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Diverse etiology of hyperlipidemia among hospitalized children in Western region of Saudi Arabia

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ABSTRACT

الأهداف: تحديد الأسباب المتعددة الأولية والثانوية لإرتفاع الدهون في الدم للأطفال المراجعين في عيادة الغدد الصماء .

الطريقة: اجريت هذه الدراسة القطعية في مستشفى جامعة الملك عبد العزيز في مدينة جدة، المملكة العربية السعودية في الفترة مابين يناير 2010 و2015، حيث تمت مراجعة ملفات الأطفال المراجعين لعيادة الغدد الصماء وعددهم 253 طفلاً تتراوح أعمارهم من الولادة إلى 12 سنة. وقد تم الحصول على جميع النتائج المخبرية من نظام جامعة الملك عبدالعزيز الإلكترونية .

النتائج: من بين 253 الأطفال الذين شاركوا وُجد التمثيل الغذائي غير الطبيعي للدهون في المتلازمة الكلوية بنسبة 35.6%، مرض السكري 19.4%، متلازمة ارتفاع الغير طبيعي للدهن المجهول 19.4%، الفشل الكلوي المزمن 1.2%، مرض مزمن في الكبد 2%، الغدة الدرقية 7.1% ، من متلازمة التمثيل الغذائي وجدت في 2.8%، ومن السمنة في 4.3%. مؤشر كتلة الجسم، نسبة إلى الجنس والعمر في هذه الفئة من الأطفال كان هناك 23.2% نقص الوزن، 38.4% صحي، 8.9% زيادة الوزن، و29.5% يعانون من السمنة المفرطة .

الخاتمة: أعلى نسبة انتشار لأسباب إرتفاع دهون الدم في الأطفال كانت في متلازمة الغدة الكلوية، ويليها متلازمة إرتفاع غير الطبيعي للدهون المجهول ومرض السكري .

Objectives: To determine the various etiologies of primary and secondary hyperlipidemia among children visiting the pediatric endocrine clinic.

Methods: This is a retrospective, cross-sectional, cohort study conducted at King Abdulaziz University Hospital (KAUH), Jeddah, Kingdom of Saudi Arabia from January 2010 to 2015 that included 253 children aged from birth to 12 years old. Data were obtained by reviewing medical reports of patients who presented with hyperlipidemia to the clinic, and their laboratory investigation results using KAUH electronic "Phoenix" system.

Results: Of the 253 children who were reviewed, those who have shown to have abnormal lipid metabolism with nephrotic syndrome were 35.6%, diabetes mellitus 17.8%, primary/idiopathic hyperlipidemia 19.4%, hypothyroidism 7.1%, obesity 4.3%, metabolic syndrome 2.8%, chronic liver disease 2% and chronic renal failure 1.2%. The body mass index relative to gender and age in this group of children showed that 23.2% were underweight, 38.4% were normal weight, 8.9% were overweight, and 29.5% were obese.

Conclusion: The highest prevalence of hyperlipidemia was in nephrotic syndrome, followed by primary/idiopathic hyperlipidemia and diabetes mellitus.

Hyperlipidemia is a condition of increased lipid levels in the body. This increase imposes patients to a higher risk of diseases, primarily those involved in athersosclerotic changes to the blood vessels. Lipids are classified into several types which are; very low density lipoproteins (VLDL), low density lipoproteins (LDL), high density lipoproteins (HDL), triglycerides (TG), and total cholesterol (TC), collectively known as the lipid profile. An increase of the lipid profile is usually asymptomatic, and screening is necessary to detect it as recommended by the Expert Panel on Integrated Guidelines of National Heart, Lung and Blood institute.[1] In addition, the causes of hyperlipidemia may be classified into 2 categories; either primary causes or secondary causes. Primary causes are due

to genetic disorders, which may be inherited, either as an autosomal dominant or an autosomal recessive inheritance. Secondary causes include diseases such as nephrotic syndrome, diabetes mellitus (DM), chronic renal failure (CRF), chronic liver disease (CLD), hypothyroidism, obesity or iatrogenic due to total parenteral nutrition (TPN). Minimal research has been conducted on the etiology of hyperlipidemia in Saudi Arabia, which is crucial for setting preventable measures against it. The aim of this study was to determine the multiple etiologies of hyperlipidemia and their frequencies among the pediatric population visiting the pediatric endocrine clinic.

