DIABETES MELLITUS AND DYSLIPIDEMIA IN UREMIC PATIENTS-TREATMENT

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Abstract: Dyslipidemia has been established as a well-known traditional risk factor for cardiovascular disease (CVD) in the general population and it is well known that patients with chronic kidney disease (CKD) exhibit significant alterations in lipoprotein metabolism. In this review, the pathogenesis and treatment of CKD-induced dyslipidemia are discussed. Studies on lipid abnormalities in predialysis, hemodialysis and peritoneal dialysis patients are analyzed. In addition, the results of the studies that tested the effects of the hypolipidemic drugs on cardiovascular morbidity and mortality in patients with CKD are reported. In patients with Diabetes Mellitus (DM type 1 and DM type 2) is proven and documented that there is a high positive correlation between hyperglycemia, glycosylated hemoglobin (HbA1c) and high lipid concentration values (LDL-ch and TG) and decrease in HDL-ch concentrations micro and macrovascular consequences, cardiovascular disease (CVD), retinopathy and diabetic nephropath(1) There are verifiable evidence that patients with insulin-dependent DM or treated with oral therapy are candidates with potential risk of cardiovascular diseases, peripheral vascular diseases, stroke compared with the healthy population. In the plasma of patients with DM were detected besides high concentrations of: blood glucose, glycosylated hemoglobin (HbA1c) were also detected high concentrations of LDL-ch and triglycerides and low concentrations of HDL-ch which further help the occurrence of cardiovascular disease (CVD) and coronary atherosclerosis complications (2). Aim of the paper work was to verify and document, role and correlation of lipid dissorders (dyslipidemia) and hyperglycemia in the pace of progress and the appearance of cardiovascular diseases in patients with Diabetes Mellitus type.1 and the type 2 compared with healthy control individuals . The paper also aimed to influence positive effects of statins family in the treatment of hypercholesterolemia in patients with diabetes mellitus type 1 and type 2. In our patients treated with statins at the dose of 40 mg per day with duration of 3 months and reached a target of reducing the LDL cholesterol by 30-38%. The research was prospective cohort („ cross-section ") Totaly are included N^0 = 240 examiners of whom 120 were patients of diabetes mellitus (DM 75 with tip1 while 45 were with DM type 2) while 120 individuals were healthy you served as group controllers.For examination was used 5+ (5) ml of venous blood taken from the vein in the patient lying position in order to avoid possible variations and the influence of the position of patients on lipid fraction values (9- 12%) which occur if the blood of patients is taken from the horizontal position. Dyslipidemia in diabetic patients with diabetes is present at the initial stages of an outbreak of the disease so its drug treatment in the early stages should be the primary postulate of physicians with which obviously would help the prevention and reduction of presentation of CVD Dyslipidemia in patients with diabetic uremic patients remains unclear. We previously reported that lipid abnormalities in diabetic uremia on short-term (3 to 28 months) hemodialysis therapy were more severe than those in nondiabetic uremic patients.

Index Term: Uremia, Diabetes Mellitus (DM), blood glucose (Gl), statins.

1 INTRODUCTION

Patients with diabetes mellitus undergoing chronic hemodialysis treatment have the worst outcome on dialysis due to an increased rate of cardiovascular complications. Nearly all patients present with dyslipidemia, a prominent vascular risk factor, probably responsible for the high rate of vascular injury. Since both uremia and diabetes predispose to hypertriglyceridemia, the present study was conducted to investigate the influence of diabetes mellitus and/or hypertriglyceridemia on lipoprotein metabolism in hemodialysis patientsDiabetes is one of the most massive diseases in the modern world with a tendency to increase the size of large and mostly appears in the developed and developing world (3). Diabetes is counted as the fourth cause of mortality in developed countries. A large number of studies have verified that epidemiologyc regulation and control of sugar concentrations significantly reduced the rate of incidence of cardiovascular diseases (CVD) cerebral-vascular insults therefore the American Association for Diabetes (AAD) always provides guidance and recom-mendations on control and regulation of high values of glycemia and examination of HgbA1c in patients with DM with which measures also reduce the risk of CVD, myocardial infraction and mortality of this group of patients. The control of hyperglycemia and glycohemoglobine (HgbA1c-average value of glycemia within three months) represents one of the primary measures in pursuit of the pace of progress to diabetes, so regular controls tracking and balancing of diabetes with dyslipidemia in the early stages of the disease, obviously would influence the prevention of the appearance of early atherosclerotic processes in coronary, cerebral and peripheral arteries .We always control glycemia and HgbA1c in patients with diabetes mellitus respecting the recom-mendations of AAD.

