ATHEROGENIC INDICES IN THE ASSESSMENT OF CARDIOVASCULAR DISEASE RISK IN CHILDREN WITH OBESITY AND SUBCLINICAL HYPOTHYROIDISM

N. Akici^{1,*}, Z.E. Onal¹, T. Gürbüz¹, C. Sağ¹, S. Kiliç²

¹*Istanbul Haydarpaşa Numune Training and Research Hospital - Department of Pediatrics,*

²*Bagcilar Training and Research Hospital, Istanbul, Turkey*

Abstract

Background. The frequency of subclinical hypothyroidism (SH) in patients with obesity is increased compared with the normal population. However, data on the risk of cardiovascular disease (CVD) in patients with SH are still scarce. Lipid parameters are strong predictors of early CVD. We aimed to investigate the role of lipid indices in predicting CVD risk compared to conventional lipid components.

Methods. A total of 220 euthyroid obese children (EU) and 90 obese children with SH were included in the study. All data were collected from hospital files. Lipid indices were evaluated. Atherogenic index of plasma (AIP), cardiac risk ratio (CRR) and atherogenic coefficient (AC) were calculated. $AIP > 0.24$, $CRR > 5$ ve $AC > 3$ were considered as cardiovascular risk criteria.

Results. The presence of SH increased the risk of higher AIP and the risk of CRR, compared to euthyroid obese children.

Conclusion. Subclinical hypothyroidism in obese children may cause dislipidemia carrying a high cardiovascular disease risk.

Keywords: Atherogenic coefficient, atherogenic index of plasma, cardiac risk ratio, obesity, subclinical hypothyroidism.

INTRODUCTION

While the diagnosis of hypothyroidism is established when low levels of thyroid hormones lead to increased levels of thyroid stimulation hormone (TSH), subclinical hypothyroidism (SH) refers to increased TSH levels above the upper limit of reference range (5-10 mIU/L) at the presence of normal thyroid hormone levels (1). Recent literature revealed varied alterations of lipid parameters in hypothyroidism. In this study, we aimed to investigate the effect of SH on cardiovascular risk indices in comparison to euthyroid status in obese children.

MATERIALS AND METHOD

We performed a retrospective case-control study in an outpatient setting after obtaining the approval from the local ethics committee. Parents gave their informed, written consent for the inclusion of children in this study. A total of 310 obese patients aged between 6-18 years were included in the study. Obesity was defined as a body mass index (BMI) greater than the 95th percentile according to the standards of the Centers for Disease Control and Prevention (CDC2000). Patients with chronic diseases, a history of drug use, any other endocrine pathology or suspected syndromes associated with obesity were excluded from the study. Children were divided into two groups according to serum TSH levels as euthyroid group (EU, FT4 levels normal TSH < 5 mIU/L) and subclinical hypothyroid group (SH, FT4 levels normal. TSH levels between 5-10 mIU/L). The EU group included 92 males and 128 females whose mean age was 12.19 ± 2.65 years. The SH group consisted of 34 males and 56 females whose mean age was 12.05 ± 2.47 years (Table 1).

Findings of physical examination were recorded along with weight, height, and blood pressure measurement. Blood samples were taken following a 12-hour night fasting to assess the metabolic findings in all children. Fasting blood glucose, insulin, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), TSH, and FT4 levels were measured. The atherogenic index of plasma (AIP, $\log[TG/HDL-C]$), cardiac risk ratio (CRR, $TC/HDL-C$), and atherogenic coefficient (AC, $non-HDL-C/HDL-C$) were calculated. $AIP > 0.24$, $CRR > 5$, and $AC > 3$ were considered as cardiovascular risk criteria (2, 3).

