To Study the Prevalence of Hypothyroidism in Non-Alcoholic Fatty Liver Disease in Northern Population

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ABSTRACT

BACKGROUND

The prevalence of non-alcoholic fatty liver disease (NAFLD) in adults has been reported to be as high as 33 % making it the most common cause of chronic liver disease. Metabolic derangements are suggested to be the main cause of NAFLD. As thyroid hormone is the main regulator of energy metabolism, there may be a link between NAFLD and thyroid function.

METHODS

The study was conducted on 100 patients with diagnosis of NAFLD on ultrasonography from 1st January 2019 to 30th June 2020. These patients were further assessed for thyroid dysfunction by thyroid function tests.

RESULTS

The present study consisted of 100 patients having Non-alcoholic fatty liver disease diagnosed on ultrasonography, 47 % were having grade 1, 42 % were having grade 2 and 11 % were having grade 3 fatty liver. In the present study, 59 % were having normal FT3 levels and 41 % patients had low FT3 levels which showed no significant relationship with increasing grades of fatty liver ($p = 0.114$). In the present study, 20 % of the patients were having low free T4 levels whereas 80 % had normal free T4 levels, and free T4 levels showed inverse relationship with increasing grades of fatty liver ($p = 0.000$). 18 % patients with NAFLD had hypothyroidism (4 % subclinical and 14 % overt hypothyroid) and more percentage of patients with grade 2 and 3 fatty liver had hypothyroidism.

CONCLUSIONS

The prevalence of hypothyroidism was 18 % in patients with NAFLD. Free T4 and serum TSH levels had significant correlation with increasing grades of fatty liver. Hence, statistically significant association was found between hypothyroidism and NAFLD.

KEYWORDS

NAFLD, TSH, T3, T4

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BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) represents a broad clinical spectrum ranging from simple fatty liver to non-alcoholic steatohepatitis (NASH), which may progress to liver fibrosis, cirrhosis and hepatocellular carcinoma.[1] NAFLD is a rapidly growing diagnosis, and it is the most common cause of abnormal liver function tests worldwide.[2] The growing pattern of NAFLD prevalence is generally attributed to a global increase in the prevalence of obesity and other metabolic risk factors.[3] Advanced age and metabolic disorders, such as diabetes type 2, impaired glucose tolerance, and central obesity, are among the risk factors for NAFLD.[4] Cryptogenic cirrhosis is a term used for those patients with liver cirrhosis who lack any identifiable viral, alcoholic, autoimmune or drug-related cause of the condition. Many clinicians now believe that a considerable number of these patients have cirrhosis due to NASH.[5]

Considering the increasing incidence of NAFLD/NASH, especially in developed and developing countries, it is anticipated that cirrhosis due to these conditions may surpass other causes of cirrhosis in a near future. Therefore, understanding the pathophysiology, risk factors and new treatment options of NAFLD / NASH should be among the priorities in the field of hepatology.[4] Thyroid gland is thoroughly involved in cell metabolism, energy homeostasis, regulation of body weight, thermogenesis, lipid and carbohydrate metabolism, and adipogenesis.[6] Subclinical hypothyroidism has been reported to be associated with metabolic syndrome, cardiovascular mortality, and disturbance of lipid metabolism.[7] Considering these evidences, some studies were conducted to investigate the association between thyroid dysfunction and NAFLD / NASH.

Objectives

1. To estimate thyroid function in patients of non-alcoholic fatty liver disease.
2. To study the prevalence of hypothyroidism in patients of non-alcoholic fatty liver disease.

METHODS

The present hospital based cross sectional study was proposed to be undertaken with a total number of 100 patients of NAFLD diagnosed by ultrasonography whole abdomen, attending the department of medicine after approval from Institutional Thesis and Ethical Committee.

Inclusion Criteria

All Patients above 18 years of age with NAFLD visiting indoor and outdoor of Sri Guru Ram Das Institute of medical sciences and Research, Vallah, Sri Amritsar.

