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Investigation Roles of Erythropoietin, Testosterone, and Thyroid Hormones in Patients with Chronic Liver Disease

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ABSTRACT

Chronic liver disease (CLD) is characterized as a steady decline in liver functions that lasts longer than six months, including the generation of clotting factors and other proteins, detoxification of toxic metabolic products, and bile excretion. CLD is a continual process of inflammation, damage, and regeneration of the liver parenchyma that results in fibrosis and cirrhosis.

The study aims to determine the predictive role of erythropoietin, testosterone, and thyroid function markers in the pathogenesis of liver dysfunction in Iraqi patients.

The current research investigation was conducted out in Baquba Teaching Hospital / Diyala governorate from November 2022 to January 2023. 50 blood samples were taken from patients who came to the Baquba Teaching Hospital and those with chronic liver disease for inspection and diagnosis by the consultant doctor in the advisory units/Baquba Teaching Hospital. 30 healthy people's blood samples were taken as a control group. The serum levels of erythropoietin, testosterone, TSH, FT3, and FT4 indicators in the samples were determined using the Roche Cobas e411.

The current study's findings revealed that 61-70 and >70 years scored highest age groups (28% and 26%) than ≤40 years that scored least age groups (6%) with significant differences ($p<0.05$). The levels of erythropoietin and TSH were higher in patients than healthy. In contrast, the levels of testosterone, FT3, and FT4 were low in patients than healthy with significant differences ($p<0.05$). According to Pearson correlations, erythropoietin is a substantial positive association with FT4 ($r= 0.293$* Sig.=0.039). Depending on receiver operating characteristic (ROC) curve, the present study showed the Erythropoietin, Testosterone, TSH, FT3, and FT4 markers scored the highest sensitivity (86%, 90%, 94%, 96%, and 100%) and specificity (90%, 90%, 94%, 100%, and 72%) respectively, in screening patients with Chronic liver disease (CLD).

We came to the conclusion that illness severity increased with age. Erythropoietin, testosterone, and thyroid function are good prognostic markers in screening chronic liver disease that is associated with gonadal and thyroid disorders.

Keywords- Chronic liver disease, Erythropoietin, testosterone and thyroid function markers.

I. INTRODUCTION

Chronic liver disorders are defined as a six-month gradual worsening of liver functioning. Chronic liver disease is caused by genetic defects, toxins, excessive alcohol intake, infection, autoimmune reactions, and metabolic disorders [1]. Liver fibrosis is the result of chronic inflammation, lipid peroxidation, and necrotic assaults that degrade the liver parenchyma and produce scars. A tiny proportion of people will develop hepatocellular carcinoma and/or end-stage cirrhosis [2]. Cirrhosis is the 11th major the 15th leading cause of morbidity and cause of death globally. It is distinguished by evident fibrosis and nodule formation

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as a result of persistent injury [3].

The three main causes of cirrhosis-induced mortality at the moment are alcohol misuse (27.3% in males and 20.6% in females), hepatitis C virus (25.5% in males and 26.7% in females), and hepatitis B virus (HBV; 31.5% in males and 24.0% in females) [4]. Obesity-related non-alcoholic fatty liver disease (NAFLD; presently 7.7% in males and 11.3% in females) is extremely common worldwide and is associated with hepatic fat accumulation without a history of alcohol abuse. As a result, it is also predicted to contribute to an increasing percentage of deaths in the future [5].

