The Corellation Between The Values Of Hba1c And Cholesterol, Triglycerides, Hdl, Ldl And Treatment Of Hyperlipidemia In Patients With Diabetes Type 2 In Tetovo Region

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ABSTRACT: The aim of this study is analysis of correlation between the values of HbA1c and cholesterol, triglycerides, hdl, ldl and treatment of hyperlipidemia in patients with diabetes type 2 in tetovo region.

MATERIAL METHOD: we measured the values of glucose, HbA1c and lipids in 80 patients with DM type 2. The number of patients with comorbidity was 68 from which 27 were male and 41 were female patients. The blood was collected in close system with 2 tubes. For serum we used a tube without anticoagulant (clot activator) in which we analysed Glucose, Cholsterol, Triglycerides, LDL, HDL.

For blood a tube with anticoagulant K2EDTA was used where the glicolysed Haemoglobin HbA1c was measured.

RESULTS: The peak age group in both genders was 51 – 60. There was significant correlations between the levels of HbA1C in all three measurements $p<0.01$, between HbA1C and triglyceride with level of significance $p<0.05$, between cholesterol and triglycerides during all three measurments with $p<0.01$, and between Triglycerides and Ldl with $p<0.01$ for the first measurment and $p<0.05$ for the secon measurment.

There was no significance in values of cholesterol, triglycerides, Hdl nd Ldl levels among the group with T2DM only na T2DM and comorbidity patients.

CONCLUSION: There was no significnce between T2DM only and T2DM with comorbidity group becouse this was an observational study over 12 months period where all the patiends had before started with appropriate therapy.

We can conclude that if the therapy is correct and patients comply with lifestyle chnges also, there are no significance in levels of HbA1c, glucose and lipids in patiends with T2DM and T2DM with comorbidity.

Key words: T2DM, comorbidity, therapy

INTRODUCTION

Patients with diabetes mellitus have a higher risk for cardiovascular heart disease (CHD) than does the general population, and once they develop CHD, mortality is higher**.** Good glycemic control will reduce CHD only modestly in patients with diabetes. Therefore, reduction in all cardiovascular risks such as dyslipidemia, hypertension, and smoking is warranted. The focus of this article is on therapy for dyslipidemia in patients with type 2 diabetes. Patients with the metabolic syndrome (insulin resistance) share similarities with patients with type 2 diabetes and may have a comparable cardiovascular risk profile. Diabetic patients tend to have higher triglyceride, lower high-density lipoprotein cholesterol (HDL), and similar low-density lipoprotein cholesterol (LDL) levels compared with those levels in nondiabetic patients. However, diabetic patients tend to have a higher concentration of small dense LDL particles, which are associated with higher CHD risk. Current recommendations **(according to American hearth association AHA scientific statement)** are for an

LDL goal of less than 100 mg/dl (an option of < 70 mg/dl in very high-risk patients), an HDL goal greater than 40 mg/dl for men and greater than 50 mg/dl for women, and a triglyceride goal less than 150 mg/dl. Nonpharmacologic interventions (diet and exercise) are first-line therapies and are used with pharmacologic therapy when necessary. Lowering LDL levels is the first priority in treating diabetic dyslipidemia. Statins are the first drug choice, followed by resins or ezetimibe, then fenofibrate or niacin. If a single agent is inadequate to achieve lipid goals, combinations of the preceding Drugs may be used. For elevated triglyceride levels, hyperglycemia must be controlled first. If triglyceride or HDL levels remain uncontrolled, pharmacologic agents should be considered. Fibrates are slightly more effective than niacin in lowering triglyceride levels, but niacin increases HDL levels appreciably more than do fibrates. Unlike gemfibrozil, niacin selectively increases subfraction Lp A-I, a cardioprotective HDL. Niacin is distinct in that it has a broad spectrum of beneficial effects on lipids and atherogenic lipoprotein subfraction levels. Niacin produces additive results when used in combination therapy. Recent data suggest that lower dosages and newer formulations of niacin can be used safely in diabetic patients with good glycemic control. Current evidence and guidelines mandate that diabetic dyslipidemia be treated aggressively, and lipid goals can be achieved in most patients with diabetes when all available products are considered and, if necessary, used in combination

Pathophysiology of diabetic dyslipidemia

The pathogenesis of diabetic dyslipidemia is not known, but many data suggest that insulinic resistance has the major role in it.[1], [2], [3], [4]. The main reason is the elevation of free fatty acids by fatty cells who are insulin resistant the elevated level of fatty acids with the presence of glycogen in the liver initiated the production of triglycerides, which stimulates the secretion of apolipoproteine B (Apo B) and VLDL cholesterolin. The altered ability of insulin to inhibiy the production of free fatty acids causes elevation of hepatic VLDL, which correlates with the accumulation of hepatic fat.[5], [6].

