CONCENTRATION OF APOLIPOPROTEIN-B $_{100}$ (Apo-B $_{100}$) and LIPOPROTEIN [(a) Lp (a)] AT PATIENTS WITH DIABETES MELLITUS

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Abstract:

Patients with diabetes have 3 or 4 times higher risks of coronary disease compared with the healthy population. One of the main factors of developing atherosclerosis at patients diagnosed with DM is the abnormalities appeared in apolipoprotein B-100 and Lp (a). At DM patients it is proven that it exists a high correlation between the concentration of Apolipoprotein B-100, Lipoprotein - (a), diabetic nephropathy, micro and macro albuminuria as well as diabetic retinopathy (1). One of the most common complications of DM is: micro and macro vascular changes. Insulin depended patients or patients treated with oral insulin are potential candidates for diseases such as: renal diseases, diabetic retinopathy, coronary diseases and cerebral insult - compared with the healthy population or patients with different etiological disease. **Purpose:**

The purpose of this paper work is to be verified and documented the relation, role and correlation of Apolipoprotein-B100 (b-Lp, Apo-B100, Apo-LDL) and lipoprotein(a) (Lp(a)) in the appearance of the atherosclerotic processes of the patients with DM compared with the group examined of healthy patients.In the plasma of the patients with DM is detected (except high concentration of glucose, Apo-B100, Lp(a),LDL-ch, Triglycerides, Protein C Reactive (PCR) and low concentration of HDL-ch) Apolipoprotein-A1 (Apo-A1), that indicates a silence inflammation process at patients with DM, this inflammation speeds the developing process of atherosclerosis in cerebral or peripheral arteries(2).

Index term:

Apolipoprotein-B100 (Apo-B100), Lipoprotein-a (Lp - a), Diabetes Mellitus (DM), Atherosclerosis (Ath), Glucose (Gl), Glycated Hemoglobin (HbA1c), Lipidic profile (LT, ChT, TG, HDL-ch and LDL-ch).

1 INTRODUCTION:

Diabetes is the most common disease in the modern world with high inclination reach, mostly is presented in the transitional and developed states in the world where diabetes as a disease is rated in the fourth place for its mortality. According to statistical studying in world level over 154 million people of the adult community suffers from diabetes, most of them diagnosed with type II diabetes (over 85 - 95 % of 154 million adults).

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The early stages of diabetes are characterized with lipid disorders with particular emphasis on the rise of Apo-B100 and Lp(a), compared with patients that suffer from other diseases, which indicates the early monitoring of this disorders may be a crucial fact on preventing atherosclerosis at patients with DM either type I or II. There are documented facts that the disorder of apolipoproteins at patients with DM are associated with high level of lipids, in consideration of this fact in our study except for the determination of apolipoproteins in our DM patients we also measured the lipidic profile (Total cholesterol (TCH), Triglycerides (TG), Total Lipids (TL), HDL-ch, and LDL-ch), glycemia (Gl) and glycated hemoglobin (HbA1c).

Diabetes today represents a mayor socio-economic problem because of the high material costs that as a disease requires (3). These patients must be on constant monitoring because of the ability to develop atherosclerosis in the early stages of DM as well as the monitoring of the derivate diseases of atherosclerosis in nervous, cardiovascular systems. High concentration of Apo-B100 and Lp-a are independent risk factors in the developing of atherosclerosis disease not only in the patients with DM also in the patient that doesn't suffer from DM. Even though diabetes as a disease is old, its definition often is a debate topic full of controversy that originates from the different criteria of diagnostication of DM form World Health Organization. The definition of diabetes only as a chronic disease associated with disorders of carbohydrate metabolism doesn't complete the main meaning of this cosmopolite disease that daily takes giant epidemic steps as the most spread chronic disease. According to contemporary opinions

diabetes is a disease with multifactor etiology, its main characteristic is hyperglycemia associated with carbohydrate, lipid and protein metabolic disorders that are manifested with total or relative absence of insulin, insulin resistance or it is appeared as a combination of all the factors mentioned above. Apolipoproteins are compound proteins of the lipoproteinemic macromolecule, and they are specific for every single class of lipoproteins (8). They bound with the lipids of the molecule using the hydrophobic nature of fatty acids form phospholipids and the polar part of the polypeptide range (a process of interaction of ions between phospholipids and the amino acidic couples that are electricity contra - charged - of the alpha helix of the apoprotiein).

