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Lipid control in patients with and without Type 2 Diabetes Mellitus (T2DM). The experience of a special unit of a second grade hospital

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Abstract

Introduction: The prevalence of T2DM is worryingly increasing; the current understanding that T2DM is a metabolic disorder rather than a single disease makes the management of patients with T2DM challenging. In parallel, dyslipidemia is a fundamental risk factor for atherosclerotic cardiovascular disease (ASCVD) that can be reversible under pharmaceutical measures and lifestyle changes. Given that the risk of ASCVD is already elevated for patients with T2DM, the lipid management is of great importance to them.

Patients and Methods: Patients with dyslipidemia (*n*= 114) with T2DM (*n1*= 36) and without T2DM (*n2*= 78) were included. The patients were treated with statin ± anti-diabetic agent. Smokers (> 5 packet-years) and patients with Chronic Kidney Disease (CKD) were excluded. They were under medical supervision in our Lipid, Diabetes and Metabolism Unit for at least 12 months. There were follow-up appointments once every 3 months for the first year and a full lipid profile, HbA1c and BMI were recorded.

Results: After one year under medical supervision, 8% of the patients with T2DM and 31% of the patients without T2DM had a totally normal lipid profile. The LDL and the triglyceride (TG) goal in the two groups were achieved by 11% / 46% and 31% / 67% respectively. LDL-C, non-HDL-C and TG

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achievement rates were higher in patients without T2DM (p <0.05). 56% of the patients with T2DM achieved HbA1c levels ≤ 6,5%.

Conclusion: The statistically significant difference in the lipid control between the patients with and without T2DM is a characteristic of the diabetic dyslipidemia. Intensive medical supervision is of paramount importance for those patients.

Key words: lipids; lipoproteins; cholesterol; LDL; diabetes mellitus; diabetic dyslipidemia

1. Introduction

T2DM has unarguably become a global health problem, keeping a steady increase in developed and developing countries.[1] The situation is getting more and more alarming, considering that the rates of childhood obesity are rising, which leads to T2DM becoming more and more common in teenagers and young adolescents.[2] T2DM, atherogenic dyslipidemia and obesity synthesize a classic triptych for atherosclerotic cardiovascular disease (ACVD) and this fact is well documented.[3] Patients with T2DM are by definition prone to macrovascular and microvascular disease and complications which are attributed to the injurious effects of chronic hyperglycemia. Nonetheless, major studies failed to show the desired positive effects on cardiovascular risk from intensive glycemic control alone.[4,5] The nature of T2DM is quite complex and insulin resistance seems to play an important role in it; the extreme manifestation of insulin resistance is better known as the metabolic syndrome.[6] Obesity and genetic predisposition are both correlated with insulin resistance which is, in turn, strongly associated with hypertension, dyslipidemia, diabetes and their complications.[7] Therefore, intensive hypolipidemic and antihypertensive therapy as well as low-calorie, low-fat diet and body mass index (BMI) reduction is advised, aiming at diminishing the residual cardiovascular risk. Pharmaceutical agents and lifestyle changes have place in treatment. Yet, goals are hard to achieve and even harder to maintain. The management of patients with T2DM is a real challenge as a majority of these patients show poor adherence to the suggested therapy and the recommendations of health care providers.[8] The need for close follow-up after the diagnosis of T2DM has led to the formation of special Diabetes Units in our country which contribute to the primary and secondary prevention of diabetes and its complications. We undertook a retrospective study on the patients with dyslipidemia, with and without T2DM who are under medical supervision in our Lipid, Diabetes and Metabolism Unit, trying to discover the possible differences in the lipid control between the two groups. Additionally, we tried to investigate the results of our efforts to reduce their ACVD.

2. Patients and Methods

2.1. Data source

Medical charts of the patients who were under medical supervision in the Lipid, Diabetes and Metabolism Unit of the General Hospital of Trikala, Thessaly, Greece were retrospectively reviewed and only those who had at least one year continuous follow-up in our Unit were approved.