During fetal life, the liver produces erythropoietin (EPO), but after birth, the kidney becomes the primary site of production. It is possible that anemia, hypoxia, and renal hypoperfusion could cause a rise in EPO, or that EPO will have a hepato-protective and regenerative effect [6]. A class of steroid hormones known as "sex steroids," or "sex hormones" for short, are androgen, estrogen, and progesterone. They play a vital role in both the reproductive and non-reproductive systems, supporting processes like hair growth, lipid metabolism, puberty, body fat distribution, and reproduction. In particular, the adrenal cortex, the gonads (testes and ovaries), and the placenta all manufacture them in large quantities [7]. The body's homeostasis and preventive measures against infertility, obesity, and hair/bone loss are achieved by complex control of the circulating and tissue levels of sex hormones [8]. Since basic and clinical studies have shown that sex hormones can significantly impact the pathophysiology of obesity, type 2 diabetes, cardiovascular disease, and non-alcoholic fatty liver disease (NAFLD), as well as be used as novel therapies for these conditions, the roles of sex hormones in metabolic diseases have garnered a great deal of attention in recent decades [4]. The meta-analysis study showed that lower testosterone is associated with the severity of liver diseases in males, while the relationship between sex hormone binding globulin (SHBG) and severity of liver diseases is still to be further verified [9].

The connection between non-alcoholic fatty liver disease (NAFLD) and thyroid disorders has drawn significant attention due to the significance of thyroid hormones in lipid metabolism and energy homeostasis, which contribute to the onset and progression of NAFLD. However, the results of studies examining this relationship range from a strong association to no association [10]. In the meanwhile, there is still disagreement on the relationship between euthyroid people's non-alcoholic fatty liver disease (NAFLD) and free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH). For instance, high-normal FT3 and low-normal TSH are independently linked to a greater prevalence of liver disorders, but not by FT4, according to a research conducted on middle-aged and elderly euthyroid people [11]. The Lifelines A high-normal FT3 level was shown to be independently related with liver disorders, but not with TSH, according to a cohort study [12]. Few research have examined the relationship between thyroid function in the euthyroid range and liver fibrosis in non-alcoholic fatty liver disease (NAFLD). The goal of the current study is to ascertain how thyroid function, testosterone, and erythropoietin indicators relate to the etiology of liver dysfunction in Iraqi patients.

II. METHODOLOGY

Samples collection

The current study was conducted in Baquba Teaching Hospital / Diyala governorate for the time from November 2022 to January 2023. 50 blood samples were collected from patients who came to the Baquba Teaching Hospital and those with Chronic liver disease (CLD) and the consultant physician's examination and diagnosis in the Baquba Teaching Hospital's advising units. Thirty healthy individuals gave blood samples, which were used as a control group. Patients and healthy participants ranged in age from under 40 to over 80.

Methods

To isolate the serum, five ml of human blood were spun at 3000 rpm for 5 minutes. Serum levels of erythropoietin, testosterone, TSH, FT3, and FT4 markers in the samples were measured by Roshe Cobas e411. The procedural protocol that came with the kit and was provided by the manufacturer was followed for doing this test.

Statistical analysis

First, the Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine if the parameters for erythropoietin, testosterone, TSH, FT3, and FT4 indicators were normal. The student t test was utilized to ascertain the significance of the differences between the two groups, and the parameters that pass the normality tests (non-significant difference) were displayed as Mean± SD. Additional factors were presented as percentages and numbers, and the Pearson-Chi-square test was used to identify significant variations in frequency. The nature and strongly of the association between parameters was assessed by Pearson correlation (r). Receiver operating characteristic (ROC) curve was used to determine area under the curve (AUC), sensitivity, and specificity of parameters. $P \leq 0.05$ was measured significant. Our data were analyzed using SPSS v. 21.0 and Graph pad prism v.6 statistical software.

III. RESULT

1. Age groups of liver dysfunction patients

Results of present study showed there is significant differences ($p<0.05$) among age groups of patients, where the 61-70 and >70 years scored highest age groups (28% and 26%) than ≤40 years that scored least age groups (6%) (figure 1).