Management of dyslipidemia in diabetes mellitus

Management of dyslipidemia in people with diabetes mellitus, just like in any other individual, starts with a thorough evaluation that aims to identify secondary causes that might contribute to the abnormal lipid profile.[8] Lifestyle changes, including increased physical activity and dietary modifications, are the cornerstones of management.[7], [9]. Many people with T2DM are overweight and benefit from caloric restriction. The highest priority for diabetic individuals who have poor glycemic control should be to achieve near-normal blood-glucose levels, in the expectation that this approach will also improve dyslipidemia.[10], [11]. However, many individuals with T2DM continue to have abnormal plasma lipid profiles, despite having achieved their glycemic.

Lipid-lowering agents

Statins

Statin therapy is recommended as the initial pharmacological treatment for lowering LDL-C levels in patients with type 2 diabetes who either have overt CVD or are over 40 years old and have increased CVD risk [18], [20]; however, even with adequate LDL-C lowering via statin therapy, CVD risk remains high in many patients [18], [19]. The beneficial effects of statin treatment are thought to be mediated predominantly via lowering of LDL-C levels, although effects on HDL-C and other lipoproteins may also play a role [19]. Statin treatment lowers non-HDL-C more than apoB [21], and reaching the apoB target usually requires more intensive therapy than that required to achieve the non-HDL-C goal [22], [23]. Common adverse events associated with statin use include gastrointestinal upset and muscle aches, although dose-related hepatoxicity and myotoxicity are the most clinically significant adverse events [24]. Caution is recommended in patients with severe renal impairment (creatinine clearance < 30 mL/min). Studies have shown that high-dose statin

therapy is effective in achieving LDL-C goals and associated with favorable effects on lipoprotein subfractions in patients with type 2 diabetes, which may translate into clinical benefits in terms of anti-atherogenic potential and a subsequent reduction in the risk of adverse cardiovascular outcomes [25], [26].

Other lipid-lowering therapies

Niacin has been used to treat dyslipidemia in patients with type 2 diabetes for over half a century [27]. Although niacin is the most effective agent for raising HDL-C levels, high doses can worsen hyperglycemia [20]. Additional adverse events associated with niacin include flushing, itching, nausea, gastrointestinal upset, hypotension, and tachycardia [24], [27]. It has been suggested that combination lipid-lowering therapy (eg, a statin with a fibrate or niacin) may be necessary for patients with diabetic dyslipidemia to achieve optimal lipid levels; however, to date, such strategies have not been adequately evaluated for their long-term effect on CVD risk reduction or safety compared with lipid-lowering monotherapy [18], [20]. Furthermore, the risk of myopathy is thought to be greater when niacin is used with a statin [27]. Niacin plus laropiprant - a prostaglandin D_2 receptor antagonist and antiflushing agent - has been used successfully to improve the lipid profile with reduced niacin-associated flushing in patients with type 2 diabetes [28]. In 2 large randomized studies in patients with primary hypercholesterolemia or mixed dyslipidemia, the combination of niacin, laropiprant, and simvastatin significantly improved lipid parameters with a similar tolerability profile versus niacin/laropiprant alone, but with an increase in flushing and other niacin-related adverse effects versus statin alone [29], [30].

Ezetimibe, a selective cholesterol absorption inhibitor, is an effective lipid-lowering agent when used as monotherapy and is useful in patients who are unable to tolerate statin therapy [27]. Ezetimibe can also be used in combination with statin therapy for greater lipid-lowering efficacy. Ezetimibe plus atorvastatin, for example, can provide LDL-C lowering equivalent to that achieved with high-dose atorvastatin, but with better tolerability in some patients, and may be a useful adjunctive therapy in patients with type 2 diabetes who have demonstrated an inadequate response to statin treatment [31].

Fibrates are useful for lowering TG and non-HDL-C levels and increasing HDL-C, yet results from trials in patients with type 2 diabetes have been controversial [32]. In the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study in 9795 patients with type 2 diabetes, fenofibrate did not significantly affect the primary endpoint, coronary event rate, relative to placebo (11% reduction) [33]. Nevertheless, FIELD did show that combination therapy with a statin and fenofibrate is safe. Recent results from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study provided further insight into whether the combination of a statin and a fibrate is safe and provides CVD benefits beyond statin therapy alone. In this study in 5518 patients with type 2 diabetes, there was no difference between combination therapy with a statin and fibrate compared with statin therapy alone with respect to the primary outcome (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) [34]. Common adverse events associated with fibrates include gastrointestinal disturbance, rash, headache, pancreatitis, myalgia, and myotoxicity (in rare instances - and possibly more likely with gemfibrozil than with fenofibrate [35]). Adjuvant fibrate therapy is not recommended in patients with severe renal dysfunction, severe hepatic dysfunction, and preexisting gall bladder disease [24].

MATERIAL AND METHODS

In our study we have analysed 80 patients with DM type 2 in total from which 68 (27 male and 41 female) were with comorbidity (hyperlipidemia and obesity).

Patients with T2DM received treatment with metformin and glinides. Patients with T2DM and

comorbidity were additionally treated with statins and fibrates for hyprlipidemia.

