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The Effect of Treatment Types on Plasma Levels of Lipoproteins, Apolipoproteins and LCAT in Type II Diabetes Mellitus

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Abstract: In this studry 32 hyperglycemic patients with type II DM were treated with diet (7 patients), with gliclazide, an oral antidiabetic agent (10 patients), or with insulin (15 patients). The levels of liporoteins, apolipoprotein A and B and LCAT enzyme are measured before the therapy and 3 weeks after the achievement of glycemic control. Treatment types are compared with each other and with control group (10 normal persons) triglyseride (TG) and VLDL levels which were found to be high in all of the patients decreased in all groups to levels similar to control group. TC (total cholesterol), LDL, TC/HDL, LDL/HDL levels found high before treatment in the OAD (oral antidiabetic) group ($p<0.05$) were similar to control values after treatment in the OAD levels of all groups before the treatment were similar to control group, but afterwards it was significantly high in the OAD group. Apo B level decreased after the therapy only in the OAD group ($p<0.05$).

The higher levels of Apo B/Apo A in the OAD and insulin group before the treatment declined in both groups with the therapy and were indifferent from control group in the OAD group. LCAT levels didn't change in any of the conditions. Between treatment groups there was no difference in lipoprotein, Apo A, Apo B and LCAT levels before and after the treatment. There was a positive correlation between fasting blood glucose level (FBGL) and TG and Apo B/Apo A, insulin level and Apo B and Apo B/Apo A, TG and T.C, Apo B and LDL/HDL, LDL and Apo B, HDL and Apo A, but a negative correlation between the activity and insulin level and macrovascular complications of the disease, HDL and proteinuria.

In conclusion, in patients with uncontrolled type II DM lipid metabolism in altered and with achievement of metabolic control these alterations regress independent of treatment type and the most beneficial alteration has been observed in the OAD group.

Key Words: Diabetes Mellitus, Plasma Lipoproteins, Apolipoproteins, LCAT.

Introduction

One of the dominant characteristics of diabetes mellitus (DM) is the change in lipoprotein metabolism. In cases with type II DM, the changes in lipoprotein metabolism play a role in the development of macrovascular complications and they are important factors leading to an increase in mortality and morbidity. In type II DM it has been reported that the peripheric vascular disease in 5 fold higher and the mortality due to atherosclerotic heart disease is 2-3 fold higher than the normal population (1). Therefore, in the treatment of DM, along the glycemic control the effects of treatment type on lipoprotein metabolism play an important role in the development of macrovascular complications.

Hence in our study in cases of type II DM with non regulated glycemic control we intended to study the changes in lipoprotein metabolism and the effects of glycemic control and treatment type on the changes in lipoprotein metabolism after the glycemia has been regulated.

Material and Method

The study population consisted of 32 DM patients, partly new diagnosed and partly from the patients who were followed up in the department of endocrinology and a control group of ten healhy volunteers. In the selection of the patients following criteria were taken into account:

1. Fasting blood glucose level (FBGL) 140 mg/dl, postprandial glucose level (PGL) 200 mg/dl and above.

2. HbAıc above 6%

3. The absence of any disease apart from DM which can influence lipid levels.

4. The absense of any treatment which can influence lipid levels.

5. The absense of ketoacidosis and chronic alcoholism.

6. The treatment type should be applied for the first time.

The patients were starified into 3 groups according to treatment:

Diet group: consisting of 7 patients, 4 men and 3 women, aged between 42-65 (mean 51.4±3.4) receiving only diet therapy.

Oral antidiabetic group (OAD): consisting of 10 patients, 5 men and 5 women, aged between 41-66 (mean:55.2±2.8) and receiving in addition to diet 80-320 mg/day gliclazide according to fasting blood glucose level.

Insulin group: consisting of 15 patiens, 6 mean and 9 women, aged between 30-67 (mean:58±3) receiving in addition to diet therapy conventional insulin therapy in a dose of 35-90 U/day

All of the patients were hospitalized and in addition to detailed history, physical examination and laboratory investigations, examinations to find out DM complications were made. The patients were charged out from the hospital after the regulation of blood glucose concentration and were called for an outpatient visit after 3 weeks. In this period they were warned not to change their activities. At the next visit all of basic parameters are controlled again.