2.2. Definitions

Accoring to the Hellenic Diabetes Association guidelines[9], a person was considered to be a "patient with T2DM" when one or more of the following criteria were fulfilled:

- Fasting Plasma Glucose FGP ≥ 126mg/dL.
- Random Plasma Glucose ≥ 200mg /dL, AND symptoms of hyperglycemia, namely polyuria, polydipsia, weight loss.
- Abnormal Oral Glucose Tolerance Test (OGTT) (75-g glucose/ 2 h)

Dyslipidemia is used as a synonym to hyperlipidemia. The decision of the statin therapy was made according to each patient profile and the 10-year

Table 1. The targets that the patients included in our study had to achieve during the follow-up in our Lipid, Diabetes and Metabolism Unit

TARGETS	Patients with dyslipidemia included in the study non-FH individuals	
	With T2DM	Without T2DM
LDL-C	< 70 mg/dl	< 115 mg/dl
Non-HDL-C	< 100 mg/dl	< 145 mg/dl
HbA1c	≤ 6.5%	
TG	< 150 mg/dl	
BMI	Between 18.5 and 24.9	

risk of developing ASCVD, according to the Hellenic Heart SCORE as mentioned in the updated guidelines of the Hellenic Society of Atherosclerosis for the diagnosis and treatment of dyslipidemia.[10] The body mass index (BMI) is defined as the body mass divided by the square of the body height and is expressed in kg/m^2.

2.3. Patients and methods

Finally 114 patients with dyslipidemia were included in the study and 36 of them suffered from T2DM as well. Patients with chronic kidney disease (stage > II), smokers (>5 packet-years) and those > 75 years old were excluded. None with homozygous familial hyperlipidemia or an autoimmune disease was in the study. There were follow-up appointments once every 3 months for the first six months and then once per year. All the patients were thoroughly examined. Moreover, FGP, glycated hemoglobin (HbA1c), total cholesterol (Chol), low density lipoprotein (LDL-C), high density lipoprotein (HDL-C) and triglycerides (TG) were tested. The blood samples were taken after a 12 hour-fast. When serum TG were measured > 200 mg/dl, the LDL-C levels were directly measured. The body mass index (BMI) of each patient was calculated as well. All the patients were treated with statins and the patients with T2DM were treated with one or more anti-diabetic agents as well. 14 patients were newly diagnosed with dyslipidemia and therefore they were statin-naïve. The rest of the patients had already been receiving statin ± antidiabetic treatment and the necessary interventions were made in an effort to achieve lipid and HbA1c targets levels (**Table 1**)[10]. There was no intervention in the patients' possible anti-hypertensive or antiplatelet therapy. All the patients were advised to follow a low fat and low cholesterol diet and to do physical aerobic exercise of medium intensity at least four times a week for at least 30 minutes. The outcome on the lipid profile of our patients was considered by the difference of the values of the above parameters at the beginning of the follow-up and at the end of the first year of supervision.

An ADVIA 1800 Clinical Chemistry System (Siemens Healthcare) was used for the photometric analysis of the blood samples.

2.4. Targets

According to the Greek[10] and European[11] Guidelines, the target for the patients who were included in our study are seen in **Table 1**.

Notably, there is a sub-group of patients without T2DM who are advised to achieve LDL-C levels < 100 mg /dl and those are patients with Familial Hypercholesterolemia (FH), autoimmune diseases, uncontrolled hypertension as well as heavy smokers. Yet, heavy smokers had been initially excluded from our study and none of our patients had FH, uncontrolled hypertension or autoimmune disease. Therefore, the LDL-C and non-HDL-C targets for all the patients without T2DM who were included in our study were 115 mg/dl and 145 mg/dl respectively.