Methods. *Definitions.* Nephrotic syndrome is a disease characterized by the presence of proteinuria >3.5 mg/dl, hypoalbuminemia <25g/dL, generalized edema and high serum cholesterol concentration. Hyperlipidemia is related to the hypoproteinemia and low serum oncotic pressure of nephrotic syndrome, which then leads to reactive hepatic protein synthesis, including that of lipoproteins. Next, diabetes mellitus is a disorder of hyperglycemia due to the body's inability to secret insulin, or to respond to secreted insulin appropriately or both. Diagnostic values relied upon in our study were fasting plasma glucose (FPG) value ≥126 mg/dl (7.0 mmol/l), 2-h plasma glucose (PG) value of ≥200 mg/dl (11.1 mmol/l) and an HbA1c ≥6.5% as recommended by American Diabetes Association.[2] Chronic renal disease is defined as the presence of kidney damage markers (blood, urine, or imaging) for ≥3 months, indicating structural or functional kidney abnormalities, with or without a decreased glomerular filtration rate (GFR), or a GFR <60 ml/min for ≥3 months, with or without kidney damage.[3]

Hypothyroidism is a condition in which the thyroid gland is underactive and doesn't produce enough thyroid hormone, which can lead to intellectual disability and profound developmental delays if untreated. Its diagnosis was made by the presence of elevated thyroid stimulating hormone (TSH) levels, and decreased free thyroxine (T4) levels. The normal reference values used were TSH 0.36- 4.7mIU/L, free T4 12-22 pmol/L.

Primary (familial) hypercholesterolemia is a heritable, single gene disorder that produces a clinical pattern of severe hypercholesterolemia due to accumulation of LDL in the plasma, and cholesterol deposition in the tendons and skin. High levels of lipid profile were defined as a TC, 4.4-5.2 mmol/l; LDL-C, 2.9-3.4 mmol/l; and TG, 0.8-1.1 mmol/l (0-9 years) or 1-1.5 mmol/l (10-19 years). High levels were defined as the following: TC, 5.2 mmol/l; LDL-C, 3.4 mmol/l; and TG, 1.1 mmol/l (0-9 years) or 1.5 mmol/l (10-19 years) as recommended by The American Academy of Pediatrics and the Expert Panel sponsored by the United States National Heart, Lung, and Blood Institute cited earlier. Metabolic syndrome was diagnosed by the presence of 2 or more of the following: insulin resistance and impaired glucose tolerance, elevated TC and TG concentrations, low circulating HDL-C concentrations, abdominal obesity, and high blood pressure. Body mass index (BMI) was calculated by dividing weight (in kilograms) by the height squared (in meters). Then, it was expressed as a percentile of the values on the Centers for Disease Control and Prevention BMI charts[4] (**Table 1**).

Data collection. This retrospective, cross-sectional, cohort study was conducted by reviewing the medical records of all the children with hyperlipidemia following up at the Pediatric Endocrinology Clinic at King Abdulaziz University Hospital (KAUH), Jeddah, Kingdom of Saudi Arabia (KSA) between January 2010 and January 2015. A total of 253 children between the ages 0 and 12 years were included in the study. All laboratory data was obtained using KAUH electronic Phoenix system. Missing data from the files of the patients was obtained by directly contacting the patients or their parents, and a verbal consent was taken by the parents prior to initiating the study, which was performed according to the principles of Helsinki Declaration. The data collected compromised of age, gender, race, lipid profile (LDL, HDL, TG, TC), liver function tests (aspartate, aminotransferase [AST], alanine aminotransferase [ALT], albumin, and bilirubin concentrations), renal

Table 1 - Frequency/percentage for each BMI category of the population on whom which the research was conducted.

BMI	Frequency	%
Underweight	44	(23.2)
Normal weight	73	(38.4)
Overweight	17	(8.9)
Obese	56	(29.5)
Total	253	(100)
BMI - body mass index		

function tests (urea and creatinine concentrations), fasting blood glucose level (FBG), random blood glucose level, glycated hemoglobin level (HbA1c), weight, height, family medical history, drug history, and past medical history. Patients included in the study were those who have shown the presence of hyperlipidemia according to KAUH laboratory values with TC >5.2 mmol/l, LDL >3.4 mmol/l or TG >1.13 mmol/l. Exclusion criteria involved children aged >12 years, incomplete data, children on medication, or refusal to participate by the child or parent. The Research and Ethics committee at the KAUH in Jeddah approved the study.

Statistical Analysis. Statistical analysis was carried out with the help of a biostatistics specialist. The data were entered, coded, and analyzed using the Statistical Package for Social Science (SPSS Inc., Chicago, IL, USA), version 16. The correlation coefficients were calculated and the relationships BMI, TC, LDL, HDL, and TG were assessed using Pearson correlation coefficients. Simple descriptive statistics were reported as proportions for qualitative variables and as mean and standard deviation for quantitative variables, such as the mean cholesterol, LDL, HDL, and TG levels for the various BMI categories. An independent t-test was used to find the difference in BMI among males and females. *p*-values less than 0.05 were considered significant, unless otherwise specified.

