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A Study of Association of Level of Thyroid Hormone with Non-Alcoholic Fatty Liver Disease

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Abstract

Background

Studies reveal that thyroid hormones play a critical role in the pathogenesis of non-alcoholic fatty liver disease (NAFLD), but its role in NAFLD still remains controversial. Our objective was to find the association of thyroid hormone levels in patients with NAFLD as it has implications on the prevention of hypothyroidism and NAFLD.

Methods

Hospital based, cross-sectional, observational study was conducted in the Department of Medicine, Pt.JNM Medical College and Dr. BRAM Hospital; DKS PGI & Research Centre, Raipur (C.G.), comprising 84 patients of NAFLD between September 2018 and August 2019, to evaluate thyroid hormone levels by biochemical tests.

Results

A total of 84 patients were included. Majority of them i.e. 26.2% were from 51-60 years. Male to female ratio was 1.4:1. After adjusting for the cofounders, it was found that the prevalence of overt hypothyroidism was 20.2% and subclinical hypothyroidism was 7.1%. Prevalence of reduced FT4 was 26.2% and elevated TSH was 27.4%. On

comparing mean FT4 among all the three grades, the difference was statistically not significant ($p>0.05$) but TSH level was significantly higher in NAFLD grade 3 followed by grade 2 and vary according to the severity of NAFLD. Association of hypothyroidism with grading of NAFLD was found to be statistically significant ($p<0.05$).

Conclusion

There was no association between FT4 and NAFLD but significant association of increased TSH with grading of NAFLD was established. Significant association was found between hypothyroidism and NAFLD in this study.

Keywords

Non-alcoholic fatty liver disease, hypothyroidism, subclinical hypothyroidism, association

Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases that is emerging as a global public health problem.[1]NAFLD comprises of a spectrum of clinicopathological entities ranging from simple fatty liver (NAFL with fat accumulation in more than 5% of hepatocytes) to steatohepatitis (NASH characterized by hepatocyte ballooning and lobular inflammation ± fibrosis) that might progress to liver cirrhosis and rarely to hepatocellular cancer, in the absence of secondary causes or alcoholic liver disease. Its prevalence has increased enormously in the last three decades due to the global obesity epidemic and accompanied insulin resistance (IR).In a general population, prevalence numbers for NAFLD are thought to be approximately 10-24% worldwide.[1] The disease occurs when fat forms more than 10 to 15% of the liver's weight. The disease involves a wide range of liver diseases but occurs in people who either do not drink alcohol or only use moderate amounts of alcohol (i.e. less than 20 g/d in men and less than 10 g/d for women).[2]NAFLD is associated with obesity, insulin resistance, type 2 diabetes mellitus (T2DM), hypertension, hyperlipidemia, and metabolic syndrome. It has been found in previous studies that the hypothyroid metabolic state is concomitantly found in NAFLD and may be related to the development of NAFLD.[3]The physiological role of thyroid gland has been explored extensively because it is significantly involved in energy homeostasis, lipid and carbohydrate metabolism, regulation of body weight and adipogenesis.[4,5] Thus, thyroid dysfunction can affect lifelong health.

Hypothyroidism is classified into subclinical hypothyroidism and overt hypothyroidism. Subclinical hypothyroidism is defined as a disease with an elevated thyroid-stimulating hormone (TSH) level than normal range, normal serum free thyroxine (fT4) level and absence of obvious clinical manifestation. Overt hypothyroidism is considered to be a disease with an elevated TSH level and a lower fT4 level, and it may be accompanied by obvious clinical symptoms.[6] Studies have revealed that both overt hypothyroidism and subclinical hypothyroidism are associated with cardiovascular disease and mortality. Other studies showed that either overt or subclinical hypothyroidism may be associated with chronic kidney disease, dementia and fractures.[7-9]

Moreover, there are obvious relations between hypothyroidism and metabolic changes which include insulin resistance (IR), dyslipidemia, obesity and therefore, have important roles in the development of NAFLD. [10]

It is of importance that the lower levels of thyroid hormones in hypothyroidism can increase the

cholesterol levels, low-density lipoproteins and triglyceride due to the delivery of hepatic fatty acids, but decrease the level of high-density lipoprotein (HDL), and thus can affect lipid metabolism. Therefore, patients having overt hypothyroidism often have fatty infiltration of the liver and thus have a higher risk for NAFLD. TSH can directly increase hepatic gluconeogenesis, repress hepatic bile acid synthesis, and cause hypercholesterolemia by decreasing HMG-CoA reductase phosphorylation, which further leads to the development of NAFLD. Finally, elevated oxidative stress markers can be observed in hypothyroidism patients and oxidative stress in liver tissue among hypothyroidism patients can cause cellular injury and IR via reducing beta-oxidation of fatty acids and increasing peroxidation of lipids.[10]

