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Study of Some Hormonal and Biochemical Parameters among Patients with Chronic Liver Diseases

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Abstract

It has been revealed previously that chronic liver disease (CLD) may be associated to hormonal fluctuations. The current study, therefore, aimed to evaluate some hormones in CLD patients compared with non-CLD individuals. This case control study was conducted at Gastroenterology and Hepatology Teaching Hospital, Medical city, Baghdad, Iraq during December 2021 to May 2022. One hundred and twenty male patients with CLD (age:14-75 years) and 120 control males (age: 24-70 years) were involved in this study. Serum samples were taken from all individuals and were then analysed for many tests which included hormones (Cortisol, testosterone, prolactin, insulin and thyroid stimulating hormone TSH); biochemical analysis (Prothrombin time PT, international normalized ratio INR and albumin); liver enzymes (aspartate aminotransferase AST, alanine aminotransferase ALT, alkaline phosphatase ALP and gamma glutamyl transferase (GGT)) and interleukins (Interleukin 13 IL-13 and transforming growth factor TGF). Some hormones such as cortisol, prolactin and insulin significantly increased in CLD patients while other hormones (testosterone and TSH) significantly decreased in CLD patients compared with the controls. Results also showed significant increase in liver enzymes among CLD patients. These changes in the hormones and liver enzymes levels may be related with significant increase in INR and albumin which were significantly higher in CLD patients than in the control group. Finally, IL-13 increased significantly in CLD patients while no significant differences were noticed between CLD and control regarding TGF levels. It can, therefore, be concluded that hormonal imbalance can affect people with liver conditions. and that this hormonal imbalance may be associated with high levels of liver enzymes.

Keywords: Chronic liver disease, Cortisol, IL-13, Prolactin, TGF, TSH.

دراسة بعض المعايير الهرمونية والكيمولحيوية لدى مرضى أمراض الكبد المزمنة

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الخلاصة

ارتبطت امراض الكبد مؤخرا مع التقلبات الهرمونية بشكل كبير. لذلك هدفت الدراسة الحالية الى تقييم مستويات بعض الهرمونات لدى المرضى الذين يعانون من امراض الكبد المزمنة ومقارنتها مع غير المصابين بامراض الكبد المزمنة. اجريت هذه الدراسة في المدة الزمنية المحصورة بين كانون الاول من العام 2021 و ايار من العام 2022 في مستشفى امراض الجهاز الهضمي و الكبد التعليمي، بغداد–العراق. تم شمول 120 مريضاً من الذين يعانون من امراض الكبد المزمنة(العمر:14–75 سنة) و 120 شخصا من غير المصابين بامراض الكبد المزمنه (العمر:24–70 سنة). تراوحت اعمار المشاركين بين (14–75) سنة. جُمعت عينات مصل الدم من جميع المشاركين وخضعت جميعها لمجموعة من التحاليل المختبرية والتي شملت كل من الفحوصات الهرمونية (الكورتيزول، التيستوستيرون، البرولاكتين، الانسولين و الهرمون المحفز للغدة الدرقية) ، الفحصوصات الكيموحياتية (زمن البروثرومبين، النسبة المعيارية الدولية و الالبومين) , فحوصات انزيمات الكبد (ناقل امين الاسبارتات, ناقل امين الالنين, ,انزيم الفوسفاتيز القلوي و ناقل الببتيد غاما غلوتاميل) و فحوصات المدورات الخلوية (انترلوكين–13 و عامل النمو المحول). اشارت النتائج الى وجود ارتفاع في بعض الهرمونات (الكورتيزول, البرولاكتين و الانسولين) لدى مرضى الكبد مقارنة بالسيطرة بينما انخفضت الهرمونات الاخرى (التيستوستريون و الهرمون المحفز للغدة الدرقية) و بشكل معنوي لدى مرضى الكبد مقارنة بالسيطرة. اشارت النتائج ايضا الى وجود ارتفاع معنوي في انزيمات الكبد في مرضى الكبد. هذه التغيرات في كل من مستوى الهرمونات و انزيمات الكبد قد ارتبط بارتفاع ملحوظ في كل من النسبة المعيارية الدولية والالبومين لدى مرضى الكبد مقارنة بالسيطرة. واخيرا ارتفع الانتروكين–13 بشكل ملحوظ لدى مرضى الكبد بينما لم يشهد عامل النمو المحول فرقا معنويا بين مرضى الكبد و مجموعة السيطرة. يمكن أن نستنتج أن عدم التوازن الهرموني يمكن أن يؤثر على الأشخاص الذين يعانون من أمراض الكبد ، وهذا الخلل الهرموني قد يترافق مع مستويات عالية من إنزيمات الكبد.