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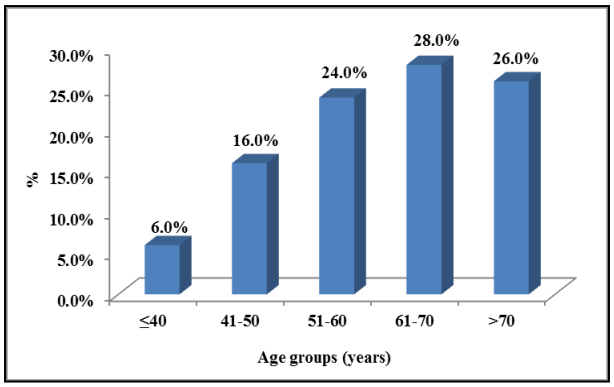

Figure 1: age groups of patients

2. Relationship of erythropoietin, testosterone and thyroid function markers with study groups

Results of conducted study showed there is significant difference ($p<0.05$) between erythropoietin, testosterone and thyroid function markers and study groups. The levels of erythropoietin and TSH were high in patients (31.12±6.25 and 5.74±0.85) than healthy (16.13±7.26 and 2.97±0.66). In contrast, the levels of testosterone, FT3 and FT4 were low in patients (9.96±3.77, 2.02±0.71, and 0.64±0.29) than healthy (24.50±6.52, 4.67± 0.44, and 1.77±0.68) (table 1 and figure 2).

Table 1: comparative mean levels of erythropoietin, testosterone and thyroid function markers between study groups

Groups		N	Mean	SD	P value
Erythropoietin	Patients	50	31.12	6.25	P<0.001***
	Healthy	30	16.13	7.26	
Testosterone	Patients	50	9.96	3.77	P<0.001***
	Healthy	30	24.50	6.52	
TSH	Patients	50	5.74	0.85	P<0.001***
	Healthy	30	2.97	0.66	
FT3	Patients	50	2.02	0.71	P<0.001***
	Healthy	30	4.67	0.44	
FT4	Patients	50	0.64	0.29	P<0.001***
	Healthy	30	1.77	0.68	