Table 2. Characteristics of enrolled patients. Values are expressed as percent or mean +/- SEM (standard error of mean)

			Enrolled Patients N=114				P
			Patients with T2DM 31.6		Patients without T2DM 68.4		
SEX	Male		41.7		39.7		0.948
	Female		58.3		60.3		
Age			60.06 ± 1.75		58.69 ± 1.55		0.598
BMI			29.62 ± 1.2		25.99 ± 0.74		0.012
LDL-C			158.12 ± 5.6		136.57 ± 9.35		0.041
nonHDL-C			196.07 ± 7.22		191.52 ± 9.53		0.699
TG			289.5 ± 37.41		196.53 ± 23.86		0.044
HbA1c			7.3 ± 0.25				
STATINS	Atorvastatin	10mg	5.3	11.4	9.6	41.2	
		20mg	6.1		29.8		
		40mg	0		1.8		
	Simvastatin	20mg	6.1	8.7	9.6	15.7	
		40mg	2.6		6.1		
	Rosuvastatin	5mg	5.3	7.9	5.3	10.6	
		10mg	2.6		5.3		
	Pravastatin	20mg	1.8	3.6	0.9	0.9	
		40mg	1.8		0		
	Statin monotherapy		87.2		76.5		
	Statin + ezetimibe		12.8		23.5		

2.5. Statistical analysis

SPSS version 24.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Continuous variables are presented as mean ± standard error of mean (SEM), and categorical variables are shown as percentages and numbers. Normally distributed continuous variables were compared using the Student's t-test. χ^2-test was used for identifying the significance in the differences for categorical variables. P values below 0.05 ($p < 0.05$) were considered to be statistically significant.

3. Results

3.1. Patient Enrollment & characteristics

114 patients with dyslipidemia (47 men and 67 women) were included in the study. All of them were under medical supervision in our Lipid, Diabetes and Metabolism Unit for at least 12 months. The characteristics of the patients are summarized in **Table 2**. BMI, LDL-C levels and TG levels seem to be significantly higher in patients with T2DM than those without T2DM.

3.2. Comparison of LDL-C, non-HDL-C and TG target level achieving rates between the patients with T2DM and without T2DM

LDL-C and non-HDL-C target level achievement rates were 11% and 8% in patients with T2DM and these rates were 46% and 48%, respectively, in patients without T2DM. Comparing the TG levels