Results. The study included 253 children of whom 114 (45.1%) were girls and 139 (54.9%) were boys. The nationality was Saudi for 94 (37.5%) children. The mean age of the boys was 3 years, and the mean age of the girls was 4 years. The frequency of children with hyperlipidemia for each disease was recorded alongside with their lipid profile (**Figure 1**). For the 45 (17.8%) children with diabetes mellitus, the mean random glucose level was 18.7 mmol/l, mean fasting glucose level was 6.1 mmol/l, and mean HbA1c was 19.6. For the 3 (1.2%) patients diagnosed with chronic renal failure, the mean blood urea nitrogen (BUN) concentration was 13.9 mmol/l, and the mean creatinine concentration was 2.10 mmol/l. For the 5 (2%) children diagnosed with chronic liver disease, the mean AST concentration was 2.5 u/l, mean ALT concentration was 1.8 u/l, mean albumin concentration was 27.5 g/l, and mean bilirubin concentration was 119.3 mmol/l. For the 21 (8.3%) children diagnosed with Hypothyroidism, the mean triiodothyronine (T3) concentration was 4.6 mmol/l, mean T4 concentration was 16.7 mmol/l, and mean TSH concentration was 8.8 mmol/l. Body mass index, relative to gender and age, indicated that 28 (14.7%) of the boys were underweight, 39 (20.5%) boys were of healthy weight, 10 (5.3%) boys were overweight, and 30 (15.8%) boys were obese. For the girls, 16 (8.4%) girls were underweight, 34 (17.9%) girls were of healthy weight, 7 (3.7%) girls were overweight, and 26 (13.7%) girls were obese.

A family history of a medical disease was present for 41 (16.2%) children, and 135 (53.4%) children had no family history of a medical disease; the data was missing for the remaining 77 (30.4%) children. A family history of hypercholesterolemia was present for 3 (1.2%) children and absent for 247 (97.6%) children; the data
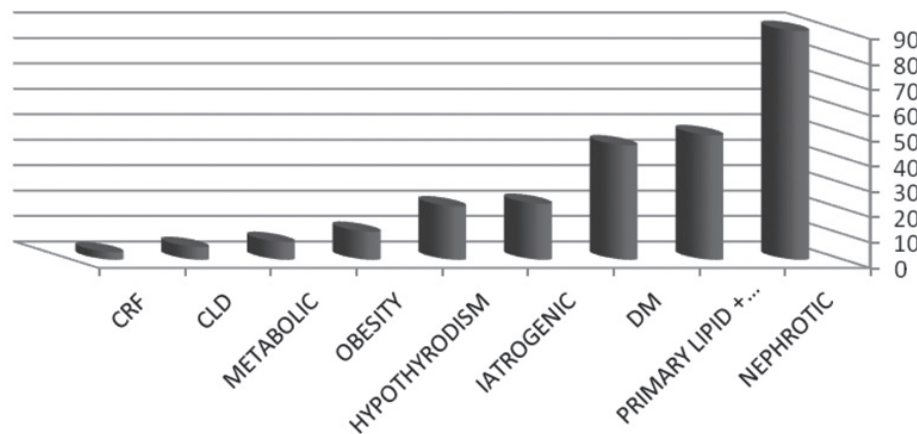

Figure 1 - Frequency of hyperlipidemia in various etiologies. X axis - diagnosis, Y axis - number of patients, CRF - chronic renal failure, CLD - chronic liver disease, DM - diabetes mellitus

was missing for 3 (1.2%) children. A family history of premature death was present for 20 (8.0%) children but absent for 157 (62.1%) children, and the data for 76 (37.2%) children was missing.

Discussion. Abnormal lipid metabolism is reportedly common in patients with kidney disease,[5] particularly nephrotic syndrome (**Table 2**); the most common known lipid abnormalities with nephrotic syndrome are hypercholesterolemia, hyperlipidemia of LDL and hypertriglyceridemia. Decreased plasma oncotic pressure stimulates hepatic lipoprotein synthesis resulting in hypercholesterolemia, diminished clearance might also play a role in the development of hypercholesterolemia. Impaired metabolism is primarily responsible for nephrotic hypertriglyceridemia.