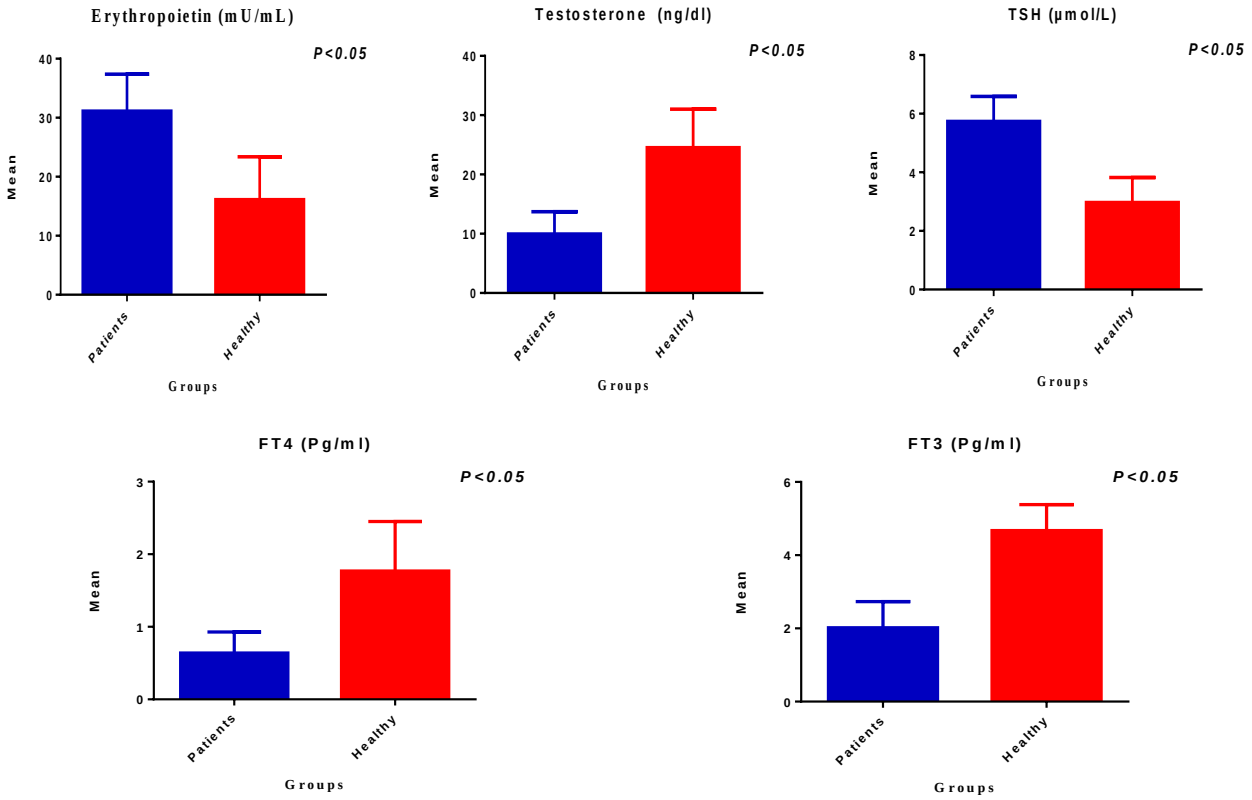

Figure 2: comparative mean levels of Erythropoietin, Testosterone and thyroid function markers between study groups

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3. Correlation relationship among Erythropoietin, Testosterone and thyroid function markers in patients with Chronic liver disease.

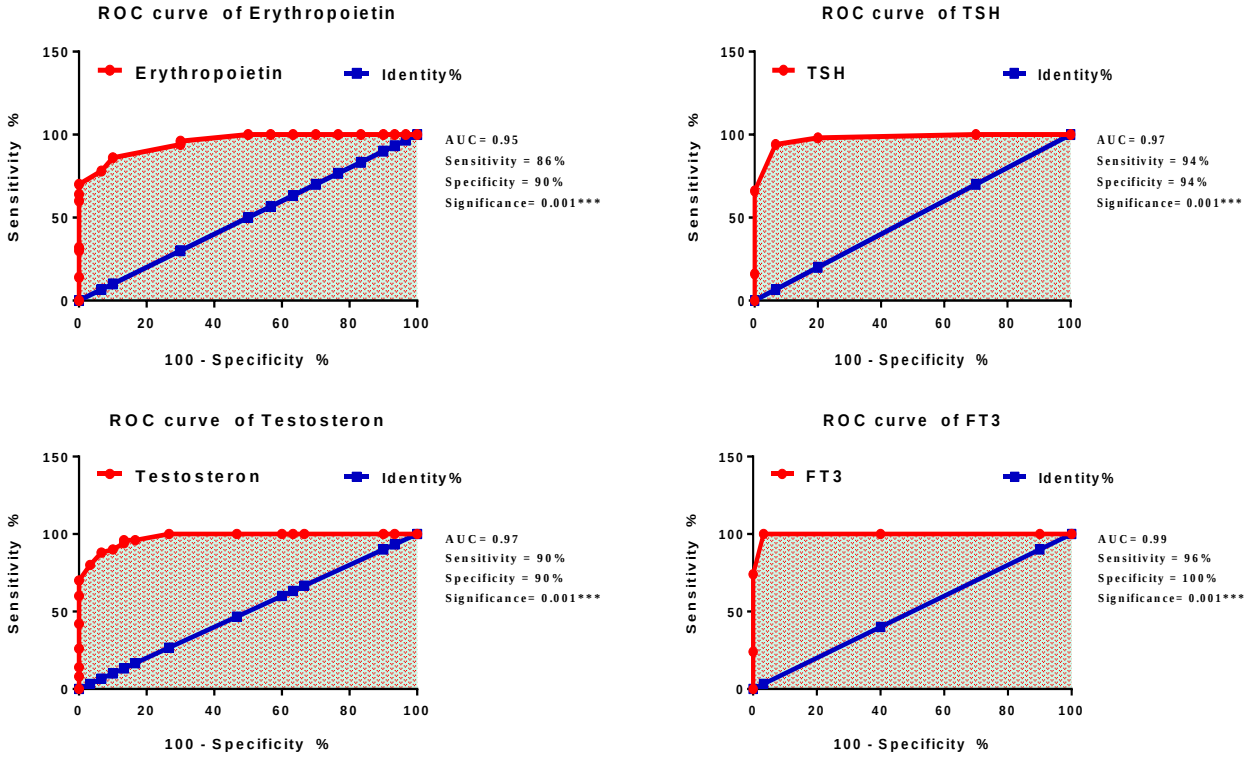
Results of present study showed there is positive and negative correlations among erythropoietin, testosterone and thyroid function markers. Importantly, erythropoietin is significant positive correlate with FT4 (r= 0.293* Sig.=0.039) (table 2).