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Recent years the incidence of unregulated diabetes and diabetic nephropathy and not only in the US and Europe but also the Balkans has an increase of 38% -42% which is due to: unregulated treatment of diabetes, psychostress, adiposity unrespected hygiene and dietary measures, excess consumption of fatty foods and disregard of ordinated therapy, smoking, physical inactivity, oxidative stress etc.Therefore, in recent years doctors always suggests that measurement and monitoring of blood glucose and lipid control to be one of the goals and measures mandatory for doctors of primary and secondary practice to what will be considerably decreased the incidence of SKV. So in the initial stages of presentation of Diabetes (DM) have dyslipidaemia and dyslipoproteinemia disorders with increased concentrations of LDL-ch, TG and HDL-ch reduction compared with patients with other diseases, so early examination of these disorders can significantly affect the prevention of the appearance of cardiovascular diseases (CVD (6.7). There are documented facts that the disorders of blood glucose and HgbA1c everytime in patients with DM are also associated with disturbance of lipid and therefore we decide to make our paper examinations lipid profile (total Cholesterole (CHT), Triglycerides(TG) Total lipid (TL), HDL and LDL-ch)], glycemia (Gl) and glycosylated hemoglobin (HbA1c) in patients with diabetes-insulin users and patients treated with oral therapy. Patients with Diabetes Mellitus (DM) are at higher risk for early atherosclerosis and its consequences to the cerebrovascular system, cardiovascular and peripheral artery atherosclerosis compared with healthy population (4,5). Besides lipid abnormalities patients with DM have the disturbance of apolipopro-teins . Apol-ipoproteines are integral protein of lipoproteinemic macro-molecule specific to each class of them (8) . Are related to lipid molecule using hydrophobic properties of fatty acids from phospholipids and polar part of the polypeptide chain (the process of inter-ionic reaction between phospholipids couples and opposite-charged amino acid alpha-helix electric to apoproteine. As factors underlying the appearance of cardiovascular diseases, cerebrovascular and early atherosclerosis in patients with DM apolipoproteines have an important role in metabolic disorders (9-11). Genetic factors of cardiovascular diseases, cerebrovascular and sclerotic processes are counted: the disruption of reverse transport of HDL-ch, cumbersome expression of B-receptors compared with E-receptors, reducing the conversion of VLDL to IDL and LDL ch (12). The function of apolipoproteins is that they allow plasma lipid hydrosolubility in water ($C_{h,}$ TG, FL) of macromolecular complex-forming hydrosolubile lipoprotein (apolipopro-proteins) that are transported by the blood. The exact pathogenesis of diabetic dyslipidemia is not yet known; however, a large number of evidence suggest that insulin resistance has a central role in the development of this pathological phenomenon. The main cause of diabetic dyslipidemia is the release of fatty acids by increasing insulin-resistant fat and increased flux of free fatty acids in the liver in the presence of adequate stores of glycogen, which is still draining triglycerides encourages production, which in turn stimulates its secretion apoliproteines-B (apo-B), Lp (a). and VLDL cholesterol. Diabetes mellitus – type 1 and generally well controlled rarely is associated with hyperlipidemia except diabetic ketoacydosis often associated with hypertriglyceridemia due to the increased release of tissue fatty acids (13-17). Pathological consequences of hypertriglyceridemia mostly appear to lipoprotein metabolism and early artherosclerotic manifestation. Anytime Diabetes is associated with high risk of cardiovascular disease (CVD) .Menagment of diabetic dyslipidemia is a key element in a multi-factorial approach to prevent the occurrence of CVD in patients with diabetes. Patients with diabetes have a higher absolute risk of coronary disease presenting as patients without diabetes equally but with coronary disease, acute myocardial infarction and congestive heart failure, high prevalence of

