



## ASSOCIATION BETWEEN HYPOTHYROIDISM AND NAFLD

<sup>1</sup>Somnath Verma, <sup>2</sup>Arti Mona, <sup>3</sup>Rajesh Minia, <sup>4</sup>Rahul Khajuria

<sup>1</sup>Department of Internal Medicine, Senior Resident, Government Medical College, Jammu (J&K), India

<sup>2</sup>Department of Anesthesiology, Postgraduate, Sher-I-Kashmir Institute of Medical Sciences (SKIMS), Soura, J&K, India

<sup>3</sup>Department of Internal Medicine, Senior Resident, Government Medical College, Jammu (J&K), India

<sup>4</sup>Department of Internal Medicine, Senior Resident, Government Medical College, jammu (J&K), India

Conflicts of Interest: Nil

Corresponding author: *Somnath Verma*

### Abstract:

NAFLD is a chronic liver disease with a histological spectrum ranging from steatosis alone to non-alcoholic steatohepatitis (NASH), the latter having an increased risk for progression to cirrhosis. The prevalence of NAFLD in adults has been reported to be as high as 33% making it the most common cause of chronic liver disease. It is possible that hypothyroidism can be contributing to the dyslipidemia in NAFLD, which is a common abnormality in these patients. Early identification of at-risk patients is important since treatment of the hypothyroidism may reduce the risk of NAFLD and potential complications.

**MATERIALS AND METHODS:** The present prospective, observational study was conducted on 50 subjects presenting with clinical features/biochemical evidences suggestive of thyroid dysfunction. Exclusion criteria included were <18 year age, with any hepatitis virus infections, hemochromatosis, elevated alcohol consumption, intake of iodine or antithyroid agents.

**RESULTS:** A total of 50 subjects fulfilling inclusive criteria were taken up for study. These included four (8%) subjectives with features suggestive of subclinical hypothyroidism and 46 (92%) with those of clinical hypothyroidism. A total of 12 (24%) subjects with spectrum of steatosis alone to non-alcoholic steatohepatitis (NASH) were diagnosed ultrasonographically. All these subjects had features of clinical hypothyroidism.

Hypothyroidism enhances the degree of insulin resistance in NAFLD patients and may increase the already elevated lipolysis and free fatty acid delivery to the liver and thereby accelerate liver injury in NAFLD. Hypothyroidism primarily causes elevation in cholesterol and low density lipoproteins and also affects the synthesis, mobilization and degradation of all aspects of lipid metabolism. Early identification of at-risk patients is important since treatment of the hypothyroidism may reduce the risk of NAFLD and potential complications.

**Keywords:** Hypothyroidism, Non alcoholic fatty liver disease (NAFLD), non alcoholic steatohepatitis (NASH)

## INTRODUCTION

The world faces a burden of thyroid disease that has reached epidemic proportions (**Zhou et al., 2016**). Subclinical hypothyroidism (SCH) defined as an elevated serum thyroid-stimulating hormone (TSH) concentration and normal free thyroxine (FT<sub>4</sub>) level, the most common thyroid dysfunction which is often accompanied by lipid metabolic disorders, is an independent risk factor for atherosclerosis (odds ratio = 1.9), myocardial infarction (OR = 3.1), and nonalcoholic fatty liver disease (NAFLD) (hazard ratio = 2.21) (**Xu et al., 2012**).

Increased hepatic fat content, in the absence of excessive alcohol consumption or other specific causes of steatosis, has been called non-alcoholic fatty liver disease (NAFLD) (**Stefan et al., 2008**).

NAFLD is a chronic liver disease with a histological spectrum ranging from steatosis alone to non-alcoholic steatohepatitis (NASH), the latter having an increased risk for progression to cirrhosis. The prevalence of NAFLD in adults has been reported to be as high as 33% making it the most common cause of chronic liver disease (**Browning et al., 2004**). 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 (**Bugianesi et al., 2005**).

It is possible that hypothyroidism can be contributing to the dyslipidemia in NAFLD which is a common abnormality in these patients (**Toledo et al., 2006**). The antisteatotic and triglyceride reducing effects of a liver-selective thyroid receptor (TR) agonist on livers with fatty liver have been described. Therefore

hypothyroidism may exacerbate the preexisting lipid abnormalities in NAFLD (Cable et al., 2009).

Overt hypothyroidism has been associated with the development of NAFLD (Ittermann et al., 2012). The prevalence of NAFLD, as diagnosed by ultrasound and the exclusion of other causes of hepatic steatosis, in patients with treated hypothyroidism was 30.2% compared with 19.5% in the control population (Chung et al., 2012).