We have analysed venous blood for all hunger conditions. The analysis were made by a device which is integrated automatic device that simultaneously can do the biochemical analysis, electrolytes and immunologic analysis. The device is consisted of 3 modules, biochemical which uses photometry, ISE module with multisensory technology and HM module which is heterogenic immunologic, respectively. The blood was collected in close system with 2 tubes. For serum we used a tube without anticoagulant (clot activator) in which we analysed Glucose, Cholsterol, Triglycerides, LDL, HDL. For blood we used tube with anticoagulant K_2EDTA where we measured the glicolysed Haemoglobin HbA1c.

The blood from the tube without anticoagulant was centrifuged 10-15 minutes with 3000 rotations in order to devide serum from the elements of the blood. The serum from supernatant was collected with automatic pipets (200-300μl) and put to the device for analysis.

The tube with K_2EDTA has been well mixed and put into cuvettes and analysed. We have measured te levels of Glucose, Cholsterol, Triglycerides, LDL, HDL. The parameters of all the patients were measured every 3 months for 1 year. The analysis were done in clinical hospital of Tetovo, Macedonia.

The referent values for Glucose and HbA1c were taken the values proposed from WHO (Gl=3.5-6.5 mmol/l, HbA1C %=4.4% -6.6 %).

RESULTS

The overall number of patients is 80 from which 48 are female and 32 male. The number of patients only with DM II is 12 and those having DM II plus hyperlipidemia, hypertension and obesity is 68. From this group 27 are male and 41 are female. The most affected age group was 51 – 60.

The test about age og the patients and level of lipids showed significance in male patients. Tgilycerids had a negtive correlation with $p<0.01$, while Hdl had positive corelation $p<0.05$ and Ldl had no significance. In female group the age and the level of lipids showed no significant correlation. When tested all togeather, there was no statistically significancebetween age nd level of lipids becouse the number of female patients was higher in this study, table 1.

Table1 . the corelation between the age and lipids in patients

Male patients	Hb A1c - M1	Hb A1c - M2	Hb A1c - M3	Hol esterol - M1	Hol esterol - M2	Hol esterol - M3	trigl iceride - M1	trigli cerid e - M2	trig lice rid e - M3	Hdl - M1	Hdl - M2	Hd l - M3	Ldl - M1	Ldl - M2	Ldl - M3
HbA1c - M1	1	,233	,331	-,041	-,051	-,017	,076	,008	,022	,075	-,004	,019	-,032	-,030	-,140
HbA1c - M2	,233	1	,830(**)	-,141	,016	,102	,267	,331	,354(*)	,232	-,245	-,184	,139	,021	-,188

HbA1c - M3	,331	,830(**)	1	-,053	-,015	-,014	,333	,245	,225	,288	-,130	-,100	,073	-,047	-,254
Holesterol - M1	-,041	-,141	-,053	1	,616(**)	,351(*)	,476(**)	,452(**)	,273	-,063	-,252	-,270	,348	,286	-,028
Holesterol - M2	-,051	,016	-,015	,616(**)	1	,748(**)	,321	,394(*)	,329	-,104	-,214	-,271	,389(*)	,370(*)	,039
Holesterol - M3	-,017	,102	-,014	,351(*)	,748(**)	1	,251	,397(*)	,471(**)	-,155	-,305	-,292	,280	,322	,141
trigliceride - M1	,076	,267	,333	,476(**)	,321	,251	1	,866(**)	,707(**)	-,074	-,328	-,313	,470(**)	,397(*)	,051
trigliceride - M2	,008	,331	,245	,452(**)	,394(*)	,397(*)	,866(**)	1	,847(**)	-,227	-,481(**)	-,360(*)	,555(**)	,509(**)	,107
trigliceride - M3	,022	,354(*)	,225	,273	,329	,471(**)	,707(**)	,847(**)	1	-,112	-,317	-,165	,366(*)	,370(*)	,115
Hdl - M1	,075	,232	,288	-,063	-,104	-,155	-,074	-,227	-,112	1	,381(*)	,423(*)	,028	,026	,100
Hdl - M2	-,004	-,245	-,130	-,252	-,214	-,305	-,328	-,481(**)	-,317	,381(*)	1	,686(**)	-,182	-,122	,153
Hdl - M3	,019	-,184	-,100	-,270	-,271	-,292	-,313	-,360(*)	-,165	,423(*)	,686(**)	1	-,237	-,140	,116
Ldl - M1	-,032	,139	,073	,348	,389(*)	,280	,470(**)	,555(**)	,366(*)	,028	-,182	-,237	1	,893(**)	,408(*)
Ldl - M2	-,030	,021	-,047	,286	,370(*)	,322	,397(*)	,509(**)	,370(*)	,026	-,122	-,140	,893(**)	1	,681(**)
Ldl - M3	-,140	-,188	-,254	-,028	,039	,141	,051	,107	,115	,100	,153	,116	,408(*)	,681(**)	1