mortality(18,19) Lipid disorders ie diabetic dyslipidemia (atherogenic dyslipidemia) are always manifested by increased levels of triglycerides and LDL cholesterol and reduced level of cholesterol proatherogen-HLD-ch. Diabetic dyslipidemia is often helped by insulinemic resistance and is present even before the diabetes. Small dense particles of LDL are more atherogenic due to their high sensitivity by increasing oxidative modification and the growth of taking the fat from the arterial wall. Overall, 30-40% of patients with diabetes suffer from diabethic dyslipidemia. All current national guidelines (NCEP- National Cholesterol Education Program) on the treatment of diabetic dyslipidemia as main target values have reduced the TG and LDL-ch and they suggest for LDL-c values from 100 to 70 mg / dl (20,21,22) as the optimal value for preserving the risk of coronary disease. NCEP recommendations association 2005 for the start of treatment of diabetes dyslipidema of hypercholesterolemia namely with statin should be started when the values of LDL-ch are> 100 mg / dl to gain target effects of treatment with decreases in LDL-ch of 30-40 %%, no pre-Liner LDL cholesterol levels, thus the lower the degree of risk of CVD.Results of many studies on the treatment of diabetic dyslipidemia and verified results have proven very successful during treatment with statine.In the case treatment with statin did not give proper effect to then preferably combined therapy, statin and niacin or statin with holestipol or holestiramin or fibrates with but any means combination niacin and fibrates between statins family due to the harmful effects of myositis or rhabdomyolysis consequences (23-27). Improvement and regulation of blood glucose values regardless of the type of dyslipidemia treatment has shown positive effects in improving lipid values. Beneficial effects in improving lipid abrevations in tip2 diabetic patients with oral therapy have shown metformin and rapaglinid treatments. There is documented evidence of these drug's influence on the improvement of diabetes and lipid disorders is closely linked with reduced levels of triglycerides and increased HDL-ch values (28,29,30). Hypertriglyceridemic and diabetic patients showed reduced lipase activity and increased LDL oxidation. Furthermore, they accumulated a fraction of small, dense LDL, and LDL was predominantly taken up via the scavenger-receptor pathway in peritoneal macrophages. This study elucidates the distinct influence of diabetes and/or hypertriglyceridemia in hemodialysis patients on cellular LDL metabolism via specific and nonspecific metabolic pathways. Furthermore, it underscores the cumulative impact of these pathologic entities on impairment of lipoprotein metabolism and increase of cardiovascular risk. Patients with renal failure undergoing chronic hemodialysis treatment are known to be at increased atherogenic risk (1). In diabetic patients on hemodialysis treatment, morbidity and mortality are even higher compared with nondiabetic patients. One of every two patients with non-insulin-dependent diabetes mellitus (NIDDM) dies during the first 3 yr of hemodialysis treatment, and in more than 60% the cause of death is of vascular origin (2). Dyslipidemia is common in uremic and nonuremic patients with diabetes mellitus and is regarded as playing a major role in the progression of atherosclerosis (3,4). One main component of such dyslipidemia is impaired uptake of LDL via LDL-receptor-mediated pathways, which has recently been described for diabetic subjects (5,6), hypertriglyceridemic patients (7,8), and hemodialysis patients (9). In addition to uremia and dialysis-induced changes of lipoprotein metabolism, alteration of receptor-mediated lipoprotein pathways in diabetic hemodialysis patients could be due to modifications in lipoprotein composition and configuration via glycosylation (10,11). Enrichment of small, dense and triglyceride-rich LDL in diabetes mellitus has been described before (12). This alteration in distribution of LDL subfractions may additionally diminish receptor-specific uptake because small and triglyceride-rich LDL are known to exhibit impaired affinity to the LDL-receptor. Because hydrolysis of triglyceride-rich lipoproteins is dependent on lipoprotein lipase and hepatic lipase activity, changes in enzyme activity may considerably influence lipoprotein metabolism, preferably affecting triglyceride-rich lipoproteins. Besides uremic factors leading to impaired lipase activity in patients with renal failure, chronic heparin treatment in hemodialysis patients might deplete endothelial lipase stores, resulting in hypertriglyceridemia based on an increase in half-life of triglyceride-rich lipoproteins.

2 Material and Methods Used

The research was prospective cohort (,, cross-section ") Totaly are included N^0 = 240 examiners of whom 120 were patients of diabetes mellitus (DM 75 with tip1 while 45 were with DM type 2) while 120 individuals were healthy you served as group controllers.For examination was used 5+ (5) ml of venous blood taken from the vein in the patient lying position in order to avoid possible variations and the influence of the position of patients on lipid fraction values (9- 12%) which occur if the blood of patients is taken from the horizontal position. Blood taken for examination inserted into the vial with a few drops heparin (5ccm serum) were sent for analysis in the laboratory of Clinical Hospital of Tetovo and parallely from a vial from the same patient was sent to the Institute of Clinical Laboratory in Skopje, in order to be verified and calibrated results obtained Of the patients with DM (120) -54 (45%) of them were girls with an average age: 56.40 □12.80 but- 66 (55%) were male, with an average age: 59.50 □14:50 years.Group controller sound examination (voluntary blood donors) also were 54 (45%) women and 66 (55%) men with an average age identical: 15:00 □58.60 years. Of the total number of patients = N^0 = 120with Type-1 diabetes mellitus (DM Tip1 th insulin dependent) were 75 while 45 were patients with Type-II diabetes mellitus (DM type 2 th treated with oral hypoglycemic), table number 1 .. Patients who were insulin dependent are counted as Type-1 while patients independent of insulin but with oral therapy, count as type-2 DM. So together with examination of concentrations of lipid profile, glycemia and the glicosylated hemoglobin (HbA1c) we made the determination of BMIx (Body Mass Index-tabel . no. 4). In all patients and the control group were analyzed lipid values of blood glucose and hemoglobin that is glycosylated within 3 months. The methods of determining the concentrations of lipid profile, blood glucose (Gl) and HbA1c are identified in the table of number 2. As a reference value for Gl and HbA1c values were taken according to criteria proposed by the World Health Organization (WHO) - {(Gl = 3.5-6.5 mmol / l, (HbA1c% = 4.4% -6.6% T All analyzes are provided according to the study protocol and detected in the laboratory of the Institute of Clinical Laboratory of the University Clinical Center of the Medical Faculty in Skopje.