The data with respect to subclinical hypothyroidism are more variable with some studies identifying it as an independent risk factor for the presence of hepatic steatosis after correcting for confounding variables (Xu et al., 2012). The prevalence of hypothyroidism among a cohort of 246 patients with biopsy-proven NAFLD was 21 vs 9.5% in 430 age-, gender-, race- and BMI-matched controls (Pagadala et al., 2012). In addition, the prevalence of hypothyroidism in patients with NASH is higher than those with more benign disease (Carulli et al., 2013).

Early identification of at-risk patients is important since treatment of the hypothyroidism may reduce the risk of NAFLD and potential complications.

## MATERIALS AND METHODS

The present prospective, observational study was conducted on subjects presenting with clinical features/biochemical evidences suggestive of thyroid dysfunction..

Following subjects were excluded from the study:

- ❖ <18 years
- ❖ With incomplete laboratory results
- ❖ With past or present hepatitis B or hepatitis C virus infections
- ❖ Hemochromatosis or elevated alcohol consumption (>40 g/day in males and >20 g/day in females)
- ❖ Intake of iodine, antithyroid agents or thyroid hormones
- ❖ Missing ultrasonographic data on hepatic steatosis
- ❖ Missing data on BMI or metabolic syndrome

Patient history, including demographics, past medical history, family medical history, medication history as well as nicotine and alcohol use and nutritional habits was noted down in a predesigned proforma. Body height, body weight, hip, and waist circumference

was measured. The body-mass index (BMI) and the waist-to-hip ratio (WHR) were calculated according to recommendations of the World Health Organization (WHO).

Each subject underwent following laboratory investigations: random glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST),  $\gamma$ -glutamyl transferase (GGT), alkaline phosphatase (AP), C-reactive protein (CRP), albumin, lipid profile, thyroid-stimulating hormone (TSH), triiodothyronine (TT<sub>3</sub>), thyroxine (TT<sub>4</sub>) and anti-thyroid autoantibodies (Anti-TPO). The reference values taken in the present study was as per ASCOMS and Hospital Laboratory, which are as follows:

Serum levels TSH: 0.270 to 4.20  $\mu$ IU/mL

Serum levels of T<sub>3</sub>: 1.30 to 3.10 nmol/L

Serum levels of T<sub>4</sub>: 66.0 to 181.0 nmol/L

The ultrasound examinations were performed under standardized conditions. The liver was assessed with respect to size, the presence of focal lesions, and the presence of hepatic steatosis. The degree of steatosis was assigned to classes of “none” (grade 0), “mild” (grade I), “moderate” (grade II) and “severe” (grade III).

## Statistical analysis

The data was presented and analyzed using appropriate statistical methods. Data was presented as mean for variables with a normal distribution. Statistical differences between groups were evaluated by the chi-square test for categorical variables. A p-value of <0.05 was considered statistically significant.

## OBSERVATIONS

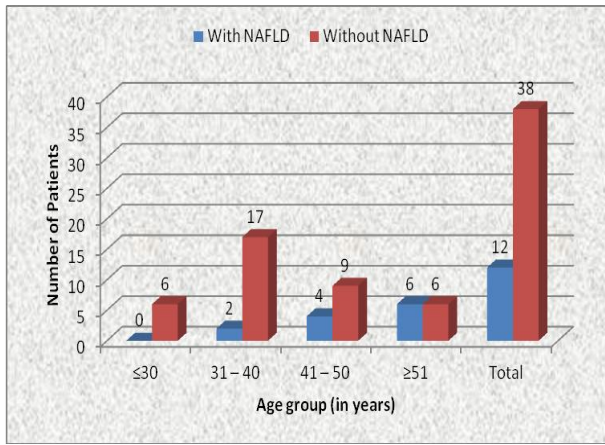
Subclinical hypothyroidism (SCH) was defined as an increase in serum thyroid stimulating hormone (TSH) above normal range (0.27 – 4.20  $\mu$ IU/mL) with normal concentration of serum thyroxine (66.0 – 181.0 nmol/L) and tri-iodothyronine (1.30 – 3.10 nmol/L), while clinical hypothyroidism (CH) was defined as an increase in serum TSH above normal range with a decrease concentration of thyroxine and tri-iodothyronine. Accordingly, there were 4 (8%) subjects with features suggestive of SCH and 46 (92%) with those of CH.