Female patients	Hb A1c - M1	Hb A1c - M2	Hb A1c - M3	Holesterol - M1	Holesterol - M2	Holesterol - M3	trigliceride - M1	trigliceride - M2	trigliceride - M3	Hdl - M1	Hdl - M2	Hdl - M3	Ldl - M1	Ldl - M2	Ldl - M3
HbA1c - M1	1	,483(**)	,404(**)	-,040	-,014	-,107	,207	,213	,099	,000	,130	,114	,105	,135	,024
HbA1c - M2	,483(**)	1	,800(**)	-,161	-,157	-,222	,199	,232	,232	,131	,321(*)	,268	,414(**)	,322(*)	,217
HbA1c - M3	,404(**)	,800(**)	1	-,051	-,128	-,129	,152	,106	,104	,223	,394(**)	,317(*)	,318(*)	,274	,233
Holesterol -	-	-	-	1	,722	,543	,566	,462	,414	-	,009	,033	,176	,127	,121

M1	,040	,161	,051		(**)	(**)	(**)	(**)	(**)	,058					
Holesterol - M2	-,014	-,157	-,128	,722 (**)	1	,762 (**)	,395 (**)	,397 (**)	,421 (**)	-,187	,063	,010	,305 (*)	,297 (*)	,219
Holesterol - M3	-,107	-,222	-,129	,543 (**)	,762 (**)	1	,169	,212	,294 (*)	-,084	,093	,037	,097	,201	,199
trigliceride - M1	,207	,199	,152	,566 (**)	,395 (**)	,169	1	,897 (**)	,739 (**)	-,088	,141	,004	,211	,141	,172
trigliceride - M2	,213	,232	,106	,462 (**)	,397 (**)	,212	,897 (**)	1	,867 (**)	-,252	,176	,005	,173	,144	,222
trigliceride - M3	,099	,232	,104	,414 (**)	,421 (**)	,294 (*)	,739 (**)	,867 (**)	1	-,223	,221	,078	,175	,146	,189
Hdl - M1	,000	,131	,223	-,058	-,187	-,084	-,088	-,252	-,223	1	-,019	-,120	,282	,247	,146
Hdl - M2	,130	,321 (*)	,394 (**)	,009	,063	,093	,141	,176	,221	-,019	1	,677 (**)	,295 (*)	,353 (*)	,304 (*)
Hdl - M3	,114	,268	,317 (*)	,033	,010	,037	,004	,005	,078	-,120	,677 (**)	1	,195	,230	,251
Ldl - M1	,105	,414 (**)	,318 (*)	,176	,305 (*)	,097	,211	,173	,175	,282	,295 (*)	,195	1	,899 (**)	,644 (**)
Ldl - M2	,135	,322 (*)	,274	,127	,297 (*)	,201	,141	,144	,146	,247	,353 (*)	,230	,899 (**)	1	,762 (**)
Ldl - M3	,024	,217	,233	,121	,219	,199	,172	,222	,189	,146	,304 (*)	,251	,644 (**)	,762 (**)	1

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

In table 2 we have shown the corelation between the lipids and HbA1c. There was significant corelation between the levels of HbA1c at all 3 measurements, $p<0.01$.

Significant corelation between HbA1c at second measurment and triglycerids with 0.05 significance. The levels of triglycerides is getting lower at second and third measurment. There was a signifikant corelation between the levels of HbA1c and Ldl during the measurments as levels of Ldl drop, $p<0.05$.

Levels of cholesterol also dropped significantly during measurments, $p<0.01$. There was a significant corelation between levels of cholesterol and triglycerides during all three measurments, $p<0.01$. as cholsterol levels drop, triglycerides drop also.

Triglycerides aslo showel significant corelation at all three measurments, $p<0.01$, as well as with the levels of Ldl with $p<0.01$ for the first measurment and $p<0.05$ for the secon measurment.

The corelation between the levels of Hdl was significant also in second and third measurement at 0.01 level.

There was no sugnificance between the levels of Ldl at any measurment.

Table 2. the corelation between the lipids and HbA1c

	HbA1c - M1	HbA1c - M2	HbA1c - M3	Holesterol - M1	Holesterol - M2	Holesterol - M3	trigliceride - M1	trigliceride - M2	trigliceride - M3	Hdl - M1	Hdl - M2	Hdl - M3	Ldl - M1	Ldl - M2	Ldl - M3
HbA1c -	1	,370(*	,376(*	-,029	-,015	-,078	,167	,154	,086	,013	,089	,090	,061	,093	-,016

