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ORIGINAL ARTICLES

Management of Dyslipidemia in Patients with Diabetes Mellitus and Cardiovascular Disease

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Abstract

Introduction: Diabetes mellitus and cardiovascular diseases remain the leading causes of death worldwide. There are approximately 366 million people with diabetes globally, and by 2030, it is projected that this number will reach 520 million, or 6.3% of the world's population, affected by diabetes. Dyslipidemia and diabetes are the main contributors to cardiovascular diseases. Diabetic dyslipidemia is characterized by disturbances in all lipid fractions (increased triglycerides, increased LDL-cholesterol, and low HDL-cholesterol levels).

Purpose of the study: This study aimed to assess hyperlipidemia as a risk factor for cardiovascular disease in patients with diabetes Mellitus.

Materials and Methods: The study was a prospective cohort ("cross-sectional").

Results: A total of 200 participants were included: 100 patients with diabetes mellitus (60 with type 1 and 40 with type 2), and 100 healthy individuals serving as controls. Among the diabetes patients (100), 45 (45%) were female, with a mean age of 58.00 ± 14.00 years, while 55 (55%) were male, with a mean age of 59.60 ± 12.00 years. The control group comprised 100 voluntary blood donors, 45 (45%) women and 55 (55%) men, with a mean age of 58.40 ± 13.60 years. The results are shown in the following tables (numbers 3-6).

Conclusion: Dyslipidemia and hyperglycemia are the principal risk factors and are independent of the development of premature atherosclerosis and cardiovascular disease. Treating primary or secondary dyslipidemia early is crucial and can significantly help prevent early atherosclerotic processes and cardiovascular diseases. Recent studies on the treatment of dyslipidemia have shown a strong positive effect of statins (40 mg dose), which appear to help prevent cardiovascular disease.

Keywords: dyslipidemia, cardiovascular disease, diabetes mellitus.

Introduction

Diabetes mellitus (DM) is a globally prevalent chronic disease that in 2019 caused over 1.5 million deaths worldwide. Diabetes coexisting with dyslipidemia is the leading cause of cardiovascular diseases (CVD) in patients with DM.

Diabetic dyslipidemia is characterized by increased concentrations of triglycerides (TG), LDL-C (Low-Density Lipoprotein Cholesterol), and Lp(a) (Lipoprotein(a)), and decreased HDL-C (High-Density Lipoprotein Cholesterol), with LDL-C levels predominating at 91.20. The epidemiology of dyslipidemia varies by region, age, gender, and ethnicity, and is influenced by genetic and environmental factors.

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The global prevalence of dyslipidemia in adults is estimated to range from 20% to 80%. Awareness, treatment, and control of dyslipidemia are also low in many countries of the world, especially in low- and middle-income countries [3].

The incidence of dyslipidemia is usually asymptomatic and often coexists with other risk factors (such as hypertension, obesity, oxidative stress, inflammation, sedentariness, smoking, physical inactivity, etc. A large-scale trial demonstrated that lowering LDL cholesterol by 1 mmol/L reduced the risk of major vascular events by approximately 20%, regardless of the baseline LDL level.

A meta-analysis of 26 randomized trials found that statin therapy reduced the risk of all-cause mortality by 10%, coronary mortality by 18% and mortality from cerebral stroke by 9%.

Results from a U.S. study estimated that the annual cost of dyslipidemia was $34.4 billion in 2006, of which $19.7 billion was attributable to direct medical costs and $14.7 billion to indirect costs [4, 5].

Hyperglycemia is a significant contributor to the development of hypertriglyceridemia (HTG); therefore, glycemic control and normalization also affect the dyslipidemic profile.