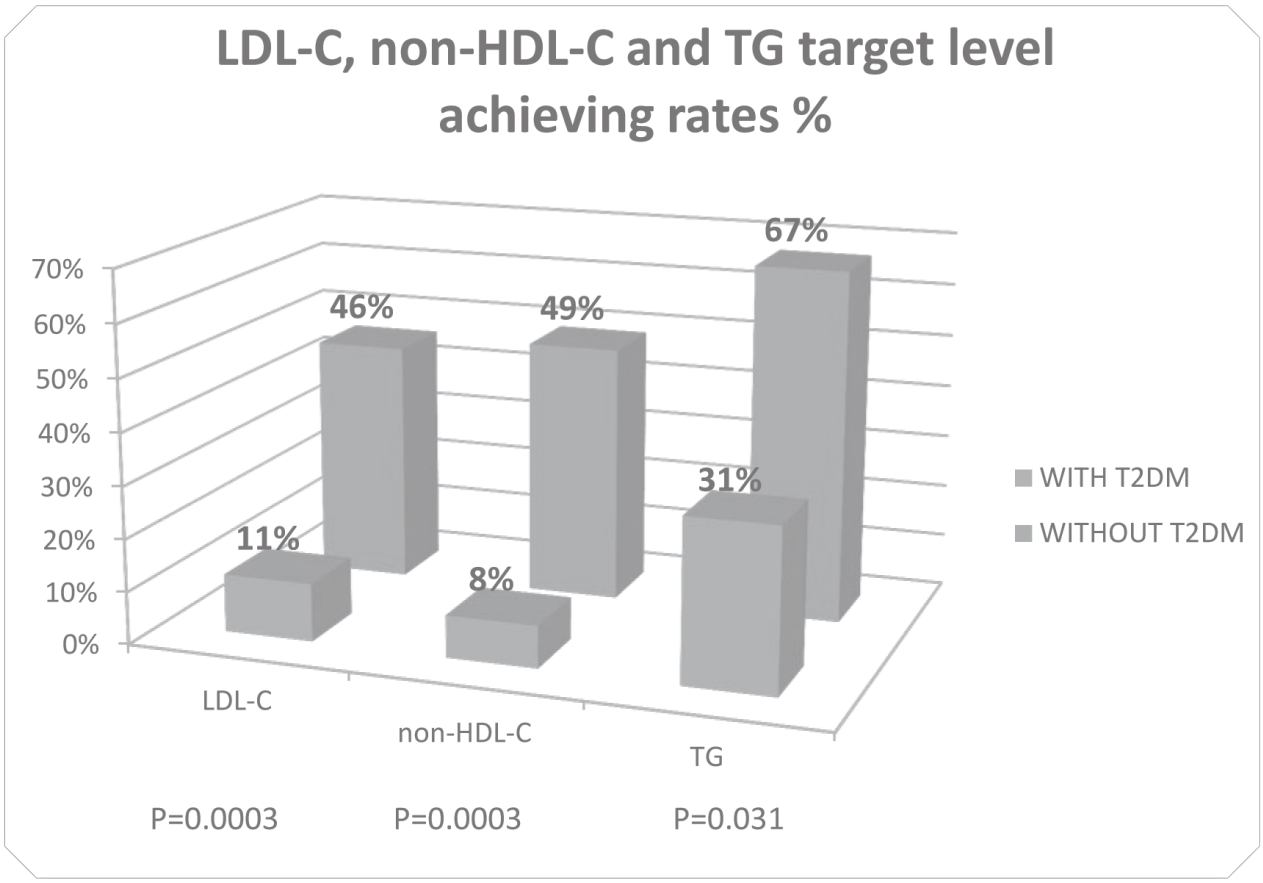

Figure 1. The differences between patients with and without T2DM in the LDL-C, non-HDL-C and TG target level achieving rates were statistically significant

between the two groups, 31% of the patients with T2DM and 67% of the patients without T2DM managed to achieve the target levels. (**Figure 1**)

3.3. Comparison of HbA1c levels of the patients with T2DM at the beginning and at the end of the 12-month-supervision

As shown in **Table 4**, the reduction in the HbA1c levels in the dislipidemic patients with T2DM who were under medical supervision in our Lipid, Diabetes and Metabolism Unit was statistically significant. 56% of the patients with T2DM managed to achieve HbA1c levels ≤ 6,5%.

3.4. Comparison of LDL-C, non-HDL-C, TG and BMI of the patients with T2DM at the beginning and at the end of the 12-month-supervision

The lipid profile seems to be improved in the patients with dyslipidemia and T2DM at the end of the follow-up, but the reduction of LDL-C is not statistically significant. Additionally, only 8% managed to achieve all their targets. As far as BMI is concerned, the results were not encouraging. This phenomenon is usual in patients with T2DM and is attributed to many antidiabetic agents, especially insulin.

3.5. Comparison of LDL-C, non-HDL-C, TG and BMI of the patients without T2DM at the beginning and at the end of the 12-month-supervision

The majority of the patients improved their lipid profile. 31% of them had a totally normal lipid profile. The reduction of all the cardiovascular risk parameters was proved to be statistically significant (**Table 3**).