The subjects underwent ultrasonography for the presence of hepatic steatosis. A total of 12 (24%) subjects with spectrum of steatosis alone to non-alcoholic steatohepatitis (NASH) were diagnosed. All

these subjects had features of clinical hypothyroidism. Following observations were made while studying association of SCH/CH with non-alcoholic fatty liver disease (NAFLD) in subjects aged 18 to 65 years.

**Agewise comparison of study subjects with and without NAFLD**

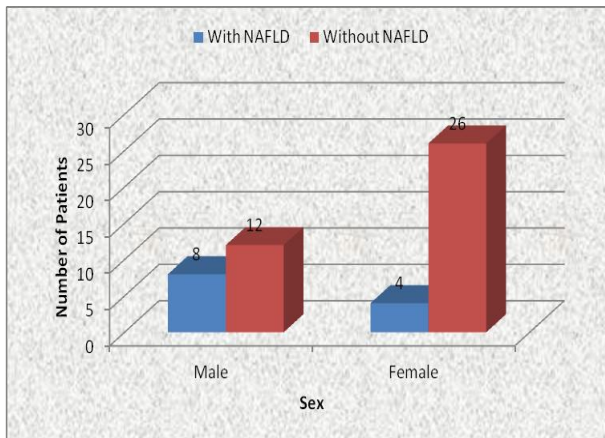
Out of 12 subjects with NAFLD, 6 (50%) subjects are in their 5<sup>th</sup> decade of life, while 4 (33.33%) are in their 4<sup>th</sup> and 2 (16.67%) are in their 3<sup>rd</sup> decade of life. The mean age of subjects with NAFLD is significantly more than that of subjects without NAFLD (49 vs 39.47 years, p=0.001).



**Fig. 1: Bar chart showing agewise distribution of study subjects with and without NAFLD**

**Sexwise comparison of study subjects with and without NAFLD**

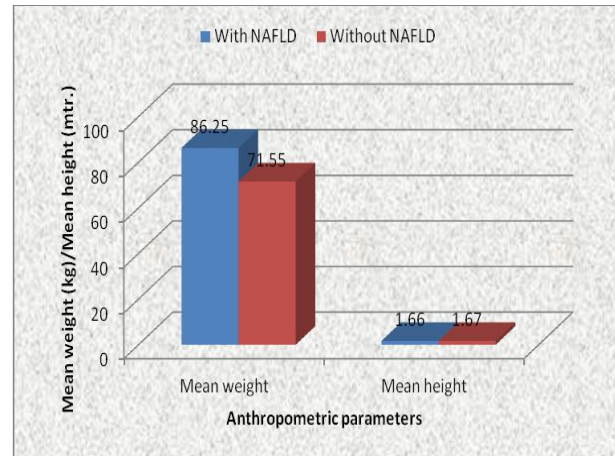
There were 8 (66.67%) male and 4 (33.33%) female subjects with NAFLD, while there were 12 (31.58%) male and 26 (68.42%) female subjects without NAFLD. The difference in gender between the two groups was statistically significant (p=0.04).



**Fig. 2: Bar chart showing sexwise distribution of study subjects with and without NAFLD**

**Comparison of study subjects with and without NAFLD according to mean weight and mean height**

Subjects with NAFLD have significantly more mean weight as compared to that of subjects without NAFLD (86.25 vs 71.55 kg, p<0.0001). However, mean height of subjects of both the groups( 1.66 VS 1.67 metres is comparable, p=0.56).

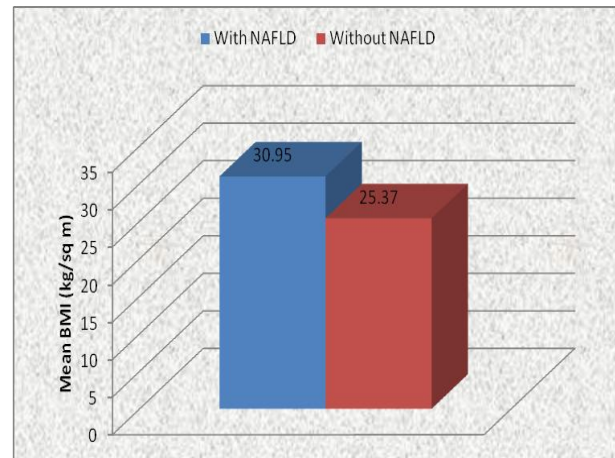


**Fig. 3: Bar charts showing mean weight and mean height of study subjects with and without NAFLD**

**Comparison of study subjects with and without NAFLD according to body mass index (BMI)**

Subjects with NAFLD have significantly higher mean BMI as compared to that of subjects without NAFLD (30.95 vs 25.37 kg/m<sup>2</sup> p<0.0001).