The most effective strategy for managing dyslipidemia is to optimize diet and lifestyle. The first-line drugs for the treatment of hypocholesterolemia are hydroxy-3-methylglutaryl-CoA reductase inhibitors (statins), which, in addition to lowering LDL, also decrease TG concentrations by 10-34%. For control and the most efficient treatment of hypertriglyceridemia, drugs from the fibrate group contribute more to reducing CVD risk. Dyslipidemia also enhances the transfer of cholesterol esters from HDL to LDL and VLDL (Very Low-Density Lipoprotein) via the action of cholesterol ester transfer protein, thereby reducing HDL's ability to remove excess cholesterol from blood vessels. Some possible signs and symptoms of dyslipidemia include: xanthoma, xanthelasma, arcus senilis (a gray or white ring around the cornea caused by cholesterol deposits at the border of the cornea and indicating high blood cholesterol levels), lipemia retinalis (a milky appearance in the retinal vessels due to elevated triglycerides in the blood, which may signal severe hypertriglyceridemia), and ischemia of the lower limbs (peripheral artery disease caused by narrowing or blockage of the arteries supplying blood to the legs due to atherosclerosis).

This condition is typically characterized by pain or cramps during physical activity (e.g., standing or exercise) and is relieved by rest. Angina pectoris is a symptom of coronary artery disease, caused by the narrowing or blockage of the arteries that supply the heart with blood due to atherosclerosis [7, 8, 9].

This finding is consistent with the results of a recent study by *Grant et al.* (18), who also reported a high prevalence of suboptimal HDL-c levels in patients with type 2 diabetes, with nearly half (49.5%) of patients exhibiting low HDL-c levels [10].

Of particular note, in patients with diabetes and low HDL-C and elevated TG, the most common lipid therapy was statin monotherapy (in 37% of patients), and only 17% received any niacin or fiber therapy to target suboptimal TG levels [11, 12, 13].

These results are also consistent with those reported by *Klingman and colleagues* [21], who evaluated data from the 1999–2000 National Health and Nutrition Examination Survey to assess the status of dyslipidemia management in the US adult population and to determine whether treatment patterns were consistent with guideline recommendations.

Numerous studies have shown that glycemic control significantly reduces the incidence of CVD; therefore, the American Diabetes Association (ADA) provides guidelines and recommendations for managing hyperglycemia. Glycemia, glycosylated hemoglobin (HgbA1c), and lipids in patients with DM also reduce the risk of CVDs.

Control of hyperglycemia and glycosylated hemoglobin (HbA1c) is a primary measure for monitoring disease progression; therefore, normalizing glycemia and dyslipidemia in the early stages of the disease would undoubtedly affect the incidence of early atherosclerotic processes in the coronary, cerebral, and peripheral arteries. In recent years, the incidence of uncontrolled diabetes and diabetic nephropathy not only in the USA and Europe, but also in the Balkans has increased by 38%-42%, therefore, doctors always suggest that measuring and monitoring blood glucose and lipid control should be one of the goals and mandatory measures for doctors with CKD (chronic kidney diseases) to reduce the incidence of CVDs [14, 15] significantly.

Patients with DM are at higher risk for early atherosclerosis and its consequences in the cerebrovascular system, cardiovascular, and peripheral artery atherosclerosis compared to the healthy population.

The exact pathogenesis of diabetic dyslipidemia is still not fully known; however, a large amount of evidence suggests that insulin resistance plays a central role in the development of this pathological phenomenon in diabetes [16].

The National Cholesterol Education Program (NCEP) guidelines for the treatment of diabetic dyslipidemia focus on lowering TG and LDL-c, and they suggest LDL-ch values from 100 to 70 mg/dl as the optimal value for maintaining the risk of coronary heart disease [17-23].

Improvement and regulation of blood glucose levels, regardless of the type of dyslipidemia treatment, have been shown to positively affect lipid levels. Treatments with metformin and rapaglinide have demonstrated beneficial effects on lipid reduction in patients with type 2 diabetes who are on oral therapy.

There is documented evidence that the effects of these drugs in improving diabetes and lipid disorders are closely

related to reductions in triglyceride levels and increases in HDL-cholesterol levels.