Table number 1: Reference Values and methods by authors whose blood glucose concentrations are determined, HbA1c and Lidids profiles are Presented in table 1.

Parameters Examined	Reference Values	Authors
LT	4-10g / l	ZOLLNER & Kirsch [74]
TG	0.68-l, 70 mmol / l	Buccola G. & H. David [75]
TCH	3, l, 5.2 mmol / l	CC. Allain et al [76]
LDL-ch	<3,4mmol / l, danger of adults:> 4.1 mmol / 1	Friedewalde & Fredricks on[77]
HDL-ch	> 1,6mmol / 1, danger of adults: <0.9 mmol / 1	WARNICKE G. et al [78]
Glicemia (Gl)	3.5-6.5 mmol / L	Turbidimetric, Cobas Integra 400
HbA1 c%	4.4-6.6%	Turbidimetric, Cobas Integra 400

Table no.2: Presentation of diabetes patients under therapy

Tot. pacients-N^{o} = 120	DM type 1 (insulin-dependent)	DM type 2 (oral hypoglicemic)
	75	45

Table no. 3: Distribution of patients by sex and age average

Gender	Number	The average age
Men	66 (55%)	59.40± 14.60
Women	54 (45%)	58.00 ±13.50

Table no. 4: Distribution of the control group average by gender and age

Gender	Number	The average age
Men	66 (55%)	57.00±12.80
Women	54 (45%)	58.50± 13:00

The average age of patients was male gender-59.40±14.60 , while female sex was-58.00 ±13.50, the average age difference between male and female according to statistics is nonsignificant $p = 0.0005$, which indicates a homogeneous groups (tab. 2)

Table. No.5: Distribution of patients according BMIx: male = 75 and female = 45

BMIx	Male	Female
Poor Feeding	18	10
Normal feed	28	15
More feed	24	12

Obesity instance II-a	5	8

According table number 4. Differences between patients according to statistics is *nonsignificated p <0.0005* and shows that working for homogeneous groups of patients.

3 Statistical processing of material examined

Values obtained of the blood glucose, HbA1c% and lipids (Kol.Total, TG, HDL-ch, LDL-ch) and control group are presented with mean values and standard deviation X □SD. In the results were also calculated correlation coefficient "r "statistical value of p ,," less that1% (p <0.0001). Statistics comparative lipid parameters between the two groups were analyzed to test the so-called Studentov ,, t "while for examples dependent or independent and non-parametric tests were used tests: Mann-Whitney-U. significant statistics differences between the group of patients and control group obtained values of the parameters of lipids, glycemia and HbA1c% were analyzed to test the so-called ,, Anonova Two-Factor "statistical Worth ,, p 'lesser of 5 %, namely p<0.0005.

Results obtained:

The results obtained from the examination of blood glucose, HbA1c, lipid, (Kol.Total, TG, HDL-ch, LDL-ch) and the results obtained from the control group are presented in tables.2 and 3. Tables itself noted that the two groups of patients (DM Type-1 and DM-type 2) are verified high concentrations of lipids and HbA1% with significant statistical difference for *p <0.0001,* compared with control group. Between values obtained of patients (with DM Type-1 and Type-2 DM) did not notice any significant difference facts that are consistent with many other studies (31,32). Lipid parameters presented a significant increase of the concentrations of: LDL-ch and TG and low concentrations of HDL-ch of the two groups of patients with DM compared with the results from acquired by the group controller.

Table number 6: Presentation of the average Values of the Parameters analyzed to Examine patients with type 1 DM - the insulin-dependent N ^{0} = 75 before treatment with hyppolypemic therapy.

Parameters	Number of patients	Average	Minimum	Maximum	± SD
HbA1c%	76	10.80	6.80	13.60	5.70
Glycemia	75	9.60	7.6	14.20	3.40
TL	75	7.80	3.90	9.50	2.10
TG	75	3.70	1.26	4.60	0.80
TCh	75	5.60	2:50	7.80	2.10
HDL-ch	75	1:00	0.70	2.15	0.85
LDL-ch	75	4.60	4.20	5.90	0.90

Table number 7: Presentation of the average Values of the Parameters analyzed to Examine patients with type 2 DM dependent N ^{0} = 45 (oral hypoglocemic) -Before hippolypemic THERAPY TREATMENT.

