RESEARCH ARTICLE

Dyslipidaemia in children with Type 1 diabetes: Experience from a tertiary care hospital

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Abstract

Objective: To determine the lipid profile of children with type 1 diabetes, and to identify the risk factors associated with dyslipidaemia.

Method: The cross-sectional study was conducted at Indus Hospital's Korangi campus from January 2021 to March 2022, and comprised children of either gender aged up to 15 years having type 1 diabetes. Data included fasting lipid profile, thyroid-stimulating hormone level, tissue transglutaminase immunoglobulin A, serum immunoglobulin A level, urine analysis, urine-albumin creatinine ratio, and glycated haemoglobin level. Data was analysed using SPSS 21.

Results: Of the 40 children, 24(60%) were boys and 16(40%) were girls. The overall median age was 8 years (interquartile range: 3.75-10 years), median body mass index was 15.9kg/m^2 (interquartile range: 14.2-16.6kg/m^2), and median duration of diabetes was 2 years (interquartile range: 1.7-4.5 years). Dyslipidaemia was seen in 22(55%) children, and gender had no significant association with it ($p>0.05$). Median total cholesterol, triglyceride, high-density lipoprotein-cholesterol and low-density lipoprotein cholesterol values were significantly higher in children with dyslipidaemia ($p<0.05$). Also, children with dyslipidaemia had significantly higher blood pressure values compared to those not having dyslipidaemia ($p<0.03$).

Conclusion: Lipid profile abnormalities were common in non-obese children with type 1 diabetes, and elevated blood pressure was significantly associated with dyslipidaemia in such children.

Key Words: Dyslipidaemia, Type 1 diabetes, Paediatric endocrinology, Lipid profile, Glycaemic control, Socioeconomic factors, Hypertension, Nephropathy, Celiac disease, Micro-albuminuria.

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Introduction

Type 1 diabetes mellitus (T1D) is a chronic disorder of glucose homeostasis characterised by an absolute insulin deficiency state, resulting in abnormal carbohydrate and lipid metabolism. The pathogenesis includes autoimmune destruction of pancreatic beta (β) cells; believed to be triggered by genetic or environmental risk factors.[1] The reported prevalence of T1D is approximately 2-3 per 1,000 in Pakistan.[2]

Children with diabetes are at a risk of developing micro-vascular and macro-vascular complications. Dyslipidaemia is one of the macro-vascular complications. Evidence shows that children with T1D are prone to developing dyslipidaemia regardless of glycaemic control .[2] However, longer duration of diabetes, higher median age, higher glycated haemoglobin (HbA1c) values, elevated body mass index (BMI), puberty and low physical activity make the risk of dyslipidaemia more pronounced among such children.[3-5]

Evidence has also shown that T1D children with dyslipidaemia have 2-4 times greater risk of developing atherosclerosis compared to children without diabetes.[6] Atherosclerosis, in turn, leads to increased risk of cardiovascular diseases among these children.[7] To prevent complications of dyslipidaemia and cardiovascular diseases in T1D, the International Society for Paediatric and Adolescent Diabetes (ISPAD) has recommended lipid profile screening for children with diabetes, and endorses pharmacologic therapy when low-density lipoprotein-cholesterol (LDL-C) concentration is >130mg/dL.[8]

Different socioeconomic conditions and diverse dietary habits of a population may change risk factors of dyslipidaemia in a particular geographic area. Furthermore, cut-off points used for definition of dyslipidaemia in Pakistan are not uniform, and, updated information based on international, validated laboratory cut-off values is necessary to fill the gaps in knowledge.

The current study was planned to determine the lipid

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profile of children with T1D, and to identify risk factors associated with dyslipidaemia.

Subjects and Methods

The cross-sectional study was conducted at Indus Hospital's Korangi campus in Karachi from January 2021 to March 2022 after approval from the institutional ethics review committee. Children were enrolled using a purposive sampling method.

The sample size was calculated using the WHO sample size calculator, taking the prevalence of type 1 diabetes mellitus (T1DM) as 1.02% from a previous study[9], with a 5% margin of error and 95% confidence level, resulting in a required sample size of 18 participants. Indus Hospital is a free, multi-disciplinary tertiary care hospital. A free-of-cost paediatric diabetes clinic is run weekly in the outpatient department (OPD) of the hospital. Children with TID are treated with multiple daily insulin injections, using ultra-short-acting and basal insulin. Blood pressure was measured using an age-appropriate cuff. Children are routinely screened for diabetes-associated dyslipidaemia, nephropathy, hypothyroidism, and Coeliac disease at the time of diagnosis and annually thereafter. Lipid profile is collected after fasting of at least 8 hours. Children are also screened for micro-vascular complications, including ophthalmological and neurological examinations, yearly. Dietary and lifestyle modifications are advised to children who have dyslipidaemia and nephropathy. Pharmacotherapy is advised if conservative management fails. Gluten-free diet is recommended to children diagnosed with Coeliac disease.