M1		*)	*)												
HbA1c - M2	,370(**)	1	,801(**)	-,170	-,104	-,105	,220	,263(*)	,252(*)	,150	,069	,065	,284(*)	,193	,050
HbA1c - M3	,376(**)	,801(**)	1	-,062	-,100	-,098	,214	,152	,133	,233(*)	,202	,167	,222(*)	,166	,073
Holesterol - M1	-,029	-,170	-,062	1	,699(**)	,500(**)	,527(**)	,455(**)	,391(**)	-,057	-,072	-,044	,218	,170	,079
Holesterol - M2	-,015	-,104	-,100	,699(**)	1	,762(**)	,370(**)	,399(**)	,404(**)	-,164	-,037	-,077	,327(**)	,319(**)	,161
Holesterol - M3	-,078	-,105	-,098	,500(**)	,762(**)	1	,202	,282(*)	,360(**)	-,097	-,050	-,068	,161	,240(*)	,180
trigliceride - M1	,167	,220	,214	,527(**)	,370(**)	,202	1	,885(**)	,723(**)	-,081	-,049	-,116	,320(**)	,235(*)	,127
trigliceride - M2	,154	,263(*)	,152	,455(**)	,399(**)	,282(*)	,885(**)	1	,855(**)	-,235(*)	-,089	-,132	,333(**)	,277(*)	,180
trigliceride - M3	,086	,252(*)	,133	,391(**)	,404(**)	,360(**)	,723(**)	,855(**)	1	-,192	,027	,002	,240(*)	,218	,165
Hdl - M1	,013	,150	,233(*)	-,057	-,164	-,097	-,081	-,235(*)	-,192	1	,084	,017	,199	,191	,133
Hdl - M2	,089	,069	,202	-,072	-,037	-,050	-,049	-,089	,027	,084	1	,678(**)	,092	,178	,248(*)
Hdl - M3	,090	,065	,167	-,044	-,077	-,068	-,116	-,132	,002	,017	,678(**)	1	,017	,100	,203
Ldl - M1	,061	,284(*)	,222(*)	,218	,327(**)	,161	,320(**)	,333(**)	,240(*)	,199	,092	,017	1	,889(**)	,548(**)
Ldl - M2	,093	,193	,166	,170	,319(**)	,240(*)	,235(*)	,277(*)	,218	,191	,178	,100	,889(**)	1	,735(**)
Ldl - M3	-,016	,050	,073	,079	,161	,180	,127	,180	,165	,133	,248(*)	,203	,548(**)	,735(**)	1

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

In table 3 we have the data of the lipids of patients with T2DM compared to patients with T2DM plus comorbidity. The t – test showes no significance in ean values of cholesterol, triglycerides, Hdl nd Ldl levels among 2 groups. Here the number of patients with comorbidity was reduced becouse the number of patients only with diabetes was 12.

Table 3. corelation of mean values of lipids between two groups (T2DM -1 only and T2DM + comorbidity - 2)

	PATIENTS.	N	Mean	Std. Deviation	Std. Error Mean
cholesterol - M1	1,00 - COMORBID	15	5,6600	,59976	,15486
	2,00 – T2DM ONLY	12	5,8067	,35607	,10279

cholesterol - M2	1,00 - COMORBID	15	5,3933	,66383	,17140
	2,00 T2DM ONLY	12	6,0750	,63550	,18345
cholesterol - M3	1,00 - COMORBID	15	4,8600	,56795	,14665
	2,00 – T2DM ONLY	12	5,9583	,77631	,22410
triglyceride - M1	1,00 - COMORBID	15	2,0707	,88874	,22947
	2,00 – T2DM ONLY	12	2,2725	,87897	,25374
triglyceride - M2	1,00 - COMORBID	15	1,9073	,71559	,18476
	2,00 T2DM ONLY	12	2,0700	,86109	,24857
triglyceride - M3	1,00 - COMORBID	15	1,7233	,60935	,15733
	2,00 – T2DM ONLY	12	1,9200	,63883	,18442
Hdl - M1	1,00 - COMORBID	15	1,1260	,23068	,05956
	2,00 T2DM ONLY	12	1,2217	,38984	,11254
Hdl - M2	1,00 - COMORBID	15	1,2607	,31782	,08206
	2,00 T2DM ONLY	12	1,2442	,40804	,11779
Hdl - M3	1,00 - COMORBID	15	1,2673	,31217	,08060
	2,00 – T2DM ONLY	12	1,1242	,34849	,10060
Ldl - M1	1,00 - COMORBID	15	2,8447	1,03567	,26741
	2,00 – T2DM ONLY	12	2,2300	1,20030	,34650
Ldl - M2	1,00 - COMORBID	15	3,0900	,77556	,20025
	2,00 – T2DM ONLY	12	3,0583	,81403	,23499
Ldl - M3	1,00 - COMORBID	15	3,4200	,59426	,15344
	2,00 – T2DM ONLY	12	3,6167	,36639	,10577

Levenes test for equality of variances of two groups also showed no significance between the levels of cholesterol, triglycerides, Hdl and Ldl. Table 4.