There are studies that showed lower free T4 to be an independent risk factor for NAFLD and increased serum levels of TSH to be an independent risk factor for NASH. These findings, therefore, emphasizes the role of thyroid dysfunction in the development of hepatic steatosis and more serious forms of NAFLD. Thus, it highlights the need for screening of thyroid function in NAFLD and early identification of at-risk patients since treatment of the hypothyroidism may reduce the risk of NAFLD and its potential complications. [11,12]

Objective

To know the association of thyroid hormone level in patients with non-alcoholic fatty liver disease.

Methods

This study is a hospital based, cross sectional, observational study which was conducted in the Department of Medicine, Pt. Jawaharlal Nehru Memorial Medical College & associated Dr. Bhim Rao Ambedkar Memorial Hospital, Raipur; DKS Postgraduate Institute & Research Centre, Raipur (C.G.), between a period of September 2018 and August 2019.It includeda total of 84 diagnosed patients of NAFLD with age > 18 years.

Sampling Technique

Simple random sampling method

Inclusion Criteria

Patients with definite diagnosis of NAFLD by ultrasound examination, having age greater than 18 years.

Exclusion criteria

Patients with age group less than 18 years or having any liver disease other than NAFLD or NAFLD in the context of other liver diseases i.e. chronic viral hepatitis, auto-immune hepatitis, hemochromatosis or drug induced hepatitis. Patients with increased alcohol consumption (male>40g/d, female>20g/d) or with history of intake of iodine, anti-thyroid agents or thyroid hormones were also excluded from our study group.

Data collection

A cross-sectional survey is conducted in which patients over 18 years are assessed for fatty liver disease by ultrasound examination. Information is obtained from each participant concerning demographics, alcohol intake, tobacco smoking, medical history and medication use. Following exclusion of subjects with past or present hepatitis B or C virus infections, hemochromatosis, auto-immune or drug induced hepatitis, intake of iodine, anti-thyroid agents or thyroid hormones and adjusting for all the possible confounders, a total of 84 subjects with fatty liver disease is evaluated for thyroid hormone levels by biochemical tests such as TSH and FT4 levels. After comparing the results, a relationship is established

between non-alcoholic fatty liver disease and thyroid dysfunction.

Statistical Analysis and Methods

Data was collected by using a structured proforma. Data thus was entered in MS excel sheet and analysed by using SPSS 24.0 version IBM USA. Qualitative data was expressed in terms of percentages and proportions. Quantitative data was expressed in terms of Mean and Standard deviation. Association between two qualitative variables was seen by using Chi square/ Fischer's exact test. Comparison of mean and SD within same groups was done by using paired t test to assess whether the mean difference between groups is significant or not. Descriptive statistics of each variable was presented in terms of Mean, standard deviation, standard error of mean. Correlation between two quantitative variables was assessed by using Pearson's correlation coefficient test (r). A p value of <0.05 was considered as statistically significant whereas a p value <0.001 was considered as highly significant.