In the current study, T1D children aged up to 15 years were included. Children with known hereditary diseases that affect lipid metabolism, like familial hyperlipidaemia, and children who were already on lipid-lowering medications were excluded.

Clinical features and laboratory investigations done at the time of enrollment were included after taking informed consent from the caregivers of the children. A predesigned questionnaire was used to collect information about clinical features and lab parameters. Demographic characteristics, dietary history, lifestyle details, physical activities, height, weight, BMI and BP of the children were noted. Lab investigations included fasting lipid profile, thyroid-stimulating hormone (TSH) level, tissue transglutaminase immunoglobulin A (tTG-IgA), serum immunoglobulin A (IgA) level, urine detailed report (DR), urine-albumin-creatinine ratio (ACR), and HbA1c level.

Glycaemic control was categorised on the basis of ISPAD guidelines.[8] Good control was taken as HbA1c 6-7.5%. fair as 7.6-9.9% and poor as ≥10%.

Physical activity level was categorised into mild, moderate and vigorous, with mild activity meaning regular daily activities, like household chores and walking, moderate activity indicating climbing stairs, bicycling, playing cricket, badminton, playing on school playground, swinging, or climbing, and vigorous activity meaning running, swimming, jumping rope, several competitive sports, football, basketball, or jogging.

Dyslipidaemia was identified as per the guidelines[8] on the basis of LDL-C ⩾100mg/dl, or high density lipoprotein-cholesterol (HDL-C) ≤35mg/dl, or total cholesterol (TC) ⩾200mg/dl, or triglycerides (TG) ⩾150mg/dl.

Diabetic nephropathy was classified as micro-albuminuria (ACR 30-300mg/g) and macro-albuminuria (ACR >-300mg/g). Coeliac disease was diagnosed on the basis of serum tTG-IgA >20U/ml on two occasions along with suggestive symptoms.

Hypothyroidism was diagnosed when TSH >6mIU/L was noted along with low free thyroxin (T4) levels in relation to age-specific range. Hyperthyroidism was labelled when TSH <6 mIU/L was noted along with raised T4 levels.

Hypertension was defined as the median value 95th percentile of at least three independent measurements. Prehypertension meant systolic BP (SBP) and/or diastolic BP (DBP) between 90th and 95th centile in all ages. While hypertension meant BP ≥95th centile (<13 years) or SBP ≥130mmHg and/or DBP ≥80mmHg (≥13 years)[8]

Data was analysed using SPSS 21. Since data was not normally distributed, median values with interquartile range (IQR) were was used to express quantitative variables, while frequencies and percentages were used for categorical variables. Categorical variables were analysed using chi-square test or Fisher's exact test, while Mann-Whitney U test was used for quantitative variables. P<0.05 was considered significant.

Results

Of the 40 children, 24(60%) were boys and 16(40%) were girls. The overall median age was 8 years (IQR: 3.75-10 years), median BMI was 15.9kg/m2 (IQR: 14.2-16.6kg/m2), and median duration of diabetes was 2 years (IQR: 1.7-4.5 years). Median calories consumed were 932 (IQR: 650.7-1316.5) per day. Median HbA1c was 10.9% (IQR: 9.0-14.1%). Hypothyroidism was found in 1(2.5%) and Coeliac disease in 3(7.5%). Diabetes-associated nephropathy was observed in 9(22.5%) children out of whom 6(66.7%) also had dyslipidaemia. Overall, dyslipidaemia was seen in

Table-1: Demographic characteristics.

Clinical Parameters Median (IQR) & n (%)		Macronutrients Parameters Median (IQR) & n (%)	
Age at Diagnosis	8 (3.75-10)	Total Calories/day	932 (650.7-1316.5)
		CHO Calories/day	474 (384-789)
Gender,%		Protein Calories /day	150 (94-199)
Male	24(60)		
Female	16(40)		
BMI, Kg/m^2	15.9 (14.2-16.6)	Fat Calories /day	270 (168.7-355.5)
Duration of Diabetes, Y	2 (1.7-4.5)	**THYROID PROFILE**	
BP Diastolic, mm/Hg	59 (55.7-20.5)	TSH, mIU/L	1.5 (1.1-2.38)
BP Systolic, mm/Hg	101 (97.7-115.5)		
LIPID PROFILE		**COELIAC DISEASE**	
Total Cholesterol, mg/dl	144 (104.5-184)	tTG IgA,U/ml	2.5 (1.7-24.3)
Triglycerides, mg/dl	69.50 (56.75-155.5)		
LDL-C, mg/dl	80.50 (54.5-112)	**NEPHROPATHY**	
HDL-C, mg/dl	44 (37.7-49.5)	Urine ACR	11.59 (6.6-24.0)
GLYCAEMIC CONTROL			
HbA1c	10.9 (9.0-14.1)		