FT4 and TSH were measured by a homogeneous sequential chemiluminescent immunoassay based on

*Correspondence to: Narin Akıcı MD, Haydarpaşa Numune Education and Research Hospital, Department of Pediatrics, Tıbbiye Cad. No: 23 Selimiye Üsküdar, 34668, Istanbul, Turkey, E-mail: narinakici@yahoo.com

Table 1. Anthropometric and metabolic findings of groups

	Control n:220	SH n:90	P
Age (years)	12.19±2.65	12.05±2.47	0.759
Gender	Male n (%)	34 37.7%	0.105
	Female n (%)	56 62.3%	
Height (cm)	152.42±13.97	148±18.08	0.133
Weight (Kg)	70.28±18.78	69.82±19.86	0.896
Height-SDS	0.72±1.32	0.71±1.11	0.346
Weight-SDS	2.76±0.72	2.57±0.99	0.213
BMI (kg/m ²)	30.72±4.58	30.44±3.55	0.706
BMI-SDS	2.68±0.44	2.68±0.52	0.93
Systolic blood pressure (mmHg)	115.96±23.3	118.96±12.51	0.566
Diastolic blood pressure (mmHg)	74.45±12.53	73.22±9.1	0.677
Glucose (mg/dL)	91.59±6.73	93.07±7.82	0.177
Insulin (mU/L)	18.01±10	18.21±10.18	0.912
HbA1c (%)	5.7±0.3	5.6±0.4	0.095
Cholesterol (mg/dL)	179.97±35.13	174.46±28.86	0.345
Triglyceride (mg/dL)	133.68±64.74	120.19±52.56	0.209
LDL-C (mg/dL)	114.96±30.46	105.71±28.52	0.082
HDL-C (mg/dL)	42.12±7.59	44.75±11.41	0.110
TSH (mU/L)	2.86±1.06	6.91±1.34	0.0001
FT4 (ng/dL)	1±0.24	0.89±0.18	0.002

LOCI technology using Siemens Healthcare System (Behring Inc.). Plasma glucose levels were measured by the glucose oxidase method. Serum insulin concentrations were measured by radioimmunoassay (RIA) using a commercial kit (Bio-Rad). HbA1c was measured by HPLC (high performance liquid plasma chromatography) method (BioRad Laboratories Ltd). Plasma cholesterol and TG were measured enzymatically with an RA-1000 Autoanalyser. HDL-C was also measured in the RA-1000 after precipitation of apo-B containing lipoproteins. LDL-C was calculated according to Friedewald's Formula ($\text{LDL-C} = \text{Total Cholesterol} - (\text{VLDL-C} + \text{HDL-C})$, $\text{VLDL-C} = \text{Triglyceride}/5$).

Statistical analysis was performed using the program NCSS 2007 (Number Cruncher Statistical System, Kaysville, Utah, USA). Descriptive data were presented in numbers and percentages or mean and standard deviations, where appropriate. After performing the normality test, the groups were compared via dependent t-test and Mann Whitney U test for normally and non-normally distributed variables, respectively. Categorical variables were compared through chi-square test whereas the association of variables was demonstrated by using Pearson correlation test. An overall 5% of Type-I error level was used to infer statistical significance.

RESULTS

There was no statistically significant difference among the mean age, gender, weight, height, BMI,

systolic and diastolic blood pressures, and levels of glucose, insulin, HbA1c, serum lipid parameters (TC, TG, LDL-C, and HDL-C) between SH and EU groups ($p > 0.05$). As expected, there was a statistically significant difference among the mean levels of TSH and FT4 between the groups ($p < 0.05$). The study groups did not significantly differ in terms of AIP, CRR, and AC ($p > 0.05$). In SH group, 31.9% had $\text{AIP} > 0.24$, 18% had $\text{CRR} > 5$, and 51.6% had $\text{AC} > 3$. In EU group, 16% had $\text{AIP} > 0.24$, 12.7% had $\text{CRR} > 5$, and 40.8% had $\text{AC} > 3$.