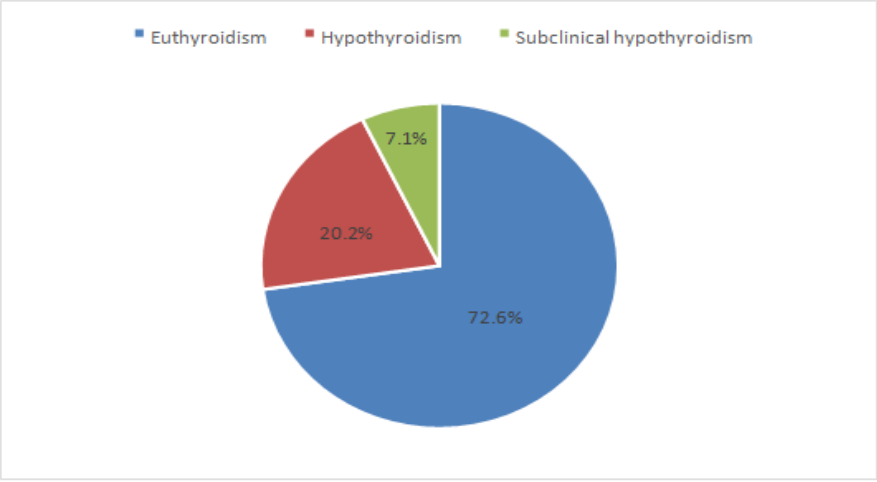
Grading of NAFLD

Grading of NAFLD was done as per standard criteria accepted by American Gastroenterology Association i.e. an increase in hepatic echogenicity as a reference, the presence of enhancement and lack of differentiation in the periportal intensity and the vascular wall due to great hyper echogenicity in the parenchyma (Roti **Agrawal et al.** 2008).

	GRADE I	GRADE II	GRADE III
FATTY LIVER	Slight diffuse increase in the fine echoes. Liver appears bright as compared to the cortex of the kidney. Normal visualisation of diaphragm and intrahepatic vessel borders.	Moderate diffuse increase in the fine echoes. Slightly impaired visualisation of the intrahepatic vessels and diaphragm.	Marked increase in the fine echoes. Poor or no visualisation of intrahepatic vessel borders, diaphragm and the vessels.

Results

Fig 1: Distribution according to type of thyroid abnormality



Prevalence of overt hypothyroidism in our study was 20.2% and that of subclinical hypothyroidism was 7.1%.

Table 1: Age wise distribution of thyroid abnormality

		Type of thyroid abnormality						Total
		Euthyroidism		Hypothyroidism		Subclinical hypothyroidism		
		No	%	No	%	No	%	
Age group in years	< 30	10	16.4	0	0.0	0	0.0	10
	31-40	14	23.0	4	23.5	0	0.0	18
	41-50	10	16.4	5	29.4	6	100.0	21
	51-60	15	24.6	7	41.2	0	0.0	22
	61-70	8	13.1	1	5.9	0	0.0	9
	> 70	4	6.6	0	0.0	0	0.0	4
	Total	61	100.0	17	100.0	6	100.0	84

Chi square test-26.53, p-0.003 (<0.05), Significant

Out of 17 patients with hypothyroidism, majority i.e. 7(41.2%) were from 51-60 years followed by 5(29.4%) from 41-50 years and 4(23.5%) from 31-40 years age group whereas all 6 patients with subclinical hypothyroidism were from 41-50 years age group. This difference in the proportion between age groups was found significant ($p<0.05$).

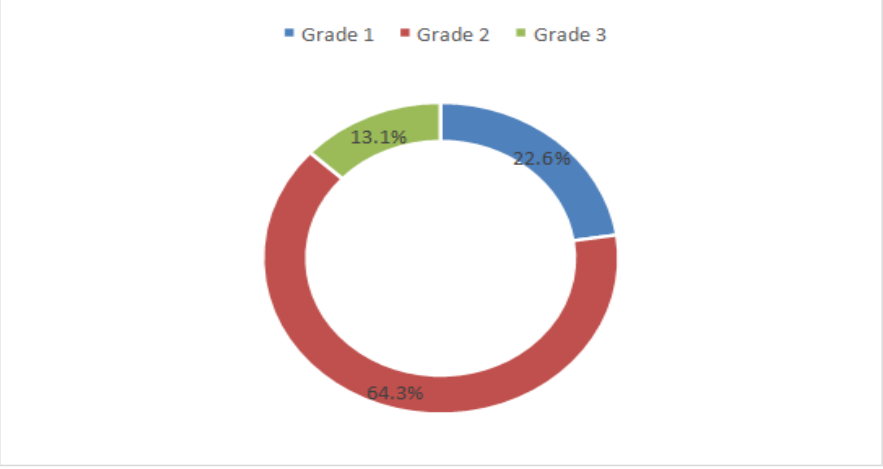
Table 2: Gender wise distribution of thyroid abnormality

		Type of Thyroid Abnormality						Total
		Euthyroidism		Hypothyroidism		Subclinical hypothyroidism		
		No	%	No	%	No	%	
Gender	Male	39	63.9	6	35.3	4	66.7	49
	Female	22	36.1	11	64.7	2	33.3	35
Total		61	100	17	100	6	100	84

Chi square test-4.67, p-0.097 (>0.05), Not Significant

Proportion of hypothyroid males were 35.3% as against 66.7% of subclinical hypothyroidism males. Proportion of hypothyroid females were 64.7% as against 33.3% of subclinical hypothyroidism females. This difference in the gender wise proportion was found to be statistically not significant ($p>0.05$).

