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The Role Of Thyroid Hormone Receptor **B** In Patients With Non-Alcoholic Fatty Liver Disease

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Abstract

Background: *Nonalcoholic fatty liver disease (NAFLD) includes all phases and grades of the disease. It is defined as a group of people in which at least 5% of hepatocytes display macrovesicular steatosis and there is no clear cause of steatosis, such as alcohol, drugs, malnutrition, or genetic diseases.*

About two-thirds of people with type 2 diabetes and high blood pressure and high cholesterol have fat in their livers. Thyroid hormone (TH) is an important factor in how the liver processes glucose, cholesterol, and lipids. Thyroid hormone receptors (THRs) are part of the nuclear receptor superfamily. They act as transcription factors that need ligands to work.

Objective: *determine the Role of thyroid hormone receptor β in Patients with NAFLD*

Patients and Methods: *From June 1, 2024, to June 15, 2025, a study took place at Azadi Teaching Hospital. There were 90 people in the trial, 60 of whom had NAFLD and 30 who were healthy. The study employed a spectrophotometer to measure high-density lipoprotein (HDL), triglyceride (TG), and cholesterol. The ELISA washer and reader can also be used to quantify TSH, THR-β, and thyroid hormones (T3 and T4).*

Result: *Patients' ages range from 20 to 65 years. Serum level of THR-β was measured and compared to control group, it was significantly lower in patients with NAFLD.Thyroid hormone (T3, T4) also were measured and they were significantly higher in patient group than control group, while TSH level was lower in patients than controls. Measurement of triglyceride and cholesterol reveal higher level in patient than control while HDL level was significantly lower in NAFLD.*

Keywords: *Nonalcoholic fatty liver disease, thyroid hormone receptor, thyroid hormone, lipid profile*

INTRODUCTION

Liver cells that have The nonalcoholic fatty liver (NAFL) is marked by a fatty liver mass greater than 5% without overt symptoms of inflammation or harm to the liver cells [(1)]. Stress-induced metabolic syndromes are the root cause of NAFLD, a disorder that affects the liver. Cirrhosis, hepatocellular carcinoma, nonalcoholic steatohepatitis (NASH), and nonalcoholic hepatic steatosis (NAS) are all on the spectrum of liver diseases. The hallmarks of NASH are inflammation between lobules, fibrosis or lack thereof, and hepatocyte ballooning degeneration [(1,2)].

In order to avoid and treat NAFLD and its repercussions, it is critical to diagnose these various phases of NAFLD, especially NASH [(3)]. Biopsy of liver is still the clinical standard for a conclusive diagnosis of NAFL or NASH, even if imaging and clinical characteristics can raise strong suspicions about a person [(4).] More than half of individuals with NAFLD are without symptoms, and the disease may silently have progressed to cirrhosis [(5)]. The most obvious symptoms detected at primary stages among persons with NAFLD include right upper quadrant discomfort and fatigue [(6)].

Proven factors of risk for NAFLD involve metabolic syndrome and its hallmarks, which include obesity, type 2 diabetes, hypertension, and dyslipidemia. Other endocrine diseases that have potential to aid the development of NAFLD include adrenal insufficiency, thyroid dysfunction, growth hormone deficiency, and polycystic ovarian syndrome [(7).]

The thyroid gland regulates many physiological process in the body through the synthesize and secretion of thyroid hormones into the bloodstream [8]. These hormones have an impact on the cardiovascular system, musculoskeletal system, central nervous system, adipose tissue, and liver. Although T4 is primarily made by the thyroid gland, the most potent thyroid hormone, systemic T3, is mainly created when T4 is deiodinated in peripheral tissues [8]. The hypothalamus-pituitary axis regulates the secretion of thyroxine by the thyroid gland. The pituitary gland is stimulated to secrete additional thyrotropin and intracellular cyclic adenosine monophosphate (cAMP) when the hypothalamus secretes thyrotropin-releasing hormone (TRH), which binds to G protein-coupled TRH receptors on the thyrotrope. When TSH binds to a specific receptor on thyroid follicular cells, it stimulates the release of TH [9].