We found that the presence of SH increased the risk of $\text{AIP} > 0.24$ by 2.4-fold (95% CI, 1.37-4.32) (Table 2). SH also increased the risk of $\text{CRR} > 5$ by 1.68-fold (Table 3) and that of $\text{AC} > 3$ by 1.55-fold (95% CI, 0.95-2.55), (Table 4). The latter risk elevation of AC was not statistically significant among boys (0.98; 95% CI, 0.45-2.16; 95% CI) but was preserved among girls (2.14; 95% CI, 1.13-4.08). The risk of $\text{AIP} > 0.24$ associated with SH was 1.64-fold in boys compared to 3.23-fold in girls. While the risk of $\text{CRR} > 5$ was increased by 3.42-fold (95% CI, 1.44-8.14) in girls with SH, we found no significant risk change in obese boys. We detected no association of serum TSH and FT4 levels to AIP, CRR, and AC values in the study groups (Table 5).

DISCUSSION

Thyroid hormones play an important role in the regulation of basal metabolism, thermogenesis,

Table 2. Evaluation of AIP in SH and EU groups among genders

Sex	Thyroid function status		AIP>0.24	AIP<0.24	Total
Male	Hypothyroid	n (%)	10 (28.6)	25 (71.4)	35 (100.0)
	Euthyroid	n (%)	17 (19.5)	70 (80.5)	87 (100.0)
	Total	n (%)	27 (22.1)	95 (77.9)	122 (100.0)
Female	Hypothyroid	n (%)	19 (33.9)	37 (66.1)	56 (100.0)
	Euthyroid	n (%)	17 (13.7)	107 (86.3)	124 (100.0)
	Total	n (%)	36 (20.0)	144 (80.0)	180 (100.0)

AIP, atherogenic index of plasma; SH, subclinical hypothyroidism; EU, euthyroid obese patients.

glucose and lipid metabolism, food intake, and fat oxidation (4). Obesity and mild hypothyroidism are frequently coexisting diseases. On the other hand, it is critical that SH may be undiagnosed and missed in obese children. Recent literature has suggested that the predictive cardiovascular risk factors for atherosclerotic changes in adulthood begin to occur in childhood. The Bogolusa Heart Study demonstrated that body mass index, systolic and diastolic blood pressure, TG, TC, LDL-C, and HDL-C were associated with an increased risk of early atherosclerotic changes in children (5).

Thyroid hormone regulates the synthesis and metabolism of lipids by decreasing intestinal cholesterol absorption and increasing hepatic cholesterol synthesis (6,7). Yadav *et al.* performed a study on 27 children aged 11 ± 2.4 years with SH, where they reported higher BMI, waist-to-height ratio, LDL-C, TG, TG/HDL-C ratio, fasting insulin levels, HOMA-IR values and lower FT4 and HDL-C levels compared to euthyroid subjects. The authors further reported a positive correlation of BMI to TG and TG/HDL-C ratio in children with SH (8).

Few studies revealed higher SBP and DBP in children and adolescents with higher TSH levels (9,10). Cerbone *et al.* reported normal blood pressure levels and did not find any significant difference in SBP and DBP in children with SH compared to euthyroid patients (11), consisting with the findings from the study of Yadav *et al.* (8). The results of our study were similar with these two studies indicating that the presence of SH did not change blood pressure levels, as compared to euthyroidism.

Although the relation between overt hypothyroidism and atherosclerosis is well documented, the association of SH to increased risk of atherosclerotic

disease is still controversial (12,13). This risk elevation seems to be caused by cardiovascular changes related with dyslipidemia, insulin resistance, and diastolic dysfunction which are observed also in mild SH (14-17). Although we did not identify insulin resistance and diastolic dysfunction in our SH patients, altered lipid profile indicating dyslipidemia (high LDL-C, high TG, and low HDL-C level) was detected compared to euthyroid group.

Marwaha *et al.* reported lower HDL-C and higher LDL-C and TG levels in children and adolescents with SH and TSH>10 mIU/L. The authors further reported that TSH levels were positively and FT3 and FT4 levels were negatively correlated with TC and LDL-C (18). Another study from South India reported higher levels of TC, TG and higher levels of HDL-C in children with SH (9). Nader *et al.* also demonstrated that TG levels were positively correlated with TSH levels and inversely correlated with FT4 levels (19). Paoli-Valeri *et al.* reported no change in levels of TG, TC, LDL-C but a decrease in HDL-C in four-month follow-up of children with SH (20). Cerbone *et al.* demonstrated normal TG, TC, and LDL-C levels but lower HDL-C levels in patients with SH (11). They documented an increased AIP and plasma TG/HDL-C ratio indicating an atherogenic risk profile, as these were considered as useful indices to identify subjects carrying cardiovascular disease risk (21, 22).