As a main factor that contributes in the arteriosclerosis (disease of nervous, cardiac and peripheral arteries) in the early stage of DM is the disorder of apolipoproteins (9, 10, and 11). The genetic factors that help on manifesting atherosclerosis in the cardio vascular and neruo vascular systems are: disorders on the reverse transport of HDL-cholesterol (12), low expression of B-receptors compared with E-receptors, reduced convertion of VLDL on IDL and LDL (13). Apolipoproteins are distingue-ished from each other by the structure (primary, secondary, tertiary), physical and chemical attributes and by the specific function of the lipoprotein that contains in itself.

Types of apolipoproteins: Apolipoprotein - A (Apo-A) with five subclasses ApoA-$_{1,2,3,4,5}$; Apolipoprotein-B (Apo-B) with two subclasses Apo-B$_{100}$ and Apo-B$_{48}$; Apolipoprotein-C with three subclasses ApoC-$_{1,2,3}$; Apoliprotein-E with 4 subclasses Apo-E$_{1,2,3,4}$; Apoliprotein-D Apo-A ; Apoliprotein-F Apo-F ; Apoliprotein-G Apo-G,Apoliprotein-H Apo-H,Apoliprotein-S Apo-S.

In the structure of lipoproteins except its typical representer, the molecule is combined with a mayor number of apolipoproteins , that's why the classification of lipoproteins is proposed to bee by the representer of the lipoproteinemic family such as: Lp-A, Lp-B, Lp-C, Lp-D, Lp-E...) depending on the apoprotein that is formed by. The function of apolipoproteins is to transfer the plasmatic lipids with their hydro-solubility affinities (Ch, TG, FL) forming a macromolecular complex (hydro-soluble) that floats through the blood. The apoproteinal disorders are genetically determined as well as their function that are basically defined for each and one of them (14). Apolipoprotein-B100 (β-Lp, ApoB-$_{100}$, apo-LDL) is a dominant apoprotein in the class of LDL, VLDL,IDL,Lp(a) and of a small amount of hilomicroenes (HM). Apo-B100 is a ligand of B/E receptors in LDL-ch macromolecules. Apo-B100 *is syntetysed in the liver*. The referent values of apolipoprotein-B100 (Apo-B100) are: 0.7-1.6 g/l for male and 0.6-1.5 g/l for female gender. In the total composition of Apo-B$_{100}$ is a participant and Apo-B$_{48}$. Apo-B$_{100}$ consists 43% α- helix, 21% of β-bonds, 16% of β-spirals and 20% random structures. High concentrations of

