Lipid Profile in Children with Insulin Dependent Diabetes Mellitus

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Abstract

Objective: To evaluate serum lipids in children with type 1 diabetes mellitus and its relation to glycemic control, in comparison with matched controls.
Setting: Basrah Maternity and Children Hospital, Basrah, Iraq.
Method: Lipid profile was studied in 32 children (17 males and 15 females) with type 1 diabetes mellitus from October 1999 to September 2000. Seventy seven non-diabetic children (35 males and 42 females) admitted with acute illness in the same hospital were selected as controls.
Results: The age and BMI was similar in both groups. The mean total cholesterol, triglycerides, HDL-C, LDL-C, VLDLC and LDL-C/HDL-C ratio were significantly higher in diabetic children compared to control group. There was no significant difference in the levels of Ape 0 and Apo B in both groups.
Conclusion: Children with type I diabetes should be screened for serum lipids as significant lipid abnormalities are related to glycemic control. Both can be improved with dietary management and insulin therapy (JPMA 52:29, 2002).

Introduction

Diabetes mellitus (DM) can be found in all populations throughout the world; recent studies have suggested an increasing incidence of IDDM1. Diabetes mellitus is not a benign disease2. Development of diabetes mellitus is associated with increased mortality and high risk of developing vascular, renal, retinal and neuropathic complications1-3. There is a relationship between the degree of metabolic control and the appearance, progression and severity of these complications2,4-7. However, hyperglycemia is not the only factor involved in the pathogeneSis of long term diabetic complications. Other environmental and genetic factors play an additional role in the development of complications8. Atherosclerosis is the most common complication of DM, with the largest numbers of ischemic events occur in people with Type 2 diabetes. However, the risk of atherosclerosis is also high in Type I diabetes and may manifest at a younger age'. Coronary heart disease is a major cause of death in patients with type 1 diabetes9. Although diabetes implies a relatively poor prognosis for the individual developing the disease, there is a distinct prospect of significant improvement in prognosis with the implementation of effective existing strategies including screening for risk factors, which should include determination of lipid profile.
The aim of this study was to evaluate serum lipids in children with Type 1 diabetes mellitus (IDDM) and its relation to glycemic control, in comparison with sex and age matched non-diabetic children as controls.

Subjects and Methods

Subjects

Thirty two diabetic children and adolescents (17 males and 15 females) attending Basrah Maternity and Children Hospital, who had been diagnosed having type[1] diabetes mellitus for at least one year, were included in the study. They were not acutely ill and did not haveevidence of other diseases associated with hyperlipidemia like renal disease, liver disease or Downs syndrome.

A questionnaire form designed for the purpose of the study was filled by the same paediatrician (investigator) which included age, sex, duration of diabetes, insulin therapy, complications of the disease and family history of diabetes mellitus. A thorough physical examination was carried out on each subject. Informed consent was obtained from one of the parents.

Seventy seven healthy children (35 males and 42 females), admitted to the same hospital for acute illnesses like typhoid fever or respiratory tract infections were randomly selected as controls. The importance of the procedure was explained to one of the parents (which was usually the mother) and the child, where appropriate and an informed consent was obtained. Children with chronic illnesses and with family of history diabetes mellitus or cardiovascular disease were excluded. For each patient and control, height and weight were measured and body mass index (BMI) was calculated as wt/ht^2.

Laboratory Methods

Fasting blood samples (5 ml) were drawn from each individual participating in this study. Two millilitres was added to EDTA anticoagulant containing tubes for the estimation of glycosylated hemoglobin (HbAlc) which was carried out within a week. The remainder of the blood samples were allowed to clot at room temperature, then serum was separated and stored at 4°C until analyzed for lipid parameters within 3 days. Samples for apolipoproteins were stored at - 20°C until assayed, while serum glucose was estimated immediately. Serum concentrations of glucose , total cholesterol (TC), triglyceride (TG) and HDLcholesterol (after the precipitation by phosphotungstate and MgC_{12}) were estimated by the enzymatic method using kits from BioMerieux, France. Apolipoproteins were estimated by immunoturbidimetric method using kits supplied by BioMerieux,France. All procedures were followed according to instruction of the manufacturer. Quality control sera from BioMerieux were included in each assay batch for all the above analysis. The interassay coefficient of variation was 1.9% for glucose, 3.5% for TC and TG while that of HDL-C was 6.5%. LDL - C value was calculated using the Friedewald equation: LDL-C = TC - (HDL-C + TG/5) , while VLDL- C was calculated from the formula VLDL-C = TG / 5[10]. Glycosylated hemoglobin (HbAlc) was measured by its conversion to 5-hydroxymethyl furfural according to the method of Standefer and Eaton[11].