Purpose of the work:
This study aimed to evaluate hyperlipidemia as a risk factor related to CVD in patients with diabetes mellitus. The study estimates that disorders of all lipid fractions should be

Materials and Methods

The research was a prospective cohort study (not cross-sectional). It included 200 examiners, of whom 100 were patients with DM, comprising 60 with type 1 DM and 40 with type 2 DM. One hundred healthy individuals served as the control group.

For examination, 5+ (5) ml of venous blood was used, taken from the vein in the patient's lying position 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.

Of the patients with DM (100), 45 (45%) were girls with an average age of 58.00±14.00 years, while 55 (55%) were male, with an average age of 59.60±12.00 years.

The group controller sound examination (voluntary blood donors) also included 45 (45%) women and 55 (55%) men, with an average age of 58.40 ± 13.60 years. Of the total number of patients, No. 100 with Type-1 diabetes mellitus

Identified and treated with medications in the early stages of the appearance of diabetes in the entire population (DM Tip1: insulin dependent) were 60, while 40 were patients with Type-II diabetes mellitus (DM type 2 treated with oral hypoglycemic), Table 1, 1,2.

The methods used to determine the lipid profile, blood glucose (GI), and HbA1c concentrations are listed in Table 2. As a reference value, Gl and HbA1c values were taken according to the criteria proposed by the World Health Organization: Gl = 3.5-6.5 mmol/L, (HbA1c = 4.4-6.6%).

Patients who were insulin dependent are counted as Type-1, while patients independent of insulin but with oral therapy count as Type-2 DM. In addition to examining lipid profiles, glycemia, and HbA1c, we determined BMI (Body Mass Index) (Table 3).

In all patients and the control group, blood glucose and hemoglobin values were measured within 6 months.

Tot. patients-100	DM type 1 (insulin-dependent)	DM type 2(oral hypoglicemic)
100	60	40

Table 1: Presentation of diabetes patients under therapy, oral and insulin

Gender	Number	The average age ±SD	Control group	The average age ± SD
Women	45	58.40±14.00 years	45	58.40±13.60 years
Men	55	59.60±12.00 years	55	58.40±13.60 years

Table 2: Distribution of patients and control group average by gender, sex, and age average

The average age of the patients, by gender, was 59.60±12.00 years for men and 58.40±14.00 years for women. The age difference between men and women was statistically significant (p = 0.005), indicating a similar patient cohort.

Statistical processing of the material examined
Values for blood glucose, HbA1c%, and lipids (Kol.Total, TG, HDL-ch, LDL-ch), along with those from the control group, are presented as mean ± standard deviation (SD).

The results also include calculated correlation coefficients "r" and a statistical p-value of less than 1% (p<0.001). Statistical comparisons of lipid parameters between the two groups were performed using Student's t-test, for example, to assess differences in dependent variables.

Results

The results from the examination of blood glucose, HbA1c, and lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol), as well as those from the control group, are presented in Tables 2 and 3. The tables show that, in both groups, some patients (DM Type 1) exhibit variation. Independent and non-parametric tests were used: the Mann-Whitney U test. Significant statistical differences were observed between the patient and control groups. Values of the parameters of lipids, glycemia, and HbA1c% were analyzed to test the so-called, Anova Two-Factor "statistical Worth, p 'lesser of 5 %, p<0.005. Moreover, DM-type 2) was characterized by verified lipid concentrations and HbA1c levels above normal values, with a statistically significant difference (p < 0.001) compared to the control group.

Table 5 presents significant differences between the parameters examined in patients with diabetes mellitus (types 1 and 2) and the control group. The difference that appears between the average values of the examined parameters of the two groups is statistically significant (p < 0.001, compared to the control group.

