Original Article

Association between sub clinical hypothyroidism and non-alcoholic fatty liver disease in children

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Non-Alcoholic Fatty Liver Disease is defined as accumulation of fat in Liver cells in absence of excess alcohol consumption. To study the association between sub Clinical Hypothyroidism and Non-Alcoholic Fatty Liver Disease in Children. In this cross-sectional study which was done at Department of thyroid and endocrine research in the Institute of Nuclear Medicine & Allied Sciences, Delhi, 30 children in the age group of 10-18 years with Sub Clinical Hypothyroidism were compared with 30 age and sex matched controls. This entire cohort of cases and controls were subjected to anthropometric, biochemical and radiological examination. Bio chemical evaluation included estimation of Free T3, Free T4, TSH, lipid profile and Liver Function Tests. Radiological evaluation included USG of thyroid for echogenicity and presence of nodule. USG of abdomen was done to look for presence of fatty liver. In 53.3% children with sub clinical hypothyroidism had fatty liver on USG compared to 13.3% controls. The prevalence of Non-Alcoholic Fatty Liver Disease in our children was considered higher as compared to general population. Children with sub clinical hypothyroidism are at increased risk of developing Non-Alcoholic Fatty Liver Disease.

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Key words **: Sub clinical hypothyroidism, non alcoholic fatty liver disease, ultrasound.**

Non alcoholic fatty liver disease (NAFLD) is defined as accumulation of fat in liver in absence of excess alcohol consumption. NAFLDis a spectrum of liver disease that ranges from simple steatosis (fat in the liver or fatty liver) to steatohepatitis –fat with inflammation and /or fibrosis to severe fibrosis culminating into cirrhosis[1]. Non-alcoholic fatty liver disease can result in end stage liver failure requiring liver transplantation. NAFLD is associated with diabetes, insulinresistance, metabolic syndrome, obesity, hypertriglycerimia, hypothyroidism and Cushing syndrome.

The massive increase in prevalence of overweight and obesity across the globe has lead to the emergence of NAFLD as the leading cause of liver disease worldwide. In patients with type 2 diabetes, the association with NAFLD is well established and recognized. Thyroid hormones play an important role in metabolism of lipids and carbohydrate. Insulin resistance and dyslipidemia are observed in patients with subclinical hypothyroidism and few studies done in the past have suggested that sub clinical hypothyroidism may be related to hepatic steatosis[2]. The association seems biologically possible because hypothyroidism is associated with visceral obesity, metabolic syndrome and insulin resistance, all of which are closely related to hepatic steatosis.

The aim of the present study is to understand the relationship between subclinical hypothyroidism and NAFLD.

Materials and Methods

This is a cross sectional study carried outat the department of endocrine and thyroid research, Institute of Nuclear Medicine and allied science (INMAS) New Delhi, between July 2016 and October 2017. INMAS is tertiary referral Centre for management of thyroid disorders.

All the patients with sub clinical hypothyroidism in the age group of 10 to 18 years attending the thyroid clinic of INMAS were recruited for the study. They all underwent a complete physical examination, which included measurement of weight, height, BMI, systolic and diastolic blood pressure. Systolic and diastolic blood pressures were measured at right arm after 30 minutes rest in supine position using amercury sphygmomanometer.The institutional ethics committee approved the study and informed written consent was obtained from parents or legal guardians of the subjects. Age, gender, race, and body-weight matched individuals seen during the same period served as controls.

The entire cohort of children and adolescents underwent assessment of height and weight and calculation of BMI. Height was measured to the nearest 0.1 cm using a stadiometer with the subject standing straight with head

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held in Frankfurt horizontal plane. Subject's weight, without shoes and with light clothes on was measured to the nearest 0.1 kg, using an electronic scale. Height and weight measurements were taken twice and the mean of two measurements was used to calculate BMI, which was defined as the ratio of body weight to body height squared, expressed in kg/m^2. Every morning, the scale and stadiometer were calibrated with standard weight and height respectively.

Hepatic steatosis was diagnosed by ultrasound after exclusion of infectious /autoimmune hepatitis and metabolic diseases of the liver. None of the child recruited for the study had been consuming alcohol.

Laboratory Investigations :

Venous blood samples were obtained from all the subjects after 12 hours of overnight fast for the estimation of free T4, TSH,TPO, total cholesterol, triglycerides, high density lipoproteins (HDL)cholesterol, low density lipoprotein (LDL) cholesterol, liver function test.

Concentration of TSH was measured by immunochemiluminiscent procedure using Elicsys 2010 Roche analyzers (Roche, Manheim Germany).The reference range of normal value for TSH was 0.27 to 4.2 microIU/L. The reference intervals for FT3 and FT4 were 2.6–6.8 pmol/L and 12.–22 pmol/L, respectively. The threshold value for anti-TPO antibodies was 34 IU/mL.