Parameters	Number of patients	Average	Minimum	Maximum	± SD
HbA1c%	45	8.70	6.80	8.90	1.20
Glycemia	45	7.90	7.10	9:00	0.90
TL	45	7.80	5.40	12:30	3:40
TG	45	3.80	2.40	4.80	0.80
TCh	45	5.80	5.10	7.50	2.50
HDL-ch	45	1.10	0.90	2.40	0.70
LDL-ch	45	4.90	3.60	6.80	0.60

Table number 8: Presentation of the ***Mann-Whitney U-test*** for the Difference of the Values of the Parameters analyzed patients with DM type 1 and type 2 DM

Parameters	U	Z	*p-level*
Glycemia	6780.000	0.46895	0.860246
HbA1c%	8265.000	0.48280	0.006842
LT	1131.000	-0.13778	0.890417
TG	655500	-3.25744	0.001124
Cholesterol	1091.500	0.39693	0.691421
HDL-ch	687800	-3.42614	0.001240
LDL-ch	8156.000	-3.456800	0.001460

Was Recorded qual Difference Between the average seething of patients with DM type 1 and type 2 DM is josinjifikant for p <0.005, Significant Difference Was Recorded only at: *TG (p = 0.0011, HDL-ch (p = 0.001124) and LDL -CH (p = 0.00146)*

Table number 9: Presentation of the average Values of the Parameters Examined in patients with DM Type 1, Type 2 DM and control group

P atients with - DM Type 1 and Type 2 DM						Controls Group		
Saw ERS	Number	Average	Minimum	Ma ximum	± SD	Average	± SD	*p*
T L	1 20	7. 80	2. 40	12.60	2.8 0	6. 40	0.60	0 .0001
TG	1 20	3.85	2. 50	4. 80	0. 80	1. 28	0.63	0.0001
T Ch	1 20	5. 80	4. 60	7. 40	0.9 2	4.9 0	1.2 4	00:02 50
HDL-ch	1 20	1:03	0. 50	1. 15	0. 82	1.60	0. 60	0.0001
LDL-ch	1 20	4.20	3:40	5.4 0	0.9 5	3 .50	1.0 2	0.0001
Glycemia	1 20	8. 60	4.90	9.80	4.6 5	5. 60	2. 10	0.0001
HbA1c%	1 20	8. 60	5. 80	12. 40	3. 90	7.20	3. 80	0.0001

Table 9: shows significant differences-p between the parameters examined between the patients with Diabetes mellitus (type 1 and type 2) and the control group. The difference which appears between the average values of the examined parameters of the two

groups is significant statistic except total cholesterol values differ with *p> 0.0005).* The values of the parameters examined LT, TG and LDL-ch, are higher of patients with DM-1 and DM-Tip Tip 2 with p <0.0001, compared with control group. Lower values of patients with DM type 1 and type 2 DM compared with the control group were recorded only in HDL-ch for P <0.0001.

Table number 10: Indicates significant differences between the examined parameters of patients with diabetes mellitus (type 1 and type 2) and the control group after 3 months after treatment with statins.

Parameters	Number of patients	Average	Minimum	Maximum	± SD	Controls group.Average	± SD
Glycemia	120	8.10	6.80	8.90	1.25	6:40	0.60
HbA1c%	120	7.60	7100	8.70	0.80	1.28	0.63
LT	120	7.80	5:40	7.10	1:40	4.90	1.24
TG	120	2.80	2.20	2.90	0.80	1.60	0.60
Cholesterol	120	5.70	4:50	5.60	1.20	3:50	1:02
HDL-ch	120	1.18	0.80	2.70	12:50	5.60	2.10
LDL-ch	120	4:00	3.90	4.20.	0.60	7.20	3.80

From the table itself noted that the total lipid, triglycerides, total cholesterol and LDL-ch after treatment with statins doses of 12 weeks 1 tablet of 40 mg in the evening have significant reduction of their concentrations with *p = 0.0001* while the HDL fraction ch noticed a remodeling to increase its concentration, which testifies to the positive effects of statin for a double effect and the regulation of LDL hypercholesterolemia but also in increasing proatherogen HDL-ch concentration

4 DISCUSSION:

Treatment of diabetic dyslipidemia recent years often by the American Diabetes Association (ADA American Diabetes Association) has been the topic of discussion by proposing dietary and therapeutic measures on managing of dyslipidemia in patients with diabetes. There are documented facts that the patients with diabetes from lipid fractions most often manifest hypertriglyceridemia (concentration increase of triglycerides-TG) and hypercholesterolemia-increased concentrations of LDL-ch with decreased cholesterol values of proatherogen *(HDL-ch).* In particular, patients with diabetes tend to have a significant increase of oxidized cholesterol (LDLox) and a higher percentage of particles ,, fooam cells "which are highly susceptible to oxidation at high risk consequences of submitting the Cardiovascular diseases (CVD, acute myocardial infarction, angina pectoris stable and unstable coronary insufficiency ...). A large number of cohort studies suggest that dyslipidemia and concentrations of elevated TG, LDL-ch and reduced concentrations of HDL-ch are at high positive correlation and independent predictor of CVD risk (33). In recent study by group of patients 5963 from ages> 40 years with dyslipidemia and diabetes treated with statins its verified a reduction and a decrease in LDL-ch for 22% and significant reduction in symptoms of CVD appearances (34). Observational studies of ADA American Diabetes Association together with friends Medical Nutrition Therapy -MNT- have verified

