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Original Article

Thyroid function tests in overweight and obese children and adolescents with and without non-alcoholic fatty liver disease

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Abstract

Background: Hypothyroidism can play an important role in the development of non-alcoholic fatty liver disease (NAFLD). This study compared the thyroid function tests in overweight and obese children and adolescents with and without NAFLD.

Methods: This case-control study was conducted on 100 children and adolescents aged 4-18 years who referred to the endocrinology clinic of Amirkola Children's Hospital, Babol, Iran in 2021. 42 obese and overweight children with NAFLD were considered as case group and 56 persons without NAFLD as control group. They were selected after physical examination and body mass index (BMI) assessment. Then, TSH, T4, FBS, lipid profile, 25(OH) vit D3 (VD), AST and ALT levels were measured. Abdominal ultrasound was performed to survey fatty liver. T-test and Chi-score were used for analysis and $p< 0.05$ was considered significant.

Results: The mean age in both group was 11.63±2.55 and 10.07±2.61 years, respectively (P=0.004). Hypothyroidism was not seen in the groups. Two groups in terms of mean TSH (P=0.92), T4 (P=0.87), FBS (P=0.33), cholesterol (P=0.44), LDL (P=0.35), VD (P=0.07) had no significant difference. However, difference was found between the two groups in terms of the mean level of AST (P=0.003), ALT (P=0.001), TG (P=0.02), HDL (P=0.01) and BMI (P<0.001).

Conclusion: This study showed that the mean level of thyroid hormones in both groups did not have significant difference and hypothyroidism was not seen. Other studies with larger sample size and longer periods of time are suggested.

Keywords: Thyroid function test, Non-alcoholic fatty liver, Adolescence, Obesity, Overweight.

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Thyroid hormones (T3, T4) are produced by the thyroid gland under the influence of pituitary TSH. Hypothyroidism can appear at birth or be acquired in period of childhood and adolescence with or without symptoms. According to many researches, hypothyroidism is associated with obesity or may a cause of obesity (1). Central obesity can lead to metabolic abnormality with metabolic syndrome and liver damage in the form of non-alcoholic fatty liver disease (NAFLD) (2), which is considered as the main cause of chronic liver disease in children (3). Thyroid hormone is an important regulator of liver fat metabolism. This hormone through the induction of genes involved in hepatic lipogenesis, thyroid hormone couples autophagy to mitochondrial lipid oxidation, which in turn leads to ketogenesis and reverse cholesterol transport (4) A close relationship between high TSH level and NAFLD occurs in adults (5, 6). TSH plays as a mediator between obesity and NAFLD (7). NAFLD is the most common cause of abnormality in liver function tests in the world (7). Also, hypothyroidism is one of the most common diseases in the world, which plays an important role in the development of NAFLD (8).

A study conducted by Nichols et al. in 2020 between two groups with and without fatty liver showed that the mean level of TSH in the fatty liver group was higher than the control group (9). A systematic review and meta-analysis conducted by Zeqi Guo et al. in 2018, concluded that TSH level is an important risk factor in the development of NAFLD (6). On the other hand, Mantovani A (2018) in a systematic review concluded that existence of defined hypothyroidism is significantly associated with NAFLD and its severity ,but the eligible studies with their observational design does not permit to proof the casualty (10). It is commonly believed that hypothyroidism is associated with obesity and can lead to cold intolerance, bradycardia, brittle hair, dry skin, palority and myxedema (1). Therefore, considering the possible occurrence of changes in thyroid hormones in children and adolescents with NAFLD and the consequences of thyroid dysfunction in obese children and adolescents (especially those with NAFLD) and also the contradictory results in some studies and no existence of study in the field of pediatrics in Iran, we decided to investigate the mean level of thyroid hormones in overweight and obese children and adolescents with and without NAFLD.

Methods

Study type and samples: In this case-control study, 100 children and adolescents between the ages of 4-18 years with obesity and overweight referred to Amirkola Children's Hospital in 2021 were examined in terms of thyroid function tests. The inclusion criteria in the case group were obese and overweight persons, who went to the endocrinology clinic for growth monitoring in 2021 and then were referred to the gastroenterology clinic because of fatty liver disease. In the control group, there were children with similar conditions, but they were not suffering from NAFLD and were visited in the endocrinology clinic for growth monitoring.