Although recent studies had inconsistent results about lipid profile in relation to SH, they tend to support elevated TG and reduced HDL-C in hypothyroidism, which seem to be consistent with our findings. TSH levels are at the upper limit of the normal range or slightly increased in obese children,

Table 3. Evaluation of CRR in SH and EU groups among genders

Sex	Thyroid function status		CRR>5	CRR<5	Total
Male	Hypothyroid	n (%)	4 (11.4)	31 (88.6)	35 (100.0)
	Euthyroid	n (%)	16 (18.2)	72 (81.8)	88 (100.0)
	Total	n (%)	20 (16.3)	103 (83.7)	123 (100.0)
Female	Hypothyroid	n (%)	14 (25.0)	42 (75.0)	56 (100.0)
	Euthyroid	n (%)	11 (8.9)	113 (91.1)	124 (100.0)
	Total	n (%)	25 (13.9)	155 (86.1)	180 (100.0)

CRR, cardiac risk ratio; SH, subclinical hypothyroidism; EU, euthyroid obese patients.

Table 4. Evaluation of AC in SH and EU groups among genders

Sex	Thyroid function status		AC>3	AC<3	Total
Male	Hypothyroid	n (%)	17 (48.6)	18 (51.4)	35 (100.0)
	Euthyroid	n (%)	43 (48.9)	45 (51.1)	88 (100.0)
	Total	n (%)	60 (48.8)	63 (51.2)	123 (100.0)
Female	Hypothyroid	n (%)	30 (53.6)	26 (46.4)	56 (100.0)
	Euthyroid	n (%)	43 (35.0)	80 (65.0)	123 (100.0)
	Total	n (%)	73 (40.8)	106 (59.2)	179 (100.0)

AC, atherogenic coefficient; SH, subclinical hypothyroidism; EU, euthyroid obese patients.

adolescents, and adults. The TSH level was reported to be positively related with BMI (23). Progressive fat deposition was positively related to an increase in TSH and FT3 levels irrespective of insulin sensitivity and metabolic parameters. BMI of obese children were also positively associated to FT3/FT4 ratio (24). This was also consistent with our findings that showed a significant difference between the mean levels of TSH and FT4 among the study groups. James *et al.* reported higher TG/HDL-C ratio and AIP levels in SH group compared to EU group but no correlation between TSH and AIP in SH group (25), similar to our findings.

The percentage of those with AIP>0.24 was increased 2.4-fold in the presence of SH with no change in CRR>5 and AC>3 subjects. On the other

hand, further analysis by gender showed that SH increased the risk of AIP>0.24 or the risk of AC>3 and CRR>5 about 2-fold in females compared to their male counterparts. These results suggest that females are affected much more than males in terms of the lipid profile if SH is present. SH may go unrecognized in obese patients. These patients will continue to gain weight and will develop a worse lipid profile, which can end in a full circle thyroid/obesity association. This indicates the need to diagnose SH as soon as early, as it carries the risk of altered lipid parameters.

The findings of our study should be interpreted in the light of its limitations. First, it has a retrospective design with a comparably lower sample size. Another limitation was that we used the Friedewald's formula for calculation of LDL-C though, in clinical practice, it is generally used when direct measurement is unavailable or costly. However, the Friedewald's formula cannot be used for LDL-C calculation when the subject is not fasting, when serum TG is >400 mg/dL or <100 mg/dL (26) or in patients with type III or type I hyperlipoproteinemia (27). The use of this formula is also not recommended for Type II diabetes mellitus, nephrotic syndrome, and chronic alcoholic patients (28-30).

In conclusion, our study has highlighted the necessity of further larger-sized studies that would be performed in children with obesity to clarify the relationship between thyroid function status and aspects of lipid profile. These studies may contribute to decrease the cardiovascular risk which may be secondary to altered lipid profile.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA. 2004;291(2):228-238.

