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Thyroid-stimulating hormone variation within the euthyroid range and the severity of fatty liver disease in patients with type 2 diabetes mellitus: A cross-sectional study

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Abstract

Objective: To identify the relationship between thyroid-stimulating hormone levels within the euthyroid range and the severity of fatty liver disease in patients with type 2 diabetes mellitus.

Method: The cross-sectional study was conducted at the Department of Medicine, Pakistan Railways Hospital, Rawalpindi, Pakistan, from August 15, 2024, to February 15, 2025, and comprised euthyroid patients with type 2 diabetes mellitus of either gender, aged 35-65 years. Those with non-alcoholic fatty liver disease were placed in group A, while those with non-alcoholic steatohepatitis were placed in group B. The diagnosis was based on abdominal ultrasonography. Thyroid-stimulating hormone was classified as low-normal (0.5-2.5mIU/L) or high-normal (>2.5-5.0mIU/L). Alanine aminotransferase, body mass index, fasting blood sugar and duration of diabetes were recorded. Data was analysed using SPSS 27.

Results: Of the 670 patients with a median age of 48.0 years (interquartile range: 37.0-57.0 years), 520(77.6%) were female, and 150(22.4%) were male. There were 480 (71.6%) patients in group A and 190 (28.4%) in group B. Median thyroid-stimulating hormone was higher in group B than in group A (p=0.018). High-normal thyroid-stimulating hormone was more frequent in group B than group A (p=0.001). Fasting blood sugar was higher in group B (p<0.001), while body mass index was higher in group A (p = 0.001). The correlation between alanine aminotransferase and thyroid-stimulating hormone was weak overall (p=0.023). Multivariable regression showed high-normal thyroid-stimulating hormone was independently associated with non-alcoholic steatohepatitis (p<0.001).

Conclusion: Within the euthyroid range, higher thyroid-stimulating hormone levels in type 2 diabetes mellitus patients were associated with non-alcoholic steatohepatitis, which is a more severe fatty liver disease than non-alcoholic fatty liver disease. This was independent of confounders. Thyroid-stimulating hormone level within the normal range may help identify diabetic patients at higher risk of progressive liver disease.

Key Words: Non-alcoholic fatty liver disease, Metabolically-dysfunction-associated steatotic liver disease, Metabolically-dysfunction-associated steatohepatitis, Diabetes mellitus, Type 2, Thyrotropin.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a huge and growing clinical problem, affecting almost 38% of people worldwide.[1-3] In 2023, a multisociety Delphi consensus renamed NAFLD as metabolic dysfunction-associated steatotic liver disease (MASLD), and non-alcoholic steatohepatitis (NASH) as metabolic dysfunction-associated steatohepatitis (MASH).[4] Apart from its effects in the liver, NAFLD raises the risk of type 2 diabetes mellitus (T2DM). This is attributed to the shared aetiology of NAFLD and T2DM, with unhealthy lifestyles and obesity being the most common reversible risk factors in both diseases. Identifying modifiable predictors of NAFLD severity in the diabetic population is critical for early intervention.[5]

The pathophysiology of NAFLD in T2DM is complex and attributed to metabolic changes, including insulin resistance (IR), dyslipidaemia, subclinical inflammation, and oxidative stress (OS). The disease progresses from simple fatty liver to steatosis, fibrosis, cirrhosis, hepatocellular carcinoma (HCC) and even death.[6] In Pakistan, Kanwal et al. found NAFLD in 61.5% of diabetic patients undergoing routine ultrasound screening.[7] Globally, NAFLD was reported to be present in 55% to 73% of individuals with T2DM.[8] Patients with diabetes also have a higher risk of hepatic decompensation than non-diabetics.[9]

The thyroid hormone helps regulate metabolic processes, especially in hepatocytes. Disruption of thyroid hormone signalling contributes to the pathogenesis of NAFLD, especially in hypothyroidism.[10,11] Elevated thyroid-stimulating hormone (TSH) in the high-normal range correlates with a higher prevalence of NAFLD among euthyroid T2DM patients. Tan et al. studied euthyroid adults with T2DM and found that high-normal serum TSH levels were present in T2DM with NAFLD.[12]