Apo-B100 have a direct impact on developing cardiovascular atherosclerosis and early atherosclerosis. The genes of apolipoprotein-B are placed in the short chromatid of the second chromosome (2r23-r24). Apo-B protein represents a polymorphism, the mutant of Apo-100 contains high levels of cholesterol(Ch). Apo-B provides absorption of cholesterol from the hepatic tissues and extra hepatic tissues by bonding with B or E receptors enabling the extraction of the triglycerides from the liver. The high levels of Apo-B_{100} except for the patients with DM are evidenced even in other diseases such as hyperliopproteinemies: Type II-a, II-b, Type-IV, Type-V, during the pregnancy period, in the nephrotic syndrome, hyperapo-β-lypoproteinemy, usage of diuretics or high usage of β-blockers, therapy with corticosteroids, therapy with cyclosporine (CsA) and in the patients with chronic renal insufficiency. *The small lipopeotein-A (Lp/a) antigen (Apolip-oprotein/a/; Apo/a/)*is synthesized in the liver and an intracellular way with the help of two sulfide bond is connected with Apo-B100. For the first time Lp(a) is discovered by Berger in 1963(15) and it is assumed that is a variation of LDL-cholesterol (LDL-ch) and a great quan-titative marker for the risk of atheromatosis [Lp(a)-atheromatosis]. Lp(a) in the plasma circulates together with Apo-B_{100} as a proteinic base of the lipopeoteins (Lp) rich with esterified cholesterol. Low levels of Lp(a) associate with particles that have a hepatic origin rich in triglycerides. The function of Lp(a) is - competitive inhibitor of plasminogen by linking it to its receptors, inhibiting thrombolysis and increasing the percentage of thrombolytic processes. With SDS-PAGE are discovered minimum 13 izophorms (genetic variants) with different size and 66 possible phenotypes (16). Lp(a) has an ability to send the particles rich in cholesterol in the needed places for the fast regeneration ability of the cell and active synthetisation of the cell membrane as it happens in the processes of self healing of the cell. Lipopeotein(a) can be considered as a reactant in the acute phase of in injury. Lp(a) by reacting with fibrinolyse may be also a thrombogen and it may contribute in the formation of the arteriosclerotic plaque. Lp(a) is an independent risk factor for early atherosclerosis as well as an indicator of the appearance of the aterogen processes because of it high level of cholesterol in its structures - it fixes its self in the subendotelial intima, its chemical modification, being phagocyted by macrophages and forming foam cells. Apo(a) mainly it is synthesized in the liver where is bounded with Apo-B_{100} and gets excreted mostly as a part of Lp(a). The atherogenity of Lp(a) obviously is increased if its concentration in the serum is higher than 0.30 g/l and it is tightly linked with the appearance of early atherosclerosis. Apo(a) in the plasma circulates bonded with Apo-100, some studies suggest that for its elimination from the serum are needed the LDL receptors, and there are other studies that determinate that the madicamentalblocation of

LDL receptors doesn't impact the modification and the high level of Lp(a). *The gene for Lp(a) is in the six chromosomes (chromatid q26-127) its location is the same as the location of plamsinogene*. Their density is amid LDL-ch and HDL-ch. low concentration of Lp(a) are in the patients with DM, coronary diseases, acute myocardial infarct, post MI, angina pectoris and during the period of pregnancy.

2MATERIALS AND METHOS USED

As a work material was used the venal blood of 60 patients (N^o=60 from which 25 were form the female gender and 35 from the male gender) with diabetes mellitus Type-1(insulin dependent with age average = 59.50 ± 9.40) and 70 patients with Type II diabetes (treated with oral hypoglycemic) with age average = 61.40±8.40 (N^o=70) 40 were from the female gender and 30 from the male gender, as well as 80 healthy individuals that served as a controlling group with age average of = 59.46 ± 6.50. Insulin depended patients are considered as Type I DM while patients that are not depended from insulin are considered as Type II DM. The blood for examination was taken at 08:00 in the morning, in the room temperature 19-24^{0}C, patients were laid for the intervention, and it was requested the patients to be fasting for 12 hour.

Together with the concentration of apolipoprotein-B_{100}, lipoprotein (a) was analyzed and the lipidic profile, glycemy and glykolised hemoglobin (HbA1c). The method for determinating the concentration of Apo-B100, Lp(a) and the lipidic profile, glycemia and HbA1c are evidenced in the table nr.1. As referent levels for Gl and HbA1c were those designated by the World Health Organization (Gl=3.5-6.5 mmol/l ; HbA1c% = 4.4-6.6). All the analysis projected by the studying protocol was established in the Clinical Laboratory Institute of Clinical University Centre – Faculty of Medicine – Skopje.

3STATISTICAL PROCESING OF THE EXAMINED MATERIALS

The gained values of Apolipoprotein-B_{100},lipoprotein (a),glycemia and lipids (Total cholesterol, TG, HDL-ch, LDL-ch) are presented with average values and standard deviation X±SD. We tested the association between the gained variables with the regressive linear analysis: ***(y=Bx+A)*** we calculated and the correlation coefficient „**r**“thisstatistic value for „**p**“smallerthen 1% p<0.0001. The compared statistic of lipid parameters and lipoproteinic between the two groups were analyzed with the test called ***STUDENTOV,,t",*** whereas for the dependent or independent examples as well as the nonparametric tests were

used: ***Mann-Whitney-U and Wilcoxon test.*** The statistical significant of the differences between the patient's group and the checking (controlling) group for the gained values of lipids, apolipoproteins and glycemia were analyzed with the so called ***,,Anonova Two-Factor"*** test, with statistic value for "**p**" lower than **5% p<0.000**. The frecunce and distribution were tested with the test-$\mathbf{x}^2$. The value of the differences (**z**) between the average of the analyzed paramenters-arythmetical average and their proportion (**x,p**) was tested with more the 95% of occurrence or **z=1.78 SEM**. the gained results are showed in a table from, the same results are refined in a standard statistical program (Statistic for Windos,Version 6.0 A Stat. sof Tuzla OK USA).