Table 5. Comparison of AIP, CRR, AC with anthropometric measures and metabolic parameters

		AIP	CRR	AC
Age	r	-0.157	-0.009	-0.009
	p	0.077	0.916	0.916
Height	r	-0.006	0.028	0.028
	p	0.95	0.757	0.757
Weight	r	0.087	0.076	0.076
	p	0.344	0.406	0.406
Height-SDS	r	0.063	0.115	0.115
	p	0.477	0.193	0.193
Weight-SDS	r	0.116	0.035	0.035
	p	0.189	0.691	0.691
BMI	r	-0.039	-0.016	-0.016
	p	0.663	0.860	0.860
BMI-SDS	r	0.029	0.083	0.083
	p	0.746	0.345	0.345
Systolic blood pressure	r	0.121	0.126	0.126
	p	0.320	0.300	0.300
Diastolic blood pressure	r	0.02	-0.175	-0.175
	p	0.873	0.146	0.146
Glucose	r	0.115	0.015	0.015
	p	0.185	0.862	0.862
Insulin	r	0.352	0.162	0.162
	p	0.0001	0.062	0.062
HbA1c	r	0.105	0.065	0.065
	p	0.250	0.474	0.474
TSH	r	-0.018	-0.098	-0.098
	p	0.838	0.261	0.261
FT4	r	0.005	-0.140	-0.140
	p	0.950	0.106	0.106

AIP, Atherogenic index of plasma; CRR, cardiac risk ratio; AC, atherogenic coefficient.