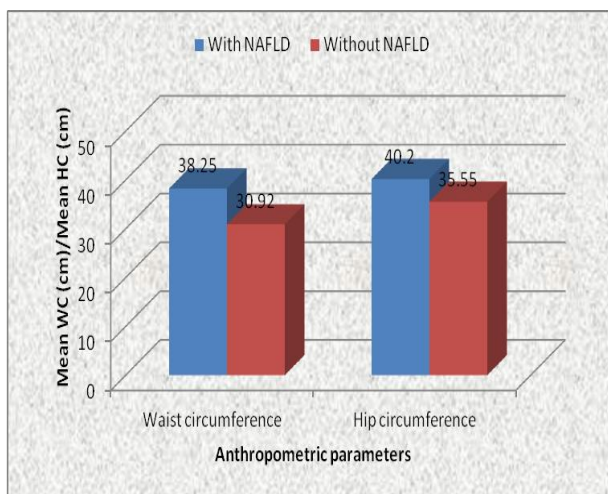
Out of 12 subjects with NAFLD, 1 (8.33%) was overweight, while rest 11 (91.67%) subjects were obese. Among subjects without NAFLD, 17 (44.74%) had normal weight, 15 (39.47%) were overweight and 6 (15.79%) subjects were obese.



**Fig. 4: Bar chart showing mean body mass index (BMI) of study subjects with and without NAFLD**

**Comparison of study subjects with and without NAFLD according to mean waist circumference and mean hip circumference**

Subjects with NAFLD have significantly more mean waist circumference as well as hip circumference as compared to those of subjects without NAFLD (38.25 vs 30.92 inches,  $p < 0.0001$  and 40.20 vs 35.55 inches,  $p < 0.0001$  respectively).

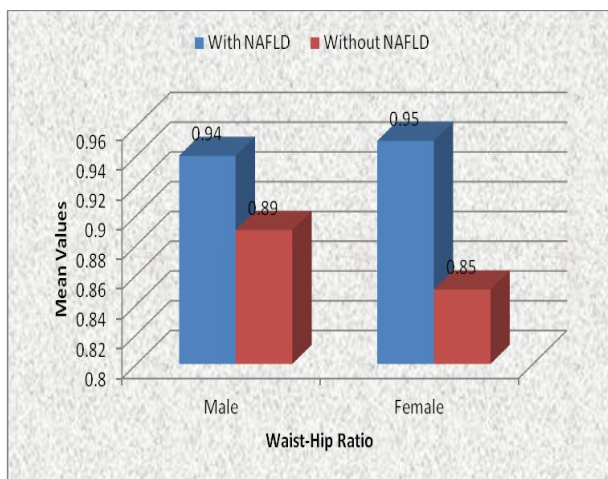


**Fig. 5: Bar chart showing mean waist circumference and mean hip circumference of study subjects with and without NAFLD**

**Comparison of study subjects with and without NAFLD according to waist-hip ratio**

Mean waist-hip ratio of male subjects with NAFLD (n=8) is significantly more than that of male subjects without NAFLD (n=12) (0.94 vs 0.89,  $p = 0.0002$ ).

Mean waist-hip ratio of female subjects with NAFLD (n=4) is significantly more than that of female subjects without NAFLD (n=12) (0.95 vs 0.85,  $p = 0.0002$ ).

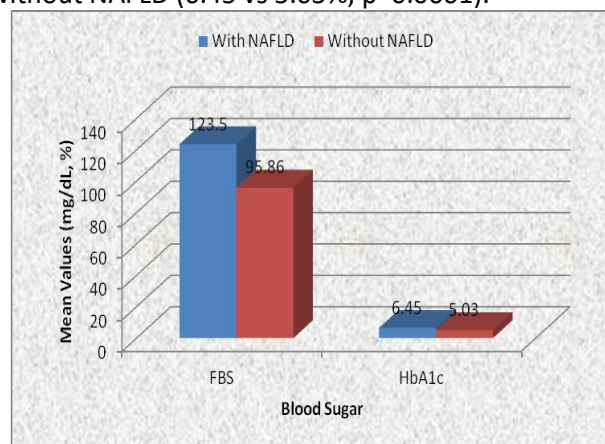


**Fig. 6: Bar chart showing mean waist-hip ratio of study subject with and without NAFLD**

**Comparison of study subjects with and without NAFLD according to blood sugar**

Mean fasting blood sugar in subjects with NAFLD is statistically more than that of subjects without NAFLD (123.5 vs 95.86 mg/dL,  $p = 0.008$ ).