Exclusion criteria in both groups included a history of liver and biliary, renal, infectious, vascular, blood and autoimmune diseases, celiac disease, metabolic disorders, hyperlipidemia, diabetes mellitus, obesity and overweight in the context of chromosomal syndromes, taking drugs affecting liver function, vitamin D (VD) use in the last 4 months, previous history of hypothyroidism and levothyroxine use.

Sample size and Sampling method: According to studies (9), taking into account, the effect size of 0.41 for the comparison of TSH index in two groups at the confidence level of 95% and power of 80% and the ratio of 1 to 1 in both case and control groups with a sample size of 100 samples was determined.

Assessment of physical examination and body mass index: First, after taking a complete history, all adolescents were subjected to a physical examination and their height and weight were measured. The children's weight was measured with a Balas digital scale made in Iran and their height was measured with a stadiometer. Then, according to the body mass index (BMI) curve by gender, persons whose BMI was below the 5th percentile were considered underweight, between the 5th and 85th percentile were normal, between the 85th and 95th percentile were overweight, and above than 95th percentile were considered as obese (9). If they were normal in history and physical examination in terms of other aspects (except overweight and obesity), they were included in the study.

Ultrasound assessment: The selected persons were considered for abdominal ultrasound and liver/thyroid function tests in endocrinlogy and gastroenterology clinics. Ultrasound was performed by a radiologist with a Toshiba Aplio-300 machine made in Japan. Children were divided in two groups with and without NAFLD based on ultrasound findings and liver enzyme levels. In children with liver involvement and having the criterion of fatty liver in ultrasound, or children with increased liver enzymes (if negative in terms of other causes), they were placed in the group with NAFLD (case group). Children who did not have findings in favor of fatty liver in ultrasound, were placed in the group without NAFLD (control group). Compared to biopsy, ultrasound of the liver has 89% specificity and 93% sensitivity in detecting fat deposition in fatty liver (11).

The sonographic criteria of fatty liver included the following: diffuse increase in echogenicity of the liver much more than the echogenicity of the right kidney and decrease in the penetration of sound waves, which is shown as a weak image of the echogenicity of the triad port and the right hemi-diaphragm. Sonographic criteria for grading of fatty liver included the following: a mild increase in liver echogenicity as grade 1, a moderate increase in liver echogenicity limited to the diaphragm and intrahepatic vessels as grade 2 and with a severe increase in liver echogenicity limited to the diaphragm and intrahepatic vessels as well as in the area of behind the right lobe of the liver, as grade 3 (12).

Evaluation of laboratory parameters: Fasting blood sugar (FBS) was measured by photometric laboratory

method in mg/dL and Pars test kit made in Iran with a normal range of 60-100 mg/dl (13). Lipid profile including triglyceride (TG), total cholesterol, HDL and LDL was done by photometric laboratory method and Pars test kit made in Iran. The normal range for TG and total cholesterol was considered below 200 mg/dl and for HDL more than 40 mg/dl (13). VD was measured by ELISA laboratory method and ideal measurement kit made in Iran and normal level of 30 to 70 ng/ml was considered (1). Liver enzymes (SGOT & SGPT) were measured by photometric laboratory method, with a kit made in Iran, and normal values for SGOT for ages 3 to 19 years, 15 to 45 U/L and normal values for SGPT for ages 1 to 19 years U/L, 5 to 45 U/L were considered (13). The level of TSH and T4 was measured by the laboratory ELISA method and Pishtaz kit made in Iran. The normal level of TSH for ages between 5 months and 20 years was 0.5 to 5.5 mIU/L. So the TSH level >5.5 mIU/L with normal level of T4 was considered as subclinical hypothyroidism. The normal level of T4 for children 3 to 10 years old, 5.5 to 12.8 µg/dl and for those older than 10 years old, 4.2 to 13 µg/dl were considered (13, 14).

Statistical Analysis: Data were analyzed by SPSS 22 software and using descriptive statistical tests, t-test and Chi-score and $p< 0.05$ was considered significant.