TABLE 4. corelation of mean values of lipids between two groups (T2DM -1 only and T2DM + comorbidity - 2) with Levene`s test for Equality of Variances

	Levene's Test for Equality of Variances		t-test for Equality of Means						
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
Holesterol - M1	5,306	,030	-,747	25	,462	-,1467	,19643	-,55122	,25788
Holesterol - M2	,044	,836	-2,701	25	,012	-,6817	,25233	-1,20135	-,16198
Holesterol - M3	2,509	,126	-4,247	25	,000	-1,0983	,25859	-1,63092	-,56575
trigliceride - M1	,010	,920	-,589	25	,561	-,2018	,34255	-,90732	,50366
trigliceride - M2	,004	,947	-,536	25	,596	-,1627	,30323	-,78719	,46185
trigliceride - M3	,083	,775	-,816	25	,422	-,1967	,24109	-,69320	,29987
Hdl - M1	7,224	,013	-,794	25	,434	-,0957	,12042	-,34367	,15234
Hdl - M2	1,197	,284	,118	25	,907	,0165	,13955	-,27090	,30390
Hdl - M3	,055	,817	1,125	25	,271	,1432	,12728	-,11898	,40531
Ldl - M1	2,296	,142	1,428	25	,166	,6147	,43033	-,27162	1,50095
Ldl - M2	1,036	,318	,103	25	,919	,0317	,30702	-,60065	,66399
Ldl - M3	1,723	,201	-1,002	25	,326	-,1967	,19628	-,60090	,20757

DISCUSSION

Type 2 diabetes is associated with a characteristic atherogenic lipid pattern of elevated serum TGs, low serum HDL-C levels, and a preponderance of small, dense LDL particles. Disturbance of lipid metabolism linked to insulin resistance may be the primary event in the development of type 2 diabetes. The majority of adults in the United States with type 2 diabetes do not have optimal lipid profiles based on national guidelines. In order to reduce the risk of CVD in patients with type 2 diabetes, physicians must initiate early and effective lipid-lowering therapy. Although the first priority of treatment is to lower LDL-C in patients with type 2 diabetes, the atherogenic pattern of dyslipidemia associated with type 2 diabetes may require an advanced treatment approach that ultimately aims for full normalization of the lipid profile to decrease cardiovascular risk. Data from combined prevalence studies suggest that potentially all patients with type 2 diabetes may have an abnormal lipid profile. Despite aggressive lipid-lowering therapy, many patients with type 2 diabetes do not achieve the recommended lipid levels to reduce their CVD risk sufficiently.

Adjuvant use of a bile acid sequestrant such as colesevelam, having the dual effect of improving both glycemic control and atherogenic profile in patients with type 2 diabetes, may help improve the overall management of type 2 diabetes in some patients.

The objective of managing the patient with diabetes is to alleviate their symptoms and improve their quality of life. Treatment should not only address glycaemic control in order to reduce microvascular risk, but also focus on major risk factors for macrovascular disease including dyslipidaemia, hypertension and smoking. For the patient with diabetes, LDL-cholesterol is the major therapeutic target, with a secondary target of non-HDLcholesterol for some patients. For the majority of patients, treatment with a statin is the preferred lipidlowering therapy.Dyslipidemia contributes to the increased risk of cardiovascular disease in diabetes mellitus

The efficacy and safety of combination therapies has been the subject of several trials. The Diabetes and Combined Lipid Therapy Regimen (DIACOR) study[12] found that combination therapy with simvastatin plus fenofibrate had a superior ability than monotherapy with either drug to improve a variety of cardiovascular risk factors, including reducing levels of small dense LDL cholesterol (-0.88 mmol/l) and VLDL cholesterol (-0.259 mmol/l), and increasing HDL type 3 level (+0.06 mmol/l). The HDL-Atherosclerosis Treatment Study[13] showed that combination therapy with simvastatin plus nicotinic acid (mean daily doses 13.0 mg and 2.4 g, respectively) stops angiographically visible progression of atherosclerosis and reduces major clinical events by 60% in patients with coronary artery diseases who have low HDL cholesterol levels. Glycemic control among patients with diabetes mellitus declined mildly in the simvastatin plus nicotinic acid group, but returned to pretreatment levels after 8 months of treatment.

The efficacy and safety of two regimens that used a combination of extended-release nicotinic acid (1 g per day and 2 g per day) and simvastatin (20 mg per day in both regimens) were compared with simvastatin monotherapy (20 mg per day) for 24 weeks in 319 patients who had a high risk of CHD and predominantly mixed dyslipidemia [14]. The combination therapy resulted in greater improvements in HDL cholesterol, triglycerides, ApoB and lipoprotein (a) levels, and in the total cholesterol: HDL cholesterol ratio compared with those achieved by monotherapy. Similar results were observed in the OCEANS study (Open-Label Evaluation of the Safety and Efficacy of a Combination of Niacin ER and Simvastatin in Patients with Dyslipidemia) [15] in which the safety and efficacy of a combination of extended-release nicotinic acid and simvastatin was evaluated over 52 weeks in 520 patients with mixed dyslipidemia. Future studies with clinical-outcome end points should be carried out to determine the role of this combination therapy in the management of patients with T2DM.

