Original Article

Non alcoholic fatty liver disease in non diabetic hypothyroid patients : ascertaining the connecting links with metabolic syndrome

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To characterize the relationship between the broad spectrum of hypothyroidism and nonalcoholic fatty liver disease (NAFLD). A prospective analytical case control study with 97 subjects was conducted. The subjects were categorized as having either subclinical [thyroid-stimulating hormone (TSH) >4.1 mIU/L and normal free thyroxin (T4) level] or overt hypothyroidism [TSH >4.1 mIU/L decreased free T4]. NAFLD was diagnosed on the basis of typical ultrasonographic findings, and alcohol consumption of less than 20 g/day in the absence of other causes of liver disease. Maximum number of subjects belonged to the age group of 18-49 and 87.5% of cases were female. No significant association was observed between NAFLD and hypothyroidism (mean TSH in cases with normal liver = 3.30±0.81, mean TSH in cases with fatty liver 2.79±0.69, p=0.249). The degree of fatty infiltration did not increase significantly with the increasing level of hypothyroidism. The value of pearson correlation coefficient [r] = -0.15, however the p value for this trend was 0.25 which was statistically insignificant. Significant association was observed between NAFLD and body mass index (BMI) (mean BMI in patients with normal liver = 21.23±1.27, mean BMI in patients with fatty liver 26.28±,p<0.001) and waist circumference (WC). There was no significant association between hypothyroidism and NAFLD however increasing severity of fatty liver was strongly associated with increasing BMI and WC.

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***Key words* : Hypothyroidism, NAFLD, BMI, WC.**

Non alcoholic fatty liver disease (NAFLD) is a distinct hepatic condition and is one of the most common causes of chronic liver disease globally[1]. The definition of NAFLD requires that (a) there is evidence of hepatic steatosis by imaging or by histology and (b) there are no secondary causes for hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medications or hereditary causes of hepatic fat accumulation[2]. NAFLD includes a spectrum of hepatic dysfunctions ranging from simple steatosis to nonalcoholic steatohepatitis, cirrhosis and hepatocellular carcinoma. NAFL is defined as the presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of hepatocytes. Non alcoholic steatohepatitis (NASH) is defined as the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis.

The reported prevalence of NAFLD varies widely depending on the population studied and the definition used. The reported prevalence of biopsy proven NAFLD was found to be around 20-51% in various studies[3,4]. Today NAFLD is the most common cause of abnormal liver function tests even in India. Prevalence of the disease is estimated to be around 9-32% in the general Indian population, with a higher incidence rate amongst obese and diabetics[5]. Researchers have found various conditions associated with NALFD. Out of these obesity, type 2 diabetes mellitus, dyslipidemia and metabolic syndrome are the conditions with established associations whereas conditions like polycystic ovary syndrome, hypothyroidism, obstructive sleep apnea, hypopituitarism, hypogonadism, pancreato-duodenal resection are the conditions with emerging association[2].

There is a possible association between hypothyroidism and NAFLD. A recent study showed the increased prevalence of NAFLD in patients with hypothyroidism[6]. Various mechanisms have been postulated in the patho-

- Increasing severity of fatty liver was strongly associated with increasing BMI.
- Strong association was found between NAFLD and WC in this study.
- But no significant association was seen between NAFLD and hypothyroidism.
- Limitations: (a) Small sample size.
  (b) Studied among slected part of India.
  (c) Majority of hypothyroid cases were already on treatment – might be a confounding factor.

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genesis of NAFLD in patients with hypothyroidism. Because thyroid hormones play a fundamental role in lipid metabolism, hypothyroidism may cause hypercholesterolemia and play an essential role in the pathogenesis of NAFLD[7,8]. Another hypothesis that explains the pathogenesis of NAFLD in hypothyroid patients is the possible association of hypothyroidism with components of metabolic syndrome, NAFLD being one of these components[9-14].

Therefore, a case control study was conducted to evaluate association of NAFLD with hypothyroidism.

Aims and Objectives

To correlate serum TSH with presence of NAFLD on ultrasonography and to correlate serum TSH with markers of metabolic syndrome like BMI, WC.