Standart body weight of the cases are measured according to Broca Index and they received 20-40 kcal/kg diabetic diet according to their activities (15 % of total calories consist of protein, 35 % of fat and 50 % of carbohydrates). Body Mass Index (BMI) of the patients before and after the treatment is calculated with the formula:

BMI=Body weigt (kg)/Height^2(m^2)

The patients were stratified into 3 groups according to their activities. The patients who can manage only their own activities formed the 1st group, physically active ones or the patients maintaining regular exercises included in the 3rd group and the patients with an activity between these two groups were in the second group. For the detection of macrovascular complications the presence of angina pectoris, claudicatio intermittens and past myocardial infarction has been investigated and physical examination and ECG recording were done.

The patients without macrovascular complications, with ischemic heart disease and with previous mycocardial infarction attached were classified in to grups 0,1,2 respectively.

Before the treatment and 3 week after the control of glycemia blood specimens were taken after a 12 hour fast and fasting blood glucose level, one-hour postprandial glucose, insulin, HbA_{1c}, total cholesterol (TC), HDL-cholesterol and trigliserid (TG) levels were measured. An aliquot of serum was taken from blood specimens and refrigerated at -35°C in a deep freeze for investigations of Apo A, Apo B and lecithin cholesterol acyltranferase (LCAT) enzyme. HbA_{1c} is measured with microcolon chromatography method (N:3 -6 %). Fasting insulin levels (FIL) were measured by radioimmunoassay (RIA) (N:0-30 uIU/ml). Protein was measured in 24 hour urine sample with the modified Purdy method quantitatively and creatinine was determined by alkaline picrat method. Fasting blood glucose level (N:70-110 mg/dl), TC (N:112-253 mg/dl), TG (N:25-170 mg/dl) levels were determined with a Dacos autoanalyser.

LDL and VLDL levels were calculated by Friedwald formula. Apo A and Apo B levels were measured immunoturbometrically. LCAT enzyme was determined by the calorimetric method of Nagasaki T and Akanuma Y. except two patients in insulin group (2).

For the statistical evaluation of the data, t-test, x^2 test, Pearson and Spearman's correlation analysis were used.

Results

The characteristics of control group and treatment groups are given in Table 1. Laboratory findings and statistical comparisons of all groups and of control group are summarized in Table 2 and 3.

1. The fasting blood glucose levels decreased in diet group ($p<0.01$), in insulin and OAD group ($p<0.001$) statistically significantly after therapy.

2. In our cases prominent hyperinsulinemia has not been detected. Only in the OAD group a significant increase in comparison to control group before the therapy is detected ($p<0.05$), but after the therapy it became similar to levels in control group.

3. In all of the treatment groups the most prominent change was observed in the levels of TG and VLDL before the treatment. TG and VLDL levels which were

Table 1. The characterictics of control group and treatment group

		CONTROL GROUP n=10	DIET GROUP n=7	OAD GROUP n=10	INSULIN GROUP n=15
AGE (yrs)		53.100 ± 2.69	51.429 ± 1.85	55.200 ± 2.79	58.067 ± 3.07
WEIGHT (kg)		69.600 ± 2.15	88.857 ± 5.18	74.650 ± 3.71	66.467 ± 3.00
BMI (kg/m2)		27.609 ± 0.45	32.964 ± 1.55	29.058 ± 1.08	26.041 ± 1.55
HbAlc (%)		3.920 ± 0.39	7.911 ± 0.75	10.334 ± 1.12	10.467 ± 0.77
DURATION OF DM (yrs)			1.543 ± 1.00	4.250 ± 1.66	9.433 ± 2.31
PBGL (mg/dl)		80.400 ± 1.42	172.571 ± 14.12	274.800 ± 24.45	331.000 ± 29.57
INSULIN (uIU/ml)		22.200 ± 1.00	22.857 ± 2.81	29.800 ± 2.43	28.133 ± 5.36
ACTIVITY	1	2 (20 %)	2 (28.6 %)	4 (40 %)	9 (69 %)
	2	7 (70 %)	4 (57.1 %)	6 (60 %)	4 (26.7 %)
	3	1 (10 %)	1 (14.3 %)	-	2 (13.3 %)
MACROVASCULER	0	-	6 (85.7 %)	7 (70 %)	8 (53.3 %)
COMPLICATIONS	1	-	1 (14.2 %)	3 (30 %)	5 (33.3 %)
	2	-	-	-	2 (13.3 %)

Table 2. Before (BT) and after treatment (AT), all of the therapy groups statistical findings.