BMI: Body mass index, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, CHO: Carbohydrate, TSH: Thyroid-stimulating hormone, tTG-IgA: Tissue transglutaminase immunoglobulin A: IgA: Immunoglobulin A, HbA1c: Glycated haemoglobin, ACR: Albumin-to-creatinine ratio, BP: Blood pressure, IQR: Interquartile range.

Table-2: Comparison between dyslipidaemia and non-dyslipidaemia groups.

(Median) (IQR)	DYSLIPIDAEMIA		p – value
	PRESENT (22)	ABSENT (18)	
CLINICAL PARAMETERS			
Age at assessment	11 (6-12)	11 (8-12)	0.386
Age at Diagnosis	8.50 (4.75- 9.25)	8 (4.75- 11)	0.689
BMI	16.3 (14.1- 17.9)	15.2 (14.2- 16.3)	0.169
BP diastolic	69.50 (58-76)	66.50 (59.50-70)	0.446
BP Systolic	110 (97.5-121.25)	104.5 (101-110)	0.121
Duration of Diabetes	2 (1-3)	1 (1-4)	0.538
LIPID PROFILE			
Total Cholesterol	160.5 (153.7- 177.2)	134.5 (120.7- 150.5)	0.001
Triglycerides	116 (73.75- 191.2)	71 (61.5- 94.2)	0.002
HDL-C	37.5 (31.75-44)	43.5 (40.7-49.7)	0.003
LDL-C	111 (99-130.5)	77.5 (63.50-85.50)	0
BLOOD GLUCOSE			
HbA1c	12 (9.1-13)	14.1 (9.9-16.6)	0.754
MACRONUTRIENTS PARAMETERS			
Total Calories/day	813 (540.7-1053.2)	837 (688.2-1026)	0.459
CHO Calories/day	58.1 (76-141.5)	55.8 (50.7-62.9)	0.742

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22(55%) children, and gender had no significant association with it (p>0.05). Among the subjects with dyslipidaemia, 11(50%) had single lipid abnormality, while the other 11(50%) children had mixed dyslipidaemia. Among the children who had multiple elevated lipid markers, 3(27.6%) had deranged cholesterol, TG and LDL-C levels, while 6(54.4%) had combined TG, LDL-C and HDL-C abnormalities, and 2(18%) had deranged LDL-C and HDL-C levels. The most prevalent lipid abnormality was raised LDL-C 11(50%), followed by hypertriglyceridaemia and low HDL-C 9(40%).

Median TC, TG, HDL-C, and LDL-C values were significantly higher in children with dyslipidaemia (p<0.05). Also, children with dyslipidaemia had significantly higher BP values compared to the non-dyslipidaemia subjects (Table 2).

Discussion

The current study analysed the frequency of dyslipidaemia in children with T1D. Generally, dyslipidaemia has been reported more in T1D females[6,10] because of increased adiposity, poor glycaemic control and increased waist-to-height ratio among them.[11] However, no gender preponderance was observed in the current study probably because of a smaller number of females in the cohort.

Over the past decades, data on T1D has increased exponentially and there is documented association of overweight and increased BMI with dyslipidaemia among such children.[12] Insulin resistance in overweight individuals with T1D may be associated with an increased risk of vascular complications.[13] The current findings demonstrated no significant association of BMI with dyslipidaemia. In fact, most patients were underweight with a median BMI of 15.9kg/m^2. Also, calories consumed from fats were 28,9% of the total calories. It can be argued that although BMI is a predictor of weight status, it is not the preferred method of measuring adiposity; dyslipidaemia in the current sample may have been related to inadequate control. Future studies are needed to determine the association of BMI with dyslipidaemia among Pakistani children. Moreover, the current study observed no effect of diabetes duration on dyslipidaemia. The discrepancy could be attributed to the study's small sample size.

