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"FREQUENCY OF HYPOTHYROIDISM IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE"

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Abstract

Introduction: *The prevalence of non-alcoholic fatty liver disease (NAFLD) in adults has been reported to be high, making it the most common cause of chronic liver disease. Metabolic derangements are suggested to be the main cause of NAFLD. The aim of our study was to determine the frequency of hypothyroidism in patients with non-alcoholic fatty liver disease*

Objective: *To determine the frequency of hypothyroidism in patients with non-alcoholic fatty liver disease at a tertiary care Hospital, Karachi*

Setting: *This study was conducted in department of Internal Medicine, Liaquat National Hospital, karachi*

Study Design; *Cross Sectional study*

Duration of study; *6 months from 24th June 2023 to 24th Dec 2023*

Subject & methods: *All patients who fulfilled the inclusion criteria in the department of Department of General Medicine, Liaquat National Hospital, Karachi were included in the study. After taking informed and written consent history was taken, clinical examination was done and serum TSH, free T3 and free T4 levels were checked to reach the outcome i-e hypothyroidism.*

Result: *Total of 149 patients with non-alcoholic fatty liver disease were included. 81 patients (54.4%) were males & 68 patients (45.6%) were females with the mean age of 42.295±9.986 years. Hypothyroidism was noted in 19 (12.8%) patients.*

Conclusion: *In conclusion the frequency of hypothyroidism in patients with non-alcoholic fatty liver disease was not much low, it increases with the decrease in age and increase in BMI & predominant in female gender.*

INTRODUCTION

Fatty liver is also known as hepatic steatosis. It happens when fat builds up in the liver. Having small amounts of fat in liver is normal (<5%), but too much (>5%) can become a health problem. There are two types of fatty liver, alcohol fatty liver disease (AFLD) and nonalcoholic fatty liver disease (NAFLD).[1]

Nonalcoholic fatty liver disease (NAFLD) is chronic liver disease with a high incidence worldwide[1]. NAFLD has a spectrum comprised of fatty liver, nonalcoholic steatohepatitis (NASH), advanced fibrosis, and cirrhosis. CHB and NAFLD commonly cause cirrhosis and hepatocellular carcinoma (HCC)[2]

An increasing number of diseases have been reported to be linked to NAFLD, such as cardiovascular disease, type 2 diabetes, chronic kidney disease, hypothyroidism and cancer.[3,4]

Hypothyroidism is a common disease of the endocrine system that affects lifelong health. The physiological role of the thyroid gland has been taken seriously by many scholars, not just because of the critical role of thyroid hormones in cell metabolism and energy homeostasis.[5] Previous studies on the hypothyroidism patients indicated that lower thyroid hormone caused insulin resistance, metabolic disorders, and NAFLD.[6] In Parikh et al[7] study the prevalence of hypothyroidism in NAFLD was 16.8 %. Subclinical hypothyroidism and low-normal thyroid function are associated with NASH and fibrosis according to the TSH levels.[8] From lifeline cohort study, higher FT3is associated with NAFLD in euthyroid subjects.[9]

Although thyroid function has been demonstrated to be associated with non-alcoholic fatty liver disease (NAFLD) in different population, the prevalence and features of NAFLD in hyperthyroidism have not been reported.[10] Previous studies propose that hypothyroidism might play a crucial role in the pathogenesis of non-alcoholic fatty liver disease (NAFLD) but findings from published studies on the relationship between hypothyroidism and NAFLD are still controversial.[11]

The rationale of study is to determine the frequency of hypothyroidism in patients with non-alcoholic fatty liver disease (NAFLD). The literature on this topic is scarce locally, this study will provide local statistics of hypothyroid induced NAFLD. The results could be different locally because of difference in ethnicity, life style and eating habits. In addition, this study will be helpful in emphasizing that NAFLD patients should have thyroid profile test mandatory. This will help early diagnosis and treatment of hypothyroidism.

OBJECTIVE:

To determine the frequency of hypothyroidism in patients with non-alcoholic fatty liver disease at a tertiary care Hospital, Karachi

OPERATIONAL DEFINITIONS:

Non-Alcoholic Fatty Liver Disease:

was defined on the basis of ultrasound imaging and will be diagnosed as NAFLD on the presence of any one or more of the following features on ultrasonography

1. Diffuse hyper echogenicity of liver parenchyma.
2. Impaired or no visualization of portal vein borders.
3. Impaired or no visualization of diaphragm.
4. Impaired or no visualization of posterior part of right lobe of liver.
5.