Similarly, Mean glycosylated haemoglobin in subjects with NAFLD is statistically more than that of subjects without NAFLD (6.45 vs 5.03%,  $p = 0.0001$ ).

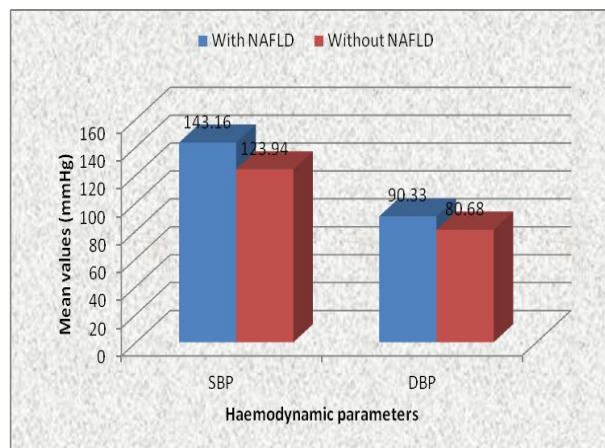


**Fig. 7: Bar chart showing mean blood sugar levels of study subjects with and without NAFLD**

**Comparison of study subjects with and without NAFLD according to hypertension**

Mean systolic blood pressure in subjects with NAFLD is statistically high than that of subjects without NAFLD (143.16 vs 123.94 mmHg,  $p = 0.01$ ).

Similarly, mean diastolic blood pressure in subjects with NAFLD is statistically high than that of subjects without NAFLD (90.33 vs 80.68 mmHg,  $p = 0.005$ ).

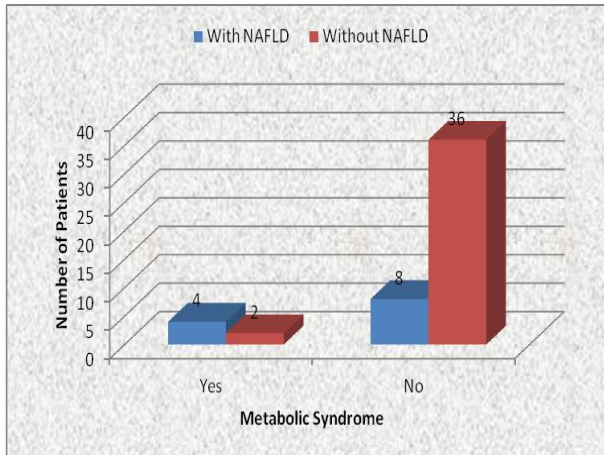


**Fig. 8: Bar chart showing mean SBP and mean DBP of study subjects with and without NAFLD**

**Comparison of study subjects with and without NAFLD according to metabolic syndrome**

Metabolic syndrome is present in 4 (33.33%) subjects with NAFLD and in 2 (5.26%) subjects without NAFLD.

The comparison between the two groups is statistically significant ( $p=0.02$ ).

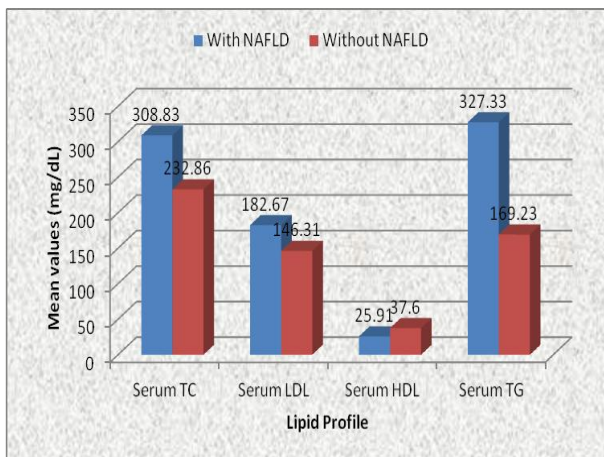


**Fig. 9:** Bar chart showing distribution of study subjects with and without NAFLD according to metabolic syndrome

**Comparison of study subjects with and without NAFLD according to lipid profile**

Mean serum total cholesterol, mean serum low density lipoprotein and mean serum triglycerides in subjects with NAFLD are significantly higher than those of subjects without NAFLD (308.83 vs 232.86 mg/dL,  $p<0.0001$ ; 182.67 vs 146.31 mg/dL,  $p=0.003$ ; 327.33 vs 169.23 mg/dL,  $p<0.0001$  respectively).