By altering the metabolism of fats and carbohydrates, THs control a variety of metabolic processes. They regulate hepatic insulin sensitivity, inhibit hepatic gluconeogenesis, and encourage the breaking down and release of lipid

alongside de novo lipogenesis in the liver [10]. T3 levels have an effect on lipolysis and cholesterol clearance; when they're low, the opposite is true; when they're high, lipolysis improves and body weight drops [11]. In contrast to T3, whose molecular activity is reliant on nuclear thyroid hormone receptors (THRs), ligand-dependent transcription factors, T4's binding affinity to THR is approximately ten times lower, and its potential direct effects are less obvious.

[12]. Two isoforms (THRα, THRβ) are encoded by two THR genes. The heart and bones are where THRα is most commonly expressed. Although it is also found in other organs such the kidney, retina, and central nervous system, in hepatocytes, THRβ is found in the highest amount.

In reality, the THR-β pathway is exclusive to the liver and lowers levels of LDL, Apo lipoprotein B (Apo B), and lipoprotein a (Lap(a)) through its effects on mitophagy, cholesterol production, de novo lipogenesis, and β-oxidation of fatty acids. Individuals who carry THRβ gene mutations that do not affect gene function are more likely to develop fatty liver disease and exhibit resistance to thyroid hormone [13,14].

By modulating the expression of multiple other nuclear receptors, the THR regulates glucose metabolism in addition to lipid metabolism.Thyroid hormones can stimulate the production of 3-hydroxy-3methylglutarylcoenzyme A, or HMG-CoA reductase, the enzyme that starts the process of cholesterol manufacture.

Furthermore, triiodothyronine (T3) has the ability to activate the LDL receptor gene and upregulate LDL receptors by attaching to particular sections of the genome that are receptive to thyroid hormone. Another factor that controls HDL metabolism is thyroid hormones. The expression of the regulatory sterol element binding protein-2 (SREBP-2) is boosted by thyroid hormones and is crucial for modulating cholesterol metabolism.

Triglyceride (TG) levels are decreased because T3 increases lipoprotein lipase, which breaks down TG-rich lipoproteins [15].

Protein transporters like liver fatty acid-binding proteins (L-FABPs), fatty acid transporter proteins (FATPs), and fatty acid translocases (FATs) help move free fatty acids around in the liver's cells when thyroid hormones (T3 and T4) bind to their respective gene receptors.

A decrease in TG clearance and an increase in TG hepatic absorption can be caused by THs, which can enhance intrahepatic lipolysis through lipophagy in hepatocytes via THR-β [16].

Aim and objective: Estimation the level of thyroid hormones (T3, T4), TSH, THR-β and lipid profile in NAFLD patients and compared with control group.

Patients and Methods

There were sixty NAFLD patients whose ages ranged from twenty to sixty-five years old. These individuals were diagnosed by ultrasound after being brought to the gastrointestinal unit at Azadi teaching hospital.

Participants were interviewed using a researcher-created questionnaire that inquired about their age, weight, height, smoking status, chronic diseases, and treatment regimen, among other demographic details. Thirty healthy individuals will also serve as controls in the study.Blood samples (4-5 ml) were drawn from patients and healthy people and transferred to gel tubes. After 15 minutes of centrifugation at 3000 rpm, serum was extracted. Until the tests were conducted, the serum was kept at -20 °C.

The tests which were performed include THR-β, T3, T4, TSH using ELISA technique and lipid (Triglyceride, cholesterol, HDL) using spectrophotometer technique

Statistical analysis

We used the SPSS program, which is a statistical package for the social sciences, to determine the level of statistical significance. Unless the P value was less than 0.05, we did not consider the difference between the two groups to be statistically significant. We then expressed the results as (mean ± standard deviation).