Table 2: correlation relationship among Erythropoietin, Testosterone and thyroid function markers in patients with liver dysfunction

		Erythro poietin	TSH	FT4
Erythropoietin	Pearson coefficient (r)	1	0.125	0.293*
	Sig.		0.388	0.039
Testosterone	Pearson coefficient (r)	-0.118	0.181	-0.195
	Sig.	0.413	0.209	0.174
FT3	Pearson coefficient (r)	-0.083	0.243	0.046
	Sig.	0.567	0.089	0.752
FT4	Pearson coefficient (r)	0.293*	-0.117	1
	Sig.	0.039	0.420	

4. Receiver operating characteristic (ROC) curve of Erythropoietin, Testosterone and thyroid function markers

Results of present study showed the Erythropoietin, Testosterone, TSH, FT3, and FT4 markers scored highest sensitivity (86%, 90%, 94%, 96%, and 100%) and specificity (90%, 90%, 94%, 100%, and 72%) respectively, in screening patients with Chronic liver disease (CLD) (figure 3).



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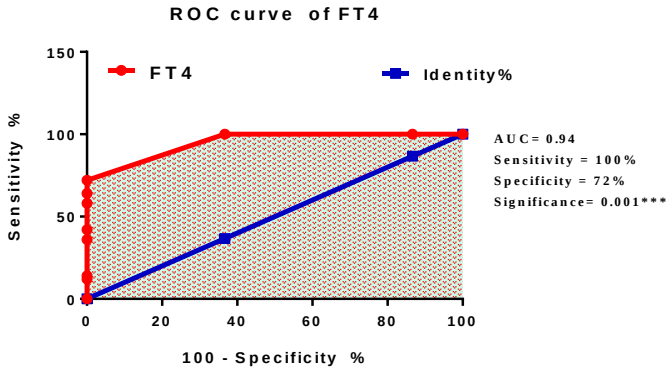

Figure 3: ROC curve of Erythropoietin, Testosterone and thyroid function markers

IV. DISCUSSION

The conducted study revealed the liver diseases are increased with age progression, and these results matched with results [13]. As the primary metabolic organ of the body, the liver ages more slowly than other organs and has a higher capability for regeneration, according to study findings [14]. As we age, our liver cells undergo changes due to a variety of stresses and the possibility of developing long-term liver illnesses such as non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH) and hepatocellular carcinoma (HCC) increases [15]. Research has demonstrated that these illnesses develop more quickly in the elderly and can sometimes result in end-stage liver disease requiring liver transplantation. The management of chronic liver disease in the elderly is a difficult task that need for both a customized strategy and ongoing research to identify more safe and efficient therapeutic options [13].

Recent study showed the age rather than duration of type 2 diabetes (T2D) predicts liver-related events in patients with nonalcoholic fatty liver disease (NAFLD) and T2D. Patients with T2D and NAFLD should be screened for advanced liver disease beginning around age 50 [16].The increase occurrence of liver diseases with age progression related with several causes such as organ dysfunction, chronic diseases, impaired immune status, and may be sample size.