Mean high density lipoprotein in subjects with NAFLD is significantly lower than that of subjects without NAFLD (25.91 vs 37.60 mg/dL,  $p=0.0005$ ).

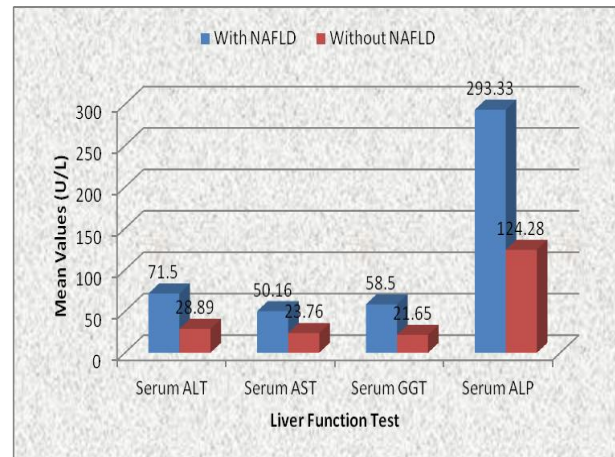


**Fig. 10:** Bar chart showing mean lipid profile of study subjects with and without NAFLD

**Comparison of study subjects with and without NAFLD according to liver function test**

Mean serum ALT (SGPT), mean serum AST (SGOT), mean GGT and mean serum ALP are significantly higher in subjects with NAFLD than those of subjects

without NAFLD (71.5 vs 28.89 U/L,  $p<0.0001$ ; 50.16 vs 23.76 U/L,  $p<0.0001$ ; 58.5 vs 21.65 U/L,  $p<0.0001$ ; 293.33 vs 124.28 U/L,  $p<0.0001$  respectively)

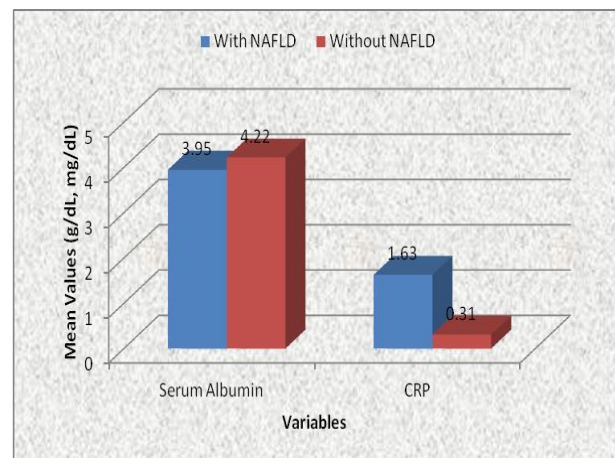


**Fig. 11:** Bar chart showing mean values of liver function test of study subjects with and without NAFLD

**Comparison of study subjects with and without NAFLD according to serum albumin and C-reactive protein levels**

Mean serum albumin in subjects with NAFLD is significantly lower as compared to that of subjects without NAFLD (3.95 vs 4.22 g/dL,  $p=0.01$ ).

Mean CRP in subjects with NAFLD is significantly higher as compared to that of subjects without NAFLD (1.63 vs 0.31 mg/dL,  $p<0.0001$ ).

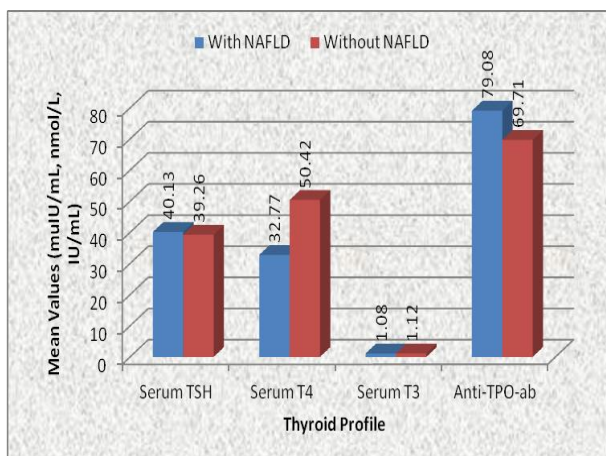


**Fig. 12:** Bar chart showing mean serum albumin and mean C-reactive protein levels in study subjects with and without NAFLD