Results

Results of demographic information: After consideration of inclusion and exclusion criteria, 100 children and adolescents (58 children in the control group and 42 children in the case group) were selected. In the case group, 10 (23.8%) and 32 (76.2%) were girls and boys, respectively, and 50% of them equally were girls and boys in the control group. Overall, the mean age of the children was 10.7±2.68 years (11.63±2.55 and 10.07±2.61 years in case and control groups, respectively). Between the two groups in terms of gender (P=0.01) and mean age (P=0.004), the difference was statistically significant. The mean BMI in the case and control groups was 29.49±5.51 kg/m^2 and 25.41±4.70 kg/m^2 respectively, with a statically significant difference ($p<0.001$).

The results of laboratory parameters: The mean level of TSH and T4 in the control group was 3.72±1.97 mIU/L and 8.31±1.61 µg/dl, respectively and these amounts in the case group were 3.78±2.23 mIU/L and 8.26±1.43 µg/dl, respectively, which had no significant difference (P=0.92 and P=0.87). There was no case of hypothyroidism in the case and control groups. Also, there was not a significant difference between the two groups in terms of the mean level of FBS (P=0.33), cholesterol (P=0.44), LDL (P=0.35) and VD (P=0.07). However there was a statistically significant difference between the two groups in terms of the mean level of AST (P=0.003), ALT (P=0.001), TG (P=0.02) and HDL (P=0.01).

In this study, children with fatty liver were divided into two subgroups of grade 1 and 2, 22 (52.4%) and 20 (47.6%) persons respectively, but it did not happen fatty liver of grade 3.No significant difference was found in terms of age (P=0.78) and gender (P=0.92) in these two subgroups. In the grade 1, all 22 people were obese, and in the grade 2, 2 (4.9%) individuals were overweight and 18 (95.1%) were obese, with no significant difference (P=0.23). The mean level of TSH and T4 in the grade 1 was 3.33±2.28 mIU/L and 8.38±1.34 µg/dl and in the grade 2, was 4.25±2.12 mIU/L and 8.14±1.55 µg/dl, respectively which did not have significant difference (P=0.08 and P=0.59). The two subgroups of grade 1 and 2 in terms of the mean level of TSH (P=0.08), T4 (P=0.59), FBS (P=0.87), TG (P=0.51), cholesterol (P=0.35), HDL (P=0.67), LDL (P=0.92) and VD (P=0.76) had no statistically significant difference. However, in terms of AST and ALT, difference was found between the two subgroups (p=0.001) (table 2).

Table 1. Comparison of laboratory factors between the case and control groups

Groups / Values	With Fatty Liver(case)	Without Fatty Liver(control)	P-Value
FBS (mg/dl)	92.73±7.60	94.30±6.39	0.33
TSH (mIU/L)	3.78±2.23	3.72±1.97	0.92
T4 (µg/dl)	8.26±1.43	8.31±1.61	0.87
AST (IU/L)	30.04±19.01	20.96±7.86	0.003
ALT (IU/L)	41.20±3.66	18.98±8.99	0.001

Groups / Values	With Fatty Liver(case)	Without Fatty Liver(control)	P-Value
TG (mg/dl)	163.27±85.99	128.88±75.05	0.02
CHOL (mg/dl)	172.43±35.83	168.24±28.76	0.44
HDL (mg/dl)	41.04±11.01	44.03±7.62	0.01
LDL (mg/dl)	100.46±25.07	95.73±24.50	0.35
Vit D3 (ng/ml)	22.95±10.31	23.75±12.40	0.73

Fasting blood sugar (FBS); Thyroid Stimulating Hormone (TSH); Thyroxine (T4); Aspartate Aminotransferase (AST); Alanine Aminotransferase (ALT); Triglycerides (TG); Cholesterol (CHOL); High-density Lipoprotein (HDL); low-density Lipoprotein (LDL);Vitamin D3 (Vit D3).