	OAD BT-AT	BT OAD-CONTROL	AT OAD-CONTROL	INSULIN BT-AT	BT INSULIN-CONTROL	AT INSULIN-CONTROL	DIET BT-AT	BT DIET-CONTROL	AT DIET-CONTROL
Hba1c (%)		**			***			*	
AGE (yrs)		ns			ns			ns	
WEIGHT (kg)	*	ns	ns	ns	ns	ns	*	**	**
BMI (kg/m2)	*	ns	ns	ns	ns	ns	**	**	**
FIL (uIU/ml)	ns	*	ns	*	ns	ns	ns	ns	ns
FBGL (mg/dl)	***	***	***	***	***	**	***	***	***
TG 'mg/dl)	ns	*	ns	***	*	ns	**	*	ns
T.C (mg/dl)	ns	**	*	ns	ns	ns	ns	ns	ns
HDL (mg/dl)	*	ns	*	ns	ns	ns	ns	ns	ns
VLDL (mg/dl)	ns	*	ns	***	*	ns	**	*	ns
LDL (mg/dl)	ns	*	ns	ns	ns	ns	ns	ns	ns
T.C / HDL	ns	*	ns	ns	ns	ns	ns	ns	ns
ldl / HDL	ns	*	ns	ns	ns	ns	ns	ns	ns
APO A (mg/dl)	ns	ns	ns	ns	ns	ns	ns	ns	ns
APO B (mg/dl)	*	*	ns	ns	ns	ns	ns	ns	ns
APO B / APO A	*	**	ns	ns	**	*	ns	ns	ns
LCAT (nmol/ml/hrs)	ns	ns	ns	ns	ns	ns	ns	ns	ns

*p<0.05 **p<0.01 ***p<0.001

significantly higher than control group (p<0.05) decreased to levels similar in the control group after the correction of the glycemia, this decline was most prominent in insulin group (p<0.001).

4. Before the treatment T.C, LDL, LDL/HDL, TC/HDL levels were higher than the control group only in the OAD group (p<0.05), but after the treatment all of them decreased. LDL, LDL/HDL, TC/HDL levels were indifferent from control group.

5. HDL level wasn't low in any of the groups and only in OAD group it did increase after the treatment (p<0.05).

Table 3. Before (BT) and after treatment (AT), all of the therapy groups and control group's labotarory findings.

	BT DIET GROUP n=7	AT DIET GROUP n=7	BT OAD GROUP n=10	AT OAD GROUP n=10	BT INSULIN GROUP n=15	AT INSULIN GROUP n=15	CONTROL GROUP
HbA1c (%)	7.911±0.75		10.334±1.12		10.467±0.77		3.920±0.39
AGE (yrs)	51.429±3.44		55.200±2.79		58.067±3.07		53.100±2.69
WEIGHT (kg)	88.857±5.18	87.000±4.81	74.650±3.71	73.750±3.57	66.467±3.00	66.300±2.83	69.600±2.15
BMI (kg/m2)	32.464±1.54	32.303±1.52	29.058±1.08	28.700±1.03	26.040±1.55	25.959±1.46	27.609±0.45
FIL (uIU/ml)	22.857±2.81	22.857±2.34	29.800±2.43	23.200±2.32	28.133±5.36	37.467±6.02	22.200±1.10
FBGL (mg/dl)	172.571±14.12	115.571±9.35	247.800±24.45	113.200±6.71	331.000±29.57	117.267±5.31	80.400±1.42
PGL (mg/dl)	267.429±31.37	181.286±10.69	323.500±29.85	168.000±8.22	412.000±34.39	162.000±7.07	
TG (mg/dl)	181.714±27.37	141.143±20.75	180.100±20.01	150.700±10.18	193.000±21.93	146.600±16.88	112.600±16.77
TC (mg/dl)	219.429±13.83	216.000±13.53	240.800±14.30	231.100±12.88	227.267±19.38	221.533±15.26	183.600±13.13
HDL (mg/dl)	49.286±4.48	44.429±3.03	45.200±3.35	52.500±3.07	41.400±3.31	46.133±4.18	44.100±1.81
VLDL (mg/dl)	36.343±5.47	28.229±4.15	37.000±4.85	30.140±2.03	38.600±4.49	29.720±3.38	22.520±3.35
LDL (mg/dl)	133.800±12.63	143.314±12.20	158.600±10.99	148.460±11.82	144.520±15.99	142.827±13.38	116.980±11.63
T.C/HDL	4.597±0.44	4.971±0.41	5.514±0.44	4.470±0.40	5.662±0.56	5.058±0.54	4.243±0.35
LDL/HDL	2.839±0.36	3.296±0.35	3.662±0.33	2.971±0.37	3.634±0.46	3.345±0.46	2.712±0.28
Apo A (mg/dl)	115.329±8.19	110.443±7.04	115.750±4.27	107.480±4.89	101.040±8.85	96.440±6.99	107.950±7.17
Apo B (mg/dl)	132.571±7.31	130.286±10.89	154.500±12.33	130.500±11.61	122.420±11.37	118.860±9.96	108.160±12.95
Apo B/Apo A	1.176±0,09	1.183±0.05	1.345±0.09	1.204±0.08	1.445±0.12	1.262±0.09	0.981±0.07
LCAT (nmol/ml/hrs)	44.970±17.00	44.10±8.14	37.719±3.63	43.513±1.72	43.189±6.53	48.902±6.10	39.579±6.50