**Comparison of study subjects with and without NAFLD according to thyroid profile**

Mean serum TSH, mean serum T3 and mean anti-TOP-ab levels in subjects with NAFLD are comparable with those of subjects without NAFLD (18.51 vs 16.21  $\mu$ U/ml,  $p=0.05$ ; 1.08 vs 1.12 nmol/L,  $p=0.81$ ; 79.08 vs 69.71 IU/mL,  $p=0.62$ ). However, mean serum T4 level

in subjects with NAFLD is significantly less as compared to that of subjects without NAFLD (32.77 vs 50.42 nmol/L,  $p < 0.0001$ ).



**Fig. 13:** Bar chart showing mean thyroid profile of study subjects with and without NAFLD

## DISCUSSION

Thyroid dysfunction is an independent risk factor for nonalcoholic fatty liver disease. Hypothyroidism enhances the degree of insulin resistance in NAFLD patients and may increase the already elevated lipolysis and free fatty acid delivery to the liver and thereby accelerate liver injury in NAFLD. Hypothyroidism primarily causes elevation in cholesterol and low density lipoproteins and also affects the synthesis, mobilization and degradation of all aspects of lipid metabolism. Early identification of at-risk patients is important since treatment of the hypothyroidism may reduce the risk of NAFLD and potential complications.

A total of 50 subjects fulfilling inclusive criteria were taken up for study. These included four (8%) subjects with features suggestive of subclinical hypothyroidism and 46 (92%) with those of clinical hypothyroidism. A total of 12 (24%) subjects with spectrum of steatosis alone to non-alcoholic steatohepatitis (NASH) were diagnosed ultrasonographically. All these subjects had features of clinical hypothyroidism.

**Liangpunsakul and Chalasani (2003)** in their case-control study to find out the association between hypothyroidism and non-alcoholic steatohepatitis (NASH), reported mean age  $\pm$  SD of  $49 \pm 13$  years, with 59% female patients, which is similar to the present study.

**Eshraghian et al. (2013)** also reported all measured anthropometric indices including weight, BMI, waist

circumference, hip circumference and waist-hip ratio significantly higher among individuals with NAFLD compared to those without NAFLD ( $p < 0.001$ ), which is similar to our study.

**Gokmen et al. (2016)** evaluated the effects of metabolic parameters and thyroid dysfunction on the development of non-alcoholic fatty liver disease (NAFLD). They also found that the mean waist circumference and body mass index values were significantly ( $p = 0.01$ ) higher in the patients with NAFLD compared to those without it. They listed both these indices as independent risk factors for NAFLD.

In the present study, mean fasting blood sugar and mean glycosylated haemoglobin in subjects with NAFLD was statistically more than that of subjects without NAFLD ( $p = 0.008$  and  $p = 0.0001$ ). Similarly, mean systolic and diastolic blood pressures were statistically high in NAFLD group as compared to non-NAFLD group ( $p = 0.01$  and  $p = 0.005$ ).

**de Araujo Souza et al. (2012)**, while reviewing 96 clinical and experimental studies, cohorts, meta-analysis and systematic reviews pointed out that hypertension and type-2 diabetes mellitus were risk factors related to NAFLD in the context of metabolic syndrome.

**Eshraghian et al. (2013)** also reported that higher mean systolic and diastolic blood pressures were associated with presence of NAFLD ( $p < 0.001$ ), which is in agreement with our study. However, they did not find any association of fasting plasma glucose with NAFLD.

**Hazlehurst and Tomlinson (2013)** examined the association and causal relationship between endocrinopathies and the development of NAFLD. They added that the rising prevalence of NAFLD is fuelled by the epidemic of obesity, type 2 diabetes and insulin resistance.

In the present study, metabolic syndrome was present in 33.33% subjects with NAFLD and in 5.26% subjects without NAFLD. The comparison between the two groups was statistically significant ( $p = 0.02$ ).

**Eshraghian et al. (2013)** detected metabolic syndrome in 30.70% participants with NAFLD and in 12.05% participants without NAFLD ( $p < 0.001$ ), which is comparable to our study.

**Posadas-Romero et al. (2014)** found that subclinical hypothyroidism with fatty liver was associated with increased odds of metabolic syndrome, insulin

resistance and coronary artery calcification in a sample of 753 subjects.