Another study in patients with newly-diagnosed T2DM also found that high-normal TSH and higher free T3 (FT3) were associated with a greater prevalence of NAFLD.[13] Even non-diabetic euthyroid populations show variation in TSH and free thyroid hormones that correlates with the incidence of NAFLD. For example, high-normal FT3 and low-normal TSH have been associated with developing NAFLD in middle-aged and older euthyroid subjects in cohort studies.[14]

Although the relationship of NAFLD with T2DM has been studied to some extent, it remains unclear whether TSH variations (high-normal versus low-normal) are also associated with the severity of liver disease, that is, the degree of steatosis, inflammation and fibrosis, in T2DM, especially when euthyroid status is preserved.[15] A study by Huang et al. in euthyroid patients with NAFLD and T2DM found a positive correlation between alanine aminotransferase (ALT) and FT3, and a negative correlation between ALT and TSH.[10]

To our knowledge, this link has not been extensively studied. The current study was designed to address this gap by examining the relationship between TSH levels within the euthyroid range and the severity of fatty liver disease in patients with T2DM.

Patients and Methods

The cross-sectional study was conducted at the Department of Medicine, Pakistan Railways Hospital, Rawalpindi, Pakistan, from August 15, 2024, to February 15, 2025. After approval from the institutional ethics review committee reference no. Riphah/IIMC/IRC/24/1052, dated: 27th June 2024 of Pakistan Railways Hospital, Rawalpindi (which operates under the administrative management of Riphah Islamic International Medical college and thus shares the same ethics review committee), the sample size was calculated using the MedCalc Statistical Software (MedCalc Software Ltd, Ostend, Belgium version 23.7.1) based on a correlation of -0.108[10] between ALT and TSH with alpha (α) value 0.05 and beta (β) value 0.20. The sample was raised using a non-probability consecutive sampling technique from among inpatients and outpatients diagnosed with T2DM who were assessed for NAFLD or NASH on ultrasonography and euthyroidism. Informed consent was obtained from all the participants. T2DM patients of both genders aged 35-65 years who were found to have NAFLD or NASH, as well as TSH levels within the normal range (0.5-5.0mIU/L), were enrolled. Patients with acute complications of diabetes, acute cardiovascular events, severe chronic kidney disease (CKD) with glomerular filtration rate (GFR) <60ml/min, alcohol users, those with hepatitis B and C, malignant tumour, severe hepatic disease (liver function test values >1.5 times the upper normal reference) and pregnant women were excluded.

The patients underwent abdominal ultrasonography using a 2–7 MHz probe (Mindray DC-70 ultrasound system; Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China), performed by a single consultant radiologist with >5 years of experience. NAFLD was diagnosed when at least two of three findings were present: a diffuse increase in liver near-field ultrasound echo (bright liver), liver echogenicity greater than

that of the kidney with blurring of vascular structures, and gradual attenuation of the far-field ultrasound echo. NASH was characterised by a hyperechoic liver (greater echogenicity than the kidneys), blurring of vascular structures, and deep attenuation on ultrasonography. Those with NAFLD were assigned to group A, while those with NASH were assigned to group B.

TSH levels were divided into low-normal (0.5-2.5mIU/L) and high-normal (>2.5-5mIU/L). The 2.5mIU/L cut-off for separating low-normal from high-normal TSH has been used in earlier studies of euthyroid adults,[16] and high-normal TSH within the euthyroid range has been linked to NAFLD in T2DM.[12]

Blood samples for fasting blood sugar (FBS), liver function tests (LFT), including serum ALT, and TSH were sent to the institutional laboratory at no cost to the patients. Serum TSH was measured in the hospital's central laboratory by an automated chemiluminescence immunoassay. The assay and the analyser were kept the same for all patients, thereby avoiding inter-assay variation. The laboratory euthyroid reference range for TSH was 0.5-5.0mIU/L.

Data was analysed using SPSS 27. The Shapiro-Wilk test indicated that the numerical variables were not normally distributed, so they were summarised as medians with interquartile range (IQR) and analysed using non-parametric tests. The recorded numerical variables were age, height, weight, body mass index (BMI), duration of T2DM, FBS, ALT and TSH. Categorical variables, such as gender, BMI category, diagnosis, disease severity, and euthyroid TSH category, were reported as frequencies and percentages. The two groups were compared using the Mann-Whitney U test for numerical variables and the chi-square test for categorical variables. In contrast, the association of baseline variables with ALT and TSH was assessed using Spearman's rank correlation. To reduce confounding, a multivariable binary logistic regression was fitted with disease severity (NASH vs NAFLD) as the outcome and TSH, age, gender, BMI, FBS, duration of T2DM, and ALT as predictors. $P \leq 0.05$ was considered statistically significant.