1. Introduction

Chronic liver disease (CLD) is classified as a persistent inflammatory condition of the liver (lasting more than six months) that destroys the liver parenchyma and hinders its ability to repair, ultimately leading in fibrosis and cirrhosis [1]. The primary cause of morbidity and mortality is thought to be chronic liver disease which is also placing an increasing burden on the healthcare system. In 2010, the National Centre for Health Statistics (NCHS) and Centre for Disease Control and Prevention (CDC) reported 31,903 fatalities from CLD and cirrhosis. In the upcoming ten years, it is anticipated that this number would rise steadily [2]. Non-alcoholic fatty liver disease (NAFLD), alcohol-related liver disease, viral hepatitis, various genetic metabolic disorders and autoimmune liver diseases are the main causes of chronic liver disease [3, 4]. Approximately 15% of instances of chronic liver disease are idiopathic as well [5]. While non-alcoholic fatty liver disease is the fastest-growing cause of chronic liver disease and is thought to affect 25% of the world's population on average, that number rises to 95% in morbidly obese people. Alcohol-related liver disease is still considered as the non-viral chronic liver disease that is most frequently associated with cirrhosis deaths [6]. Although non-alcoholic fatty liver disease (NAFLD) first appears to be a benign condition. However, in a substantial percentage of people, it can advance to non-alcoholic steatohepatitis (NASH) [7]. It is undeniable that liver diseases studies have evaluated the aspartate aminotransferase to alanine aminotransferase ratio (AST/ALT ratio) in recent years Studies have been conducted on patients with liver disease that was both acute and chronic and came from various sources. Numerous studies have shown the clinical importance of the AST/ALT ratio in the diagnosis process of patients with chronic hepatitis virus infection, and these variables are accessible, easy to use and reasonably priced [8–11].

Many circulating hormones that keep endocrine homeostasis in the body are involved in the biological functions as well as the metabolism of the liver. The liver and all endocrine organs have multiple, ongoing interactions and feedback mechanisms because both are involved in a wide range of metabolic processes. It consequently becomes a target during numerous metabolic and endocrine problems, and vice versa, liver diseases are frequently linked to hormonal irregularities [12]. Various research has reported the correlation between CLD and hormonal fluctuation [13-15]. Some people have also spoken about endocrine issues related to CLD. Short stature, delayed puberty, hepatic osteodystrophy, hypogonadism, relative adrenal insufficiency and sick euthyroid syndrome are the most prevalent endocrine symptoms in CLD [13-14]. The current study aimed to evaluate cortisol, testosterone, prolactin, insulin and TSH in CLD patients compared with non-CLD individuals.

2. Materials and Methods

2.1 Individuals and Study Design

This study was a case control study achieved from December 2021 to May 2022, at Gastroenterology and Hepatology Teaching Hospital, Medical city in Baghdad, Iraq. A total of 240 adult males were included in this study. One hundred and twenty of them were diagnosed with CLD. The diagnosis was based on some clinical and biochemical examinations which were done by gastrointestinal tract (GIT) specialist. The mean age of the CLD patients was 44.17 ± 13.4 years (Range: 14-75 years). The other individuals (n=120) were considered as control group with the mean age of 40.25 ± 12.08 (Range: 24-70 years). Permission was given by all individuals involved in this investigation. The study procedure was permitted according to the ethics team, College of Science, University of Baghdad, through the authentication letter provided by them (CSEC/1221/0081).

2.2 Hormones Analysis

Cortisol, testosterone, prolactin, insulin and thyroid stimulating hormone (TSH) hormones were analysed in CLD patients and control individuals. All hormones were assessed using a sandwich enzyme-linked immunosorbent assay (ELISA). All evaluations were conducted in accordance with the manufacturer's instructions available with the ELISA kits (My BioSource, China) of each hormone. All samples were examined in a 96-well plate which was then examined with an ELISA reader operating at 450 nm wavelength.

2.3 Biochemical Analysis

2.3.1 Liver Enzymes:

Liver enzymes, AST, ALT and ALP were assessed using liver enzymes kit (Abbott, USA). All of the enzymes were measured using ABBOTTc4000 chemistry analyser (Abbott, USA) based on the manufacturer’s instruction found in the kits. Gamma glutamyl transferase (GGT) was measured for all participants using ELISA kit (My BioSource, China) according to the instructions available with the kit. All samples were then analysed and read at 450 nm wavelength.

2.3.2 Prothrombin Time (PT) and International Normalized Ratio (INR) Analysis

Both prothrombin time (PT) and international normalized ratio (INR) were evaluated for all participants using BCS XP analyser (Siemens, Germany). The assessment procedure was done according to the instructions that came with the kit.