that patients who have used more healthy diet and increased physical activity (normal body weight) had decreased the triglycerides and LDL-ch to increase levels of HDL cholesterol and have had less symptoms of CVD (35,36,37). A large number of clinical studies for effects of treatment of diabetic dyslipidemia targeting the scope of medication therapy (statins, fibrates, niacin holoestipol, holestiramin) as target values for effective treatment have been proposed: LDL-ch are <2.60 mmol / l in HDL cholesterol are = 1.02 mmol / l), and triglycerides levels are = 1.7 mmol / l) .The females HDL-ch levels may be higher due to estrogenes. Recommendations for treatment of dyslipidemia are always followed on the basis of recommendations and consensus proposed by the ADA and NCEP-National Cholesterol Education Program (38) . Hypertriglyceridemia may be a risk factor for CVD in people with initial diabetes .Initial hypertriglyceridemia therapy is consisted of dietary preventive measures such as: changes of way of life, weight loss, increased physical activity, limited consumption of saturated fats, reducing carbohydrates consumption , and reducing alcohol consumption, balancing diabetes (oral therapy or insulinemic) and then if the aforementioned measures do not show proper effects to then start therapy with medication Group of fibrates (gemfibrozil, fenfibrat, Clofibrat etc.) or in the cases of high hypertriglyceridemia fibrates may be combined with Niacin (<2 g / day. *Often the clinicians presented the question of when and in which value of Tg should start treating hypertriglyceridemia? Decision* to initiate pharmacological therapy depends on the judgment of the clinician - it must begin between triglyceride levels from 2:30 to 4:50 mmol / l). The therapeutic combination of statins family and fibrates is prohibited due to the extremely high side effects of myositis and rhabdomyolysis. In case of high dyslipidemia these combinations are preferred therapy, statins with nicotinic acid, statins with holestiramin or holestipol, fibrates with nicotinic acid, fibrates with holestiramin and holestipol, nicotinic acid with holestiramine or Holetipol. Choosing statins family should depend mainly

on lowering LDL necessary to achieve the goal of LDL-ch value of <100 mg / dL [2.60 mmol / l]). The use of statin therapy with high dose (eg 80 mg) to treat dyslipidemia in patients with high levels of LDL- ch and TG also shall be limited to because of side effects (increased transaminases and pain muscle) and therefore to these patients therapy should be started with the dose of 40 mg once a day and be accessed and the normalized target values after dosage laboratory examination shall be reduced to 20 mg per day.Patients with type 1 diabetes who are in good controled glycemia tend to have normal levels of lipoprotein, unless they are overweight.Contained lipoprotein may be abnormal, but the effects of these anomalies in relation to CVD are unknown. Aggressive treatment of diabetic dyslipidemia decreases significantly the risk of CVD in patients with diabetes. The main purpose of therapy is to reduce the concentrations of LDL-ch to ≤ 100 mg / dL [2.60 mmol / l]. Initial pharmacological therapy consists and should be with the use of statins family. In case of submission of an intolerance to statins family then preferably be combined therapy also with other hypolipidemic (such as niacin, holestipol, holestiramin, etc). Treatment of high levels of thriglycerids be treated with fibric acid derivatives (gemfibrozil, fenofibrates) or niacin .

the result of unregulated diabetes we have manifestations of the disturbances in micro and macrovascular levels (39). There are documented facts that a large number of patients with DM are potential candidates for more comorbid conditions ranging from cardiovascular disease (ischemic heart disease, acute stroke infarction, angina pectoris unstable, left ventricular hypertrophy, congestive heart weakening, stroke, peripheral vascular disease, vascular complexity diabetic, diabetic retinopathy, diabetic nephropathy, etc. All of the aforementioned diseases are the main cause of frequent and morbidity and mortality of patients with unregulated diabetes (40-45) therefore the American Association of Diabetes always suggests the maintenance and regulation of normal glycemia values. Irregular checks and not balancing the glycemia is counted as one of risk factors for cardiovascular diseases and rapid progression of chronic renal damage in patients with diabetes whether they are insulin users or have oral hypoglycemic therapy (46-52). Numerous epidemiological studies and the American Association for Diabetes (AAD) have verified and documented that the regulation and regular check of glycemia decrease the risk of cardiovascular disease and myocardial infarction and their complications with which is reduced the rate of mortality of diabetic patients .Concentration of the hemoglobin that is glicolysilated HgbA1c (which represents the average value of glycemia within three months) is calculated as above standard risk assessment of CVD in patients with DM (53,54,55). American Association for diabetes (ADA American Diabetes Association)always calls and suggests for mandatory screening of hemoglobin glicolysilated values in order to appropriately make decisions for treatment of diabetes in order to reduce further diabetic complications [56 57). The results of the acquired from the lipid profile showed a high disorder for both groups of patients examined (also those with Type 1 DM also those with DM-Tip.2) that complies with all studies on disorders profiles of lipoproteins in patients with DM. CVD presentation of the CVD and mortality rates in diabetic patients except increased sugar level also affect many other factors such as: metabolic imbalance lipoapoprotein Apo-B and Lp (a), disordered metabolism of carbohydrates, disorder of coagulation factors, arterial hypertension, smoking, secondary hyperparathyroidism, sedenterity,, oxidative stress etc. (58). Chronic hyperglycemia combined with dyslipidemia and hyperapolipoproteinemia increase the risk of morbidity and mortality from cardiovascular diseases in uremic patients with diabetes treated with terminal chronic hemodialysis. Besides disorder of carbohydrate metabolism diabetes as a chronic metabolic disorder impairs and other substances .Thus during diabetes predominates unraveling protein metabolism that is expressed by decreases in total protein level in the blood, and its special ingredients, such as: Albumins and globulins and all globulins ingredients such as: alpha globulins, especially gamma the globulins which are protective antibodies for the