Table nr. 1: The referent values and methods by which the authors allocated the concentration of Apo-B100, Lp (a), glycemia, HbA1c and the lipid profile – are presented in this table.

Examined parameters	Referent values	Authors
LT	**4-10 g/l**	**Zollner &Krisch[17]**
TG	**0.68 - 1.70 mmol/l**	**G. Buccola& H. David [18]**
TCh	**3,l-5,2 mmol/l**	**CC. Allain et al [19]**
LDL-ch	**<3,4mmol/l, high risck:> 4,1 mmol/1**	**Friedewalde& Fredrickson[20]**
HDL-ch	**>1,6mmol/1, high risk: < 0,9 mmol/1**	**G. Warnick et al [21]**
ApoB-100	**0.5 – 1.60 g/l**	**Imuno-turbidimetrikeRifai N[22]**
Lp(a)	**< 30 mg/dl**	**Imuno-turbidimetrikeRifai N[22]**
Glicemia(Gl) mmol/L	**3.5-6.5**	**Aparat COBAS-INTEGRA 400**
HbA1 c %	**4.4-6.6**	**Aparat COBAS-INTEGRA 400**
TCh	**3,l-5,2 mmol/l**	**G. Buccola& H. David [18]**

4 GAINED RESULTS

The gained results from the examination of Apolipoprotein-B100, Lipoprotein(a), glycemia, HbA1c, lipids (Total cholesterol, TG, HDL-ch, LDL-ch) and the results of the controller group are presented in the table nr 2 and 3. From the tables we can see that both of the groups (DM – type I and DM type-2) the concentration of Apo-B100 and Lp(a) are high, with a significant statistical difference p<0.0001 compared with the controlling group (the healthy individs). The values among the patients with DM type I and DM type II didn't have any significant difference – facts that correlate with many other studies

(23, 24). A significant growth was seen in the percentage of the lipid parameters such as: TG, LDL-ch, triglycerides and low level of concentration of HDL in both of the patients either with DM type I or DM type II compared with the results of the controlling group (healthy people (samples)).

Table nr. 2. Presentation of average values analyzed at patients with DM type I – patients insulin depended ad-N0=60 and patients with DM type II (with oral hypoglycemic) – N0=70

Parameters	Number	Average	Minimum	Maximum	± SD
Patients with Diabetes Mellitus –Type 1 (Insulin dependent- N^0=60)					
HbA1c %	**60**	**9.8**	**6.0**	**14.60**	**6.80**
Glycemia	**60**	**10.08**	**7.80**	**14.00**	**2.80**
LT	**60**	**7.41**	**2.50**	**15.00**	**2.13**
TG	**60**	**3.90**	**1.40**	**4.60**	**0.78**
Cholesterol	**60**	**5.80**	**1.30**	**6.80**	**1.37**
HDL-ch	**60**	**1.20**	**0.50**	**3.90**	**0.84**
LDL-ch	**60**	**4.50**	**1.40**	**5.00**	**0.89**
Lp(a)	**60**	**49.70**	**18,00**	**171.60**	**46.80**
ApoB-$_{100}$	**60**	**2.98**	**0.71**	**2.80**	**0.75**
Patients with Diabetes Mellitus-type 2- oral hypoglycemic - N^0=70)					
Glycemia	**70**	**6.90**	**4.20**	**8.70**	**2.80**
HbA1c %	**70**	**8.20**	**5.40**	**8.70**	**3.50**
LT	**70**	**7.34**	**5.60**	**11.50**	**1.39**
TG	**70**	**3.82**	**1.30**	**4.80**	**0.78**
Cholesterol	**70**	**5.60**	**0.80**	**7.60**	**1.97**
HDL-ch	**70**	**1.12**	**0.50**	**2.30**	**0.50**
LDL-ch	**70**	**4.30**	**2.10**	**4.60**	**0.79**
ApoB-100	**70**	**2.60**	**0.84**	**2.96**	**0.83**
Lp(a)	**70**	**42.80**	**10.00**	**85.9**	**38.60**

