Association of Subclinical Hypothyroidism and Dyslipidemia in Children and Adolescents

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Research article

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Abstract

Background: Correlation of higher levels of TSH and dyslipidemia in children is controversial. This study was designed to assess the relation between lipid profile components and TSH levels in children.

Method: This cross-sectional study was performed in a growth assessment clinic in Shiraz. Children aged between 2 to 18 years that came to the clinic from January till April 2018 were considered. TSH levels equal or above 5 and lower than 10 mIU/L with normal FT4 were considered as subclinical hypothyroidism.

Results: 666 children were euthyroid while 181 had subclinical hypothyroidism. Mean total cholesterol in euthyroid children was 160.50 ± 29.070 mg/dl and in SH group 161.39 ± 28.694 mg/dl ($P=0.713$). Mean LDL-C in euthyroid children was 90.96 ± 24.996 mg/dl and in SH group 89.10 ± 23.852 mg/dl ($P=0.369$). Mean HDL-C in euthyroid children was 47.94 ± 10.560 mg/dl and in SH group 49.04 ± 10.361 mg/dl. ($P=0.211$). Mean non HDL-C in euthyroid children was 112.56 ± 27.696 mg/dl and in SH group 112.35 ± 28.136 mg/dl. ($P=0.929$). Mean triglyceride in euthyroid children was 104.98 ± 54.934 mg/dl and in SH group 113.83 ± 91.342 mg/dl ($P=0.215$). There was no significant difference in mean serum total cholesterol, LDL, HDL, non-HDL and triglyceride levels between euthyroid and subclinical hypothyroid. Adjusted correlation was not significant between TSH levels and any lipid profile component.

Conclusion: By comparing the results of this study with other studies, it is evident that lipid disorder in subclinical hypothyroid children does not have a specific pattern.

Introduction

Subclinical hypothyroidism is defined as elevated TSH levels while T4 or FT4 levels are normal.[1] It is a common disorder with a prevalence of 1 to 10% in Adult Community, [2, 3] while in the pediatrics population subclinical hypothyroidism is slightly lower than 2%.[2, 4] Elevated TSH levels are linked with obesity[5], and they are found to be reversible after weight loss, whether being attained through bariatric surgery or diet.[6, 7]

Subclinical hypothyroidism in adults has been linked to higher chances of cardiac disease,[8–14] insulin resistance and neuromuscular and neurobehavioral alteration.[10, 15–18]

Several studies have correlated subclinical hypothyroidism in adults with higher levels of total cholesterol, LDL, non-HDL, TG and lower levels of HDL.[19–21] However in study by Meisinger et al only higher triglyceride was correlated with higher levels of TSH in male participants. Higher levels of total cholesterol and LDL-C was only true for female participants.[22]

Correlation of higher levels of TSH and dyslipidemia in children is controversial. Some studies have showed higher levels of TC, LDL and TG with increase in TSH.[23–27] Conversely another study showed higher levels of TG as the only positive correlation with increase in TSH.[28]

Studies about the association of dyslipidemia and subclinical hypothyroidism in children show different results. This cross sectional prospective study was designed to compare lipid profiles including TG, Total Cholesterol, LDL-c and HDL-c in euthyroid vs. subclinical hypothyroid children.

Methods

This study was conducted as part of a larger project on serum lipid and thyroid profile in southern Iranian children and adolescents; details of which are available in another research paper.[29] In short, children with an age of 2 to 18 years that came to a growth assessment clinic in the city of Shiraz for routine growth follow up from January till April 2018 were selected for the study. After consent from their parents, they were checked for serum Total cholesterol, LDL-c, HDL-c, Non-HDL-c, TG, TSH and FT4 levels simultaneously in a non-fast state. For this study, inclusion criteria were: 1- age of 2–18 years; 2- presence of normal free T4 ($0.8–1.8$ ng/dL) ; 3- TSH between 0.3 and < 10 mIU/L. Exclusion criteria were 1- Those children who were on levothyroxine therapy at the time of assessment; 2- Ongoing use of medications that may interfere with thyroid function test or lipid profile such

as anti-thyroid medications, corticosteroids, oral contraceptives, thiazides; 3- Familial Hyperlipidemia; 4- Diseases that may affect lipid profile such as DM, kidney disease, rheumatologic disease, other endocrine disease.