In the present study, 45 children (17.8%) had diabetes mellitus. A number of lipoprotein abnormalities have been observed in the untreated, hyperglycemic patient with diabetes mellitus. In a study carried out in Egypt,[6] the lipid profiles of 60 children with type 1 diabetes mellitus were compared with those of healthy children in the general population, dyslipidemia is significantly more frequent in children and adolescents with type 1 DM compared with non-diabetic peers. In addition, HbA1c concentrations were significantly related with TC and non-HDL-C concentrations.[7] Quantitative and qualitative abnormalities occur via lipoproteins in patients with diabetes. Quantitative involve the increased level of TG and decrease in HDL cholesterol levels, whereas the qualitative abnormality occurs by increased VLDL particle size and an increase in triacylglycerol content of both LDL and HDL.[8]

Dyslipidemia is a common finding among children with chronic kidney disease. It is associated with lower GFR, nephrotic proteinuria, and non-renal factors, such as age and obesity. There are various factors involved in the pathogenesis of dyslipidemia in CKD, including increased levels of triglycerides, triglyceride-rich lipoproteins, decreased levels of high-density lipoproteins, and aberrations in serum VLDL and IDL.[9,10] Consequently, it is a cause of major concern for patients with CKD, because it has been found that the prevalence of coronary heart disease secondary to CKD is higher, and thus the mortality rates are also increased.

Hypothyroidism has previously shown to be a contributing factor to hyperlipidemia; a cross-sectional study conducted in Hail, KSA, where search of the patient database for new patients with thyroid dysfunction between January 2011 and June 2012 showed elevated serum TC, TG, and LDL-C concentrations, and decreased serum HDL-C, which predisposes patients to atherogenic changes.[11] Furthermore, the oxidation of plasma cholesterol is increased due to 2 main mechanisms that include altered binding patterns and increased cholesterol levels.[12]

Regarding BMI, hyperlipidemia occurs much more frequently among overweight and obese children. The typical pattern is one of elevated serum LDL-C and TG concentrations and decreased HDL-C concentration. Our study has shown that as the BMI increases, so does the lipid profile, thus demonstrating a clear positive correlation between both.

Familial hypercholesterolemia (FH) is a genetic syndrome characterized by a high LDL-C concentration from birth. It is an autosomal dominant disorder caused by defects in the LDLR gene that encodes for the Apo B/E (LDL) receptor.[13] The associated impairment in the function of these receptors results in reduced clearance of LDL particles from the circulation and therefore elevated plasma LDL-C. In addition to LDL receptor defects, the phenotype of FH can be seen with mutations in the PCSK9 gene or mutations in the gene that codes for apolipoprotein B.

Table 2 - Mean cholesterol concentrations in children visiting the endocrine clinic by diagnosis.

Diagnosis	LDL (mmol/l)	HDL (mmol/l)	Total cholesterol level at first high measurement (mmol/l)	Total cholesterol at highest measurement (mmol/l)	Triglycerides (mmol/l)
Nephrotic syndrome	5.7	1.4	8.8	9.02	2.8
Diabetes mellitus	3.4	1.3	4.9	4.9	2.6
Chronic renal failure	3.8	Null	5.7	4.7	2.4
Hypothyroidism	4.3	0.9	4.8	5.7	3.4
Primary lipid + Idiopathic	3.5	0.8	5.9	4.7	2.9
Obesity	3.9	1.1	5.7	5.8	2.04
Metabolic	5.00	Null	5.1	5.7	3.5
Iatrogenic	4.04	0.6	3.5	3.6	3.6
LDL - low density lipoprotein, HDL - high density lipoprotein					

Finally, metabolic syndrome consists of several core laboratory items including a raised TG level, a decreased HDL-C level, and elevated fasting plasma glucose concentration. Clinically, it is also associated with increased abdominal obesity and an increased blood pressure.[14] Dyslipidemia in metabolic syndrome is attributed to an increased flux of free fatty acids to the liver, which promotes TG synthesis, and subsequently VLDL production. Increased VLDL, together with decreased LPL activity due to insulin resistance, causes accumulation of TG-rich lipoproteins, including proatherogenic remnants. Further increased activities of cholesteryl ester transfer protein and hepatic triglyceride lipase result in low HDL-C, and small, dense LDL concentrations.[15]

In conclusion, different etiologies of hyperlipidemia have demonstrated different pathophysiology that lead to the alteration of lipid profile. The result of this study has shown that the most common cause of hyperlipidemia in children visiting the endocrinology clinic of KAUH was due to nephrotic syndrome, which according to researches cited earlier is one of the main features for diagnosing this renal disease. Diabetes mellitus was the second most common etiology for hyperlipidemia due to its various mechanisms in increasing a patient's lipid profile. The least number of patients visiting the clinic with hyperlipidemia were those with CRF. Finally, according to our study, obesity was not considered a major etiology of hyperlipidemia.

Research on Dyslipidemias in pediatric age group is very limited, and not many resources are available. This research will be a valuable resource for others who are looking further into the etiologies of hyperlipidemia, and may be used as a guide for setting preventive measures against hyperlipidemia including management guidelines and improving the lifestyle of the patients through proper diet and exercise. It will increase the public awareness regarding this disorder, and will help the community find further methods of avoiding complications brought by it.

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