The use of drug combinations as first-line therapy might become more popular with the advent of fixed-dose combination pills; however, clinical experience with this approach is limited. The combination of a statin and a fibrate or nicotinic acid increases the risk of rhabdomyolysis, and, therefore, these agents should be used at reduced doses and in patients who are at the least risk of adverse drug interactions. If the dose of nicotinic acid is limited to less than 2 g per day, its effect on insulin resistance is modest [17]. Nevertheless, in some patients with impaired glucose tolerance, initiation of nicotinic-acid treatment might precipitate overt diabetes mellitus. In addition, a significant number of patients (up to 30%) might not tolerate the adverse effects associated with this therapy. Extended-release nicotinic acid administered once daily seems to be better tolerated than short-acting nicotinic acid [17]. .Although some insulin sensitizers, such as pioglitazone, have substantial favorable effects on serum triglyceride and HDL cholesterol levels (independent of their effects on blood-glucose control), these drugs are not approved for use in the treatment of dyslipidemia. [16].

The characteristic features of diabetic dyslipidemia are high plasma triglyceride concentration, low HDL cholesterol concentration and increased concentration of small dense LDL cholesterol

The most likely cause of diabetic dyslipidemia is the increased free fatty-acid flux, secondary to insulin resistance. Although drug therapy for dyslipidemias must be individualized, most people with diabetes mellitus are candidates for statin therapy and often need to be treated with multiple agents to achieve therapeutic goals.

CONCLUSION

The results from our statistical analysis correspond with the values of many previous studies. There was a significant corelation between HbA1c and triglycerides, between cholesterol and triglycerides ans between triglycerides and Ldl.

There was no significnce between T2DM only and T2DM with comorbidity group becouse this was an observational study over 12 months period where all the patiends had before started with appropriate therapy.

We can conclude that if the therapy is correct and patients comply with lifestyle chnges also, there are no significance in levels of HbA1c, glucose and lipids in patiends with T2DM and T2DM with comorbidity.

References

[1]. Taskinen MR (2003) Diabetic dyslipidaemia: from basic research to clinical practice.*Diabetologia* **46**: 733–749

[2]. Krauss RM and Siri PW (2004) Dyslipidemia in type 2 diabetes. *Med Clin North Am***88**: 897–909

[3]. Del Pilar Solano M and Goldberg RB (2005) Management of diabetic dyslipidemia.*Endocrinol Metab Clin North. Am* **34**: 1–25

[4]. Chahil TJ and Ginsberg HN (2006) Diabetic dyslipidemia. *Endocrinol Metab Clin North Am* **35**: 491–510

[5]. Frayn KN (2001) Adipose tissue and the insulin resistance syndrome. *Proc Nutr Soc***60**: 375–380

[6]. Adiels M *et al*. (2007) Acute suppression of VLDL1 secretion rate by insulin is associated with hepatic fat content and insulin resistance. *Diabetologia* **50**: 2356–2365

[7]. Expert panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001) Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* **285**: 2486–2497

[8]. Hachem SB and Mooradian AD (2006) Familial dyslipidaemias: an overview of genetics, pathophysiology and management. *Drugs* **66**: 1949–1969

[9]. Bantle JP *et al*. (2008) Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. *Diabetes Care* **31** (Suppl 1): S61–S78

[10]. Haffner SM and American Diabetes Association (2004) Dyslipidemia management in adults with diabetes. *Diabetes Care* **27** (Suppl 1): S68–S71

[11]. Taskinen MR (2002) Controlling lipid levels in diabetes. *Acta Diabetol* **39** (Suppl 2): S29–S3

[12]. May HT *et al*. (2008) Comparison of effects of simvastatin alone versus fenofibrate alone versus simvastatin plus fenofibrate on lipoprotein subparticle profiles in diabetic patients with mixed dyslipidemia (from the Diabetes and Combined Lipid Therapy Regimen study). *Am J Cardiol* **101**: 486–489

[13]. Zhao XQ *et al*. (2004) Safety and tolerability of simvastatin plus niacin in patients with coronary artery disease and low high-density lipoprotein cholesterol (The HDL Atherosclerosis Treatment Study). *Am J Cardiol* **93**: 307–312

[14]. Ballantyne CM *et al*. (2008) Comparison of the safety and efficacy of a combination tablet of niacin extended release and simvastatin vs simvastatin monotherapy in patients with increased non-HDL cholesterol (from the SEACOAST I study). *Am J Cardiol* **101**: 1428–1436 |

[15]. Karas RH *et al*. (2008) Long-term safety and efficacy of a combination of niacin extended release and simvastatin in patients with dyslipidemia: the OCEANS study.*Am J Cardiovasc Drugs* **8**: 69–81

[16]. Mooradian AD *et al*. (2002) The role of thiazolidenediones in the treatment of type 2 diabetes. *Treatments in Endocrinology* **1**: 13–20

[17]. Shepherd J *et al*. (2005) Nicotinic acid in the management of dyslipidaemia associated with diabetes and metabolic syndrome: a position paper developed by a European Consensus Panel. *Curr Med Res Opin* **21**: 665–682

[18]. Goff DC Jr, Gerstein HC, Ginsberg HN, Cushman WC, Margolis KL, Byington RP, Buse JB, Genuth S, Probstfield JL, Simons-Morton DG. Prevention of cardiovascular disease in persons with type 2 diabetes mellitus: current knowledge and rationale for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol. 2007;99:4i–20i.