6. Apo A level didn't show a significant change in any of the groups whereas Apo B level was detected significantly high in OAD group before the treatment ($p<0.05$), but after the treatment in became similar to levels in control group.

7. Apo B/Apo A level was found higher than control group in OAD and insulin groups before the treatment ($p<0.01$), after the treatment a decrease was observed in both groups, with a more prominent pattern in the OAD group.

8. The achievement of glycemic control with gliclazide and insulin therapy resulted in a statistically insignificant increase in the activity of LCAT.

9. The comparison of treatment groups with each other revealed no statistical change in lipoprotein levels before and after the therapy.

10. Thereas a positive correlation between fasting insulin level and Apo A and Apo A/Apo B ($p<0.05$) and a negative correlation between fasting insulin level and activity ($p<0.001$).

11. A positive correlation is detected between fasting blood glucose level and TG and Apo A/Apo B.

12. Thereas a positive correlation between TC value and TC, TC/HDL, LDL/HDL and Apo B value ($p<0.01$) an a negative correlation between TG and activity ($p<0.001$).

13. Between LDL and VLDL levels and Apo B, a positive correlation is detected ($p<0.001$), HDL level is in positive correlation with Apo A ($p<0.01$) and in negative correlation with proteinuria ($p<0.05$).

14. Macrovascular disease symptoms are negatively correlated with activity ($p<0.01$).

15. A correlation between blood lipids and the duration of diabetes, HbA_{1c} retinopathy and neuropathy symptoms could not be defined.

Discussion

In the decision of therapy plan for diabetic patients the effect of therapy on chronic complications should be considered. In diabetes mellitus blood lipid levels are under the influence of factors like age, physical activity, body weight, BMI, the duration of diabetes, the level of glycemic control, complications specific for diabetes and facting insulin level (1, 3, 4).

In our study, age and level of physical activity was similar in all of the treatment groups and in comparison of each group with control group.

In diet group where the body weight was the highest, we detected a positive correlation between body weight and TG and VLDL and in insulin group between BMI and fasting insulin level. This correlation is compatible with previous studies (5, 6).

Our findings support studies reporting that lipid levels are independent of the duration of the diabetes (7, 8). Age in as in comparable studies in our study a positive correlation between fasting blood glucose level and TG, VLDL, Apo A was detected, but an association with HDL wasn't found (8-12).

Thereas a negative correlation between HDL level and only proteinuria among the diabetic complications. In the literature this correlation is explained by the urinary loss of HDL and ApoA (13). Our finding suggests that macrovascular complication risk is increased in patients with proteinuria.

Fasting insulin level in accepted as a sensitive criterion for the development of atherosclerosis (14). In our study we detected a significant association between insulin level and ApoB and ApoB/ApoA values as also being remarkable indicators of the development of atherosclerosis.