Results

Of the 942 T2DM patients screened, 670(71.1%); 480(71.6%) in group A and 190(28.4%) in group B. TSH categories within the euthyroid range were noted in the two groups (Table 1).

Overall, there were 520 (77.6%) female and 150 (22.4%) male patients, with a median age of 48.0 years (IQR: 37.0-57.0 years). Median values for BMI, FBS, and TSH were significantly different between the groups ($p<0.05$), whereas age, diabetes duration, and ALT level did not differ significantly ($p>0.05$). There were 144(30%) patients with high-normal TSH values in group A compared to 82(43.2%) in group B ($p<0.05$) (Table 2).

The overall correlation between ALT and TSH was weak (Spearman $\rho=0.088$, $p=0.023$). Within group B, ALT and TSH showed a moderate positive correlation (Spearman $\rho=0.348$, $p<0.001$), but there was no such correlation in group A ($\rho=-0.007$, $p=0.879$). Baseline characteristics across TSH categories (Table 3) and the correlation of baseline characteristics with ALT and TSH in the two groups (Table 4) were noted.

Multivariable logistic regression showed that high-normal TSH was independently associated with NASH (adjusted odds ratio [aOR]: 2.05; 95% confidence interval [CI]: 1.43-2.95; $p<0.001$). When TSH was entered as a continuous value, each 1mIU/L rise increased the odds of NASH by about 25% (aOR: 1.25; 95%CI: 1.09-1.44; $p=0.002$). Higher BMI was associated with lower odds of NASH (aOR: 0.96, 95% CI: 0.94-0.99; $p=0.005$). Age, gender, FBS, duration of T2DM and ALT levels were not independent predictors (Table 5).

Discussion

Thyroid hormones are key regulators of lipid metabolism, hepatic mitochondrial function and insulin sensitivity.[17-19] Even within the euthyroid range, higher TSH levels may reflect early thyroid dysregulation or a compensatory response to hepatic stress. This is relevant in T2DM patients, where IR and chronic inflammation already predispose them to hepatic lipid accumulation. [20,21]

In the present study of 670 T2DM patients, within the euthyroid TSH range, those with more severe liver disease (NASH versus NAFLD) had higher median TSH, with a significantly greater proportion in the high-normal TSH bracket in the NASH group. The overall correlation between TSH and ALT was weak, indicating that TSH variation across the euthyroid range was only loosely associated with this single liver injury marker. The link was stronger inside the NASH group ($p<0.001$).

These findings partly align with recent literature. A meta-analysis found that high TSH is significantly associated with greater liver fibrosis and a higher risk of NAFLD, especially when combined with abnormal thyroid hormone levels. In that study, high FT3 levels were also associated with an increased risk of NAFLD. The results echoed the pattern of higher TSH in NASH, although the overall correlation between TSH and ALT was weak ($\rho=0.088$).[10]

A study indicated that in euthyroid adults with biopsy-proven NAFLD, those in the high-normal TSH range had a stronger link with NASH severity, especially in the presence of genetic risk variants.[18] This suggests there may be modifiers (genetic, metabolic) affecting how TSH variation shows up in liver damage.[19,20] The present study did not assess genetic polymorphisms, which might explain some divergence.

Another recent work reported that increased TSH was associated with worsening steatosis over time and with histological markers of NAFLD/NASH even when overt thyroid dysfunction was excluded.[21] This longitudinal association suggests a temporal sequence, which cross-sectional designs like the current study's cannot firmly establish.

The median TSH difference between NAFLD and NASH was modest in the current study. Among the metabolic factors, poor glycaemic control was consistent with the expected pattern, with higher FBS in the NASH group. BMI was higher in the NAFLD group than in the NASH group, whereas diabetes duration did not differ between the groups. In the current cohort, TSH and glycaemic control tracked disease severity more closely than BMI did. This supports the view that TSH variation may be one of many risk modulators, with metabolic factors having more robust effects.[22-24]

The current study has several strengths, including a large sample size of 670 patients, which provides sufficient statistical power to detect meaningful group differences. Grouping patients into NAFLD and NASH helped assess disease severity rather than the simple presence or absence of fatty liver. The analysis was also restricted to individuals with euthyroid TSH levels to focus on subtle variations within the normal range. Cross-tabulation and multivariable logistic regression were used to account for potential confounders.