RESULT

Thyroid hormone receptor β estimation

The levels of THR-β were estimated in the serum of both healthy control group and patients group with diagnosed NAFLD .The result of the estimation was analyzed statistically and found that there was significance decrease at the probability of (P value <0.05) in the concentration of THR-β in patients,where it was (1.830 ± 0.464) and increase in control group where it was (3.006 ± 0.692) shown in figure-1

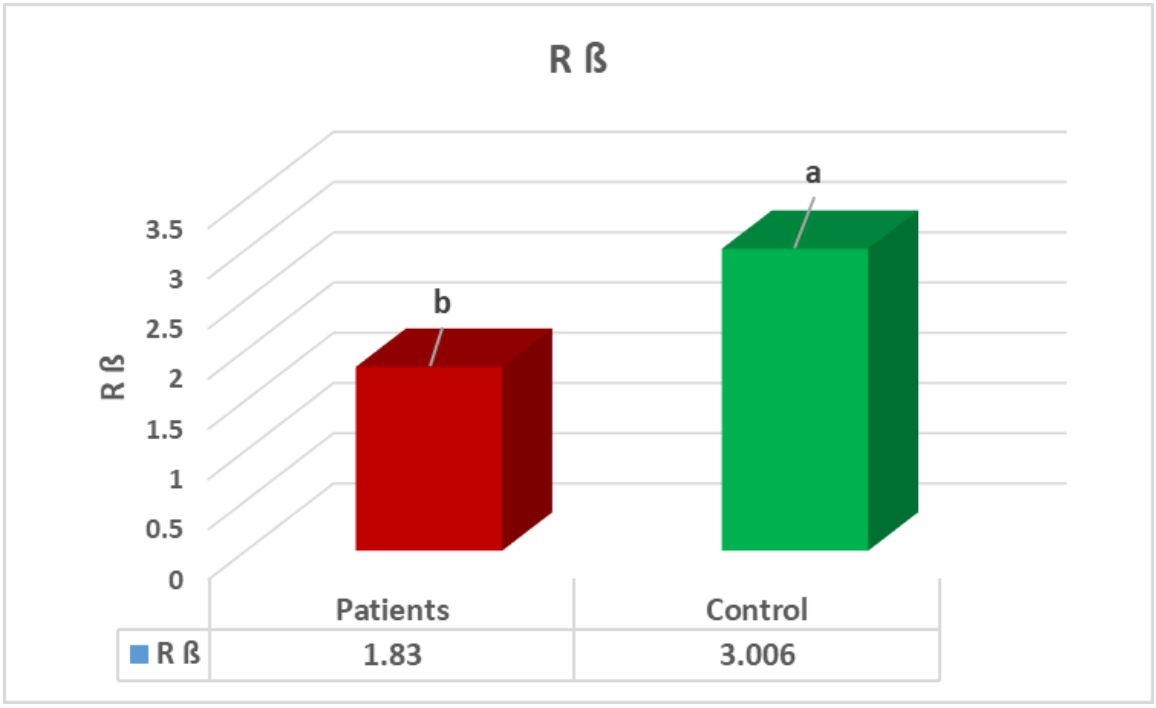

Figure-1 Level of THR-β in both NAFLD and control group

Estimation of thyroid function test:

Levels of both thyroid hormones were estimated in patients group and compared with healthy control group a statistically significant increase was noted at the probability level of P ≤ 0.05, where the values of Mean ± SD for T3 in healthy and NAFLD patients were

Lipid Profile

The results from the table-2 demonstrate that the levels of lipids (triglyceride, cholesterol, very low-density lipoprotein, and LDL) in the NAFLD group were noticeably greater than those in the control group (TRI 226.2 ± 28.0 vs. 195.5 ± 17.3, chol 212.4 ± 20.9 vs. 180.5 ± 12.5, VLDL 45.27 ± 5.63 vs. 39.08 ± 3.45, LDL 130.4 ± 21.6 vs. 87.0 ± 15.6NAFLD patients also had lower HDL levels than healthy controls (36.82±6.76 vs. 55.80±8.51).