Hypothyroidism:

TSH greater than or equal to 5mU/l and free T3 <0.6 pg/ml and/or free T4 was <5 pg/dl.

Hypertension:

Patients on antihypertensive medications for ≥ 3 months, controlled blood pressures

Diabetes millets (DM):

Patients having HbA1C > 6.5 for > 1 year, on antidiabetics

Smoking:

A person who smokes at least five cigarettes a day for at least one year or who is ex-smoker (who smoked at least five cigarettes a day for at least one year) will be labeled a smoker.

Dyslipidemia:

Patients having serum cholesterol >200mg/dl and/or serum triglyceride level >150mg/dl Height was measured by inch tap in meters, weight was measure by weight machine in kilogram, BMI was calculated by

weight in kg divided by height in meter square (kg/m^2).

MATERIAL AND METHODS

SETTING:

This study was conducted in department of Internal Medicine, Liaquat National Hospital, Karachi.

STUDY DESIGN:

Cross Sectional study

DURATION OF STUDY:

6 months from 24th June 2023 to 24th Dec 2023

SAMPLE SIZE:

Sample size calculated on the basis of the following
Frequency of hypothyroidism in patients with NAFLD=16.8% [7]
Confidence level=95%
Margin of error=6%
Sample size (n) = 149 no: of patients with NAFLD
Formula $n= z^2p (1-P) /d^2$

SAMPLE TECHNIQUE:

Non probability consecutive sampling

SAMPLE SELECTION:

Inclusion Criteria

- Patients with age of 18-70 years.
- Either gender
- Patients with nonalcoholic fatty liver disease for ≥1 year as per operational definition

Exclusion Criteria

- Patients already diagnosed as chronic liver disease 2ndry to viral or alcoholic hepatitis
- Patients having ascites on ultrasound.

DATA COLLECTION PROCEDURE:

This study was performed after taking approval from the ethical review committee of the institute and CPSP. Patients attending outpatient clinics in the department of internal Medicine, Liaquat National Hospital, Karachi with NAFLD as per operational definition meeting the inclusion criteria was included in this study after taking informed written consent. Brief history regarding demographic variables like name, medical record number, age & sex and clinical history regarding place of living, co-morbidities i-e hypertension and smoking will be taken followed by clinical examination. Patient was assessed to diagnose hypothyroidism by doing TSH, free T3 and free T4 levels done from institutional diagnostic laboratory by taking blood sample following all aseptic measures by pathologist. Levels of TSH greater than or equal to 5mU/l and free T3 <0.6 pg/ml and/or free T4 <5 pg/dl was labeled as hypothyroidism. All demography, clinical history i-e place of living, co-morbidities i-e hypertension and smoking was recorded by a principal investigator on a predesigned Performa. Exclusion criteria was followed strictly to avoid effect modifiers.

DATA ANALYSIS:

All the data was entered into SPSS 22 version and was analyzed by using the same software. Values was presented as mean ± standard deviation or median (IQR) for non-normal data, Shapirowilk test was used to check normality of data for quantitative variables like age, height, weight, BMI. Simple frequency and percentage was computed for the gender, place of residence (urban/ rural), education level (primary/ intermediate/ graduation or more/ illiterate), co-morbid i-e DM, hypertension, smoking & dyslipidemia (yes/no) and hypothyroidism (yes/ no). Stratification with respect to the age, gender, BMI, place of residence, education level and DM, hypertension, smoking & dyslipidemia was done to control the effect modifiers. Post stratification chi-Square or Fischer exact test was applied and *P*-value ≤0.05 was considered as significant.

RESULT:

A total of 149 patients with non-alcoholic fatty liver disease were selected to conduct this study.
In our study 81 patients (54.4%) were males & 68 patients (45.6%) were females (as shown in Table-3).
The mean age was 42.295±9.986 years. The distribution of age groups is presented in Graph-I. The descriptive statistics of age is presented in Table-1.
The mean height was 165.194±8.219 cm, the mean weight was 73.563±10.797 kg, the mean BMI was 26.171±20.092 kg/m^2 & the mean duration of nonalcoholic fatty liver disease (NAFLD) was 4.536±1.648 years. The distribution of BMI groups is

presented in Graph-II. The descriptive statistics of height, weight, BMI & duration of nonalcoholic fatty liver disease (NAFLD) is presented in Table-2.