847 children including 366 (43.2%) boys and 481 (56.8%) girls had full inclusion criteria and were selected for this study. For precise calculation of BMI, SDS-BMI and BMI percentile, UptoDate calculators, which are based on CDC growth charts, were used. Serum TSH and lipid profile were measured using Cobas e411 Analyzer (Mannheim, Germany) with electrochemiluminescence immunoassay (ECLIA) method and Dirui CS- T240 Auto chemistry Analyzer (Changchun, China) using Pars Azmoon kits(Iran) respectively. Assay performance was controlled using Elecsys PreciControl Universal for serum thyroid profile and TrueLab N and TruLab P for lipid profile. Auto Analyser was calibrated using Elecsys TSH CalSet and TruCal U. Inter-assay coefficients of variation (CVs) for TSH are 1.56% for 1.37 mIU/L and 0.08% for 8.62 mIU/L respectively while inter and intra assay coefficient of variations were 3.2 and 2.29% for total cholesterol and 1.6 and 1.49% for triglyceride respectively.

Signed informed consent was obtained from all participants and or their parents. The study was approved by the Kazeroon Azad University of Medical Sciences research ethics committee. (reference 1398.125)

Abnormal lipid profile cutoffs are based on the 2011 statement of the National Heart, Lung, and Blood Institute's (NHLBI) Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents and the 2008 American Academy of Pediatrics' (AAP) policy statement. (Table 1)

TSH levels equal or above 5 were considered abnormal. All participants with high TSH levels were considered for a second remeasurement. For these participants, second TSH levels were considered for the study.

For analysis, the study group was divided into two age groups: 2–9 and 10–18 each representing before start of puberty and after start of puberty respectively. Participants with TSH levels equal or above 5 mIU/L and lower than 10 mIU/L with normal free T4 levels were categorized as Subclinical Hypothyroid children. Relation between serum TSH and each lipid profile component (dependent variable) was evaluated using partial variable correlation, adjusted for age, gender and BMI Z-score. Comparisons were performed by using chi_squared test for categorical variables in table 4 and by Student t-test for continuous variables in table 3. A value of $p < 0.05$ was considered statistically significant in all comparisons with confidence interval of 95%. All statistical analysis were performed using SPSS software version 25.0 (SPSS, Chicago, IL, USA).

Results

Based on Table 2, of the 847 children in this study, 666 had TSH levels between 0.3–4.9 IU/ml and were considered as euthyroid while 181 who had TSH levels of 5–9.9 mIU/L and were considered as subclinical hypothyroid participants. There was no significant statistical difference in mean age between euthyroid and subclinical hypothyroid participants. (9.96 ± 3.40 years vs. 9.98 ± 3.28 , $P = 0.945$) 42.8% of euthyroid and 44.8% of subclinical hypothyroid were male. ($p = 0.637$) Overall, subclinical hypothyroid children had higher BMI Z-scores than euthyroid children. ($p = 0.012$) (Table 2)

Table 3 shows mean levels of lipid profile components in euthyroid and subclinical hypothyroid children and the subgroups of 2–10 and 10–18 years of age participants. Overall, there was no significant statistical difference in any of the lipid profile components between euthyroid and subclinical hypothyroid children and in the subsequent age related subgroups. (Table 3)

Table 4 shows the prevalence of dyslipidemia in each of the lipid profile components in euthyroid and subclinical hypothyroid children and their respective age groups. Overall, there was no significant statistical difference in prevalence of any of the lipid profile dyslipidemias between euthyroid and subclinical hypothyroid children and in the subsequent age related subgroups. (Table 4)

Table 5 shows the association of TSH levels and each of the lipid profile components based on partial correlation method adjusted for age, gender and BMI Z-score. No correlation was seen between TSH levels and any of the lipid profile components. Use of logistic regression was forgone due to the results of this study. (Table 5)

Discussion

Based on our study, we found no correlation between TSH levels and lipid profile components. We also found no difference in mean levels of serum lipid levels between euthyroid and subclinical hypothyroid patients.

In a study by Unal E et al on 38 subclinical hypothyroid children in comparison to a control group, Subclinical hypothyroidism lead to an increased dyslipidemia (increased TC and LDL)[23] and in a study by Witte T et al showed that there is significant positive association between TSH and all non-HDL parameters (total cholesterol, LDL-C, and triglycerides) in children.[24] Another study by Cerbone M showed that triglyceride to high-density lipoprotein-cholesterol ratio ($P = 0.01$), and high-density lipoprotein-cholesterol were significantly lower ($P = 0.003$) in SH subjects compared with controls.[25]

In the study by Paoli-Valeri M et al on 17 children with subclinical hypothyroidism, subjects with subclinical hypothyroidism had significantly lower HDL-C levels.[26]. In the latest study by Dahl AR, et al on 228 children with subclinical hypothyroidism showed that Mild SCH in children and adolescents was associated with higher rates of elevated total cholesterol and elevated non-HDL cholesterol.[27].