Exclusion Criteria

1. Presence of hepatitis B or C infection.
2. Presence of haemochromatosis.
3. Intake of iodine, antithyroid agents or thyroid hormones.
4. Chronic alcoholic liver disease.
5. Diabetes Mellitus.
6. Intake of drugs like Dopamine, Corticosteroids, Amiodarone and Phenytoin.

The present study was a cross-sectional study carried out on 100 adult patients diagnosed as having non-alcoholic fatty liver disease by ultrasonography, visiting Sri Guru Ram Das Institute of Medical Sciences and Research. Patients having age of < 18 years, chronic hepatitis B or C, haemochromatosis, taking iodine, antithyroid drugs or thyroid hormones, chronic alcoholic liver disease, diabetes mellitus and intake of drugs like dopamine, corticosteroids, amiodarone and phenytoin were excluded from the study. Detailed history and clinical examination was conducted on all patients and they underwent routine investigations and thyroid function test (free T3, free T4, and TSH).

Statistical Analysis

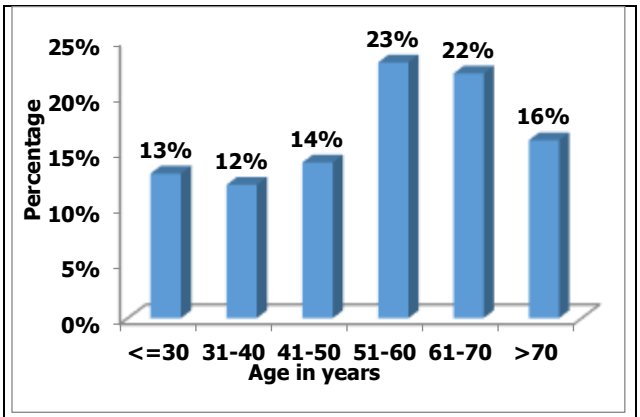
The data collected was compiled and entered in a spreadsheet computer program (Microsoft Excel 2010) and then was exported to data editor page of SPSS version 20 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics included computation of percentages, means and standard deviations. The statistical tests applied for analysis were Pearson's chi-square test, test and one way analysis of variance. For all tests, confidence interval and p-value was set at 95% and ≤ 0.05 respectively.

RESULTS

The mean age was 54.81 years with maximum number of patients (45 %) being in the age group of 50-70 years. Out of 100 patients 41 were females and 59 were males. The male to female ratio was 1.43. On ultrasonography, 47 % patients were diagnosed to be having grade 1, 42 % grade 2 and 11 % grade 3 fatty liver. Out of 47 patients having grade 1 fatty liver, 26 (55 %) had a normal FT3 levels, whereas 21 (45 %) were having low FT3 levels according to their age group. Out of 42 patients having grade 2 fatty liver, 29 (69 %) had a normal FT3 levels, whereas 13 (31 %) were having decreased FT3 levels. Out of 11 patients having grade 3 fatty liver, 4 (36 %) had a normal free T3 levels and 7 (64 %) had decreased free T3 levels. Thus abnormality in free T3 levels increased from 31 % in grade 2 to 64 % in grade 3 fatty liver, but the relationship was not statistically significant ($p = 0.114$). Mean value of serum free T3 was 2.61 ± 0.79.

Out of 47 patients having grade 1 fatty liver, 43 (91 %) had normal free T4 levels, whereas only 4 (9 %) patients were having decreased free T4 levels. Out of 42 patients having grade 2 fatty liver, 33 (79 %) had a normal free T4 levels, whereas 9 (21 %) had decreased free T4 levels. Out of 11 patients having grade 3 fatty liver, 4 (36 %) had normal free T4 levels.7 patients (64 %) had decreased free T4 levels i.e. almost more than half of the patients with

Grade 3 fatty liver were having decreased free T4 levels. As such 9 % patients with fatty liver grade 1, 21 % with grade 2 and 64 % with fatty liver grade 3 had low free T4 levels. Thus with increasing grades of fatty liver more percentage of patients had low free T4 levels which was statistically significant (p = 0.000).Mean value of serum free T4 was 1.09 ± 0.38.