Residence was urban in 73(49%) & rural in 76(51%) patients, as shown in Table-4.

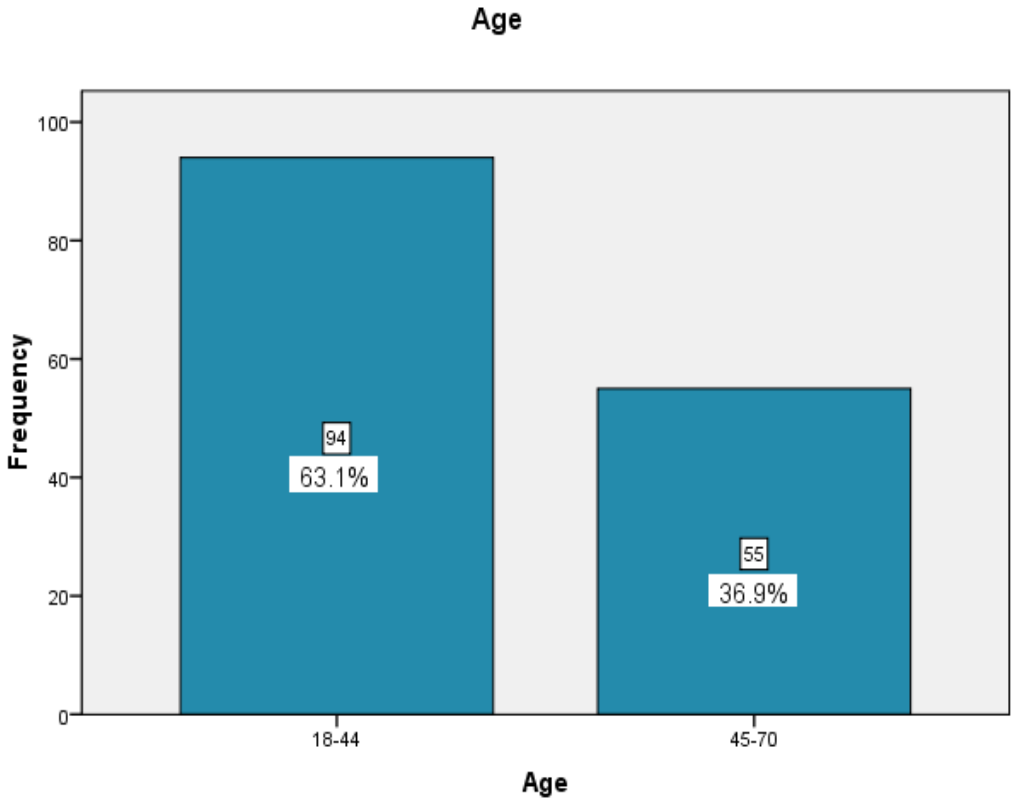
Education level was primary in 36(24.2%), intermediate in 52(34.9%) & graduation or more in 35(23.5%) patients, as shown in Table-5.

DM was seen in 21(14.1%) patients, hypertension was noted in 24(16.1%) patients, dyslipidemia was seen in 16(10.7%) patients & smoking was noted in 23(15.4%) as shown in Table-6.

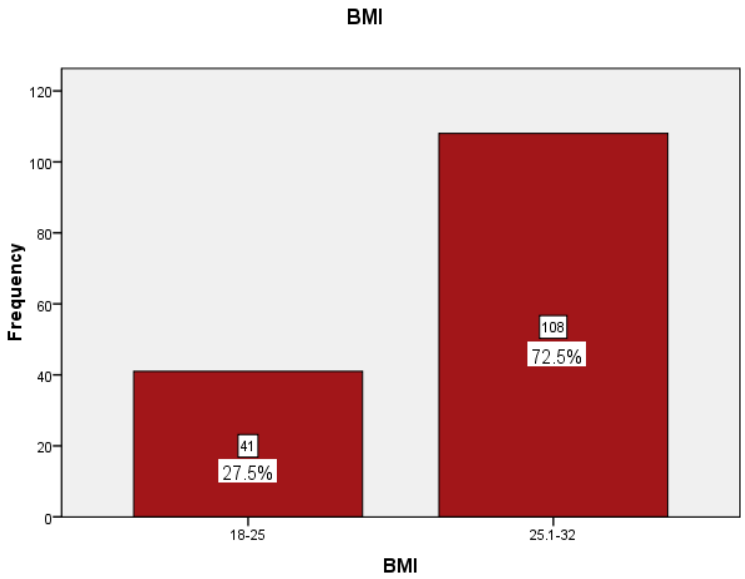
In our study Hypothyroidism was noted in 19 (12.8%) patients, as shown in Table-7.