Table nr. 3: Presentation of average analyzed values about urea (in the plasma serum in mmol/l), kreatinin (in the plasma serum with mmol/l) and uric acid (in the plasma serum in μmol/l) and GFR defined by the Cocroft and Gault form presented in ml/min at patients with DM type I insulin dependent – N0=60 in the beginning of the study:

Parameters	Average values	± SD
Potassium (mmol/l)	4.6	0.80
Urea(mmol/l)	14.2	2.6
Kreatinin(mmol/l)	314.0.0	58.0
Uric acid(μmol/l)	370.0	80.0
GFR (by Cocroft&Gault)	42.0 ml/min	4.0

Table nr 4: Presentation of average analyzed values for urea (in the serum), kreatinin (in the serum), uric acid (in the serum) and GFR defined by the Cocroft and Gault formula presented in ml/min at patients with DM type I- insulin dependent – N0=60 after 12 months

Parameters	Average values	± SD
Potassium (mmol/l)	5.0	0.60
Urea (mmol/l)	18.6	2.4
Kreatinin (mmol/l)	392.0	12.0
Uric acid(μmol/l)	420.0	14.0
GFR (by Cocroft&Gault)	30.0 ml/min	6.2

Table nr 5: Presentation of average analyzed values for urea (in the serum presented in mmol/l) kreatinin (in the serum presented in mmol/l) uric acid (in the serum presented in μmol/l) and GFR defined by the Cocroft and Gaulin ml/min at patients with DM type II treated with oral hypoglycemic- N0=70 in the begging of the study:

Parameters	Average values	± SD
Potassium (mmol/l)	4.5	0.40
Urea (mmol/l)	13.5	2.4
Kreatinin (mmol/l)	365.0	15.0
Uric acid (μmol/l)	370.00	15.0
GFR (by Cocroft&Gault)	45.0 ml/min	7.2

Table number 6: presentation of average analyzed values for urea (in the serum presented in mmol/l) kreatinin (in the serum presented in mmol/l) uric acid (in the serum presented in μmol/l)

and GFR defined by the Cocroft&Gault ml/min at patients with DM type II-treated with oral hypoglycemic-N^0=70 after 12 months:

In the tables we can notice that between the parameters of the two groups of patients with DM (Depended insulin 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 nr 7: introduction of **Mann-Whitney U** – test – the distinguition of the differences of parameters values of the DM-Type I and DM Type II

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	655.500	-3.25744	**0.001124**
Cholesterol	1091.500	0.39693	0.691421
HDL-ch	1071.500	0.52814	0.597400
LDL-ch	1137.500	-0.09513	0.924210
ApoB-100	1900.500	-3.33788	**0.005453**
Lp(a)	1092.500	-0.39037	**0.006562**

The difference between the average values of the patients with DM-Type I and DM – Type II is not significant for **p<0.0005**, a significant difference was registered only in TG, Apo-B100, Lp(a) (p=0.0011, p=0.0054, p=0.0065)

Table nr 8: presentation of the average values of the examined parameters with DM Type I, DM Type II and controlling group

Examined group - DM -Tip 1 and DM- Tip 2						Controlling group		
Parameters	Number	Average	Minimum	Maximum	**± SD**	Average	± SD	***p***
LT	130	7.62	2.50	12.60	2.82	6.50	0.60	0,0001
TG	130	3.85	2.40	4.60	0.70	1.30	0.63	0.0001
ChT	130	5.34	4.20	7.30	0.91	4.95	1.22	0.0210
HDL-ch	130	1.03	0.40	1.30	0.80	1.60	0.60	0.0001
LDL-ch	130	3.90	1.80	4.80	0.92	3.40	1.03	0.0001
ApoB-100	130	2.94	1.40	2.90	0.80	1.05	0.20	0.0001
Lp(a)	130	54.22	9.40	120.60	32.80	23.50	7.10	0.0001
Glycemia	130	8.70	4.90	9.80	4.60	5.20	2.00	0.0001
HbA1c %	130	8.20	5.60	12.60	3.80	6.80	3.50	0.0001