organism (59,60.61, 62).). Protein breakup is clinically manifested with stopping of body growing.In diabetics there are sensitive turbulences of lipids values .As we know the main lipids are : cholesterol, triglycerides, phospholipids and free fatty acids . These lipids in blood are not free but circulate with other substances as lipoproteins . First disorder of fatty metabolism in diabetes is the increasing of lipolysis process (melting of fats) that occurs during the gluconeogenesis. This causes the increase in blood of free fatty acids which serve as the starting point for excess production of some biochemical substances which are called ketone bodies and therefore for the emergence of diabetes ketoacidosis. Lowering diabetes by activation of many metabolic pathways, emerges the increase of the cholesterol and hypercholesterolemia and hypertriglyceridemia . On the other side for genetic reasons yet not finally clarified blood level rise occurs for some lipoproproteins such as increased LDL (which carries blood cholesterol) of VDLD (which carries in blood endogenous triglycerides) and decrease of HDL (lipoproteins that removes cholesterol from the blood, also referred to as " clearing factor ") Increased cholesterol, endogenous triglyceride LDL and VLDL and HDL reduction, separately or combined between them form the phatobiochemic and pathophysiologic basis of birth and acceleration of the atherosclerotic process that damages mostly large caliber medium caliber arteries in clinical practice known as atherosclerosis (63). Treatment of diabetic dyslipidemia recent years set by the American Diabetes Association (ADA American Diabetes Association) has been the topic of discussion by proposing dietary and therapeutic measures on the management of dyslipidemia in patients with diabetes mellitus. Patients with type 2 diabetes are potential candidates to four fold risk of cardiovascular disease presentation (CVD) compared with the population which suffers from other diseases. There are documented facts that the patients with diabetes from lipid fractions and often manifest hypertriglyceridemia (concentration increase of triglycerides-TG) and hypercholesterolemia-increased concentrations of LDL-ch with decreased cholesterol values of proatherogen *(HDL-ch).* In particular, patients with diabetes tend to have a significant increase of oxidized cholesterol (LDLox) and a higher percentage of particles ,, foam cells "which are highly susceptible to oxidation at high risk of consequences of submitting the Cardiovascular diseases (CVD, acute myocardial infarction, angina pectoris stable and unstable coronary insufficiency ...). A large number of cohort studies suggest that dyslipidemia and concentrations of elevated TG, LDL-ch and reduced concentrations of HDL-ch are at high positive correlation and independent predictor of CVD risk(64) In recent study by group of patients 5963 from ages> 40 years with dyslipidemia and diabetes treated with statins its verified a reduction and a decrease in LDL-ch for 22% and significant reduction in symptoms of CVD appearances (65-66) . Observational studies of ADA American Diabetes Association together with friends Medical Nutrition Therapy -MNT- have verified that patients who have used more healthy diet and increased physical activity (normal body weight) had decreased the triglycerides and LDL-ch with increase levels of HDL cholesterol and have had less symptoms of CVD (67,68,69). A large number of clinical studies for effects of treatment of diabetic dyslipidemia targeting the scope of medication therapy (statins, fibrates, niacin holoestipol, holestiramin) as target values for effective treatment have been proposed: LDL-ch are <2.60 mmol / l in HDL cholesterol are = 1.02 mmol / l), and triglycerides levels are <= 1.7 mmol / l) .The females HDL-ch levels may be higher due to estrogenes. Recommendations for treatment of dyslipidemia are always followed on the basis of recommendations and consensus proposed by the ADA and NCEP-National Cholesterol Education Program (70.71) . Initial hypertriglyceridemia therapy is consisted of dietary preventive measures such as: changes of way of life, weight loss, increased physical activity, limited consumption of saturated fats, reducing carbohydrates consumption , and reducing alcohol consumption, balancing diabetes (oral therapy or insulinemic) and then if the aforementioned measures do not show proper effects to then start the therapy with medication Group of fibrates (gemfibrozil, fenfibrat, Clofibrat