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=0.001 while the HDL fraction chnoticed a remodeling to increase its concentration, which testifies to the positive effects of statin for a double effect and the regulation of LDL

No, of patients with DM tip1 (insulin-dependent)	Parameters examined	The value obtained from the examined parameters.
60	Glycemia	9.80±6.50
60	HbA1c	8.00±4.00
60	tCh	7.80±2.00
60	LDL-ch	4.70±0.80
60	TG	3.90±0.60
60	HDL-ch	1.06±0.80

Table 3: Presentation of the average Values of the Parameters analyzed to examine patients with type 1 DM - the insulin-dependent. No 60 before treatment with hypolipidemic therapy.

Number of patients with DM tip2	Parameters examined	The value obtained from the examined parameters.
40	Glycemia	12.00±4.00
40	HbA1c	8.60±3.00
40	tCh	6.80±2.50
40	LDL-ch	4.50±0.40
40	TG	3.60±0.90
60	HDL-ch	1.04±0.50

Table 4: Presentation of the average Values of the Parameters analyzed to examine patients with type 2 DM dependent, n=40 (oral hypoglycemic) -Before hypoglycemic therapy treatment

Patients with DM Type 1 and Type 2 DM			Controls Group		
Total number of patients with DM (F+M)	Parameters examined	Values of Parameters examined	No. of patients	Values of exam.	p
100	Glycemia	11.00±4.30	100	6.70±0.40	0.001
100	HbA1c	8.70±4.00	100	7.20±0.60	0.001
100	tCh	7.40±2.00	100	6.30±1.00	0.001
100	LDL-ch	4.70±0.80	100	3.20±0.80	0.001
100	TG	3.80±0.60	100	1.40±160	0.001
100	HDL-ch	1.07±0.20	100	1.85±1.40	0.001

Table 5: Presentation of the average Values of the Parameters Examined in patients with DM Type 1, Type 2 DM, and control group

Patients with DM Type 1 and Type 2 DM = 100.			Controls Group=100	
patients with DM tip1 and 2(F+M)	Parameters Examined	Values of Exam. Param	Values of exam.	p
100	Glycemia	8.00±0.70	6.70±0.40	0.001
100	HbA1c	7.40±1.50	7.20±0.60	0.001
100	tCh	5.40±1.15	6.30±1.00	0.001
100	LDL-ch	3.90±050	3.20±0.80	0.001
100	TG	2.50±0.30	1.40±160	0.001
100	HDL-ch	1.30±0.60	1.85±1.40	0.001

Table 6: Indicates significant differences between the examined parameters of patients with diabetes mellitus (type 1 and type 2) after 6 months of treatment with statin.

hypercholesterolemia but also in increasing proatherogenic HDL-ch concentration.

Discussion

Lipids, such as cholesterol or triglycerides, are absorbed from the intestines and transported throughout the body via lipoproteins for energy. The main contributors to these pathways are cholesterol, LDL, triglycerides, and HDL.

An imbalance in any of these factors, whether organic or inorganic, can lead to dyslipidemia [24, 25].

Dyslipidemia refers to abnormal lipid levels in the bloodstream and is a significant risk factor for CVD. Dyslipidemia refers to abnormal lipid levels in the bloodstream and is a significant risk factor for CVD.

Disturbance of these lipid levels, whether due to genetic predispositions or lifestyle factors, can lead to atherosclerosis and other cardiovascular and cerebral complications. In recent years, the treatment of diabetic dyslipidemia has often been the subject of discussion by the ADA, which has proposed dietary and therapeutic measures for the management of dyslipidemia in patients with diabetes and CVD. In particular, patients with diabetes tend to have a significant increase in oxidized cholesterol (LDLox) and a higher percentage of particles, foam cells, which are very sensitive to oxidation and risk the consequences of CVD, acute myocardial infarction, angina pectoris, stable and unstable coronary insufficiency.

Observational studies by the ADA and friends, in conjunction with Medical Nutrition Therapy (MNT), have shown that patients who adopted a healthier diet and increased physical activity [29-34].