Table 2. Comparison of clinical and laboratory factors between grades 1 and 2 in the case group

Groups / Values	With fatty liver grade 1	With fatty liver grade 2	P-value
FBS (mg/dl)	92.86±6.93	92.60±8.43	0.87
TSH (mIU/L)	3.33±2.28	4.25±2.12	0.08
T 4 (µg /dl)	8.38±1.34	8.14±1.55	0.59
AST (IU/L)	23.29±17.30	37.13±18.50	0.001
ALT (IU/L)	26.14±21.49	57.00±37.23	0.001
TG (mg/dl)	154.95±86.58	172.00±86.72	0.51
CHOL (mg/dl)	176.19±36.15	168.50±35.99	0.35
HDL (mg/dl)	43.09±13.56	38.90±7.23	0.67
LDL (mg/dl)	100.09±25.49	100.85±25.28	0.92
Vit D3 (ng/ml)	23.42±22.00	23.46±10.00	0.76

Fasting blood sugar (FBS); Thyroid Stimulating Hormone (TSH); Thyroxine (T4); Aspartate Aminotransferase (AST); Alanine Aminotransferase (ALT); Triglycerides (TG); Cholesterol (CHOL); High-density Lipoprotein (HDL); low-density Lipoprotein (LDL);Vitamin D3 (Vit D3).

Discussion

This case-control study compared the thyroid function tests in overweight and obese children and adolescents with and without fatty liver in 100 children aged 4-18 years. In this study, there was no significant difference in TSH and T4 levels between the case and control groups, as well as in children with different grades of fatty liver. In the systematic review of Zeqi Guo et al., 26 studies and 61,548 people were examined. Patients with NAFLD/ NASH (Nonalcoholic Steatohepatitis) in the adult and children/adolescent groups had higher TSH levels than the control group. However, the statistical results were inconsistent among the two groups of subclinical and overt hypothyroidism. On the other hand, the association between NAFLD and FT3/FT4 levels among the population was heterogeneous, and they concluded that TSH level, independently of thyroid hormones, may be an important risk factor for the development of NAFLD (6). A study by Nicholes et al. (2020) between the two groups with and without fatty liver showed that the mean TSH level in the fatty liver group was higher than the control group, which is in contrast with the present study. One of the possible reasons of this difference is that the Nicholes

et al.'s study was conducted over a period of 8 years, which was longer than the period of our study (9).

In the present study, the amount of AST and ALT in the case group was significantly higher than the control group and also AST and ALT in grade 2 of fatty liver were significantly higher than grade 1. Despite the increased AST level in the case group compared to the control group, there were no significant differences in thyroid function tests between the two groups. This result was contrary with finding of other reaserches (15, 16).

They illustrated that there is a positive correlation is between liver enzyme and thyroid function tests. Also, their study samples were those suffering from thyroid disorder. Also, thyroid function tests were affected by the duration and chronicity of AST level increase. Considering that this is the first study in Iran and also the small number of studies in the age group of adolescents and children in the world, the need to carry out more researches on fatty liver in children with a larger number of samples and even as a multicenter study and in a longer period of time is felt. Of course, the small number of cases in our study compared to some other studies can be attributed to conducting the study during the COVID-19 pandemic and obviously fewer patients were visiting the hospital clinic compared to other days.

Furthermore, the decrease in children's mobility during this period and their rapid weight gain, and as a result, the short period of time to develop overweight and obesity, may be mentioned as the possible reason for not observing hypothyroidism in the children of the study. Usually, the change in laboratory performance of thyroid tests requires weight gain over a longer period of time .One of the limitations of the study was the small sample size, one of the reasons was that the study was conducted during the COVID-19 pandemic, so the number of children who referred to the endocrinology clinic for growth assessment was low.

Moreover, we did not examine the trend of increasing obesity, perhaps this issue affects the level of disturbance in thyroid function tests. It is suggested to consider the rate of increase in obesity in future studies. According to the results of the study, in children and adolescents with obesity and overweight, the mean level of thyroid hormones in both case and control groups was not significantly different and hypothyroidism was not seen.

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Conflict of Interests: There was no conflict of interest.

Authors' contribution: AB drafted the manuscript, MA and MRE contributed to the design and implementation of the research and wrote the main manuscript text. SK Contributed to analysis of data. HGN and MP contributed to implementation of the research. PA revised the manuscript

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