Materials and Methods

This prospective analytical case control study was undertaken in the Department of Medicine, Moti Lal Nehru Medical College, Allahabad between March 2014 and July 2015 on a total of 97 subjects. Subclinical or overt, non diabetic, hypothyroid individuals who were of >18years of age were selected as cases. Alcohol consumption in these patients was <20gm/day for females and <30gm/day for males and they did not have any other underlying hepatic pathology. Euthyroid,non diabetic individuals who were >18 years of age and of either sex, who did not have significant alcohol consumption and those who did not have any underlying hepatic pathology were selected as controls.

Each participant completed a medical history questionnaire, an anthropometric assessment, and laboratory tests.Height and body weight were measured, and BMI was calculated as follows:

BMI = body weight (kg)/height squared (m^2).

WC was measured to the nearest millimeter at the midpoint between the lower costal margin and the anterior superior iliac crest.Systolic blood pressure and diastolic blood pressure was measured twice during the same day, and mean values were used for the study.

Baseline thyroid function (TSH and free T4, T3 levels) were measured using a commercial chemiluminescence assay. Patients were also investigated for fasting Blood glucose (FBG), post prandial blood glucose (PPBG), hepatitis B surface antigen and antibody to hepatitis C virus. Ultrasonographic examination of the liver was performed by experienced radiologist who were unaware of the clinical and laboratory information. The diagnosis of fatty liver on ultrasonography was made as follows :

The patient was made to lie in the supine and right anterior oblique positions and the examination was conducted using a low frequency convex transducer (5-7MHz) on a Philips HD7 revision 3.0 or an equivalent ultrasonography machine.

Images were recorded in the transverse sagittal and subcostal oblique views and the echo texture of liver was graded as normal, fatty echotexture, fatty liver grade 1 and fatty liver grade 2 with every grade showing successively increasing degrees of fatty infiltration.

Statistical Analysis

The data were analyzed and assessed with appropriate statistical methods within different groups. Software used is SPSS-IBM version 21. Mean and standard deviation were calculated. Student t-test and Karl Pearson correlation coefficient was used to calculate p value to find out the correlation between different variables.

Observations and Results

Out of the 97 subjects maximum number of patients were in the age group of 18-29 years (23%). In 87.5% of the subjects amongst cases were females whereas in controls 64% of subjects were females. The p value for association between presence of fatty liver and mean TSH values in controls was 0.249. The p value for association between the presence of fatty liver and mean TSH in cases was 0.145. Thus, no significant association was seen between the liver echotexture and mean TSH levels in both cases and controls (Table 1).While observing the temporal association between degree of fatty infiltration of liver with the degree of hypothyroidism, the value of pearson correlation coefficient [r]= -0.15, however the p value for this trend was 0.25 which was statistically insignificant. Thus it was inferred that the degree of fatty infiltration did not increase with the increase in degree of hypothyroidism in cases and this was also true in the controls in which the TSH was within normal limits. (Table 2, Fig 1). The value of 23 kg/m^2 is considered as the upper limit of normal range of BMI in Asian population. The liver echotexture

Table 1 — *Comparison of mean TSH value with liver echotexture in cases and control population*

Groups	USG Liver	Mean TSH (µIU/L)	± SD	No of patients (%)	p value
Controls (n=25)	Normal	3.30	0.81	3 (12)	0.249
Euthyroid	Fatty	2.79	0.69	22 (88)	
Cases (n=72)	Normal	17.29	18.30	31 (43.0)	0.145
Hypothyroid	Fatty	12.54	8.43	41 (56.9)	

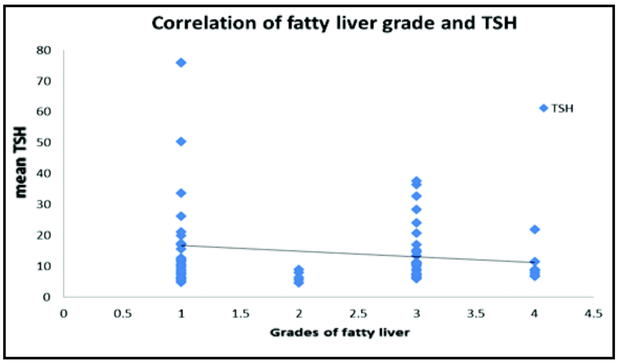

Fig1 — Pearson correlation coefficient [r]= (-0.15), p value for trend = 0.25

Table 2 — *Comparison of mean TSH values with liver echotexture (grading) in cases and control population*