Figure 2: Distribution according to NAFLD grading



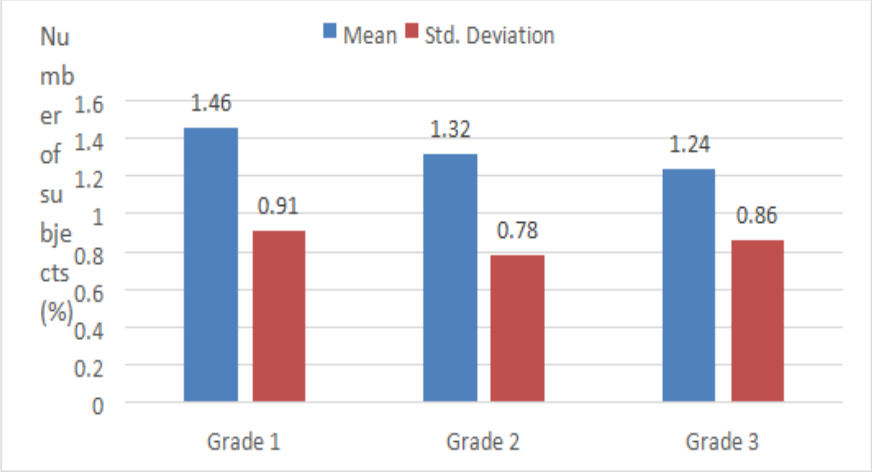
NAFLD grading revealed that majority of our patients had Grade 2 fatty liver i.e. 54(64.3%) followed by Grade 1 fatty liver in 19(22.6%) and Grade 3 fatty liver in 11(13.1%).

Table 3: Distribution according to thyroid profile

		FT 3		FT 4		TSH	
		Frequency	Percent	Frequency	Percent	Frequency	Percent
Thyroid function test	Increased	11	13.1	5	6.0	23	27.4
	Normal	64	76.2	57	67.9	61	72.6
	Reduced	9	10.7	22	26.2	0	0.0

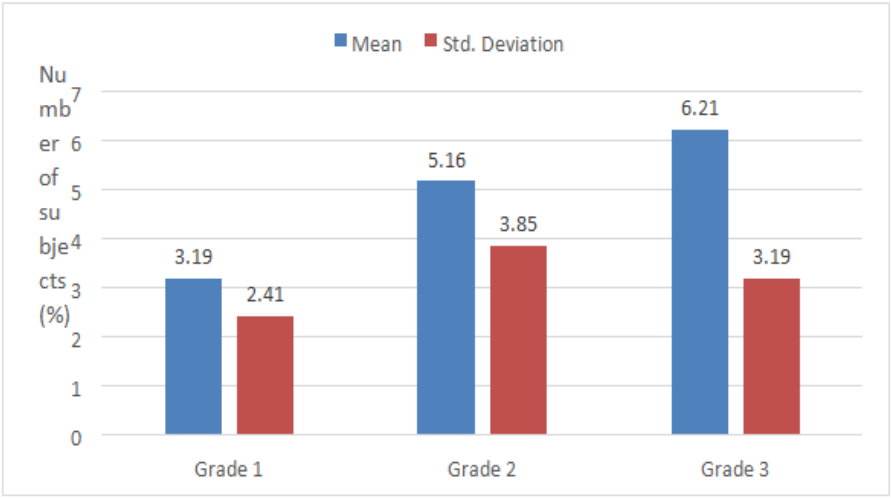
Prevalence of reduced FT3 was 10.7%, reduced FT4 was 26.2% and elevated TSH was 27.4%.