Meanwhile, Nader NS et al argued that in euthyroid children without a history of hypo- or hyperthyroidism, increasing levels of TSH and decreasing levels of free T4 are associated with higher triglyceride levels[28] and Gönül Çatlı et al, in a study on 27 subclinical hypothyroid children comparing to a control group, showed that there is similar Serum lipoprotein levels and dyslipidemia frequency between the two groups.[30].

According to our results there is no relation between mean TC, LDL-C, HDL-C, non HDL-C and TG levels in euthyroid and subclinical hypothyroid children. The same results is found in the subsequent 2–10 and 10–18 year old age groups.

There is no statistical difference between the percentage of children who have high TC, LDL-C, Non-HDL-C and TG in euthyroid and subclinical hypothyroid children. No statistical difference was also shown in percentage of children with low HDL-C between euthyroid and subclinical hypothyroid children.

According to Berenson GS, et al, in the Bogalusa Heart study, atherosclerosis will start at childhood and the effect of multiple risk factors on the extent of atherosclerosis was quite evident. One of the major risk factors in atherosclerosis is hyperlipidemia.[31]

Although L-T4 treatment exerts some beneficial effects, there is no available data regarding the impact of therapy on metabolic outcomes in SH children.[25, 30]

The mechanism of how thyroid hormones can affect lipid profile is not completely clear, but thyroid hormones reduce apoB lipoproteins via a non-LDLR pathway that leads to decreased liver apoB production.[32]

Although it is generally believed that thyroid hormones and their synthetic derivatives known as thyromimetics, can reduce serum cholesterol by their ability to increase LDLRs but recent study showed that TH and thyroid hormone receptor- β selective agonists GC-1 and KB2115 are able to reduce serum cholesterol by inducing Cyp7a1 expression and stimulating the conversion and excretion of cholesterol as bile acids.[33].

The advantage of our study relative to other studies is that a large number of subclinical hypothyroid children are included and also this is a cross sectional prospective study. Most of the other studies on relation of TSH and serum lipid concentration are case control studies spanning several years.

Conclusion

From this study, it can be concluded that that high TG is the most common lipid disorder in SCH patient, followed by high non HDL-C. In addition, by comparing the results of this study with other studies, it is evident that lipid disorder in SCH children does not have a specific pattern.

Abbreviations

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Non-HDL-C, non-low-density lipoprotein cholesterol; TG, triglycerides; BMI, body mass index; TSH, thyroid stimulating hormone; FT4, free T4; CI, confidence interval; CDC, center for disease control and prevention.

Declarations

Availability of data and materials: The datasets used during the current study are available from the corresponding author on reasonable request.

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Contributions

AshH: Collected the data, performed data analysis, interpreted the data and wrote the manuscript AsaH: Designed the study, Involved in critical revision of the manuscript. All authors read and approved the final version of the manuscript.

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Ethics declarations

Ethics approval and consent to participate: Signed informed consent was obtained from all participants and or their parents. The study was approved by the Kazeroon Azad University of Medical Sciences research ethics committee. (reference 1398.125)

Consent for publication: Not applicable.

Competing interests: The authors declare that they have no competing interests.

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Tables

Table 1. Definition of lipid levels in children from the 2011 Expert Panel Integrated Guidelines for Cardiovascular Health and Risk reduction in Children and Adolescents			
Category	Acceptable mg/dL (mmol/L)	Borderline mg/dL (mmol/L)	High
TC	<170 (4.4)	170 to 199 (4.4 to 5.2)	≥200 (5.2)
LDL-C	<110 (2.8)	110 to 129 (2.8 to 3.3)	≥130 (3.4)
Non-HDL-C	<120 (3.1)	120 to 144 (3.1 to 3.7)	≥145 (3.8)
TG			
• 0 to 9 years	<75 (0.8)	75 to 99 (0.8 to 1.1)	≥100 (1.1)
• 10 to 19 years	<90 (1 mmol/L)	90 to 129 (1 to 1.5)	≥130 (1.5)
Category	Acceptable	Borderline	Low
HDL-C	>45 (1.2)	40 to 45 (1 to 1.2)	<40 (1)
Abbreviations: TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Non-HDL-C, non-low-density lipoprotein cholesterol; TG, triglycerides			

Table 2. Anthropometric characteristics of the study subjects.			
	Euthyroid (666)	Subclinical Hypothyroid (181)	P value
Age	9.96 ± 3.40	9.98 ± 3.28	0.945
Gender (Male)	42.8%	44.8%	0.637
Height (cm)	135.20 ± 19.48	137.16 ± 18.37	0.226
Weight (kg)	38.66± 20.22	41.31± 19.44	0.116
TSH (mIU/L)	2.52 ± 1.16	6.90 ± 1.52	<0.001*
FT4 (ng/dl)	1.40 ± 0.25	1.43 ± 0.26	0.242
BMI Z score	0.16 ± 1.84	0.55 ± 1.80	0.012*
BMI	19.76 ± 6.14	20.98 ± 7.39	0.024*
Abbreviations: BMI, body mass index; TSH, thyroid stimulating hormone; FT4, free T4.			