4. Discussion

The correlation between T2DM and cardiovascu-

Table 3. The lipid profile of the patients with and without T2DM as well as the HbA1c levels before and after the 12-month-follow-up. Values are expressed as mean +/- SEM. CI: Confidence Interval

Patients	Parameters	Time = 0	Time =12 months	95% CI of the Difference		% Change	P
Without T2DM	LDL-C	136.57 ± 9.35	110.95 ± 5.44	+7.91	+43.35	-18.76%	0.006
	nonHDL-C	191.52 ± 9.53	153.78 ± 5.91	+20.03	+55.46	-19.71%	0.000
	TG	196.53 ± 23.86	145.88 ± 13.02	+8.03	+93.28	-25.78%	0.020
	BMI	25.99 ± 0.74	25.04 ± 0.65	+0.49	+1.42	-3.66%	0.000
With T2DM	LDL-C	158.12 ± 5.60	145.06 ± 22.68	-32,15	+58,25	-8.26%	0.567
	nonHDL-C	196.07 ± 7.22	147.92 ± 4.60	+35,97	60,35	-24.56%	0.000
	TG	289.5 ± 37.41	210.28 ± 17.46	+13.55	+144.89	-27.37%	0.019
	BMI	29.62 ± 1.20	29.42 ± 1.13	-0.31	+0.71	-0.68%	0.439

lar disease is very strong; adults with T2DM are 2-4 times more likely to have cardio-vascular disease than adults without diabetes and, compared to those without T2DM, they have a 2-4 times increased risk for stroke and death from heart disease.[12] Hyperlipidemia is another major factor responsible for atherosclerosis, which is reversible and treatment results in improved cardiovascular outcomes.[13] Thus, treatment of dyslipidemia in patients with T2DM is of great importance. The phenotype of hyperlipidemia in patients with T2DM is quite different from the one of the general population. Patients with T2DM tend to have high levels of TG and very low HDL-C levels, while LDL-C levels are similar to the levels of patients with dislipidemia of the general population.[14] The pathophysiology of hypertriglyceridemia in T2DM is quite complex and is generally attributed to the hepatic overproduction of large, triglyceride-rich very-LDL (VLDL), the diminished activity of lipoprotein lipase enzyme in muscle, liver and adipose tissue because of the peripheral insulin resistance and finally to the large adipose tissue which releases large quantities of non-esterified fatty acids to the liver.[15] High TG and low HDL-C levels are core components of the metabolic syndrome as well. This syndrome, which is characterized by insulin resistance and central obesity, doubles the risk of CVD but since its components are all reversible, the early diagnosis offers an effective treatment approach.[16] In metabolic syndrome, the dyslipidemia usually occurs before diabetes and worsens with time. Not surprisingly, many individuals with metabolic syndrome experience a cardiovascular event slightly before being characterized as patients with T2DM. Obviously, they were on their way to diabetes[17] and the chronic effect of insulin resistance on the endothelial dysfunction had already been proved catastrophic. [18] Hypertension, smoking and physical inactivity are the last traditional risk factors for cardiovascular disease that have to be controlled, especially in patients with diabetes because they multiply the likelihood of suffering from ASCVD by many times.[3] Unarguably, statins play the most important role in controlling dyslipidemia in T2DM patients and in general population as well. The main aim of the therapy with statins was the achievement of the LDL-C target, or at least a reduction of LDL-C < 50% of the initial levels for the very high risk patients. Yet, in patients with dyslipidemia and T2DM, non-high-density lipoprotein cholesterol (non-HDL-C) seems to be a better predictor of CVD than LDL-C[19] and, therefore, non-HDL-C should be the second goal of the therapy. Statins are generally well tolerated; they are considered as a first-line treatment in primary and secondary prevention and should not be withheld without any good reason.[15] Additionally, it does