The present study has several limitations. The cross-sectional design precludes causal inference, so it remains unclear whether higher TSH in the high-normal range is a cause or a consequence of more severe liver disease. The reliance on ALT as the primary biochemical marker was also restrictive, as ALT does not always reflect histological severity and can remain normal even in advanced disease.[25] The absence of data on free thyroid hormones or indices of thyroid hormone sensitivity further limits the interpretation of the thyroid-liver relationship. FibroScan (transient elastography with controlled attenuation parameter) was unavailable, so steatosis and fibrosis could not be graded by elastography, a common non-invasive tool for diabetic fatty liver disease.[26,27] Abdominal ultrasound also has limits. It is less sensitive for mild steatosis and cannot reliably distinguish simple steatosis (NAFLD) from steatohepatitis (NASH), a distinction that requires histology or, increasingly, elastography-based methods.[28] Some misclassification between the two groups was, therefore, possible. Also, the diagnosis of NAFLD and NASH was based on clinical and imaging criteria instead of histology, which could add misclassification bias. A lack of genetic profiling for patatin-like phospholipase domain-containing protein 3 (PNPLA3) or transmembrane 6 superfamily member 2 (TM6SF2) polymorphisms, which are known to influence NASH risk, is another limitation. The predominantly female sample restricts the generalisability of the results to other populations and genders.

Despite the limitations, however, the trend towards higher TSH in the high-normal range among patients with NASH shows the role of thyroid axis variation as a risk stratifier in T2DM patients. This raises an important clinical implication: routine monitoring of

TSH, even within the normal range, can help identify diabetic patients at risk of progressive liver disease. Future research can use longitudinal designs to determine temporal relationships. Studies on the interaction between genetic polymorphisms and thyroid function, and interventional trials targeting thyroid modulation or metabolic optimisation, will be important for clarifying whether changes in thyroid function can alter the course of NAFLD and NASH in patients with T2DM.

Conclusion

Patients with NAFLD had low-normal TSH values, whereas those with NASH had high-normal TSH levels. This suggests that higher TSH within the normal range is associated with greater liver disease severity and may act as an early marker of disease progression. In the data, poor glycaemic control was linked with more severe disease, while higher BMI was seen more in the NAFLD group and duration of diabetes did not differ between the groups. Given the global prevalence of T2DM and the rising incidence of NAFLD in diabetic populations, more targeted screening and treatment strategies should be used so that patient outcomes may improve and the healthcare costs linked to these metabolic disorders can be lowered.

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Table 1: TSH levels in patients with type 2 diabetes mellitus with NAFLD and NASH.

TSH levels	NAFLD n=480	NASH n=190
Low-Normal (0.5–2.5 mIU/L)	336 (70.0%)	108 (56.8%)
High-Normal (>2.5–5.0 mIU/L)	144 (30.0%)	82 (43.2%)

NAFLD: Non-alcoholic fatty liver disease, NASH: Non-alcoholic steatohepatitis, TSH: Thyroid-stimulating hormone.
χ^2=10.54, df=1, p=0.001.

Table 2: Comparison of baseline characteristics between NAFLD and NASH groups.

Variable	NAFLD (n=480)	NASH (n=190)	p-value
Age (years)	**48.50 (37.00–59.00)**	**48.00 (40.00–55.00)**	0.964
BMI (kg/m²)	**27.96 (24.40–32.05)**	**25.73 (22.72–31.20)**	0.001
FBS (mg/dl)	**94.50 (84.50–109.00)**	**100.00 (92.00–118.00)**	<0.001
Duration of diabetes (years)	**5.00 (2.25–7.00)**	**5.00 (4.00–7.00)**	0.247
ALT (U/L)	**24.00 (16.00–39.00)**	**26.00 (18.00–37.00)**	0.145
TSH (mIU/L)	**1.80 (1.13–2.60)**	**2.10 (1.15–3.00)**	0.018
High-normal TSH, n (%)	144 (30.0%)	82 (43.2%)	0.001

Values are median (interquartile range). NAFLD: Non-alcoholic fatty liver disease, NASH: Non-alcoholic steatohepatitis, BMI: Body mass index, FBS: Fasting blood sugar, ALT: Alanine aminotransferase, TSH: Thyroid-stimulating hormone.

