Remuzzi Heterogeneous nature of renal lesions in type II diabetes J Am Soc Nephrol 3 1993 1458 1466

10 . Gerstein HC. Dysglycaemia: a cardiovascular risk factor. Diabetes Res Clin Pract. 1998; 40(Suppl):9–14.

11. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulpho-nylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. (UKPDS 33) Lancet. 1998;352:837–853.

12. Stratton IM, Adler AI, Neil AW, et al. Association of glycaemia with microvascular and macrovascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321:405–412

13. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada.Can J Diabetes . 2003; 27(Suppl 2):s21–s23.

14. Ferrannini E, Wahren J, Faber OK, Felig P, Binder C, DeFronzo RA. Splanchnic and renal metabolism of insulin in human subjects: a dose-response study. Am J Physiol . 1983;244:E517–E527.

15. Praga M. Therapeutic measures in proteinuric nephropathy.Kidney Int Suppl 2005; (99): S137–41.

16. Locatelli F, Del Vecchio L, Pozzoni P. Clinical benefits of slowingthe progression of renal failure. Kidney Int Suppl 2005; (99):S152–6.

17. Manske CL. Hyperglycemia and intensive glycemic control indiabetic patients with chronic renal disease. Am J Kidney Dis1998; 32(5 Suppl 3): S157–71
18. Rave K, Heise T, Pfutzner A, Heinemann L, Sawicki PT. Impact of diabetic nephropathy on pharmacodynamic and pharmacokinetic prope-rties of insulin in type 1 diabetic patients. Diabetes Care.2001;24:886–890.

19. Biesenbach G, Raml A, Schmekal B, Eichbauer-Sturm G. Decreased insulin require-ement in relation to GFR in nephropathic type 1 and insulin-treated type 2 diabetic patie-nts. Diabet Med. 2003;20:642–645.

20. Mak RH, DeFronzo RA. Glucose and insulin metabolism in uremia. Nephron. 1992;61:377–382

21.. Maack T, Johnson V, Kan ST, Figueiredo J, Sigulem D. Renal filtration, transport and metabolism of low molecular weight proteins: a review. Kidney Int. 1979;16:251–270.

22. Goldberg AP, Hagberg JM, Delmez JA, Haynes ME, Harter HR. Metabolic effects of exercise training in hemodialysis patients. Kidney Int. 1980;18:754–761.

23. System USRD: USRDS 2005 Annual Data Report. Atlas of End-Stage Renal Disease in the United States. National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Diseases: Bethesda, MD 2005.

24. Koro CE, Bowlin SJ, Bourgeois N et al. Glycemic control from 1988 to 2000 among US adults diagnosed with type 2 diabetes: a preliminary report. Diabetes Care 2004; 27: 17–20.

25. Liebl A, Mata M, Eschwege E. Evaluation of risk factors for development of complications in Type II diabetes in Europe. Diabetologia 2002; 45: S23–28.

26. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes . JAMA 2004; 291: 335–342.

27. American Diabetes Association. Tests of glycemia in diabetes (position statement) . Diabetes Care 2004; 27: S91–S93.

28. Alvestrand A. Carbohydrate and insulin metabolism in renal failure. Kidney Int. 1997; 62(52Suppl):S48–S52.

29. Carone FA, Peterson DR. Hydrolysis and transport of small peptides by the proximal tubule. Am J Physiol. 1980;238:F151–158.

30. Adrogu HJ. Glucose homeostasis and the kidney. Kidney Int. 1992;42:1266–1272.

31. Mak RH. Intravenous 1,25-dihydroxycholecalciferol corrects glucose intolerance in hemodialysis patients. Kidney Int. 1992;41:1049–1054

32. Kautzsky-Willer A, Pacini G, Barnas U, et al. Intravenous calcitriol normalizes insulin sensitivity in uremic patients. Kidney Int. 1995;47:200–206.