Groups	Fatty Liver grade	Mean TSH (µIU/L)	± SD	No of patients (%)
Controls [n=25]	Normal	3.30	0.81	3(12)
	Fatty Echotexture	2.69	0.36	4 (16)
	Fatty liver grade1	2.90	0.66	13(52)
	Fatty liver grade2	2.59	1.02	5(20)
Cases [n=72]	Normal	17.29	18.30	31(43)
	Fatty Echotexture	6.73	1.70	5(6.9)
	Fatty liver grade1	14.31	9.31	28(38.8)
	Fatty liver grade 2	9.96	5.12	8(11.1)

on ultrasound was seen to have a strong statistically significant association with the mean BMI values in both the cases (p=<0.001) and the control (p=0.006) groups (Table 3). The mean BMI values were comparable in cases and control population with similar liver echotexture. The grading of liver echotexture was significantly associated with the mean BMI values in both cases (p<0.001) and control (p=0.005) groups. The value of pearson correlation coefficient [r] = 0.77 suggested a highly positive correlation and as analyzed the subsequent increase in the severity of fatty liver followed an increasing trend with the increase in the BMI. (Table 4, Fig 2).

The upper limit of normal WC for males was 90cm and for females was taken as 80 cm. The relation between WC and mean TSH was statistically insignificant in both female controls (p=0.94) and female cases (p=0.41)(Table 5).

The relation between presence or absence of fatty liver and mean WC was found to be statistically significant in both female cases (p<0.001) and female controls (p<0.001) (Table 6).

Discussion

In this study no positive association was found between hypothyroidism and NAFLD. Even in controls where TSH was within normal limits, the upper limits of TSH were not associated with NAFLD. Xu *et al*[15] in their study on association between thyroid function and NAFLD in euthyroid elderly chinese evaluated that, serum TSH even at upper limits of normal range was associated with presence of fatty liver, however this study was done only on elderly patient hence it is difficult to generalize their result to the general population. Similarly Chung *et al*[16] in their study on NAFLD across the spectrum of hypothyroidism suggested that NAFLD was statistically significantly associated with hypothyroidism (odds ratio (OR) 1.38, 95% confidence interval (CI), 1.17–1.62, suggesting that hypothyroidism is independently associated with an increased prevalence of NAFLD. Similarly Liangpunsakul *et al*[8] retrospectively evaluated the presence of hypothyroidism in biopsy proven NAFLD and found that the prevalence of hypothyroidism was higher in patients with NAFLD. Parikh P *et al*[17] estimated the prevalence of hypothyroidism in nonalcoholic fatty liver disease in

Table 3 — *Comparison of mean BMI with Fatty liver in cases and controls*

Groups	Liver USG	Mean BMI (kg/m^2)	± SD	No of patients (%)
Control [n=25]	Normal Liver	21.23	1.27	3(12)
	Fatty Liver	26.94	1.43	22(88)
Cases [n=72]	Normal Liver	21.71	1.70	31(43.1)
	Fatty Liver	26.28	1.50	41(56.9)

Table 4 — *Comparison of mean BMI values with grading of liver echotexture in cases and controls*

Groups	Fatty liver grade	Mean BMI (kg/m^2)	± SD	No of patients (%)
Controls [n=25]	Normal Liver	21.23	1.27	3 (12)
	Fatty Echotexture	25.68	1.21	4 (16)
	Fatty liver grade1	27.00	1.11	13 (52)
	Fatty liver grade2	27.81	1.85	5 (20)
Cases [n=72]	Normal Liver	21.71	1.70	31 (43.0)
	Fatty Echotext	25.36	1.50	5 (6.9)
	Fatty liver grade1	26.43	1.55	28 (38.8)
	Fatty liver grade 2	26.58	1.25	8 (11.2)

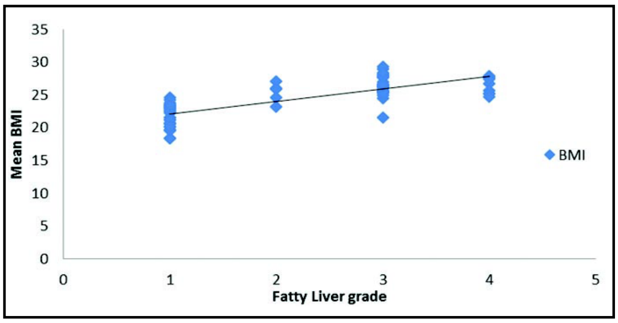

Fig 2 — Pearson correlation coefficient [r] = (0.77), p value for trend = <0.001

Table 5 — *Comparison of mean TSH values with waist circumference in males and females in cases and controls*