In the present study, mean serum total cholesterol, mean serum low density lipoprotein and mean serum triglycerides in subjects with NAFLD were significantly higher than those of subjects without NAFLD ( $p < 0.0001$ ,  $p = 0.003$ ,  $p < 0.0001$  respectively), while mean high density lipoprotein in subjects with NAFLD was significantly lower than that of subjects without NAFLD ( $p = 0.0005$ ).

Thyroid hormones induce their effects on lipid metabolism via thyroid hormone receptor  $\beta$ , which is expressed in liver (Hulbert, 2000). Thyroid hormone receptor activation results in a reduction in body weight and fat as well as a decrease in cholesterol and triglyceride levels, which takes place only in hepatocytes (Grover et al., 2003; Erion et al., 2007).

Ineck and Ng (2003) reviewed effect of subclinical hypothyroidism on serum lipids and the effects of thyroxine replacement therapy. They concluded that that subclinical hypothyroidism can potentially contribute to a pro-atherogenic lipid profile, with effects being greater at higher thyroid-stimulating hormone levels. Thyroxine replacement reduces total cholesterol and low-density lipoprotein cholesterol, with no effect on triglycerides.

Loria et al. (2009) reviewed hormonal disorders with hepatobiliary disease with particular focus to nonalcoholic steatohepatitis (NASH) and reported that hypothyroidism might lead to NASH, cirrhosis and potentially liver cancer via the development of hyperlipidemia and obesity. de Araujo Souza et al. (2012) also added that dyslipidemia to be a risk factor related to NAFLD. Lee et al. (2015) reported that serum levels of total cholesterol, triglycerides, LDL were significantly higher in the NAFLD group than those in the non-NAFLD group. Similarly, Gokmen et al. (2016) also reported that hypertriglyceridemia is an independent risk factor for NAFLD. All these results are in consonance with our study.

However, Eshraghian et al. (2013) in their study found that mean triglyceride, total cholesterol, and HDL were not associated with NAFLD. The difference between this study and our study could be because of the selection of studied subjects. While we conducted our study in subjects diagnosed with subclinical/clinical hypothyroidism, they conducted their study in subjects diagnosed with NAFLD.

In the present study, mean serum ALT (SGPT), mean serum AST (SGOT), mean GGT and mean serum ALP were significantly higher in subjects with NAFLD than those of subjects without NAFLD ( $p < 0.0001$ ,  $p < 0.0001$ ,  $p < 0.0001$  respectively), while mean serum albumin was significantly lower ( $p = 0.01$ ) and mean CRP significantly higher in subjects with NAFLD ( $p < 0.0001$ ).

Chung et al. (2012) reported that the prevalence of NAFLD and abnormal liver enzyme levels (ALT) progressively increases as the grade of hypothyroidism increases. Eshraghian et al. (2013) found that higher serum ALT and AST levels were associated with NAFLD. According to Eshraghian and Jahromi (2014), an increased serum ALT level is a surrogate biomarker for NAFLD in the absence of other causes of liver disease and an indicator for the development of diabetes, cardiovascular disease and long term adverse complications from metabolic syndrome. In the present study, mean serum TSH, mean serum T3 and mean anti-TOP-ab levels in subjects with NAFLD were comparable with those of subjects without NAFLD ( $p = 0.05$ ,  $p = 0.81$ , and  $p = 0.62$ ). However, mean serum T4 level in subjects with NAFLD was significantly less as compared to that of subjects without NAFLD (32.77 vs 50.42 nmol/L,  $p < 0.0001$ ).

Three studies indicated that lower free T4 (FT4) is an independent risk factor for NAFLD (Xu et al., 2011; Chung et al., 2012; Ittermann et al., 2012), which is in agreement with the present study. However, Carulli et al. (2013) reported that an increased serum TSH level is an independent risk factor for NASH compared to patients with NAFLD. In the present study, there was no objective of comparing patients of NASH with those of NAFLD.

Ittermann et al. (2012) detected no consistent association of serum TSH and FT3 concentrations with hepatic steatosis. In contrast, serum FT4 concentrations were inversely associated with hepatic steatosis in men (OR=0.04) and women (OR=0.06). These results are similar to those of our study.

Bano et al. (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 (OR 0.42). In line, higher TSH levels were associated with an increased risk of having clinically relevant fibrosis in NAFLD (OR 1.49). The study concluded that lower

thyroid function is associated with an increased NAFLD

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