not appear to be any threshold below which statin therapy is not beneficial.[20] On the contrary, it has been shown that for every 1 mmol/l reduction in LDL-C, there is a 9% reduction in all-cause mortality in patients with T2DM.[21] According to the Japan Atherosclerosis Society 2012 guidelines, patients aged ≥ 75 with dyslipidemia and primary prevention for coronary heart disease should be individually treated by the decisions of their attending physicians based upon the general condition of each patient.[22] On the other hand, dislipidemic patients aged 65-74 should be treated in the same way as those aged < 65 to achieve their serum lipid goals. Yet, there are clinical trials which clearly demonstrate that intervention with statins may be indicated for the elderly for primary or secondary prevention.[23] After all, the positive effects of statin therapy are pleiotropic.[24] As with glycemic control, the benefit of cardiovascular risk reduction depends upon the patient's frailty, overall health, and projected period of survival. Older patients are more likely to derive greater reduction in morbidity and mortality from cardiovascular risk reduction, particularly lipid lowering with statin therapy, than from tight glycemic control.[25] Lately, there are reports that long-term use of the majority of statins, but not all of them,[26] may provoke T2DM or deteriorate the glycemic control in established T2DM.[27,28] However, the risk is low compared to the cardiovascular benefit from LDL-C reduction. Interestingly, recent evidence show that regardless the alterations on glycemic control, CVD risk is remarkably reduced to those who develop T2DM on statin therapy.[29]

On the other hand, the effect of the anti-diabetic agents on the lipid profile can be controversial. Despite the fact that insulin increases HDL-C and metformin decreases LDL-C, TG and improves insulin resistance, sodium-glucose cotransporter -2 inhibitors are thought to increase LDL-C.[30,31] With reference to our results, BMI was inadequately controlled in both groups, especially among the patients with T2DM. It is well established that insulin, a major, widely used antidiabetic agent does not favor weight loss. It is also known that compliance with lifestyle measures is globally low.[32] As far as the lipid profile of the patients with T2DM and without T2DM is concerned, LDL-C, non-HDL-C and TG levels were decreased but in patients with T2DM the reduction in LDL-C levels did not prove to be statistically significant. Yet, statistical insignificance does not necessarily mean clinical irrelevance; statins unarguably decrease LDL-C as well as CVD risk. Despite the fact that intensive statin therapy is suggested for T2DM patients, we found lower achievement rates of LDL-C targets in T2DM group. The poorer results of LDL-C control among T2DM patients are possibly related to their personal characteristics, such as lifestyle or polypharmacy/medication non-adherence, or the nature of T2DM itself. The clinicians should try to explain the possible risks and closely follow-up those patients; they should also maximize the therapeutic lifestyle changes as well as the adherence to therapy; finally, they should educate patients and use safe and effective drugs.

To conclude, serum lipid goal attainment significantly differs between the patients with and without T2DM. Despite the fact that prescription of lipid lowering agents seems to be an everyday practice, achieving and maintaining the target levels may be a tough procedure. The problem becomes prominent when treating patients with T2DM. The complex nature of T2DM suggests that achieving the lipid goals which guarantee a reduction in cardiovascular risk can be very challenging.

5. Limitations

One limitation of the study is the relatively small number of the patients. Additionally, patients with major factors for cardiovascular risk, namely heavy smoking, uncontrolled hypertension and autoimmune diseases were either excluded or absent. Finally, we did not confront any patients suffering from FH, or patients < 20 years old.

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None.

Conflict of interest

All authors declare no conflict of interest.

Περίληψη

Ο Λιπιδαιμικός έλεγχος σε ασθενείς με ή χωρίς Σακχαρώδη Διαβήτη τύπου ΙΙ (ΣΔΙΙ) Η εμπειρία ενός Ιατρείου Λιπιδίων και Διαβήτη Δευτεροβάθμιου Νοσοκομείου

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Εισαγωγή: Ο επιπολασμός του ΣΔΙΙ αυξάνεται ανησυχητικά και η σύγχρονη θεώρησή του ως ένα σύνδρομο παρά ως μια ξεχωριστή οντότητα, κάνει την αντιμετώπισή του ιδιαίτερα απαιτητική από τους κλινικούς. Ταυτόχρονα, η υπερλιπιδαιμία παραμένει ένας θεμελιώδης παράγοντας αθηροσκληρωτικής καρδιοπάθειας, που όμως δύναται να αναστραφεί μέσω φαρμακευτικών και υγιεινοδιαιτητικών παρεμβάσεων. Οι ασθενείς με ΣΔΙΙ έχουν ήδη αυξημένο καρδιαγγειακό κίνδυνο και συνεπώς η λιπιδαιμική ρύθμιση είναι απόλυτη ανάγκη, παρόλο που οι στόχοι δύσκολα κατακτώνται και διατηρούνται.