Table-1 Level of thyroid function test in both patient and control group

Thyroid function test	Patients mean±SD N=60	Control mean±SD N=30	P value
TSH	4.014 ± 0.927	8.360 ± 1.210	0.0007[S]
T3	2.353 ± 0.774	0.703 ± 0.174	0.0006[S]
T4	40.18± 6.96	22.06 ± 3.25	0.0007[S]
T-test was *: significant at p ≤ 0.05, SD: standard deviation; S: significant; NS= Non-significant			

Table-2 Level of lipid profile in both patient and control group

Lipid profile	Patients mean±SD N=60	Control mean±SD N=30	P value
Triglyceride (mg/dl)	226.2 ± 28.0	195.5 ± 17.3	0.0003[S]
Cholesterol (mg/dl)	212.4 ± 20.9	180.5 ± 12.5	0.0004[S]
HDL(mg/dl)	36.82±6.76	55.80±8.51	0.0004[S]
LDL	130.4 ± 21.6	87 ±15.6	0.0005[S]
VLDL	45.27 ± 5.63	39.08 ± 3.45	0.0003 [S]
T-test was *: significant at p ≤ 0.05, SD: standard deviation; S: significant; NS= Non-significant			

DISCUSSION

Globally, NAFLD is the main contributor when it comes to chronic liver disease. The range of symptoms can be rather broad, starting with simple hepatic steatosis and progressing to nonalcoholic steato-hepatitis (NASH), a condition that can cause liver fibrosis and cirrhosis [17,18].

The purpose of this study was to identify the function of THR-β in the etiology of non-alcoholic fatty liver disease (NAFLD). The findings revealed that THR-β levels were lower in NAFLD patients.

A subfamily of nuclear receptors known as thyroid hormone receptors (THRs), THR-β mediates the effects of thyroid hormones and functions as transcription factors that are dependent on ligands. A

number of physiological processes, such as the regulation of mitochondrial activity, are regulated by TRs, which modulate the transcription of target genes in reaction to ligand [19].
Several parts of thyroid function's involvement in NAFLD have been discussed in earlier reviews [20]. Low thyroid function increases the risk of NAFLD as a result of a decline in liver lipase activity and triglyceride clearance, while intrahepatic triglyceride accumulation increases. [21]. This present study detects a significant increase in both THs (T3 and T4) in NAFLD patients when compared with control group while TSH level decrease in patients. No research has examined the frequency of NAFLD in people with hyperthyroidism, and there is not enough information about the relationship between TH and liver fat level in hyperthyroidism. It should be noted that patients with hyperthyroidism have been found to have oxidant stress and insulin resistance, which have both been associated with the development of NAFLD. Thus, in patients with hyperthyroidism, it is vital to investigate hepatic fat accumulation, NAFLD, and potential mechanisms Bairong Wang1,2, Baomin Wang1, Yumei Yang and their group perform study on hyperthyroidism patients and assess their relationship with NAFLD and found that there is no significant relationship between them [22]. Pathophysiology of NAFLD is largely influenced by dyslipidemia. There was mounting evidence that a person's lipid profile enhanced their risk of NAFLD in the general population [23]. Triglyceride, cholesterol, very low density lipoprotein, and LDL levels were all considerably higher in NAFLD samples compared to controls, according to the study's lipid profile analysis. Likewise, Khalil et al. discovered that low-density lipoprotein, very low-density lipoprotein, triacylglycerol, and total cholesterol were all considerably higher in patients with NAFLD. Our results are in line with theirs, unfortunately: patients with NAFLD had a lower HDL level [24].

CONCLUSIONS

The patients with NAFLD in current study present with decrease level of THR-β when compared to control group, they also show significant increase of thyroid hormone and decrease level of TSH.
Serum concentration of triglyceride, chol, VLDL and LDL were all increase in NAFLD patients conversely HDL level was decrease.
Recommendations It is recommended that more study performing about the importance of THR-βin the mechanism of NAFLD and confirm it with gene expression study.
Ethical clearance:
This study was carried out per the rules outlined in the Declaration of Helsinki. Verbal consent and analytical approval were obtained from all participants earlier than specimen collection. The biochemistry department's ethical committee of TKRIT University's Medical College looked over and approved the study protocol, as well as the subject's data and acceptance form.

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