Table 8 shows the significant differences between the parameters of the examined patients with diabetes mellitus and the control groups. The difference shown between the average values of the parameters of the two groups is with statistical significance, except in the values of the total cholesterol with **p>0.0005**. The values of the examined parameters such as LT, TG, LDL-ch, Apo-B100 and Lp(a) are higher at patients with DM-Type I and DM-Type II compared with the controlling group. Low values of the DM type I and DM Type II compared with the controlling group is only in HDL-ch.

4 DISCUTION:

The diabetic disease is characterized with high risk of micro and macro vascular diseases, that is why there is a great need for new studies that will discover new cardiovascular risk factors, especially there must be new discoveries about the complications that are tightly bonded with micro vascular diseases, among which factors lately it is shown a specially inters in the role and the high risk effect from the disorders and high concentration of lipo/apoproteis (25). some others have verified a high connection between of Apo-B100 and Lp(a) at patients with proteinuri, the above mentioned phenomena are justified by the fact that proteinuri results with high protein synthesis in the liver that corresponds with the equal highness of apoproteinsynthetisation originated from the liver, in particular this process increases the concentration of apolipoprotein and lipopeotein (a) (26). The high concentration of apolipoprotein increase the syntetisation of lipoprotein (a) as well increases the aterogenity from binding apo(a) with LDL-ch outside of hepatocytes with tendence to create Lp(a) particles, it means that the incration of the lipopeotein(a) concentration are with extra

genetic etiology. Diabetes Mellitus Type I insulin independent is characterized with hyperinsulinaemia that's why many sciences think that the concentration of insulin have a huge role in the biosynthesis of apo(a) at patients with diabetes mellitus. Diabetes Mellitus type I insulin dependent is not represented with hyperinsulinemia that's why some authors think that the high concentration of Apo-B100 and Lp(a) at patient with DM Type I are dependent from many other catabolic factors. Many authors have verified atherosclerosis in high range at patients with DM Type I and II – measured by the scale of the arterial occlusion that is in high correlation with the high concentration of Lp(a). the gained results from the lipid profile indicate a disorder for the two types of patients that are examined (either Type I or II DM) that is consistent with the lipid profile studies at patients with DM. one considerate number of the patients present a high concentration of Apo-B100 and Lp(a). This high correlation many authors connect with the first symptoms of renal damage from DM, the presence of micro or macro proteinuri at these patients (27) . it is evident that there is a need for further studies with greater diapason and with a considerable number of patients diagnosed with DM that will be monitored for a longer period as well as measurement of the atherosclerotic plaques in the carotid and peripheral arteries with Doppler, in this way will be verified and documented or demanded the theories over the aterogen-aterosclerotic effect of apolipoprotein-B100 (Apo-B100) and lipoprotein(a) as new factors and an high risk indicator for premature atherosclerosis at patients with DM. Apo-B100 and Lp(a) as enigmatic particles present in the human organism still remain un discovered.

5CONCLUSION

As a conclusion we can say that the knowledge about the mechanisms, etipopathogenesis, function, abnormalities of the polymorphism and the negative impact of apolipoproteins: Apo-B100 and Lp(a) at patients with DM type- I and DM type-II and its role in the appearance of atherosclerosis is an extraordinary impact and contributes in atherosclerosis of this patients. Preventive measurements such as dietic, therapeutic may contribute in the reduction, deceleration of the above mentioned processes at patients with DM without considering the type of diabetes, because the two groups of patients whether dependent or independent insulin users are in high risk from developing a premature atherosclerosis.

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Literature

1. 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. *NutrMetabCardiovasc Dis 2002 Jun; 12 (3) 127-131.*

2. 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.*

3. M. Bogoev. Diabetes Mellitus, Etiopatogenza, Mikrovaskularnikomplikacii, Terapija.*Skopje-2003; f:11-30.*

4. Barbara Kolleris, Martin Auinger, VeronikaResing et al. Lipoprotein(a) as a predictor of Cardiovascular Disease in a Prospectively Followed Cohort of patients With Type 1 Diabetes. Diabetes Care July 2006, Vol.29, no.7;1661-1663 .