Diabetic children were classitieci as having good control (HbAlc up to 9%), fair control (HbAlc 9-12%) and poor control (HbAlc> 12%)2.

Statistical analysis

Results were expressed as mean±SD (95% confidence interval of the mean). Differences between diabetic and control groups were assessed using the student's t test. Differences between variables in the three groups that were classified according to their glycemic control were assessed using one-way analysis of variance (ANOVA). Correlation

between variables were assessed by calculating Pearson's correlation coefficients. Differences in the number of subjects with dyslipidemia among diabetic and control groups were analyzed using Chi Square (X2) with Yates's correction. P values of < 0.05 were considered as significant.

Results

Of the 32 diabetic patients (17 males and 15 females) included in the study, 10 (31%) patients had a positive family history of diabetes mellitus (7 Type 2 and 3 Type 1). Patients were receiving a mean insulin dosage of 0.94 units per kg. of body weight (the range of insulin doses was 0.4 -1 .6U/kg), 17 patients were on twice daily regimens and 15 patients on once daily injections. The duration of diabetes ranged from 1 - 8 years (mean 3.87 years).

The control group comprised 35 males and 42 females. The mean age of diabetic children was 11.9 ± 3.7 years, while that for the control group was 10.5 ± 3.8 years (P > 0.05) (Table 1). The body mass index (BMI) was calculated for both groups; the mean BMI for diabetic patients was 17.5 ± 3.9 and for the control group was 17.8 ± 3.4 (P> 0.05) (Table 1).

Table 1. Characteristics and biochemical profile in diabetic and control children.

Variables	Diabetics No.=77	Controls difference in mean	95% CI	No.=32	P-value
Age (years)	11.9±3.7	10.5±3.8	0.19-3		>0.05
(10.5-13.2)	(9.6-11.30)				
BMI	17.5±3.9	17.8±3.4	13-1.9		>0.05
(16.1-18.9)	(17.18.6)				
Ghucose	232±92	80±11	119-186		<0.00001
(mg/dl)	(199-265)	(75.9-83)			
HbA Ic	9.8±4.2	4±0.8	4.22-7.31		<0.00001
(%)	(8.3-11.3)	(3.7.4.4)			
Cholesterol	179.6±56	129.6±30	29-71.2		<0.00001
(mg/dl)	(158.4-199)	(121.9-135)			
Triglyceride	146±95	116±34	2-61.4		0.06
(mg/dl)	(115-176)	(108-123.5)			
HDL-C	47±123	41±10	0.8-10.9		<0.02
(mg/dl)	(42.4-51.6)	(38.9-43.3)			
LDL-C	104±49	63±27	21.9-58.8		<0.0001
(mg/dl)	(86 -121)	(57-69)			
VLDL-C	30÷17	23±7	0.5-13.2		0.03
(mg/dl)	(24-36.4)	(21.8-25)			
ApoA	1.96±0.5	1.75±0.5	0.08-0.49		>0.05
(g/dl)	(1.7-2.2)	(1.6-1.9)			
Apo B	1,4±0.2	1,4±0.65	0.98-1.84		>0.05
(g/dl)	(1.23.1.48)	(1.1-1.52)			
LDL-C/HDL-C	2.3±1,2	1.59±0.8	0.21-1.17		<0.05
(1.84-2.72)	(1.4-1.8)				
Results were expressed as mean±SD					
Values in parenthesis are range as 95% confidence interval					

Biochemical Variables

The mean values of blood glucose, glycosylated hemoglobin and serum lipids are presented in Table 1. Mean fasting blood glucose and glycosylated hemoglobin values were significantly higher in diabetic patients as compared to the control group, which is an expected finding. Mean total cholesterol, HDL-C, LDL-C, VLDL-C, LDL-C / HDL-C ratio were significantly higher in diabetic children compared to the control group (P < 0.02 to < 0.0001), whereas TG level was higher in diabetic children compared to the control, but the difference was statistically marginally significant (p 0.06). However there

was no significant difference in the levels of Apo, A and Apo B in both groups.

Table 2. Blood lipids and glucose in relation to glycemic control.