etc.) or in the cases of high hypertriglyceridemia fibrates may be combined with Niacin (<2 g / day. *Often the clinicians presented the question of when and in which value of Tg should start treating hypertriglyceridemia? Decision* to initiate pharmacological therapy depends on the judgment of the clinician - it must begin between triglyceride levels from 2:30 to 4:50 mmol / l). The therapeutic combination of statins family and fibrates is prohibited due to the extremely high side effects of myositis and rhabdomyolysis. In cases of high dyslipidemia these combinations are preferred therapy, statins with nicotinic acid, statins with holestiramin or holestipol, fibratesand with nicotinic acid, fibrates with holestiramin and holestipol, nicotinic acid with holestiramine or Holetipol. Choosing statins family should depend mainly on lowering LDL necessary to achieve the goal of LDL-ch value of <100 mg / dL [2.60 mmol / l]). The use of statin therapy with high dose (pe 80 mg) to treat dyslipidemia in patients with high levels of LDL- ch and TG also shall be limited to because of side effects (increased transaminases and pain muscle) and therefore to these patients therapy should be started with the dose of 40 mg once a day and be accessed and then normalized target values after dosage laboratory examination shall be reduced to 20 mg per day.Patients with type 1 diabetes who are in good controled glycemia tend to have normal levels of lipoprotein, unless they are overweight.Contained lipoprotein may be abnormal, but the effects of these anomalies in relation to CVD are unknown (72.73)Some studies have verified that controls and normalization of glycemia may be more important and effective in patients with type 1 diabetes mellitus compared with patients with type 2 diabetes in reducing the appearance of aggressive SKV. Aggressive treatment of diabetic dyslipidemia decreases significantly the risk of CVD in patients with diabetes. Accumulated and altered LDL is predominantly taken up by scavenger receptors of macrophages favoring foam cell formation and the development of atherosclerotic plaques (41). Therefore, diabetes with hypertriglyceridemia appear to promote atherosclerosis and enhance cardiovascular risk via the influence on cellular LDL metabolism in hemodialysis patients. In the general population, several epidemiologic studies have indeed identified hypertriglyceridemia in the presence or absence of diabetes mellitus as an independent risk factor for enhanced cardiovascular morbidity and mortality (42–44). In view of these cumulative effect on impairment of lipoprotein metabolism, effective treatment of diabetes and hypertriglyceridemia in end-stage renal failure gains even more importance if renal replacement therapy becomes unavoidable. Large-scale interventional cardiovascular end point studies are required to prove whether advances in quality of life and long-term survival can be made in diabetic patients on hemodialysis.

5 Conclusion:

In conclusion we can say that the knowledge of mechanisms, ethiopathogenesis, function and abnormalities on polymorphism and the negative impact of lipids (hypetriglyceridemia and hypercholesterolemia) and unbalanced glycemia of patients with diabetes mellitus (regardless of the type of diabetes) are among risky factors and independent in presentation CVD and premature atherosclerosis. Treatment and normalization of their highest values at the initial stages of the disease is of paramount importance and can significantly affect the prevention and deterrence pace of progress to early atherosclerotic processes and cardiovascular disease in these patients. Patients with diabetes (regardless of their type- insulin dependent diabetes mellitus or treated with oral hypoglycemic) are at same and high risk from the early appearance of atherosclerosis and cardiovascular disease. Therefore, improvement, balancing and regular checkups of diabetes and lipids with medicament therapy (statins, fibrates, niacin, Holestipol, Holetiramina are the first step (per primam) in prevention and pace of progress and incidence of CVD and atherosclerotic processes . In treatment of uremic dyslipidemia in recent years a large number of studies have verified extremely high positive effects during treatment with statins (the dose of 40 mg) with what it seems is also contained and reduced the incidence of CVD presentation of diabetic patients and was also verified in our paper where we noticed a decrease in concentration of LDL-ch for 37% and 28-30% TG for facts that are consistent with other studies. We propose, based on preferences and consensus proposed by the American Association for Diabetes on the control of blood glucose, HgbA1c that treatment of diabetic dyslipidemia should be started in the initial stages of diabetes, no matter what type of diabetes whit what will be prevented visible appearances atherosclerotic phenomena (early atherosclerosis) in cardiovascular system, brain and peripheral arteries. Despite the uncertainty of results in delaying the progression of renal disease in CKD patients not on dialysis, especially in the earliest stages of CKD, it seems reasonable to use statins. Our personal opinion is that, due to the high risk of cardiac death and the safety profile, statins can be suggested in CKD patients: (1) early-mid stage at high risk of coronary or peripheral vascular disease. with nephrotic syndrome, in order to ameliorate lipid profile. already on dialysis with a previous history of coronary or peripheral vascular disease or at high risk of CVD; irrespective of the stage of CKD, at high risk of developing CV complications, even if the presumed atherosclerotic coronary risk involves only a minor, but important increased rate; and on dialysis previously treated with statins in view of the benefit on atherosclerotic complications.

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