5. Shai I, Schulze MB, Manson JE, Stampfer MJ, Rifai N, Hu FB: A prospekti study of lipoprotein (a) and risk of coronary heart disease among women with type 2 diabetes. *Diabetologia 48, 2005; 2691-2692.*

6. Maurus Marques de Almeida Holanda, RosaliaGouveiaFilizola, Maria Jose de Carvalho Costa et al. LPASMA LIPOPROTEIN (A) LEVELS –A comparasionbetwen diabetic and non diabetic patients with acute ischemic stroke. ArqNuropsiquiatr 2004;62(2-A): 233-236.

7. Nawawi HM, Muhajir M, Kian YC, et al. Type of diabetes and waist-hip ratio are important determinants of serum

lipoprotein(a) levels in diabetic patients. *Diabetes Res ClinPract 2002; 56: 221-227.*

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

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

11. Somer JB. Etal.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.*

12. Agarwal SK. et al. Prevalence of Chronic Renal Failure in adults in Delhi,India. *Nephrol Dial Transplant 2005; (20) :1638-42.*)

13. Miida T, et al. LCAT-dependent conversion of pre β1-HDL intoα-migrating HDL is severely delayed in haemodialysis patients. *J Am SocNephrol.2003;14:732-8.*

14. Assmann G, Funke H. Genetishe Diagnostic von Storungen des Lipoproteinstoffechsels. *Lab Med. 1992;16:369-74.*

15. Todorova B. Lp(a), antigen-kvalitativniikvantitativniistra`uvawaiklini~k aprimena. *doktorskadisertacija. Skopje: Medicinskifakultet; 1989.*

16. Scanu AM, Fless GM. Lipoprotein(a). Heterogeneity and biological relevance.*J Clin Invest. 1990; 85:1709-15.*

17. Zölner N. Kirchs KZ. Fotometriska-oboenametoda.*GesExp Med. 1962; 135: 545.*

18. Bucola G, David H. Quantitative determination of serum triglycerides by use of enzymes. *Clin Chem.1973;19:476-82.*

19. Allain CC, Poon LS, Chan CS, Richmond W. Enzymatic determination of total serum cholesterol.*Clin Chem.1974;20:470-5.*

20. Friedewald WT, Levy RJ, Fredrickson DS.Estimation of concentration of low density lipoprotein cholesterol without the use of the preparative ultracentrifuge.*Clin Chem.1972;18:499-502*

21. Wamick G, Benderson J, Allbers J. Quantitation of high density lipoprotein subclasses after separation by dextran sulfate and Mg+ precipitation. *Clin Chem. 1982;28:1574-61*

22. Rifai N, King ME. Immunoturbidimetric assays of apolipoproteins A-I, A-II and B in serum. *Clin Chem.1986;23(6): 957-61.*

23. Labudovic D. Toseska K. Alabakovska S. Et al. Apoprotein(a) phenotypes and plasma lipoprotein(a) concentration in patients with diabetes mellitus . *ClinBiochem. Int press 2003.*

24. Ribault A, Drou MR, Lettelier C. et al. Determination of lipoproteina (a) concentration and lipoprotein(a) molecular weights in diabetic patients. *Diabetes Metab 2000; 26: 107-112.*

25. Lundstam U, Herlitz J , et al. Serum lipids, lipoprotein(a) level ,and apolipoprotein(a) isoforms as prognostic markers in patients with coronary artery dissease. *I intern Med. 2002; 251: 111-118.*

26. Kronenberg F, Neyer U et al. The low molecular weight apo(a) phenotypes is an independent predictor for coronary artery disease in haemodialysis patients : a prospective follow-up. J Am Soc*Nefrol 1999; 10: 1027-1036.*

27. Lutfi Z. Profil na Dislipidemijata I Apoproteinskite Aberacii kaj Pacienti Lekuvani so Povtoruvani Hemodijalizi. Univerzitet „ Sv. KiriliMetodij ” Skopje Juni-2009; DoktorskaDisertacija.