Υλικό και Μέθοδος: Παρακολουθήθηκαν για τουλάχιστον 12 μήνες 114 δυσλιπιδαιμικοί ασθενείς εκ των οποίων οι 36 έπασχαν από ΣΔΙΙ και οι 78 όχι. Καπνιστές (> 5 πακέτα-χρόνια) και ασθενείς με Χρόνια Νεφρική Νόσο αποκλείστηκαν. Προγραμματίστηκαν επισκέψεις ανά τρίμηνο για το πρώτο έτος, όπου και γινόταν πλήρης λιπιδαιμικός έλεγχος, μέτρηση γλυκοζυλιωμένης αιμοσφαιρίνης (HBA1c) και Δείκτη Μάζας Σώματος (ΔΜΣ).

Αποτελέσματα: Ένα έτος μετά, 8% των ασθενών με ΣΔΙΙ και το 31% των μη-σακχαροδιαβητικών ασθενών είχαν πλήρως φυσιολογικό λιπιδαιμικό προφίλ. Η τιμή-στόχος της LDL-C και των τριγλυκεριδίων (TG) επετεύχθη από τις δύο ομάδες σε ποσοστά 11% / 46% και 31% / 67% αντιστοίχως. Τα ποσοστά επιτυχίας στις τιμές - στόχους για την LDL-C, τη non-HDL-C και των TG ήταν υψηλότερα για τους μη-διαβητικούς ασθενείς ($p < 0.05$). 56% των ασθενών με ΣΔΙΙ κατάφεραν να πετύχουν HbA1c ≤ 6.5%.

Συμπεράσματα: Η στατιστικά σημαντική διαφορά που παρατηρείται στο λιπιδαιμικό έλεγχο των σακχαροδιαβητικών και μη ασθενών αποδίδεται πιθανά στη διαβητική δυσλιπιδαιμία. Η εντατική ιατρική παρακολούθηση είναι θεμελιώδους σημασίας για αυτούς τους ασθενείς.

Λέξεις ευρετηρίου: λιπίδια, λιποπρωτεΐνες, LDL, σακχαρώδης διαβήτης, διαβητική δυσλιπιδαιμία