33. Lin S, Lin Y, Lu K, et al. Effects of intravenous calcitriol on lipid profiles and glucose tolerance in uraemic patients with secondary hyperparathyroidism. Clin Sci. 1994;87:533–538.

34. Ansari A, Thomas S, Goldsmith D. Assessing glycemic control in patients with diabetes and end-stage renal failure. Am J Kidney Dis. 2003;41:523–531.

35. Paisey R, Banks R, Holton R, et al. Glycosylated haemoglobin in uraemia. Diabet Med. 1986;3:445–448.

36. Joy MS, Cefalu WT, Hogan SL, Nachman PH. Long-term glycemic control measurements in diabetic patients receiving hemodialysis. Am J Kidney Dis. 2002;39:297–307.

37. Position statement. Standard of Medical Care in Diabetes-2007. Diabetes Care. 2007;30:s4–s41.

38. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2005;4(Suppl 3):S1–S360.

39. Tarkun I, Cetiarslan B, Canturk Z. Lipoprotien(a) concentration in patients with type 2 diabetes mellitus without cardiovascular disease: relatinoship to metabolic and diabetic complications. Nutr Metab Cardiovasc Dis 2002 Jun; 12 (3) 127-131.

40. Ogbera o A. Azenabour O A. Lipoprotein(a), C-reaktiv protein and some metabolic cardiovascular risk factors in type 2 DM. Diabetologija & Metabolic Syndrome 2010; 2:51.

41. Alaupovic P, Kostner G, Lee DM, Conathy WL, Magnani HH. Peptide composition of human plasma apolipo-proteins A, B and C. Expos Annu Bioch .Ponticelli C.et al. Lipid abnormalities in maintenance dialysis patients and renal transplant recipients.Kidney Int Suppl. 1978; 8: S 72.

42. Haas LB,Wahl PW, Sherrard DJ. A longitudinal study of lipid abnormalities in renal failure.Nephron 1983; 33:145.

43. Somer JB. Et al.B. Lipoprotein lipids in chronic renal failure and hemodialysis: the influence of etiology and implication for atherogenesis. Atherosclerosis 1979; 34:353.Med. 1972;31:145-60.

44. Miida T, et al. LCAT-dependent conversion of pre β1-HDL into alpha migrating HDL is severely delayed in haemodialysis patients. J Am Soc Nephrol.2003;14:732-8.

45. Selvin E, Marinopoulos S, Berkenblit G et al. Meta-analysis: glycosylated hemoglobin and cardiova-scular disease in diabetes mellitus. Ann Intern Med2004; 141: 421–431.

46. Menon V, Greene T, Pereira AA et al. Glycosylated hemoglobin and mortality in patients with nondiabetic chronic kidney disease. J Am Soc Nephrol 2005;16: 3411–3417.

47 . Selvin E, Coresh J, Golden SH et al. Glycemic control and coronary heart disease risk in persons with and without diabetes: the atherosclerosis risk in communities study. Arch Intern Med 2005; 165: 1910–1916.

48. Akmal M. Hemodialysis in diabetic patients. Am J Kidney Dis 2001; 38: S195–199.

49. American Diabetes Association. Standards of medical care in diabetes (position statement). Diabetes Care 2005; 28: S4–S36.

50.American Diabetes Association. Clinical practice recommendations . Diabetes Care 2006; 29: S3.

51. Ansari A, Thomas S, Goldsmith D. Assessing glycemic control in patients with diabetes and end-stage renal failure. Am J Kidney Dis 2003 ; 41: 523–531.

52.M E Williams, E Lacson Jr, M Teng, N Ofsthun and J M Lazarus. Hemodialyzed type I and type II diabetic patients in the US: Characteristics, glycemic control, and survival. Kidney International (2006) 70, 1503–1509.

Adress of the autorss:
Doc.Dr.Nexhbedin Kahremani
State University of Tetova, Medical Faculty, Tetova, Macedonia
Faculty of Medicine-Clinic for Nefrologu- Skopje,R. Macedonia
E-mail:nexhbedin.kehremani@unite.edu.mk