Graph 1. Distribution According to Age

Serum Free T4 Levels	Grades of Fatty Liver						Total	Chi-Square Value	P-Value
	Grade 1 (n=47)		Grade 2 (n=42)		Grade 3 (n=11)				
Normal	43	91 %	33	79 %	4	36 %	**80**	17.022	0.000
Low	4	9 %	9	21 %	7	64 %	**20**		

Table 1. Relationship of Serum Free t4 Levels with Grades of Fatty Liver

Serum TSH Levels	Grades of Fatty Liver						Total	Chi-Square Value	P-Value
	Grade 1 (n=47)		Grade 2 (n=42)		Grade 3 (n=11)				
<5 mIU	46	98 %	33	79 %	3	27 %	**82**	30.677	0.001
>5 mIU	1	2 %	9	21 %	8	73 %	**18**		

Table 2. Relationship of Serum TSH Levels with Grades of Fatty Liver

	Grades of Fatty Liver						Total	Chi-Square Value	P-Value
	Grade 1 (n=47)		Grade 2 (n=42)		Grade 3 (n=11)				
Normal Thyroid Function	46	98 %	33	79 %	3	27 %	**82**	33.244	0.000
Subclinical Hypothyroidism	0	0 %	3	7 %	1	9 %	**4**		
Overt Hypothyroidism	1	2 %	6	14 %	7	64 %	**14**		

Table 3. Relationship of Thyroid Status with Grades of Fatty Liver

Thyroid Status	No. of Patients	Percentage
Normal Thyroid Status	82	82 %
Subclinical Hypothyroidism	4	4 %
Overt Hypothyroidism	14	14 %
Total	**100**	**100 %**

Table 4. Distribution of Patients According to Thyroid Status

Out of 47 patients having grade 1 fatty liver, 46 (98 %) had a normal TSH levels, whereas only 1 (2 %) patient was having TSH levels of more than > 5 mIU. Out of 42 patients having grade 2 fatty liver, 33 (79 %) had a normal TSH levels, whereas 9 (21 %) had TSH levels > 5mIU. Out of 11 patients having grade 3 fatty liver, 3 (27 %) had a normal TSH levels, whereas 8 (73 %) were having TSH levels between > 5 mIU. As such 2 % patients with fatty liver grade 1, 21 % with fatty liver grade 2 and 73 % with fatty liver grade 3 had TSH level of >5 mIU. Thus with increasing grades of fatty liver more percentage of patients had high serum TSH and this relationship was statistically significant (p = 0.001). Mean value of serum TSH was 5.61 ± 11.26.

In patients having grade 1 fatty liver on ultrasonography, out of 47 patients, 46 (98 %) had a normal thyroid function, whereas only 1 (2 %) patient was having overt hypothyroidism. In patients having grade 2 fatty liver on ultrasonography, out of 42 patients, 33 (79 %) had a normal thyroid function, whereas 3 (7 %) patients were having subclinical hypothyroidism with serum TSH levels >5mIU and normal free T4 levels and 6 (14 %) patients were having overt hypothyroidism. In patients having grade 3 fatty liver on ultrasonography, out of 11 patients, 3 (27 %) had a normal thyroid function, one (9 %) had subclinical hypothyroidism and 7(64 %) were having overt hypothyroidism. As such in fatty liver grade 1, only one patient (2 %) had hypothyroidism, in fatty liver grade 2, 9 patients (21 %) had hypothyroidism out of which 3 (7 %) had subclinical hypothyroidism and 6 (14 %) had overt hypothyroidism and in fatty liver grade 3, 8 (73 %) had hypothyroidism out of which 1 (9 %) had subclinical hypothyroidism and 7 (64 %) had overt hypothyroidism. Thus, with increasing grades of fatty liver there were more percentage of patients having hypothyroidism and this relationship was statistically highly significant (p = 0.000). Thus in the present study prevalence of hypothyroidism was 18 % (4 % subclinical hypothyroid, 14 % overt hypothyroid).