Groups	Sex	Waist Circumference	Mean TSH (µIU/L)	± SD	No of patients (%)
Control [n=25]	F [16]	Normal	2.84	0.92	3 (12)
		High	2.80	0.78	13 (52)
	M [9]	Normal	3.62		1 (4)
		High	2.84	0.61	8 (32)
Cases [n=72]	F [63]	Normal	17.91	18.34	17 (23.6)
		High	13.97	12.84	46 (63.8)
	M [9]	Normal	5.66		1 (1.3)
		High	12.14	4.67	8 (11.1)

Table 6 — *Comparison of mean waist circumference with fatty liver in males and females among cases and controls*

Groups	Sex	USG Liver	Mean waist circumference	± SD	No of patients
Control [n=25]	F [16]	Normal	77.0	1.4	2(8)
		Fatty	92.5	8.0	14(56)
	M[9]	Normal	83.0		1(4)
		Fatty	94.8	1.4	8(32)
Cases [n=72]	F [63]	Normal	79.4	12.3	30(41.6)
		Fatty	97.7	8.7	33(45.8)
	M [9]	Normal	91.0		1(1.3)
		Fatty	96.8	6.6	8(11.1)

patients attending a tertiary hospital in western India and observed an association between hypothyroidism and NAFLD. However Zhang *et al*[18] in their study observed that TSH level was not an independent risk factor for NAFLD. Eshraghian *et al*[19] also observed that there was no association between hypo or hyperthyroidism and NAFLD. Rather diagnosis of NAFLD was higher among low TSH group. Thus there are various conflicting evidences regarding the association between NAFLD and hypothyroidism. However we did not observe any association between the two variables.

Further, in our study we correlated the degree of hypothyroidism with the successively increasing degree of fatty infiltration, and it was observed that successive increase in fatty infiltration of liver did not follow the gradual increasing degrees of hypothyroidism. This observation was against the observation of Chung *et al*[16] who observed that an increase of 1 IU/L of natural logged TSH was associated with a 20% increase in the prevalence of NAFLD. Our observation could be justified because of the differences in the demography and the biometric profiles of the study populations.

In this study high BMI was evaluated as a risk factor for presence of fatty liver. Kwon *et al*[20] evaluated the association of NAFLD with components of Metabolic syndrome (MetS) according to BMI in Korean adults and observed that NAFLD was positively correlated with BMI. Similarly Goland *et al*[21] observed that patients with NAFLD had a significantly higher BMI. Marchesani *et al*[22] also showed that 80% of patients with NAFLD were obese. Agrawal *et al*[23] also conducted a study to establish a relationship between NAFLD and obesity and observed a positive correlation between BMI and grades of Fatty Infiltration. Uchil *et al*[24] also evaluated in their study that frank obesity was present in 24.8% of patients whereas 52.8% of patients having NAFLD were overweight. In our study mean BMI in both cases and controls had significant association with presence of NAFLD independent of the presence or absence of hypothyroidism. Also, when comparison was done between the mean BMI with subsequently increasing degrees of fatty infiltration the correlation was found to be statistically significant.

In this study, association was also established between WC and presence of fatty liver. Duseja A *et al*[25] in their meta-analysis published that NAFLD is closely associated with MetS. Since WC is also one of the components of MetS, hence increased WC is associated with presence of NAFLD. Similarly Rocha R *et al*[26] established the association between BMI and WC with presence of NAFLD and found a positive association between the these variables. Similarly Agrawal *et al*[23] and Uchil *et al*[24] found a positive correlation between WC and presence of NAFLD. Our study holds compliance with the above mentioned various observations and the relation between presence or absence of fatty liver and mean abdominal circumference was found to be statistically significant in both female cases and controls. However the relation between presence or absence of fatty liver and mean abdominal circumference in males could not be calculated as there was only one male case and one male control with normal liver echotexture.

Limitations: Firstly, the sample size was relatively small. Secondly, the study population was confined to patients selected from a tertiary care center in eastern Uttar Pradesh; generalization of our results needs validation from other tertiary care centers. Moreover, majority of the hypothyroid cases were already on treatment, this might be a confounding factor.

Conclusion :

Increasing severity of fatty liver was strongly associated with increasing BMI. Strong association was found between NAFLD and WC. However no significant association was seen between NAFLD and hypothyroidism.

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