Dyslipidaemia in T1D is a harbinger of early cardiovascular complications, specifically increasing the risk of atherosclerosis in adolescents and young

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Protein Calories/day	112 (12.9-15.4)	118 (94-161)	0.328
Fat Calories/day	195.7 (155.2-308.2)	270 (186.3-324)	0.226
THYROID PROFILE			
TSH	1.5 (1.1-2.9)	1.49 (1.14-2.32)	0.673
IMMUNOGLOBULIN			
tTG IgA	3.8 (0.65-24.4)	2.4 (0.87- 2.59)	0.285
KIDNEY FUNCTION TEST			
Urine ACR	11.15 (6.28-25.7)	11.59 (7.27-27.2)	0.925
Gender			
Male	12/22 (54.5%)	12/18 (66.6%)	0.526
Female	10/22 (45.4%)	6/18 (33.3%)	
Normal	11/22 (50%)	15/22 (83.3%)	
Pre-hypertension (elevated BP)	5/22 (22.7%)	3/18 (16.7%)	0.034
Hypertension	6/22 (27.3%)	0	
Coeliac disease	2/22 (9.1%)	1/18 (5.6%)	0.875
Micro-albuminuria	5/22 (22.7%)	4/18 (22.2%)	1
Physical activities			
Light	7/22 (31.8%)	3/18 (16.7%)	
Moderate	15/22 (68.2%)	15/18 (83.3%)	0.464

BMI: Body mass index, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, CHO: Carbohydrate, TSH: Thyroid-stimulating hormone, tTG-IgA: Tissue transglutaminase immunoglobulin A: IgA: Immunoglobulin A, HbA1c: Glycated haemoglobin, ACR: Albumin-to-creatinine ratio, BP: Blood pressure, IQR: Interquartile range.

adults.[9,14] Previously reported prevalence of dyslipidaemia in various studies ranges between 26% and 72%.[11] In the current sample, 55% children were found to have dyslipidaemia. The possible attributing factors to dyslipidaemia in could be poor glycaemic control (median HbA1c 10.9, increased consumption of calories from carbohydrates (55%), light physical activity, hypertension, and micro-albuminuria. On further analysis, the most prevalent lipid abnormality was raised LDL-C (50%), followed by hypertriglyceridaemia (40%) and low HDL-C (40%). The distribution of lipid abnormalities was in accordance with previous data.[10,15] Glycated LDL-C binds poorly to its LDL receptor which decreases its catabolism and the glycated form is more prone to oxidation and atherogenic modification. The result has profound implications with regards to early intervention in terms of dietary and medical therapy to prevent premature cardiovascular morbidity.

In children with T1D, the prevalence of elevated BP is reportedly as high as 4-16%.[10] The current study found significant association of dyslipidaemia with elevated BP; pre-hypertension was more prevalent, while hypertension was present specifically in the group with dyslipidaemia (p=0.034) In the current cohort, the prevalence of hypertension in T1D children was 15%. Other attributing factors for hypertension could be male gender, presence of micro-albuminuria, and light physical activity, but this needs to be studied further with a larger cohort. Similar findings have been reported in previous studies.[16]

Nine subjects in the current sample had evident micro-albuminuria, and 6 of them also had dyslipidaemia. The close relation of hypertension with diabetic nephropathy is due to poor glycaemic control, obesity, insulin resistance, diabetes duration, dyslipidaemia, and male gender.[16,17] Interestingly, it is not yet proven that micro-albuminuria causes or precedes hypertension in T1D. Poor glycaemic control, hypertension and LDL-C are considered independent and significant risk factors for the development of micro-albuminuria, as evident by increased number of LDL-C particles in children with dyslipidaemia which subsequently increases their ACR.[17,18]

Three T1D children in the current sample had coeliac disease (7.5%) compared to a previous study that reported a prevalence of 4.4%[19] Another important current finding is that children with dyslipidaemia had significantly higher level of IgA anti-tTG compared to children without dyslipidaemia even though the difference was statistically not significant (p=0.30). Human leukocyte antigen (HLA) type II accounts for this genetic predisposition, leading to increased susceptibility to coeliac disease in children with diabetes. Another possible reason is that due to immune disturbances and diabetic neuropathy, the gut permeability is altered and the autoimmune target site shifts from the pancreas to the gut.[20]

The current study has limitations because the single-centre data with a small sample size means the findings cannot be generalised to the entire national population. Also, echocardiography was not done to assess cardiovascular effects of T1D, especially in children with hypertension. The relation of micro-albuminuria with dyslipidaemia needs to be studied further with a large sample while excluding all the cofounding variables.

Conclusion

Lipid profile abnormalities were common in non-obese T1D children, with elevated LDL-C being the most common. Risk factors other than dietary fat intake and poor glycaemic control also accounted for these lipid derangements. Elevated BP was significantly associated

with dyslipidaemia, while micro-albuminuria happened to occur more often in those with dyslipidaemia.

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