DISCUSSION

The present study was a cross-sectional study carried out on 100 adult patients diagnosed as having non-alcoholic fatty liver disease by ultrasonography, visiting Sri Guru Ram Das Institute of Medical Sciences and Research. Patients having age of < 18 years, chronic hepatitis B or C, haemochromatosis, taking iodine, antithyroid drugs or thyroid hormones, chronic alcoholic liver disease, diabetes mellitus and intake of drugs like dopamine, corticosteroids, amiodarone and phenytoin were excluded from the study. Detailed history and clinical examination was conducted on all patients and they underwent routine investigations and thyroid function test (free T3, free T4, and TSH).

In the present study, the 45 % patients were in the age group of 51 - 70 years of age. Mean age of the patients was 54.81 ± 17.29 years. In a study by Eshraghian A et al the mean age of patients with NAFLD was 48.20 ± 12.82 years.[8] In another study by Ludwig U et al the mean age of the patients with NAFLD was 47.7 ± 11.5 years. The patients in both these studies were in the younger age group as compared to the present study.[9]

In the present study, 59 % patients were males and 41 % were females thus having male predominance. In a study by Ulla Ludwig 70 % of the population with NAFLD were males and the remaining 30 % were females thus having male predominance.[9] In contrast in a study by Paul Samaresh et al, there was female preponderance (63.3 %) among NAFLD patients.

In the present study, 48% of the patients were having a BMI of 25 - 29.9 kg / m2 with a mean BMI of 25.10 ±2.34

kg / m^2. In a study by Eshraghian A et al, the mean BMI was 29.30 ± 5.44.[8] In the present study mean BMI was less, as obese patients with a BMI of > 30 kg / m^2 were not included, obesity being an independent risk factor for NAFLD.

In the present study, 26 % males as well as females had an abnormal waist hip ratio according to their respective reference values, whereas the remaining 74 % were having normal waist hip ratio. Mean waist hip ratio was 0.80 ± 0.16 in females and mean waist hip ratio was 0.89 ± 0.07 in males. Mean value of waist hip ratio of the patients was 0.85 ± 0.12. In a study by Ludwig U et al the mean of waist hip ratio was 0.9 ± 0.1.[9] This difference is due to the fact that obese patients were excluded in the present study.

In the present study, 47 % patients had abnormal triglyceride levels with a mean value of 150 ± 78 mg / dl, whereas only 24 % patients had abnormal cholesterol levels with a mean value of 172 ± 108 mg / dl 38 % patients had high serum LDL-C levels with a mean of 82 ± 37 mg / dl. 63 % females had decreased serum HDL-C levels of < 50 mg / dl with a mean of 36 ± 18 mg / dl. 56 % males had decreased serum HDL-C levels of < 40 mg / dl with a mean of 40 ± 21 mg / dl.

In the present study 18 % of the patients had raised serum ALT levels and 33 % had raised serum AST levels whereas 22 % had raised ALP levels. ALT levels were raised upto 2 times the upper limit of normal in 14 % of the patients whereas 4 % had ALT levels of more than 3 times the upper limit of normal. The mean value of serum ALT levels in our patients was 49 ± 60 U / L. 67% of the patients had normal serum AST levels, whereas serum AST levels were more than 2 times the normal in 21 % of the patients and 12 % of the patients had serum AST levels of more than three times the upper limit of normal. Mean serum AST level was 40 ± 27 U / L. 22% patients had raised serum alkaline phosphatase levels of > 116 mg / dl, whereas 78 % had normal serum alkaline phosphatase levels of < 116 mg / dl. Mean serum alkaline phosphatase level was 102 ± 48 mg / dl.