Hb Aic (%)	Good	Fair	Poor	P-value
7-9	9-12	12		
Number	14	*9*	*9*	
Age	12±3.3(10.2-14.2)	10.6±3.4(7.9-13)	12.6±4.6(9-16)	NS
BMI	18.5±4.4 *(15.9-21)*	15.8±1.6(14.5-17)	17.7±4.4 (14.4-21)	NS
Glucose (mg/dl)	200±91.3 (147-253)	*195.8±49.5* (157.7-233.8)	317.9±72.3 (262-373.5)	<0.01
Cholesterol (mg/dl)	149.8±33.6 (130.5-169)	180.3±51.4 (141-220)	229.6±43.2 (196-263)	<0.001
Triglyceride (mg/dl)	116.9±36 (96-138)	150±109 (66-235)	196±71 (142-251)	<0.05
HDL-C (mg/dl)	43.7±16 *(39.5-58)*	44.8±10.8 *(36.5-53)*	46.4±31 (39.3-54)	NS
LDL-C (mg/dl)	79.4±24 (66-93)	103±46.3 (67.7-138.8)	138±39 (109-169)	<0.01
VLDL-C (mg/dl)	26.9±15 *(18.4-35.5)*	33±21.5 (16.4-49.6)	32.6±16.4 (19.9-45.2)	NS
Apo-A1 (g/dl)	1.9±0.6 (1.5-2.4)	*1.96±0.5* (144-2.5)	2±0.25 (1.65-2.45)	NS
Apo-B (g/dl)	1.4-0.3 (1.2-1.6)	1.35±0.2 (1.07-1.5)	1.1±0.8 (0.99-1.23)	NS
LDL-C/HDL-C	1.6±0.7 (1.2-2)	*2.5±1.3 (1.5-3.5)*	3±1.3 (2-4.04)	<0.05

Results were expressed as mean±SD
Values in parenthesis are range as 95% confidence interval

Table 2 presents the mean blood glucose levels and lipid variables in relation to glycemic control. Diabetic patients with poor control have significantly higher levels of blood glucose, total cholesterol, triglyerides, LDL-C , LDLCl HDL-C ratio as compared to those having good glycemic control. No significant difference was found in the level of HDL-C, Apo A, Apo B and VLDL-C among the three groups. A significant correlation between most lipid variables and HbAIc levels was observed among the diabetic patients (Table 3).

Table 3. Relationship between lipid variables and HbAlc concentration.

Variables	Diabetic patients r	Control subjects r
T.Cholesterol	0.74*	0.14
Triglyceride	0.68*	0.22
HDL-C	0.015	0.099
LDL-C	0.713*	0.096
ApoA1	0.156	*-0.155*
Apo B	-0.22	*0.25*
LDL/HDL	*0.545**	0.054
VLDL-C	0.15	0.21

Values are pearson's correlation coefficients (r)
*P<0.01

It seems that these associations occur at continuous level in the diabetic group rather than at a specific level of HbAlc as intermediate values were seen in patients with fair glycemic control. No such correlations were found in the control group. There was no relationship between HDL-C, Apo A, B or VLDL-C levels and HbAlc in any of investigated groups.

The pattern of dyslipidemia in children with Type 1 Diabetes and control is shown in Table 4.

Table 4. Dyslipidemia in children with Type 1 Diabetes Mellitus and controls.

Lipid	Contro l		Type 1		P-value
			Diabetes		
parameter	n=77 No.	%	n=32 No.	%	
Total cholesterol	4	5.2	2	6	NS
170-199mg/dl	0	0	10	31	.
>200 mg/dl					
Triglyceride	10	13	11	34	0.01
>150 mg/dl					
HDL-C					
>3.	8	23	5	16	NS
LDL-C	4	5.2	13	40	0.0002
110-130 mg/dl	0	0	10	31	.
>130 mg/dl					
LDL-C/HDL-C >3.5	2	2.6	6	19	0.002
(Atherogric index)					
Extremely significant	since none	were *f*	amid in the controls		

Out of 32 diabetic patients, 10 patients (31%) had hypercholesterolemia (TC level above 200 mg/dl i.e., above the cut-off point or 95 percentile), while 2 patients (6%) had a borderline cholesterol level (170-199 mg/ dl). In comparison with the control group, 4 (5.2%) had a borderline cholesterol level and none had a total cholesterol >200 mg/dl. Hypertriglyceridemia (TG> 150 mg/dl) was present in 11 patients (34%) compared to 10 subjects (13%) in the control group (P<0.01). Hypertriglyceridemia alone was present in 4 patients, while the rest had also hypercholesterolemia. Elevated LDL-C (>130 mg/dl) was present in 10 (3 1%) diabetic patients only, whereas border level of LDL-C (110 130 mg%) was found in 13 (40%) diabetic patients as compared to 4(5.2%) in the controls (p = 0.000 1). All of the 10 diabetic patients with elevated LDL-C had hypercholesterolemia and this was associated with hypertriglyceridemia in 5 out of the 10 diabetic children. This indicated that mixed type of dyslipidemia or a combination of more than one lipid abnormalities was observed in 31% of our diabetic patients. In addition to that the LDL-C/HDL-C ratio (atherogenic index > 3.5) was significantly higher in patients with Type 1 Diabetic as compared to the control group (p= 0.002).