[19]. Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, Witztum JL. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. Diabetes Care. 2008;31:811–822. doi: 10.2337/dc08-9018.

[20]. American Diabetes Association. Standards of medical care in diabetes-2009.Diabetes Care. 2009;32(Suppl 1):S13–S61. doi: 10.2337/dc09-S013.

[21]. Sniderman AD, Furberg CD, Keech A, Roeters van Lennep JE, Frohlich J, Jungner I, Walldius G. Apolipoproteins versus lipids as indices of coronary risk and as targets for statin treatment. Lancet. 2003;361:777–780. doi: 10.1016/S0140-6736(03)12663-3.

[22]. Stein EA, Sniderman A, Laskarzewski P. Assessment of reaching goal in patients with combined hyperlipidemia: low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, or apolipoprotein B. Am J Cardiol. 2005;96:36K–43K. doi: 10.1016/j.amjcard.2005.08.006. discussion 34K-35K.

[23]. Ballantyne CM, Bertolami M, Hernandez Garcia HR, Nul D, Stein EA, Theroux P, Weiss R, Cain VA, Raichlen JS. Achieving LDL cholesterol, non-HDL cholesterol, and apolipoprotein B target levels in high-risk patients: Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapY (MERCURY) II. Am Heart J. 2006;151(975):e971–e979.

[24]. Moon YS, Kashyap ML. Pharmacologic treatment of type 2 diabetic dyslipidemia. Pharmacotherapy. 2004;24:1692–1713. doi: 10.1592/phco.24.17.1692.52340.

[25]. High-dose atorvastatin therapy achieves 25% reduction in CV events in TNT substudy of diabetic patients. Cardiovasc J S Afr. 2006;17:206–207.

[26]. Lawrence JM, Reid J, Taylor GJ, Stirling C, Reckless JP. The effect of high dose atorvastatin therapy on lipids and lipoprotein subfractions in overweight patients with type 2 diabetes.Atherosclerosis. 2004;174:141–149. doi: 10.1016/j.atherosclerosis.2004.01.016.

[27]. Nesto RW. Beyond low-density lipoprotein: addressing the atherogenic lipid triad in type 2 diabetes mellitus and the metabolic syndrome. Am J Cardiovasc Drugs. 2005;5:379–387. doi: 10.2165/00129784-200505060-00005. [PubMed] [Cross Ref]

[28]. Lauring B, Dishy V, Luo WL, Laterza O, Patterson J, Cote J, Chao A, Larson P, Gutierrez M, Wagner JA, Lai E. Laropiprant in combination with extended-release niacin does not alter urine 11-dehydrothromboxane B2, a marker of in vivo platelet function, in healthy, hypercholesterolemic, and diabetic subjects. J Clin Pharmacol. 2009;49:1426–1435

[29]. Shah S, Ceska R, Gil-Extremera B, Paolini JF, Giezek H, Vandormael K, Mao A, McCrary Sisk C, Maccubbin D. Efficacy and safety of extended-release niacin/laropiprant plus statin vs. doubling the dose of statin in patients with primary hypercholesterolaemia or mixed dyslipidaemia. Int J Clin Pract. 2010;64:727–738.

[30]. Gleim G, Liu N, Thompson-Bell S. Lipid-altering efficacy and safety profile of co-administered extended release niacin/laropiprant and simvastatin in patients with dyslipidemia [abstract 683] Circulation. 2007;116:127.

[31]. Ballantyne CM, Houri J, Notarbartolo A, Melani L, Lipka LJ, Suresh R, Sun S, LeBeaut AP, Sager PT, Veltri EP. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation. 2003;107:2409–2415.

[32]. Colhoun H. After FIELD: should fibrates be used to prevent cardiovascular disease in diabetes? Lancet. 2005;366:1829–1831. doi: 10.1016/S0140-6736(05)67668-4.

[33]. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesaniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005;366:1849–1861. doi: 10.1016/S0140-6736(05)67667-2.

[34]. Ginsberg HN, Elam MB, Lovato LC, Crouse JR, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, Goff DC Jr, Cushman WC, Simons-Morton DG, Byington RP. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362:1563–1574.

[35]. Prueksaritanont T, Tang C, Qiu Y, Mu L, Subramanian R, Lin JH. Effects of fibrates on metabolism of statins in human hepatocytes.Drug Metab Dispos. 2002;30:1280–1287.

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