Serum alanine aminotransferase (ALT)and aspartate aminotrasferase (AST) and lipid profile was estimated using CobasIntigras 400 plus Roche analyser.

Subclinical hypothyroidism was defined biochemically as a TSH value more than 4.2 m IU/L with normal levels of freeT3 and free T4.

An ultrasound examination of the liver was performed using an Esaote my lab 60 system with 3.5–5-MHz transducers. Hepatic steatosis was defined if the liver parenchyma was hyperechoic with tightly packed fine echoes and posterior beam attenuation. Ultrasound of the thyroid gland was evaluated with a high-resolution 7.5 MHz linear transducer.

Statistical Analysis

Statistical analyses were performed using the SPSS package. Data was expressed as frequencies or means with standard deviation. Geometric means was calculated for TSH, FT3, FT4, total cholesterol and HDL-C, triglycerides, and LDL. Differences between groups were tested for significance using independent sample -test for quantitative variables, and chi-square test for qualitative variables.

Results

The study group consisted of 30 consecutive cases of subclinical hypothyroidism who met the inclusion criteria. They were compared with an equal number of age and sex matched controls. The mean TSH of the study group was 17.21 ±1.619 that was significantly higher than the control group. The control group had a mean TSH of 2.2 ± 0.845. The two groups did not differ in their weight and body mass index .the serum cholesterol in the study group was 186.26±24.732 which was higher than the control group but the difference was not statistically significant. Serum triglycerides and LDL cholesterol was significantly higher in the study group than the controls (Table 1).

In 53.3% children with subclinical hypothyroidism had a fatty liver on ultrasound compared to only 13.3 % of euthyroidcontrols. The prevalence of NAFLD in our children with subclinical hypothyroidism was considerably high as compared to general population which is reported to be 20%to 30%.The prevalence of NAFLD on ultrasound and elevated tranaminsases was 26.6% in children with sub clinical hypothyroidism compared to 16.6% controls (Table 2).

Discussion

Our study has tried to assess the relationships between subclinical hypothyroidism and hepaticsteatosis in young adolescent children. The association between the two has been established in adults through various studies but the problem actually starts in childhood and therefore the lifestyle changes and other interventions need to be started right in childhood.

Several possible mechanisms may be responsible for the association between hypothyroidism and hepatic steatosis. Thyroid hormones play an important role in metabolismof fats and carbohydrates Sub clinical hypothyroidism has been associated with dyslipidemia, obesity and insulin resistance, all of which play an important role in the development of NAFLD

Table 1 — *Showing Baseline Characterstics of Participants*

Patient Characteristics	Group A (study Group) n=30	Group B (Control Group) n=30	P Valve
TSH	17.21 ±1.619	2.29± 0.845	<0.005
Weight(Kg)	70.32± 9.61	68.81± 7.146	0.153
BMI (kg/m2)	30.863±5.23	28.30±3.54	0.187
Total cholesterol (mg/dl)	186.26±24.732	167.81± 30.237	0.157
Triglyceride	116.47±23.125	110.29±18.869	<0.005
LDL	115.72±13.15	68.05±30.17	<0.005
HDL	40.89±7.17	43.10±4.516	0.031
SGOT	46.21±17.37	25.05±5.59	<0.005
SGPT	56.74±19.69	30.33±6.27	<0.005

Table 2 — *Prevalence of NAFLD and Serum Liver Enzymes in Study Participants*

Patient characteristics	Group A (n=30) TSH > 4.2 mIU/L	Group B (n=30) TSH < 4.2 mIU/L	P value
Hepatic steatosis	16(53.3%)	4(13.33%)	<0.005
Hepatic steatosis with elevated ALT	8(26.6%)	5(16.67%)	<0.005

(Continued on page 31)

(Continued from page 26)

Other reason explaining the associationbetween thyroid function andNAFLDis that sub clinical hypothyroidismis associated with hyperlipidemia. Hypothyroidism (both overt and subclinical) not only causes elevation in serum cholesterol and lowdensitylipoproteins but it also affects the degradation of all types of lipid moieties.

The increased serum levels of triglycerides in hypothyroid subjects is responsible for fatty infiltration of liver[3]. Finally, elevated oxidative stress markers can be observed in patients with clinical and subclinical hypothyroidism. Oxidative stress is one of the mechanisms of NAFLD, and oxidative stress in liver tissue among hypothyroidism patients can cause cellular injury and insulin resistance by reducing beta-oxidation of fatty acids and increasing per oxidation of lipids[4].

In a recent cross-sectional study involving 4648 health check-up subjects, Chung *et al* found that the prevalence of ultrasound-diagnosed NAFLD and abnormal ALT levels increased steadily with increasing grades of hypothyroidism[5].

Conclusion

There is evidence for the relationship between hypothyroidism and NAFLD. Children with subclinical hypothyroidism are at higher risk for NAFLD than euthyroid subjects.So, early detection of thyroid function in important for patients suffering from NAFLD.

Conflict of Interest : None

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