In the present study, out of 100 patients having non-alcoholic fatty liver disease, 47 % were having grade 1 fatty liver, 42 % were having grade 2 and 11 % were having grade 3 fatty liver on ultrasonography. In a study by Paul Samaresh et al, among patients of NAFLD, 41.7 % were found to be in grade 1, 43.3 % were in grade 2, and 15.0 % were having grade 3 fatty liver, which is consistent with the findings of present study.[10]

More percentage of patients with low free T3 levels were in higher grades of fatty liver (p = 0.114). In the study by Chung et al., which presented clear evidence of the association between hypothyroidism and NAFLD, did not also ascribe any diagnostic value to the FT3 concentration.[11] 9 % patients with fatty liver grade 1, 21 % with grade 2 and 64 % with fatty liver grade 3 had low free T4 levels. Thus with increasing grades of fatty liver more percentage of patients had low free T4 levels which was statistically significant (p = 0.000). There was an inverse relationship between low free T4 levels with increasing grades of fatty liver. In a study by Ittermann et al, a significant inverse association between the free T4 concentration of NAFLD could be demonstrated.[12] Studies by Xu et al.[13] Chung et al.[11] Ittermann et al.[12] also concluded that lower free T4 is an independent risk factor for NAFLD. Findings of these studies are consistent with the present study.

2 % patients with fatty liver grade 1, 21 % with fatty liver grade 2 and 73 % with fatty liver grade 3 had TSH level of > 5 mIU. Thus with increasing grades of fatty liver more percentage of patients had high TSH and this relationship was statistically significant (p = 0.001).Beside the inverse association with free T4, Chung et al.[11] and Xu et al.[13] identified a positive association between NAFLD and TSH. Studies by Carulli et al.[14] and Pagadala et al.[15] in addition, suggest that the serum TSH concentration is associated with the severity of the hepatic steatosis. Ittermann et al.[12] detected no consistent association of serum TSH concentrations with hepatic steatosis. Our study showed highly significant relationship between serum TSH levels and increasing grades of fatty liver. Bano et al.[16] in 2016 prospectively investigated the association between variations in thyroid function and NAFLD. They reported that higher free T4 levels were associated with a decreased risk of NAFLD. Also, higher serum TSH levels were associated with an increased risk of having clinically relevant fibrosis in NAFLD. The study concluded that lower thyroid function is associated with an increased grades of NAFLD. This is in consistence with findings of the present study as it showed significant association of free T4 and serum TSH with increasing grades of fatty liver.

In fatty liver grade 1, only one patient (2 %) had hypothyroidism, in fatty liver grade 2, 9 patients (21 %) had hypothyroidism out of which 3 (7 %) had subclinical hypothyroidism and 6 (14 %) had overt hypothyroidism and in fatty liver grade 3, 8 (73 %) had hypothyroidism out of which 1 (9 %) had subclinical hypothyroidism and 7 (64 %) had overt hypothyroidism. Thus with increasing grades of fatty liver there were more percentage of patients having hypothyroidism and this relationship was statistically highly significant (p = 0.000).

Pagadala MR et al showed 21 % of their study population was having hypothyroidism in patients with NAFLD (p = 0.000).[15] In a study by Parikh et al the number of hypothyroid patients in NAFLD was found to be 16.8 %.[17] Hypothyroidism showed a significant correlation with NAFLD with a p -value of < 0.001. In the present study 18 % patients with NAFLD had hypothyroidism (4 % subclinical and 14 % overt hypothyroid) and more percentage of patients with grade 2 and 3 fatty liver had hypothyroidism.

CONCLUSIONS

Free T3 levels had no significant relationship with grades of fatty liver. Free T4 showed an inverse relationship with the increasing grades of fatty liver. Serum TSH showed a positive correlation with increasing grades of fatty liver.

In the present study 18 % patients of NAFLD were having hypothyroidism out of which 4 % were having subclinical hypothyroidism and 14 % were having overt hypothyroidism. The prevalence of hypothyroidism in the present study was 18 % which is almost 2 times the prevalence in the general population. More percentage of patients in grade 2 and 3 fatty liver had hypothyroidism.

Patients of NAFLD should be investigated by thyroid function tests especially those in grade 2 and 3 fatty liver and thyroid replacement therapy should be started when needed.

TSH may play a critical role in development and progression of NAFLD and thyroid replacement may reverse fatty infiltration of liver. Further studies in this regard are needed.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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