The frequencies of age groups (years), gender, BMI, residence, education level, DM, hypertension, dyslipidemia, smoking & duration of non-alcoholic fatty liver disease (NAFLD) were calculated according to Hypothyroidism**.** The results are presented in Table-8, Table-9, Table-10, Table-11, Table-12, Table-13, Table-14, Table-15, Table-16 & Table-17 respectively.

In our study hypothyroidism was significantly associated with DM (0.001), hypertension (0.001), dyslipidemia (p=0.001) & & duration of non-alcoholic fatty liver disease (NAFLD) (p=0.006) while was not significantly associated with age (p=0.616), gender (p=0.251), BMI (p=0.671), residence (p=0.070), education level (p=0.864), smoking (p=0.468).



Graph-I
Frequency distribution of Age (years)



Graph-11
Frequency distribution of BMI (kg/m^2)

Table-I
Descriptive statistics of age (year)

tatistics	Age (years)
Minimum	25
Maximum	65
Mean	42.295
Std. Deviation	9.986

Table-2
Descriptive statistics of height (cm), weight (kg), BMI (kg/m^2) & duration of nonalcoholic fatty liver disease (NAFLD) (years)

Statistics	Height (cm)	Weight (kg)	BMI (kg/m^2)	Duration of nonalcoholic fatty liver disease (NAFLD) (years)
Minimum	152	49	18.30	2
Maximum	188	115	32	9
Mean	165.194	73.563	26.171	4.536
Std. Deviation	8.219	10.797	2.092	1.646

TABLE – 3
Frequency distribution of gender
(n=149)

Gender	Frequency (n)	Percentage (%)
Male	81	54.4%
Female	68	45.6%
Total	149	100%

TABLE – 4
Frequency distribution of residence
(n=149)

Residence	Frequency (n)	Percentage (%)
Urban	73	49%
Rural	76	51%
Total	149	100%

TABLE – 5
Frequency distribution of education level
(n=149)

Education level	Frequency (n)	Percentage (%)
Primary	36	24.2%
Intermediate	52	34.9%
Graduation or more	35	23.5%
Total	149	100%

TABLE – 6
Frequency distribution of co-morbidities (DM, hypertension, dyslipidemia & smoking)
(n=149)

DM	Frequency (n)	Percentage (%)
Yes	21	14.1%
No	128	85.9%
Total	149	100%
Hypertension	Frequency	Percentage

	(n)	(%)
Yes	24	16.1%
No	125	83.9%
Total	149	100%
Dyslipidemia	Frequency (n)	Percentage (%)
Yes	16	10.7%
No	133	89.3
Total	149	100%
Smoking	Frequency (n)	Percentage (%)
Yes	23	15.4%
No	126	84.6%
Total	149	100%

TABLE – 7
Frequency distribution of Hypothyroidism
(n=149)

Hypothyroidism	Frequency (n)	Percentage (%)
Yes	19	12.8%
No	130	87.2%
Total	149	100%

TABLE – 8
Hypothyroidism according to age (years)
(n=149)

Age (years)	Hypothyroidism		Total	P-value
	Yes	No		
18-44 years	11(11.7%)	83(88.3%)	94	0.616
45-70 years	8(14.5%)	47(85.5%)	55	
Total	19	130	149	

Chi-square-test was applied
P-value ≤ 0.05 considered as significant.
Not significant at 0.05 level

TABLE – 9
Hypothyroidism according to gender
(n=149)

Gender	Hypothyroidism		Total	P-value
	Yes	No		
Male	8(9.9%)	73(90.1%)	81	0.251

Female	11(16.2%)	57(83.8%)	68	
Total	19	130	149	

Chi-square-test was applied
P-value ≤ 0.05 considered as significant.
Not significant at 0.05 level