Figure 3: Comparison of FT4 between NAFLD grades



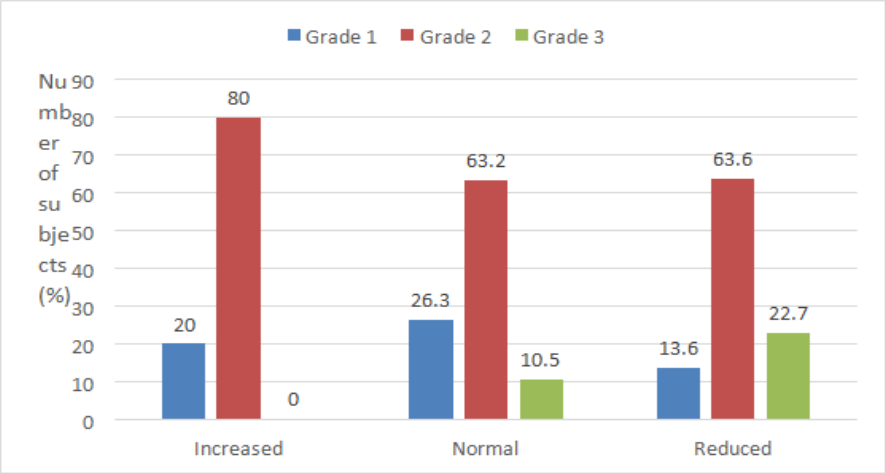
Mean FT4 in NAFLD Grade 1 was 1.46±0.91, in NAFLD grade2 was 1.32±0.78 and in NAFLD grade 3 was 1.24±0.86. When we compared FT4 among all the three grades, the difference was statistically not significant (p>0.05). It means that the FT4 levels do not vary much with respect to NAFLD grades.

Figure 4: Comparison of TSH between NAFLD grades



Mean TSH in NAFLD Grade 1 was 3.19±2.41, in NAFLD grade2 was 5.16±3.85 and in NAFLD grade 3 was 6.21±3.19. When we compared TSH among all the three grades, the difference was statistically significant ($p<0.05$). It means that the TSH level was significantly higher in NAFLD grade 3 followed by grade 2 and vary according to severity of NAFLD.

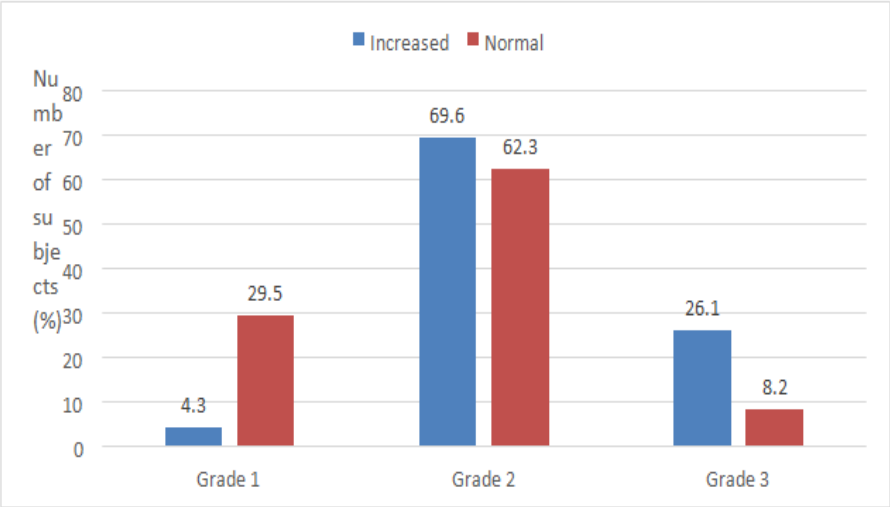
Figure 5: Distribution according to NAFLD grades and FT4



Proportion of patients with increased FT4 having NAFLD grade 2 were 80% compared to 63.2% normal and 63.6% with reduced FT4. Proportion of patients with increased FT4 having NAFLD grade 3 were 0% compared to 10.5% normal and 22.7% with reduced FT4.

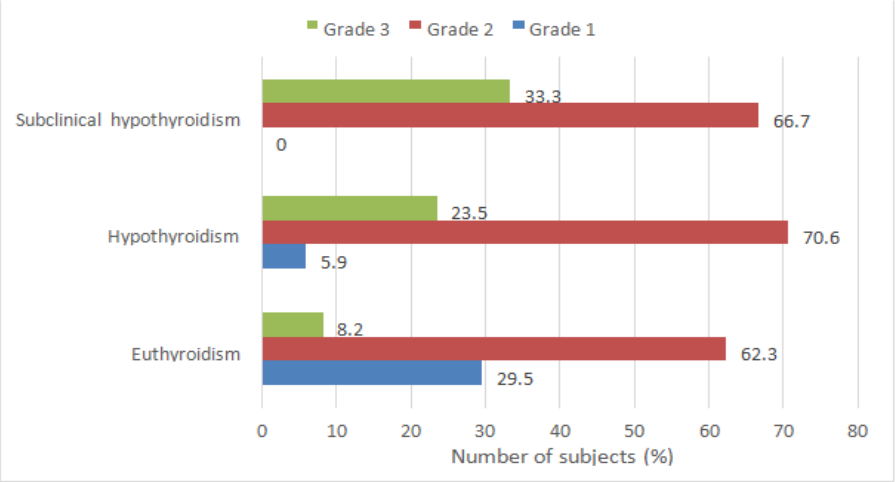
When we compared the proportion of these patients with respect to NAFLD grades and its severity, the difference was statistically not significant ($p>0.05$).It means there was no association between FT4 and NAFLD in our study.