2.3.3 Albumin Measurement

Based on the manufacturer's instructions included in the kits, ABBOTTc4000 chemical analyser (Abbott, USA) was used to quantify the albumin concentration for each participant.

2.3.4 Interleukin 13 (IL-13) and Transforming Growth Factor (TGF)

Interleukin 13 (IL-13) and transforming growth factor (TGF) were assessed using a sandwich enzyme-linked immunosorbent assay (ELISA) in accordance with the IL-13 and TGF kits' manufacturer's instructions (Fine Test, ELISA kit, China). The samples were screened in a 96-well plate at 450 nm wavelength.

2.4. Statistical Analysis

The Statistical Analysis System, (SAS) version 9.1, was used to statistically analyse the data. Using the student t-test all parameters including cortisol, testosterone, prolactin, insulin, TSH, AST, ALT, ALP, PT, INR, albumin, IL-13 and TGF were compared between the CLD and the control group. *P*-values less than 0.05 were regarded as statistically significant. Data was stated as the mean and standard deviation (mean ±SD).

3. Results

3.1 Hormones Levels

In this study, many hormones were measured both in CLD patients and control group. These hormones showed differences between the two groups. Some of them significantly increased while the others decreased significantly. All results of hormones are illustrated in Table 1. Cortisol increased significantly ($p<0.05$) in those who had CLD (28.34±2.035 ng/ml) compared with the control group who showed lower level (15.78±0.043 ng/ml) of cortisol. Whereas, testosterone decreased significantly ($p<0.05$) in CLD patients (1.76±0.011) versus control group who showed lower means of testosterone (2.95±0.045). On the other hand, prolactin levels differed significantly ($p<0.05$) between the two groups which indicated higher levels in CLD patients compared the control group where the prolactin levels were 66.6±4.2 ng/ml and 45.13±0.3 ng/ml respectively. Insulin levels also increased significantly ($p<0.05$) in CLD patients (15.6±0.19) compared with the control group (9.31±0.1). However, TSH showed significantly ($p<0.05$) low level in CLD patients' group versus control group where the TSH levels were 0.64±0.013 IU/ml and 0.97±0.033 IU/ml respectively.

Table 1: The levels of cortisol, testosterone, prolactin, insulin and (TSH) hormones in CLD patients and control group.

Hormones (Mean ±SD)	CLD Patients (n=120)	Control Group (n=120)	(*P*-value)
Cortisol (ng/ml)	28.34±2.035	15.78±0.043	(<0.05)
Testosterone (ng/ml)	1.76±0.011	2.95±0.045	(<0.05)
Prolactin (ng/ml)	66.6±4.2	45.13±0.3	(<0.05)
Insulin (ng/ml)	15.6±0.19	9.31±0.1	(<0.05)
TSH (IU/ml)	0.64±0.013	0.97±0.033	(<0.05)

3.2 Liver Enzymes

Liver enzymes were also measured in this study in both CLD and control group. The results of liver enzymes are illustrated in Table 2. Regarding all enzymes, there were noticeable variations between the two groups. AST, ALT, ALP and GGT all showed significantly higher levels (77.17 ± 6.2 IU/L, 77.86 ± 6.52 IU/L, 180.66 ±20.51 IU/L and 18.70±1.09 IU/L respectively) in CLD. While their levels were low in the control group (24.44±0.6 IU/L, 35.36±5.47 IU/L, 94.31±2.13 IU/L and 6.99±0.04 IU/L respectively)

Table 2: AST, ALT, ALP and GGT liver enzymes levels in CLD patients and control group

Liver Enzymes (Mean ±SD)	CLD Patients (n=120)	Control Group (n=120)	(*P*-value)
AST (IU/L)	77.17 ± 6.2	24.44 ± 0.6	(<0.05)
ALT (IU/L)	77.86 ± 6.52	35.36 ± 5.47	(<0.05)
ALP (IU/L)	180.66 ±20.51	94.31 ± 2.13	(<0.05)
GGT (IU/L)	18.70±1.09	6.99±0.04	(<0.05)

3.3 Prothrombin Time (PT), International Normalized Ratio (INR) and Albumin

Results showed that PT increased slightly among those who had CLD, as their values reached 12.27±0.27 second. Whereas lower PT values (11.98±0.072 second) were noticed to be lower in the control group. No significant differences were noticed between the two groups regarding PT. On other hand, significant differences (<0.05) were noticed between the two groups regarding INR. Highly significant INR was reported among CLD patients (1.24±0.3 %) versus low INR (0.89±0.06 %) in the control group. Results also showed significant differences between the two groups regarding albumin levels. Albumin raised significantly in control individuals versus its low level in patients with CLD. The means of albumin were 3.64 ±0.06 g/dl and 4.16 ±0.03 g/dl respectively.