2. Millán J, Pintó X, Muñoz A, Zúñiga M, Rubiés-Prat J, Pallardo LF, Masana L, Mangas A, Hernández-Mijares A, González-Santos P, Ascaso JF, Pedro-Botet J. Lipoprotein ratios: Physiological significance and clinical usefulness in cardiovascular prevention. *Vasc Health Risk Manag.* 2009;5:757-765.
3. Singh M, Pathak MS, Paul A. A Study on Atherogenic Indices of Pregnancy Induced Hypertension Patients as Compared to Normal Pregnant Women. *J Clin Diagn Res.* 2015;9(7):BC05-8.
4. Rosenbaum M, Hirsch J, Murphy E, Leibel RL. Effects of changes in body weight on carbohydrate metabolism, catecholamine excretion, and thyroid function. *Am J Clin Nutr.* 2000;71:1421-1432.
5. Berenson GS, Srinivasan SR, Nicklas TA. Atherosclerosis: a nutritional disease of childhood. *Am J Cardiol.* 1998;82:22T-29T.
6. Pearce EN. Update in lipid alterations in subclinical hypothyroidism. *J Clin Endocrinol Metab.* 2012;97:326-333.
7. Cooper DS, Biondi B-Subclinical thyroid disease. *Lancet.* 2012;379(9821):1142-1154.
8. Yadav Y, Saikia UK, Sarma D, Hazarika M. Cardiovascular Risk Factors in Children and Adolescents with Subclinical Hypothyroidism. *Indian J Endocrinol Metab.* 2017;21:823-829.
9. Poornachand V, Kumarasamy K, Seenivasan V, Karamath SP, Study of clinical and biochemical profile of subclinical hypothyroidism in children aged 2-12 years. *Int J Contemp Pediatr.* 2017;4:43-47.
10. Ittermann T, Thamm M, Wallaschofski H, Rettig R, Völzke H. Serum thyroid-stimulating hormone levels are associated with blood pressure in children and adolescents. *J Clin Endocrinol Metab.* 2012;7:828-834.
11. Cerbone M, Capalbo D, Wasniewska M, Mattace Raso G, Alfano S, Meli R, De Luca F, Salerno M. Cardiovascular risk factors in children with long-standing untreated idiopathic subclinical hypothyroidism. *J Clin Endocrinol Metab.* 2014;99:2697-2703.
12. Cappola AR, Ladenson PW. Hypothyroidism and atherosclerosis. *J Clin Endocrinol Metab.* 2003;88:2438-2444.
13. Cooper DS, Biondi B. Subclinical thyroid disease. *Lancet.* 2012;379:1142-1154.
14. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med.* 2000;160:526-534.
15. Duntas LH, Wartofsky L. Cardiovascular risk and subclinical hypothyroidism: focus on lipids and new emerging risk factors. What is the evidence? *Thyroid.* 2007;17:1075-1084.
16. Marotou E, Hadjidakis P J, Kollias A, Tsegka K, Peppas M, Alevizaki M, Mitrou P, Lambadiari V, Boutati E, Nikzas D, Tountas N, Economopoulos T, Raptis SA, Dimitriadis G. Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. *Eur. J Endocrinol.* 2009;160:785-790.
17. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. *Endocr Rev.* 2008; 29:76-131.
18. Marwaha RK, Tandon N, Garg MK, Kanwar R, Sastry A, Narang A, Arora S, Bhadra K. Dyslipidemia in subclinical hypothyroidism in an Indian population. *Clin Biochem.* 2011;44:1214-1217.
19. Nader NS, Bahn RS, Johnson MD, Weaver AL, Singh R, Kumar S. Relationships between thyroid function and lipid status or insulin resistance in a pediatric population. *Thyroid.* 2010;20:1333-1339.
20. Paoli-Valeri M, Guzmán M, Jiménez-López V, Arias-Ferreira A, Briceño-Fernández M, Arata-Bellabarba G. [Atherogenic lipid profile in children with subclinical hypothyroidism]. *An Pediatr (Barc).* 2005;62:128-134.
21. Castelli WP. Lipids, risk factors and ischaemic heart disease. *Atherosclerosis.* 1996;124 Suppl:S1-S9.
22. Salazar MR, Carbajal HA, Espeche WG, Aizpurúa M, Leiva Sisniegues CE, March CE, Balbín E, Stavile RN, Reaven GM. Identifying cardiovascular disease risk and outcome: use of the plasma triglyceride/high-density lipoprotein cholesterol concentration ratio *versus* metabolic syndrome criteria. *J Intern Med.* 2013;273:595-601.
23. Biondi B. Thyroid and obesity: an intriguing relationship. *J Clin Endocrinol Metab.* 2010;95:3614-3617.
24. Chomard P, Vernhes G, Autissier N, Debry G. Serum concentrations of total T4, T3, reverse T3 and free T4, T3 in moderately obese patients. *Hum Nutr Clin Nutr.* 1985;39:371-378.
25. James S.R, Ray L, Ravichandran K, Nanda S.K. High atherogenic index of plasma in subclinical hypothyroidism: Implications in assessment of cardiovascular disease risk. *Indian J Endocrinol Metab.* 2016;20:656-661.
26. Ahmadi SA, Boroumand MA, Gohari-Moghaddam K, Tajik P, Dibaj SM. The impact of low serum triglyceride on LDL-cholesterol estimation. *Arch Iranian Med.* 2008;11(3):318-321.
27. Rifai N, Warnick GR, McNamara JR, Belcher JD, Grinstead JF, Frantz M. Measurement of low-density-lipoprotein cholesterol in serum: a status report. *Clin Chem.* 1992;38:150-160.
28. Joven J, Villabona C, Vilella E, Masana L, Alberti R, Valles M. Abnormalities of lipoprotein metabolism in patients with the nephrotic syndrome. *N Engl J Med.* 1990;323:579-584.
29. Matas C, Cabré M, La Ville A, Prats E, Joven J, Turner PR, Masana L, Camps J. Limitations of the Friedewald formula for estimating low-density lipoprotein cholesterol in alcoholics with liver disease. *Clin Chem.* 1994; 40(3):404-406.
30. Rubiés-Prat J, Reverter JL, Sentí M, Pedro-Botet J, Salinas I, Lucas A, Nogués X, Sanmartí A. Calculated low-density lipoprotein cholesterol should not be used for management of lipoprotein abnormalities in patients with diabetes mellitus. *Diabetes Care.* 1993;16(8):1081-1086.