Table 3. Mean serum lipid profile components based on the subjects' thyroid status.									
	Total (847)			Age 2-10 (421)			Age 10-18 (426)		
	Euthyroid (666)	Subclinical Hypothyroid (181)	P	Euthyroid (325)	Subclinical Hypothyroid (96)	P	Euthyroid (341)	Subclinical Hypothyroid (85)	P
TChol	160.50 ± 29.070	161.39 ± 28.694	0.713	161.66 ± 29.842	160.73 ± 26.664	0.782	159.38 ± 28.314	162.14 ± 30.971	0.431
LDL- chol	90.96 ± 24.996	89.10 ± 23.852	0.369	92.54 ± 25.514	88.06 ± 21.540	0.119	89.46 ± 24.436	90.27 ± 26.302	0.788
HDL- chol	47.94 ± 10.560	49.04 ± 10.361	0.211	48.62 ± 11.077	50.09 ± 10.910	0.253	47.29 ± 10.016	47.86 ± 9.630	0.637
Non- HDL- chol	112.56 ± 27.696	112.35 ± 28.136	0.929	113.04 ± 28.081	110.64 ± 27.286	0.459	112.09 ± 27.358	114.28 ± 29.107	0.515
TG	104.98 ± 54.934	113.83 ± 91.342	0.215	97.18 ± 48.897	114.95 ± 104.861	0.111	112.40 ± 59.251	112.56 ± 73.757	0.983
Abbreviations: TChol, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; Non-HDL-c, non-low-density lipoprotein cholesterol; TG, triglycerides									

Table 4. Distribution of lipid profile abnormality based on thyroid status and age.									
	Total (847)			Age 2-10 (421)			Age 10-18 (426)		
	Euthyroid (689)	Subclinical Hypothyroid (184)	P	Euthyroid (338)	Subclinical Hypothyroid (100)	P	Euthyroid (351)	Subclinical Hypothyroid (84)	P
TChol (mg/dL)									
Acceptable (<170)	66.4%	65.7%	0.915	63.7%	65.6%	0.933	68.9%	65.9%	0.672
Borderline-high (170–199)	24.2%	23.8%		27.1%	26.0%		21.4%	21.2%	
High (≥200)	9.5%	10.5%		9.2%	8.3%		9.7%	12.9%	
LDL-chol (mg/dL)									
Acceptable (<110)	81.2%	83.4%	0.682	77.8%	85.4%	0.268	84.5%	81.2%	0.636
Borderline-high (110–129)	12.3%	9.9%		14.8%	9.4%		10.0%	10.6%	
High (≥130)	6.5%	6.6%		7.4%	5.2%		5.6%	8.2%	
HDL-chol (mg/dL)									
Acceptable (>45)	56.9%	61.9%	0.266	58.8%	63.5%	0.205	55.1%	60.0%	0.720
Borderline-low (40–45)	19.8%	20.4%		17.2%	20.8%		22.3%	20.0%	
Low (<40)	23.3%	17.7%		24.0%	15.6%		22.6%	20.0%	
Non-HDL-chol (mg/dL)									
Acceptable (<120)	64.0%	62.4%	0.661	64.6%	63.5%	0.857	63.3%	61.2%	0.213
Borderline-high (120–144)	24.2%	23.2%		21.5%	24.0%		26.7%	22.4%	
High (≥145)	11.9%	14.4%		13.8%	12.5%		10.0%	16.5%	
TG (mg/dL)									
Acceptable (<75/90)	41.0%	44.2%	0.522	38.2%	39.6%	0.967	43.7%	49.4%	0.400
Borderline-high (75–99/90–129)	26.7%	22.7%		23.7%	22.9%		29.6%	22.4%	
High (≥100/130)	32.3%	33.1%		38.2%	37.5%		26.7%	28.2%	
Abbreviations: TChol, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; Non-HDL-c, non-low-density lipoprotein cholesterol; TG, triglycerides									

Table 5. Correlation of lipid profile components with serum TSH levels.		
Lipid Profile components	Correlation coefficient (r)	P value
TChol	0 .033	0 .331
LDL-c	0 .015	0 .657
HDL-c	0 .039	0 .257
Non-HDL-c	0 .020	0 .554
TG	0 .019	0 .584
<p>Notes: Data are given in r and <i>P</i> values. Correlation coefficient was assessed by partial correlation method. Adjusted for age, sex and BMI Z-score</p> <p>Abbreviations: TChol, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; Non-HDL-c, non-low-density lipoprotein cholesterol; TG, triglycerides</p>		