TABLE – 10
Hypothyroidism according to BMI (kg/m^2)
(n=149)

BMI (kg/m^2)	Hypothyroidism		Total	P-value
	Yes	No		
18-25	6(14.6%)	35(85.4%)	41	0.671
25.1-32	13(12%)	95(88%)	108	
Total	19	130	149	

Chi-square-test was applied
P-value ≤ 0.05 considered as significant.
Not significant at 0.05 level

TABLE – 11
Hypothyroidism according to residence
(n=149)

Residence	Hypothyroidism		Total	P-value
	Yes	No		
Urban	13(17.8%)	60(82.2%)	73	0.070
Rural	6(7.9%)	70(92.1%)	76	
Total	19	130	149	

Chi-square-test was applied
P-value ≤ 0.05 considered as significant.
Not significant at 0.05 level

TABLE – 12
Hypothyroidism according to education level
(n=149)

Education level	Hypothyroidism		Total	P-value
	Yes	No		
Primary	5(13.9%)	31(86.1%)	36	0.864
Intermediate	7(13.5%)	45(86.5%)	52	
Graduation or more	5(14.3%)	30(85.7%)	35	
Total	19	130	149	

Chi-square-test was applied
P-value ≤ 0.05 considered as significant.
Not significant at 0.05 level

TABLE – 13
Hypothyroidism according to DM
(n=149)

DM	Hypothyroidism		Total	P-value
	Yes	No		
Yes	15(71.4%)	6(28.6%)	21	0.001
No	4(3.1%)	124(96.9%)	128	
Total	19	130	149	

Chi-square-test was applied
P-value ≤ 0.05 considered as significant.
Significant at 0.05 level

TABLE – 14
Hypothyroidism according to hypertension
(n=149)

Hypertension	Hypothyroidism		Total	P-value
	Yes	No		
Yes	9(37.5%)	15(62.5%)	24	0.001
No	10(8%)	115(92%)	125	
Total	19	130	149	

Chi-square-test was applied
P-value ≤ 0.05 considered as significant.
Significant at 0.05 level

TABLE – 15
Hypothyroidism according to dyslipidemia
(n=149)

Dyslipidemia	Hypothyroidism		Total	P-value
	Yes	No		
Yes	14(87.5%)	2(12.5%)	16	0.001
No	5(3.8%)	128(96.2%)	133	
Total	19	130	149	

Chi-square-test was applied
P-value ≤ 0.05 considered as significant.
Significant at 0.05 level

TABLE – 16
Hypothyroidism according to smoking
(n=149)

Smoking	Hypothyroidism		Total	P-value
	Yes	No		
Yes	4(17.4%)	19(82.6%)	23	0.468
No	15(11.9%)	111(88.1%)	126	
Total	19	130	149	

Chi-square-test was applied
P-value ≤ 0.05 considered as significant.
Not significant at 0.05 level

TABLE – 17
Hypothyroidism according to duration of non-alcoholic fatty liver disease (NAFLD) **(n=149)**

Duration of non-alcoholic fatty liver disease (NAFLD)	Hypothyroidism		Total	P-value
	Yes	No		
2-5 years	19(17.1%)	92(82.9%)	111	0.006
6-9 years	0(%)	38(100%)	38	
Total	19	130	149	

Chi-square-test was applied
P-value ≤ 0.05 considered as significant.
Significant at 0.05 level

DISCUSSION

to predict clinical outcome. The results of this study indicate that both the category and grade
Affect the outcome independently, and the higher the grade of subcategory, the greater the
chance that the ulcer will persist or that death will occur. The most important finding of this
Study is that the simple PEDIS score system can also predict the outcome and may be more ac-
curate than the more widely used system
the AUC value to confirm the diagnostic accuracy of the PEDIS score system to predict
the outcome of DFUs. The results of this study indicate that the PEDIS score system also has
excellent capacity to predict the outcome. In addition, our study shows that the PEDIS category
Scores can be summed into an aggregate PEDIS score, with a score of 7 or more being associated with a significantly greater probability of difficulties in healing. We believe that the PEDIS
score system should be applied widely in clinical
The prevalence of hypothyroidism in the United States is 3.7% as reported by the National Health and Nutritional Examination Survey (NHANES) conducted between 1999 and 2002.[210] Other studies report the prevalence of sub clinical and overt hypothyroidism to be 4–10% and 0.3–5% in the general population, respectively, and 5% in the geriatric population.[12,13]