The present study showed elevated levels of erythropoietin (EPO) in patients than healthy, and these results matched with results [17]. Erythropoietin's (EPO) primary duty is to maintain red blood cell bulk, but more and more research in recent years has pointed to a broader biological role for EPO that goes beyond erythropoiesis, such as angiogenesis and tissue protection [18]. While a fetus, the liver produces EPO; but, following birth, the kidney becomes the primary site of production. In healthy controls, the liver may produce up to 10% of the total synthesis of EPO, but it can be up-regulated to 90–100% [19]. It has been demonstrated, meanwhile, that in the absence of renally generated EPO, hepatic EPO production is insufficient to treat anemia. Although there are little data from cirrhosis patients and there is debate regarding the amount of plasma EPO in these individuals, elevated circulating EPO has been linked to a number of disorders [18]. Hepatic dysfunction, liver fibrosis, and the production of pro-inflammatory cytokines are characteristics of cirrhosis. These conditions can cause anemia, hepatic nephropathy, and arterial hypotension [20]. It is possible that anemia, hypoxia, and renal hypoperfusion could cause a rise in EPO, or that EPO will have a hepato-protective and regenerative effect [6]. Nonetheless, inadequate EPO response in end-stage cirrhosis may be explained by inflammatory feedback mechanisms, a declining co-factor level, and impaired hepatic synthesis capability [21]. According to earlier findings, EPO plays a novel function in promoting the growth and phagocytosis of Kupffer cells (KCs) as well as in drawing in monocytes in response to liver damage [22]. Another results suggest that EPO alleviated liver and mitochondrial damage induced by lipopolysaccharide (LPS), possibly via inhibition of NLR family pyrin domain containing 3 (NLRP3) signaling, and that refer to importance role of EPO as protective factor in liver against lipopolysaccharide (LPS) which causes sepsis in liver [12]. Similarity, study results showed the EPO administration could protect the kidney and liver damage induced by ischemia reperfusion (IR) [23].

The present study showed high sensitivity (86%) and specificity (90%) of EPO in screening patients with liver dysfunction, and these results refer to important of EPO in pathophysiology of hepatic diseases.

Correlation results revealed positive significant correlation between EPO and thyroid hormone (FT4) markers ($r=0.293^{*}$, Sig.=0.039) due to liver diseases that effect on kidney and thyroid functions.

The present study showed low levels of testosterone in patients than healthy, and these results matched with results [24]. The hallmark of cirrhosis is liver cell failure, a condition in which nodular fibrosis replaces healthy liver tissue and causes a variety of liver processes to slow down or stop [25]. The degree of suppression of the hypothalamic-pituitary-gonadal

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(HPG) axis, the etiology of cirrhosis, and the severity of liver disease all influence gonadal hormone dysfunction in cirrhosis [26].

Chronic liver illnesses can cause secondary or mixed hypogonadism, which combines primary and secondary hypogonadism [27]. The hypogonadism in cirrhosis mechanism is intricate. The rate of testosterone synthesis decreases in chronic liver disorders, and the peripheral conversion of testosterone into estradiol increases (because of portosystemic shunting). Hepatic aromatase activity also increases, and the hypothalamic-pituitary-gonadal axis is affected. Low free circulating testosterone and high total estradiol levels are the results of these alterations [26].