Table 3: Cross-tabulation of baseline characteristics across TSH categories within the groups.

Variables	Categories	NAFLD Low Normal N=336	NAFLD High Normal N=144	NASH Low Normal N=108	NASH High Normal N=82
Age (years)	35–50	204 (60.7%)	56 (38.9%)	52 (48.1%)	57 (69.5%)
	51–65	132 (39.3%)	88 (61.1%)	56 (51.9%)	25 (30.5%)
Gender	Female	248 (73.8%)	128 (88.9%)	96 (88.9%)	48 (58.5%)
	Male	88 (26.2%)	16 (11.1%)	12 (11.1%)	34 (41.5%)
BMI (kg/m²)	Less than 30	232 (69.0%)	80 (55.6%)	76 (70.4%)	60 (73.2%)
	More than 30	104 (31.0%)	64 (44.4%)	32 (29.6%)	22 (26.8%)
Duration of Diabetes (yrs)	1 to <6	212 (67.9%)	76 (54.3%)	64 (59.3%)	49 (63.6%)
	6 to <11	100 (32.1%)	64 (45.7%)	44 (40.7%)	28 (36.4%)
FBS (mg/dL)	≤126	276 (82.1%)	132 (91.7%)	83 (76.9%)	70 (85.4%)
	≥127	60 (17.9%)	12 (8.3%)	25 (23.1%)	12 (14.6%)

NAFLD: Non-alcoholic fatty liver disease, NASH: Non-alcoholic steatohepatitis, TSH: Thyroid stimulating hormone, FBS: Fasting blood sugar, BMI: Body mass index.
Chi-square p-values (each variable versus TSH category): NAFLD group: age <0.001, gender <0.001, BMI = 0.005, duration = 0.005, FBS = 0.007. NASH group: age = 0.003, gender <0.001, BMI = 0.672, duration = 0.547, FBS = 0.142.

Table 4: Spearman correlation of baseline characteristics with ALT and TSH.

Parameters		ALT	TSH
Age	ρ	**-.106****	**.057**
	P	**.006**	**.139**
Height	ρ	**-.039**	**.049**
	P	**.317**	**.207**
Weight	ρ	**-.051**	**.053**
	P	**.190**	**.167**

Gender	**ρ**	**.244****	**-.075**
	P	**<.001**	**.052**
BMI	**ρ**	**-.049**	**.041**
	P	**.201**	**.295**
Duration of diabetes	**ρ**	**-.074**	**.054**
	P	**.055**	**.160**

ALT: Alanine aminotransferase, TSH: Thyroid stimulating hormone, BMI: Body mass index, ρ: Spearman's correlation coefficient, P: p-value.
**correlation significant at p<0.01 level (2-tailed), *correlation significant at p=0.05 level (2-tailed).

Table 5: Multivariable logistic regression for predictors of NASH versus NAFLD.

Predictor	Adjusted OR	95% CI	p-value
High-normal TSH (vs low-normal)	2.05	1.43–2.95	<0.001
Age (years)	0.99	0.97–1.01	0.336
Male gender	1.18	0.78–1.78	0.428
BMI (kg/m²)	0.96	0.94–0.99	0.005
FBS (mg/dl)	1.00	0.999–1.005	0.136
Duration of diabetes (years)	0.99	0.95–1.03	0.749
ALT (U/L)	1.00	0.988–1.003	0.213

NAFLD: Non-alcoholic fatty liver disease, NASH: Non-alcoholic steatohepatitis, TSH: Thyroid stimulating hormone, FBS: Fasting blood sugar, BMI: Body mass index, ALT: Alanine aminotransferase, OR: Odds ratio, CI: Confidence interval.
Outcome: NASH = 1, NAFLD = 0. A model using TSH as a continuous variable gave an adjusted OR of 1.25 (95%CI 1.09-1.44, p=0.002) per 1mIU/L rise in TSH.

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AUTHORS' CONTRIBUTIONS:

SK: Concept, design, data acquisition, data collection, statistical analysis, interpretation, drafting, critical analysis and final approval.

AZ: Concept, data analysis and final approval.

KF, SK & MF: Data interpretation, revision and final approval.

QUAK: Data acquisition and drafting.