Table 3: The values of prothrombin time (PT), international randomized ratio and albumin in CLD patients and control group

Parameters (Mean ±SD)	CLD Patients (n=120)	Control Group (n=120)	(*P*-value)
PT (second)	12.27±0.27	11.98±0.072	NS
INR (%)	1.24±0.3	0.89±0.06	(<0.05)
Albumin (g/dl)	3.64 ±0.06	4.16 ±0.03	(<0.05)

3.4 Interleukin 13 (IL-13) and Transforming Growth Factor (TGF)

Results showed that IL-13 differed significantly between the two groups. It was increased in CLD patients (247.76±17.26) compared with the control group (90.16±1.68). On other hand, the results of statistical analysis indicated no significant differences between the two groups regarding TGF, although its values non-significantly increased in patients with CLD (158.33±10.16 pg/ml) versus the control group (158.33±10.16 pg/ml).

Table 4: The levels of IL-13 and TGF in CLD patients and control group.

Parameters (Mean ±SD)	CLD Patients (n=120)	Control Group (n=120)	*P*-value
IL-13(pg/ml)	247.76±17.26	90.16±1.68	(<0.05)
TGF (pg/ml)	158.33±10.16	138.38±61.04	(p=0.75)

4. Discussion

4.1 Hormones

Those with liver diseases may experience hormonal imbalance. It is well-known that both men and women who have liver illness experience hormonal fluctuation [17]. All results obtained in the current study, regarding hormone levels, confirmed that there were differences between CLD patients and the control group. These differences ranged from an increase in some hormones to a decrease in others. Cortisol levels were noticed to be significantly higher in CLD patients than the control group. According to some theories, cortisol levels are likely to be related to how severe liver failure is and may be a sign of poor prognosis [18]. This establishes a foundation for the evaluation of illness severity and prognosis using cortisol

levels. Our findings revealed that cortisol was critical to the development and severity of liver failure, and that the higher the level, the better the prognosis for patients. About 90% of circulating cortisol is bound to corticosteroid-binding globulin (CBG) and albumin (5%). About 10% of cortisol is present in its free form. Due to hypoalbuminemia, free cortisol may rise in cirrhosis. If the level of CBG declines, it could possibly get worse during critical sickness. Low production of cortisol, which is made from HDL cholesterol, is caused by the reduced cholesterol level in cirrhosis. Cortisol increases protein catabolism, decreases lipolysis, hyperglycaemia, and cytokine production, in addition to increasing vascular tone and cardiac output [18-21]. Testosterone, on other hand, dropped down significantly in those who suffered from CLD compared with the control group. This result may be due to an enhanced peripheral aromatization of androgens, a central hypothalamus-pituitary mechanism and gonadal failure [22, 23]. This result agrees with the result of [24] where they showed that men with advanced liver disease had lower testosterone levels than the controls. As well as the results of testosterone obtained in this study agree with some recent research which has shown that low testosterone is linked to an increased risk of mortality, regardless of the underlying cause of the disease, and that it is highly prevalent among men with end-stage liver disease [24-26]. The levels of prolactin also differed between CLD and the control group. Prolactin increased significantly in CLD patients compared with the control. A variation in the kind of amino acids entering the central nervous system results from decompensated liver function among those with CLD. It has been discovered that rising levels of circulating aromatic amino acids stimulate the production of false neurotransmitters, including octopamine and phenyl ethanolamine [27]. These false neurotransmitters might prevent the release of dopamine which would lead to hyperprolactinemia. Moreover, cases of hypogonadism in cirrhotic individuals linked to hyperprolactinemia have also been documented [28]. The result of prolactin illustrated in the current study agrees with the study of Jha and Kannan [29] where they showed a significant increase in prolactin among patients with liver cirrhosis.

Those with CLD had significantly higher insulin levels than its low levels in the control group. Since hyperinsulinemia is observed in CLD patients who do not have both severe hepatic parenchymal cell damage and portal-systemic shunting, increased hepatic insulin resistance is the factor associated with hyperinsulinemia in patients with liver disease [30]. Another study found that cirrhosis patients' pancreatic islets proliferate more and undergo less apoptosis than patients without chronic liver disease [31]. Our findings were consistent with earlier research suggesting that hyperinsulinemia in cirrhotic patients may occur from the pancreatic beta cells' adaptive response to enhanced insulin resistance [32]. TSH, on the other hand, revealed considerable drop among CLD patients compared with its high level in the control. According to numerous studies, there is a well-established link between thyroid dysfunction and liver disease in patients with liver disease [33]. According to a previous study which indicated that patients with liver failure had significantly lower TSH concentrations, euthyroid ill syndrome may have evolved in these people. The low TSH level seen in the current investigation was consistent with this finding [34]. Overall, it appeared that blood thyroid hormone concentrations and the severity of liver dysfunction were associated which is consistent with several other studies on cirrhotic liver diseases [35, 36].