Sexual dysfunction in men with cirrhosis of liver was found in 61% of patients in a study by [28]. A review article by [29]. notes that symptoms of feminization, testicular shrinkage, decreased libido, decreased secondary sex hair, and gynecomastia linked with impaired spermatogenesis and peritubular fibrosis are present in 50% of individuals with liver cirrhosis. Age, erectile dysfunction, lack of desire for sexual activity, and chronic illnesses including diabetes mellitus and liver and kidney failure can all contribute to libido loss. Therefore, liver failure may be the main cause of the patients' reported lack of libido. A person with chronic liver illness experiences significant psychological and physical changes that impair their libido. The study's findings on low circulating testosterone, high E2, and persistent alcohol addiction may be factors in this. Research has found that individuals with cirrhosis who experience sexual dysfunction do not see a substantial improvement after receiving a liver transplant. This may be because to permanent alterations in the pathways that produce gonadal hormones and testicular atrophy [26]. The meta-analysis study showed that lower testosterone is associated with the severity of liver diseases in males, while the relationship between sex hormone binding globulin (SHBG) and severity of liver diseases is still to be further verified [9].

According to a recent research, decreased androgen signaling may have a function in the pathogenesis of autoimmune liver illnesses and that testosterone regulates T cells in both health and autoimmunity [30].

In screening individuals with liver dysfunction, the current study demonstrated a high sensitivity (90%) and specificity (90%) of testosterone. These findings suggest that testosterone may be a prognostic component in the pathophysiology of patients with dysfunctional gonadal and hepatic hormones.

The present study showed elevated levels of TSH and low levels of FT3 and FT4 in patients than healthy, and these results matched with results [31]. Thyroid hormones play a major role in the metabolism of lipids in the liver; they can cause fat to accumulate in the liver and encourage the production of new liver tissue by binding to thyroid hormone β receptors [32]. Prior research has demonstrated that thyroid hormone derivatives, in addition to thyroid hormones themselves, play a significant role in the metabolism of lipids in the liver. 3,5-diiodo-L-thyronine (T2), a derivative of thyroid hormone, has been shown in vitro experiments to reduce excess fat in cultured hepatocytes [10].

There is strong evidence supporting the involvement of thyroid hormones and their derivatives, TSH levels, and oxidative stress in the metabolism of fat and glucose. The information that is now available suggests that there may be a causal relationship between hypothyroidism and liver disorders, both clinical and subclinical; still, obesity, metabolic syndrome, insulin resistance, and dyslipidemia are common characteristics of both hypothyroidism and liver diseases [32].

Previous study showed the high-normal serum TSH levels are significantly associated with the presence of liver diseases in T2DM patients with euthyroid function, which provide novel insight for treating these diseases [33].

Recent study showed TSH level may be an important risk factor for the development and progression of liver diseases, independent of FT3 and FT4 hormones [34].

Strong evidence from a previous study suggested that hypothyroidism may be crucial to the progression and development of liver diseases. It was discovered that elevated TSH concentrations may be a risk factor that increases the incidence of diseases, and that FT4 was negatively correlated with the risk of liver diseases while FT3 was not significantly correlated with the risk of liver diseases[35]. Even in cases where FT4 is normal, TSH elevation—even when it falls within the euthyroid range—is a stand-alone risk factor for liver disorders and may slow the development of liver fibrosis [36]. According to a recent study, FT3 levels are positively correlated with liver fibrosis presence and the degree of hepatic steatosis in NAFLD with euthyroidism [10].

Because metabolic alterations were detected when only the levels of the stimulating hormones were aberrant and the peripheral hormones were remained within the reference range, a recent study suggested that the TSH and FSH may be more related to the dysregulation of hepatic metabolism than the peripheral hormones. Elevated levels of TSH and FSH seem to function independently of one another and lead to the development of NAFLD [37]. The present study showed the TSH, FT3, and FT4 scored high sensitivity (94%, 96%, and 100%) and specificity (94%, 100%, and 72%) in screening patients with liver dysfunction, and these results refer to these markers can be considering as predictive factor in pathophysiology of patients with hepatic and thyroid disorders.

We came to the conclusion that illnesses were more severe as people aged. In the screening process for chronic liver illness linked to gonadal and thyroid

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abnormalities, erythropoietin, testosterone, and thyroid function are useful prognostic indicators.

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