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References

1. Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: Estimate for the year 2000 and projections for 2030. *Diabetes Care* 2004, 127: 1047-1053
2. Weigensberg MJ, Goran MI. Type 2 diabetes in children and adolescents. *Lancet* 2009, 373: 1743-1744
3. O'Donnell JC and Elosua R. Cardiovascular Risk Factors. Insights From Framingham Heart Study. *Rev Esp Cardiol* 2008, 61: 299-310
4. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008, 358: 2560-2572
5. Diabetes Control and Complications Trial (DCCT) Research Group. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. *Am J Cardiol* 1995, 75: 894-903
6. Kannel WB. Risk stratification of dyslipidemia: Insights from the Framingham Study. *Curr Med Chem Cardiovasc Hematol Agents* 2005, 3: 187-193
7. Reaven GM. The insulin resistance syndrome. *Curr Atheroscler Rep* 2003, 5: 364-371
8. García-Pérez L-E, Álvarez M, Dilla T, et al. Adherence to Therapies in Patients with Type 2 Diabetes. *Diabetes Therapy* 2013, 4: 175-194
9. *Hellenic Diabetes Association*. Guidelines for management of the patients with T2DM. 2013
10. Elisaf M, Pitsavos C, Liberopoulos E, et al. Updated guidelines of the Hellenic Society of Atherosclerosis for the diagnosis and treatment of dyslipidemia-2014. *Hellenic Journal of Atherosclerosis* 2014, 5: 151-163
11. European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, et al. SC Committee for Practice Guidelines (CPG) 2008-2010 and 2010- 2012 Committees. ESC/EAS Guidelines for the management of dyslipidaemias: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 2011, 32: 1769-1818
12. Wu L, Parhofe rKG. Diabetic dyslipidemia. *Metabolism* 2014, 63(12): 1469-1479
13. Cholesterol Treatment Trialists' (CTT) Collaboration, Biagen C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010, 376: 1670-1681
14. Jaiswal M, Schinske A, Pop-Busui R. Lipids and lipid management in diabetes. *Best Pract Res Clin Endocrinol Metab* 2014, 28: 325-338
15. Soran H, Schofield JD, Adam S, et al. *Diabetic Dyslipidemia Curr Opin Lipidol* 2016, 27:313-322
16. Han TS and Lean MEJ. A clinical perspective of obesity, metabolic syndrome and cardiovascular disease. *JRSM Cardiovasc Dis* 2016, 25: 2048004016633371
17. Ford ES, Zhao G, Li C. Prediabetes and the risk for cardiovascular disease: A systematic review of the evidence. *J Am Coll Cardiol* 2010, 55: 1310-1317
18. Cersosimo E, DeFronzo RA. Insulin resistance and endothelial dysfunction: The road map to cardiovascular diseases. *Diabetes Metab Res Rev* 2006, 22:423-436
19. Emerging Risk Factors Collaboration, Di Angelantonio E, Sarwar N, et al. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009, 302: 1993-2000
20. Colhoun HM, Betteridge DJ, Durrington PN, et al. CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebocontrolled trial. *Lancet* 2004, 364: 685-696
21. Cholesterol Treatment Trialists Collaborators, Kearney PM, Blackwell L, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 2008, 371: 117-125
22. Japan Atherosclerosis Society. Japan Atherosclerosis Society (JAS) guidelines for prevention of atherosclerotic cardiovascular diseases 2012. *J. Atheroscler Thromb* 2014, Suppl.2: 1-118
23. Kannel WB. Coronary heart disease risk factors in the

elderly. Am. J. Geriatr. *Cardiol* 2002, 11: 101-107
24. Bedi O, Dhawan V, Sharma PL, et al. Pleiotropic effects of statins: New therapeutic targets in drug design. *Naunyn Schmiedebergs Arch Pharmacol* 2016, 389: 695-712
25. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008, 358: 2545
26. Huang CH, Huang YY, Hsu BR. Pitavastatin improves glycated hemoglobin in patients with poorly controlled type 2 diabetes. *J Diabetes Investig* 2016, 7: 769-776
27. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: A collaborative meta-analysis of randomised statin trials. *Lancet* 2010, 375: 735-742
28. Cai R, Yuan Y, Sun J, et al. Statins worsen glycemic control of T2DM in target LDL-c level and LDL-c reduction dependent manners: A meta-analysis. *Expert Opin Pharmacother* 2016, 17: 1839-1849
29. Livingstone SJ, Looker HC, Akbar T, et al. Effect of atorvastatin on glycaemia progression in patients with diabetes: An analysis from the Collaborative Atorvastatin in Diabetes Trial (CARDS). *Diabetologia* 2016, 59: 299-306
30. Briand F, Mayoux E, Brousseau E, et al. Empagliflozin, via Switching Metabolism Toward Lipid Utilization, Moderately Increases LDL Cholesterol Levels Through Reduced LDL Catabolism. *Diabetes* 2016, 65: 2032-2038
31. Forst T, Guthrie R, Goldenberg R, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes on background metformin and pioglitazone. *Diabetes Obes Metab* 2014, 16:467-477
32. Wolf AM, Conaway MR, Crowther JQ, et al. Translating lifestyle intervention to practice in obese patients with type 2 diabetes: Improving control with activity and nutrition (ICAN) study. *Diabetes Care* 2004, 27: 1570-1576