Figure 6: Distribution according to NAFLD grades and TSH



Proportion of patients with increased TSH having NAFLD grade 2 were 69.6% compared to 62.3% normal. Proportion of patients with increased TSH having NAFLD grade 3 were 26.1% compared to 8.2% with normal TSH. When we compared the proportion of these patients with respect to NAFLD grades and its severity, the difference was statistically significant ($p<0.05$).It means there was association between TSH and NAFLD in our study.

Figure 7: Distribution according to NAFLD grades and type of thyroid abnormality



Proportion of euthyroid patients with Grade 2 NAFLD is 62.3% and grade 3 NAFLD is 8.2%. Proportion of hypothyroid patients with grade 2 NAFLD is 70.6% and grade 3 NAFLD is 23.5%. Proportion of patients with subclinical hypothyroidism having grade 2 NAFLD is 66.7% and that having grade 3 NAFLD is 33.3%. This difference in the proportion of cases was found to be significant ($p<0.05$).

Discussion

The present study showed that TSH elevation within the normal clinical range of FT4 is an independent risk factor of NAFLD and might be associated with liver fibrosis. The prevalence of NAFLD was significantly higher in patients with overt and subclinical hypothyroidism than in those with euthyroidism. TSH was independently associated with NAFLD in multivariate analysis, but FT4 was not an independent risk factor of NAFLD. It was also demonstrated that hypothyroidism is an independent risk factor for NAFLD. This indicates that hypothyroidism may directly lead to NAFLD irrespective of other metabolic risk factors.[13]

In our study, prevalence of reduced FT3 was 10.7%, reduced FT4 was 26.2% and elevated TSH was 27.4%.The prevalence of hypothyroidism was found to be 20.2% and that of subclinical hypothyroidism was 7.1%.

In this study,when mean FT4 were compared among all the three grades of NAFLD, the difference was statistically not significant ($p>0.05$). It means that FT4 level do not vary much with respect to NAFLD grades.

However, the difference in mean TSH among all the three grades was found to be statistically significant ($p<0.05$). It means that the TSH level was significantly higher in NAFLD grade 3 followed by grade 2 and vary according to severity of NAFLD.

Guo et al.have reported that the association between NAFLD and FT3 and FT4 levels was heterogeneous among the population, but the TSH level may be an important risk factor for the development and progression of NAFLD, independent of thyroid hormones.[14]

The present study also showed that hypothyroidism and increased level of TSH were significantly related to NAFLD, but the association of FT4 with NAFLD was statistically not significant.

According to the study conducted by Chung et al., a positive association was found between NAFLD and TSH. It was shown that subclinical hypothyroidism was closely related to NAFLD in a TSH dose-dependent manner, even within the normal upper TSH level range.[15]

In addition, Kim et al.in 2018reported that an increase in TSH, even within the normal clinical range of T4, was related to biopsy-proven non-alcoholic steatohepatitis (NASH) and advanced fibrosis.[16]

Accoerding to Jaruvongvanich et al., NAFLD was not found to be associated with thyroid hormone levels and hypothyroidism.[17] Conversely, results of other meta-analyses have indicated that there is an association between NAFLD and hypothyroidism.[18,19]

Conclusions

The prevalence of NAFLD grade 2 was 64.3% followed by NAFLD grade 1 i.e. 22.6% and grade 3 i.e. 13.1%.Prevalence of overt hypothyroidism in our study was 20.2% and that of subclinical hypothyroidism was 7.1%.Prevalence of reduced FT3 was 10.7%, reduced FT4 was 26.2% and elevated TSH was 27.4%. There was no association between FT4 and NAFLD. There was significant association of increased serum levels of TSH with NAFLD and its grades. Significant association was found between hypothyroidism and NAFLD in our study.

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