Discussion

There is evidence that atherosclerosis begins in early life and that hypercholesterolemia plays an important role in its evolution[12]. In pediatric age group, normal total cholesterol (TC) level should be less than 170 mgldl. A total serum cholesterol of 170-199 mgldl is border line, while that above 200 mgldl is considered to be elevated; i.e. hypercholesterolemic[13,14]. In this study, the mean total cholesterol level was significantly higher in diabetic children as compared to the control group and hypercholesterolemia was present in a significantly higher number of diabetic patients as compared to the control group. These results are in agreement with similar studies[15-18], although others did not observe such correlation[9,19] Possible explanation for variation between reports include; duration and severity of diabetes, degree of glycemic control, diet, and different laboratory methods. Furthermore, there was a significant difference in mean total cholesterol level among diabetic patients in relation to glycemic control, where poorly controlled patients have significantly higher TC levels compared to those with fair and good control. Comparable results were obtained in other studies[15,20].

Hypertriglyceridemia comprises a constellation of lipoprotein disorders and cannot be regarded as a single entity, and it is therefore necessary to consider characterizing individuals according to the sub -fractions of their lipoproteins[1]. In the present study, diabetic patients have a significantly higher serum triglyceride level compared to the control group and 34% of diabetic patients have hypertriglyceridemia (TG> 150 mg/dl) in comparison to only 13% in the control group (P<0.01). In addition to that there was a significant correlation between TG level and glycemic control. These results are similar to those reported in other studies[15'16]. It has been shown that individuals with Type 1 diabetes, who are untreated or inadequately treated have elevations in both fasting and postprandial TG levels in association with reduced activity of lipoprotein lipase21.

High density lipoproteins (HDL-C) are associated inversely with atherosclerosis and atherosclerotic diseases. In the present study, no significant difference in HDL-C levels between diabetics and controls were found, although it was higher in diabetic children. These results were similar to others[15,22,23] whereas some authors observed markedly elevated HDL-C in Type 1 diabetes[9,24,25]. Similar to others[15] we found no correlation between HDL-C level and the degree of glycemic control, whereas a negative correlation was observed by some authors[26]. Differences in treatment, physical activity, diet, relative body weight might perhaps explain some of the wide variation of HDL-C reported in Type 1 diabetes[27].

The average level of LDL-C should be less than 110 mg/dl in children, levels between 110-130 mg/dl are border line, while levels exceeding 130 mg/dl (95 percentile) are considered to be elevated[5,13]. Diabetes mellitus in general and poor glycemic control in particular were associated with significant correlation with LDL-C levels in our study. A border-line LDL-C level was found in 40% of diabetic subjects and 5.2% of the control group (p< 0.01), whereas an elevated LDL-C level was found in diabetic children only. As LDL-C level was increased in a greater proportion than that of HDL-C, the percentage of this atherogenic index (LDL-C/HDL-C > 3.5) was higher in diabetic patients (19%) than in the control group (P<0.05). In the present study, LDL-C and the LDL-C/HDL-C ratio, both generally accepted risk indicators of atherosclerosis, were found to correlate significantly with metabolic control in diabetic children. This is in agreement with previous reports[15,23,26] where it was concluded that the levels of cholesterol and LDL-C increases with deteriorating metabolic regulation. Laakso[28] suggested that the worsening

of glycemic control further deteriorates lipid and lipoprotein abnormalities. Furthermore, TC and LDL-C levels are often elevated in poor glycemic control, and the compositional changes in LDL particle may further increase the risk of coronary heart diseases.
Apo A is the major protein component of HDL, while Apo B is found mainly in LDL. Our study demonstrated no signifiant differences in Apo A and Apo B concentrations among Type 1 Diabetic children and controls. This is in common with other reports[13,29,30], while it is in contrast to other studies[13] which have demonstrated increased Apo A and B in poorly controlled diabetic subjects.
In conclusion, our fmdings indicate that screening of diabetic children for serum lipids resulted in the identification of significant lipid abnormalities and high atherogenic index, many of them were closely correlated to glycemic control. Thus lipid profile is warranted in all diabetic children with Type 1 diabetes, at least annually, in addition to improvements in blood glucose control and dietary management.

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