In our study before therapy, insulin level is high only in OAD group in comparison to control group, but declined after therapy to levels indiferent from control group. It has been reported that sulphonylurea drugs increase the number of insulin receptors and the sensitivity of the tissue to insulin, that they do not cause hyperinsulinaemia during therapy restoring phase 1 insulin release which is defective in type II DM and by this way the patients are protected from the anabolic effect of the insulin (15).

In accordance with these studies, in our patients in OAD group body weight has declined significantly after therapy.

The most frequent finding in lipid metabolism in type II DM is the increase in TG and VLDL levels (1, 3). We found TG and VLDL levels high in all of the treatment groups before glycemic control. In our study too, as in similar studies, in patients receiving diet (16), sulphonylurea (17) and insulin most prominently (18), TG and VLDL levels declined after achievement of glycemic control. The relation of macrovascular complications and TG found elevated in DM is still controversial. In some studies the correlation of TG and atherosclerosis has been shown (19). Some authors say that the low HDL level cause this association (19, 20). But in other studies it was proposed that the increase of TG and cholesterol content of VLDL result in a destruction of its structurend that this abnormal VLDL forms a risk of atherosclerosis independent of HDL level by stimulating cholesterol ester synthesis in macrophages, precursors of foamy cells (9, 21). As in the study of Noyah Al Muhtaseb et al, we found a positive correlation between TG level and T.C., T.C/HDL, LDL/HDL and Apo B, being important indicators of atherosclerosis risk in our study (12).

HDL level, an important criterion because of its inverse relation with atherosclerosis is found low especially in diabetic patients with high TG (5, 7, 18). But in our study, in spite of hypertrigliseridemia before therapy we found that HDL level was similar to control group which was quite revelant from the point of factors influencing HDL.

There wasn't a significant change in HDL level in diet and insulin group but in OAD group HDL level increased significantly in comparison to control group. In previous studies the effects of sulphonylurea drugs on HDL level gave conflicting results and became a matter of debate. The comparison of patients receiving diet, sulphonylurea and insulin therapy shows in some studies that HDL level is low only in patients receiving sulphonylurea or that with sulphonylurea therapy there isn't any beneficial effect on HDL level (11, 22). Whereas in some other studies it has been detected an increase on HDL level with sulphonylurea therapy (17, 23). In DM patients low HDL level is explained by the decreased production due to the slowing of TG and VLDL catabolism and by the increased catabolism due to increased activity of hepatic lipase (HL) (24).

It is proposed that a decrease in the activity of the enzyme LCAT which plays an important role in HDL metabolism can have a negative influence on HDL level (24). Moreover in diabetic patients is reported that the increase in the free cholesterol content of LDL and VLDL is associated with a decline in esterification rate (25). Therefore LCAT enzyme activity becomes important more and more. But in still a small number of studies done on

diabetic patients LCAT levels are found variably. In a study carried out on 80 diabetic patients HDL levels are found lower than control group, LCAT acivity similar to control group (12). In another study in patients receiving insulin therapy thereas no change in HDL levels after therapy but a decline in LCAT activity, this fact couldn't be explained (22). In our study in all treatment groups LCAT levels were similar to control group before and after therapy. ApoB, ApoB / ApoA and T.C/HDL, LDL/HDL levels which are important indicators of atherosclerosis were high in OAD group before therapy and the decline of these factors after therapy shows that the disturbed inverse - cholesterol transport is restored again. Our study in compatible with studies reporting a decline in ApoB and ApoB/ApoA levels with sulphonylurea therapy (12, 22). As in similar studies ApoB/ApoA level found high in insulin group declined with therapy and this shows that insulin therapy influences the risk of atherosclerosis positively (11, 12). In our study VLDL, TG, TC, LDL, HDL, ApoA, ApoB, ApoB/ApoA and LCAT levels didn't have a statistically significant change before and after therapy between treatment groups.

In insulin group although there was a significant increase in insulin level after therapy, it couldn't be found a statistical difference between groups. This finding suggests that the level of hyperinsulinaemia is not high enough to increase the risk of atherosclerosis. All of these findings indicate that in type II DM all of the negative changes in lipid metabolism are corrected or regress with the achievement of metabolic control and the regulation of diet in all treatment groups. Unlike some authors, we conluded that the most beneficial effect on HDL metabolism is seen on the patients receiving sulphonylurea therapy.

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