In our study frequency of hypothyroidism was 12.8% as compare to Parikh et al[14] study the prevalence of hypothyroidism in NAFLD was 16.8 %. Subclinical hypothyroidism and low-normal thyroid function are associated with NASH and fibrosis according to the TSH levels.[15] From lifeline cohort study, higher FT3is associated with NAFLD in euthyroid subjects.[16] Two previous studies with smaller sample sizes and incomplete histology reported prevalence rates of 15 and 20% for hypothyroidism in NAFLD.[17,18] Pagadala et al[19] study included a large sample size with liver histology read by a single pathologist for all the patients. It controlled for known factors associated with hypothyroidism (age, gender, ethnicity and BMI). The findings of Pagadala et al[19] study confirm an association between the presence of hypothyroidism and NAFLD.

The link between hypothyroidism and NAFLD may relate to several underlying mechanisms. Hypothyroidism has been associated with insulin resistance,[20,21] dyslipidemia[22] and obesity;[23] all of which are important components of the metabolic syndrome. In addition, hypothyroidism is also associated with the metabolic syndrome,[24] which plays an important role in the development of NAFLD.[25]

Insulin resistance in the setting of hypothyroidism has been documented and is associated with decreased responsiveness of glucose uptake in muscle and adipose tissue to insulin, as well as decreased glycogen synthesis in skeletal muscle in both animal and human studies.[26,27] These effects were alleviated by thyroid replacement. Hypothyroidism is also more common in patients with diabetes than in the general population.[28] If hypothyroidism enhances the degree of insulin resistance in NAFLD patients, it may increase the already elevated lipolysis and free fatty acid delivery to the liver and thereby accelerate liver injury in NAFLD.[29]

There is also an increased prevalence of hypothyroidism in the obese population as compared to the general population[23] with the prevalence of hypothyroidism being 10–20% in obese subjects.[23] On average hypothyroid patients weigh 15–30% more than during euthyroid state.[30] Leptin, an adipocytokine that affects thermogenesis and appetite and is an indicator of body fat content, may have a possible role in hypothyroidism and obesity.[31] Hypothyroidism patients have increased levels of leptin[32] which increases collagen production and insulin resistance in the liver.[33,34] Hypothyroidism can also increase risk of hypertension.[35] Possible mechanisms responsible for hypertension in individuals with hypothyroidism include increased peripheral vascular resistance and arterial stiffness,[36] abnormalities that occur in NAFLD patients.[37]

Up to 90% of hypothyroid patients have abnormal lipid values.[23] While hypothyroidism primarily causes elevation in cholesterol and low density lipoproteins, it also affects the synthesis, mobilization and degradation of all aspects of lipid metabolism.[38] There is increased triglyceride levels in hypothyroid subjects due to increased esterification of hepatic fatty acids with diminished lipoprotein lipase activity and decreased hepatic uptake of HDL levels in these subjects.[38] It is possible that dyslipidemia in hypothyroidism may contribute to NAFLD.[39] The antisteatotic and triglyceride reducing effects of a liver-selective thyroid receptor (TR) agonist on livers of animal models with fatty liver have been described.[40] Therefore hypothyroidism may exacerbate preexisting lipid abnormalities in patients with NAFLD.

Although the precise cause of the increased prevalence of NAFLD and NASH in hypothyroidism patients remain unclear, insulin resistance in hypothyroidism is likely to exacerbate free fatty acid influx and subsequent hepatic steatosis. Furthermore, hypothyroidism has been reported to modulate mitochondrial nitric oxide synthesis and alter mitochondrial inner membrane composition and permeability which alters respiratory gene expression and mitochondrial oxygen uptake.[41] Such abnormalities would result in increased ADP concentration and generation of reactive oxygen species.[42] The clinical importance of these findings is emphasized by the nascent but important data indicating that fatty liver may improve with liver-specific thyromimetics.[43,44]

The limitation of our study was single center study and smaller sample size, so further studies with larger sample sizes are required.

CONCLUSION

In conclusion the frequency of hypothyroidism in patients with non-alcoholic fatty liver disease was not much low, it increases with the decrease in age and increase in BMI & predominant in female gender.

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