Numerous clinical studies have investigated the effects of treating diabetic dyslipidemia, aiming to achieve effective drug therapy (statins, fibrates, niacin, cholestipol, cholestyramine) with target values for LDL cholesterol of <2.60 mmol/L and for HDL cholesterol. are = 1.02 mmol / l, and triglyceride levels are -1.7 mmol/ l. Women's HDL cholesterol levels may be higher due to estrogen's effects.

Recommendations for the treatment of dyslipidemia are typically based on guidelines and consensus statements from the ADA and the NCEP [38].

Hypertriglyceridemia may be a risk factor for CVD in people with incipient diabetes.

The fibrate group (gemfibrozil, bezafibrate, fenofibrate, Clofibrate, etc.) or, in cases of high hypertriglyceridemia, fibrates can be combined with niacin (<2 g/day. Doctors often ask: When and at what TG value should treatment for hypertriglyceridemia be initiated?

The decision to initiate pharmacological therapy depends on the physician's judgment, but it should be initiated when triglyceride levels are between 2.30 - 4.50 mmol/L. The therapeutic combination of statins and fibrates is prohibited due to the extremely high side effects of myositis and rhabdomyolysis. The use of high-dose statin therapy (eg, 80 mg) for the treatment of dyslipidemia in patients with high LDL-c and TG levels will also be limited due to side effects (elevated transaminases and muscle pain).

Therefore, for these patients, therapy should be started with a dose of 40 mg once a day. After reaching the target values, as determined by laboratory examination, the dose will be reduced to 20 mg per day, unless the patient is overweight. The primary goal of therapy is to reduce LDL cholesterol concentrations to ≤ 3.40 mmol/L.

In case of intolerance to statins, it is preferable to combine therapy with other hypo-lipidemics (such as niacin, holestipol, cholestyramine, etc.). High triglyceride levels are treated with fibrate derivatives (e.g., gemfibrozil or fenofibrate) or niacin. Irregular glycemic control and imbalance are considered as one of the risk factors for CVD and rapid progression of chronic kidney damage in patients with diabetes, whether they are insulin users or have oral hypoglycemic therapy [35].

Our lipid profile results showed a high degree of lipid disorder in both patient groups (type 1 DM and type 2 DM), consistent with prior studies on lipid disorders in patients with DM [36, 37, 38]. Patients with type 2 diabetes are at four times the risk of developing CVD compared to the population suffering from other diseases.

There are documented facts that patients with diabetes from lipid fractions most often manifest hypertriglyceridemia (increased triglyceride concentration) and hypercholesterolemia (increased LDL concentration) with decreased proatherogenic cholesterol (HDL) values [35]. First-line treatment for dyslipidemia is statins that inhibit 3-hydroxy-3-methylglutaryl-coenzyme A reductase.

Conclusion:

In conclusion, dyslipidemia and hyperglycemia are the principal risk factors and are independent of the occurrence of premature atherosclerosis and CVD. Treatment of primary or secondary dyslipidemia in the initial stages is of great importance and can significantly affect the prevention of early atherosclerotic processes and cardiovascular diseases. In the treatment of dyslipidemia in recent years, a large number of studies have verified high positive effects during treatment with statins (dose 40 mg), which appear to affect the prevention of CVD.

Abbreviations

DM - Diabetes Mellitus; CVD - Cardiovascular Diseases; TG - Triglycerides; LDL-C - Low-Density Lipoprotein Cholesterol; Lp(a),- Lipoprotein(a); HDL-C - High-Density Lipoprotein Cholesterol; HTG - Hypertriglyceridemia; VLDL - Very Low Density Lipoprotein; ADA - American Diabetes Association; HgbA1c - Glycosylated Hemoglobin; CKD - Chronic Kidney Deseases; NCEP - National Cholesterol Education Program; GI - Blood Glucose; BMI - Body Mass Index; SD - Standard Deviation; Kol.Total - Total Cholesterol; HDL-ch - HDL-cholesterol; LDL-ch - LDL-cholesterol; LDLox - Oxidized Cholesterol; MNT - Medical Nutrition Therapy;

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