4.2 Liver Enzymes

All levels of liver enzymes (AST, ALT, ALP and GGT) examined in this study showed significant increase in CLD compared with the control group. It is known from previous studies that elevated liver enzymes are evidence of the inflammation or damage that occurs in this organ. All these hormones are valid indicators of liver injury. Moreover, the rise or fall of some hormones can affect these enzymes. Zhang *et al.* presented that persons with

testosterone deficiency had significantly higher ALT. Additionally, additional research found a substantial correlation between insulin resistance and a higher risk of elevated ALT, AST, and GGT levels [37]. Earlier research has shown a substantial favourable association between AST levels and raised mean levels of TSH in patients with liver cirrhosis compared with the control group [38, 39]. The increased deposition of fat and modifications in lipid metabolism brought on by thyroid dysfunction can be employed to explain this connection [33, 40-42]. In addition to oxidative stress and lipid peroxidation, high TSH production also damages liver cells [43].

4.3 Prothrombin Time (PT), International Normalized Ratio (INR) and Albumin

Both PT and INR were reported to be greater in CLD patients matched to the control group. No significant difference was noticed between the two groups regarding PT. However, significant difference was reported between groups regarding INR. Majority of hospitalized patients with liver cirrhosis or other chronic liver diseases have coagulation problems which are linked to noticeably extended PT and high international normalized ratio (INR) values. The results of this study suggest a possible relationship between low TSH and high PT and INR readings. This finding agrees with Jao [44] who found that patients with hypothyroidism were associated with increased PT and INR. Albumin level, on the other hand, was significantly low among those with CLD. Low albumin levels in CLD patients may indicate the development of cirrhosis. A drop in plasmatic albumin is related to cirrhosis. Patients with cirrhosis experience decreased albumin synthesis and poor hepatocellular function which in advanced cirrhosis can reach a 60–80% drop [45].

4.4 Interleukin 13 (IL-13) and Transforming Growth Factor (TGF)

IL-13 and TGF levels in CLD patients were reported to be considerably greater than in the control group. In the livers of people with chronic liver disease, the rise in IL-13 is associated with progressive fibrosis and/or inflammation [46]. TGF, on the other hand, plays a crucial function in the regulation of chronic liver disease by affecting how the condition develops from the initial insult to the liver via inflammation and fibrosis to cirrhosis and hepatocellular carcinoma [47]. The synergic signalling link between these two key pro-fibrotic cytokines during fibrogenesis is a subject of ongoing discussion because TGF and IL-13 are both essential for organ fibrosis. TGF and IL-13 may collaborate to produce fibrosis under specific conditions [48]. The creation of myofibroblasts and the deposition of extracellular matrix are part of the wound-healing response brought on by liver damage-induced levels of active TGF- which also increase hepatocyte mortality and activate hepatic stellate cells and fibroblasts [47].

Reference

[1] A. Quaglia, V. A. Alves, C. Balabaud, P. S. Bhathal, P. Bioulac-Sage, J. M. Crawford, A. P. Dhillon, L. Ferrell, M. Guido, and P. Hytiroglou, "Role of aetiology in the progression, regression, and parenchymal remodelling of liver disease: implications for liver biopsy interpretation," *Histopathology*, vol. 68, no.7, pp. 953-967, 2016.

[2] Z. Ahmed, U. Ahmed, S. Walayat, J. Ren, D. K. Martin, H. Moole, S. Koppe, S. Yong, and S. Dhillon, "Liver function tests in identifying patients with liver disease," *Clinical and experimental gastroenterology*, vol. 5, pp. 301-307, 2018.

[3] P. Golabi, M. Otgonsuren, R. Cable, S. Felix, A. Koenig, M. Sayiner, and Z. M. Younossi,"Non-alcoholic fatty liver disease (NAFLD) is associated with impairment of health- related quality of life (HRQOL)," *Health and quality of life outcomes*, vol. 14, no.1, pp. 1-7, 2016.

[4] H. Arif and R. F. Thejeal, "Etiology of chronic liver disease in Iraqi children, with special emphasis on the role of liver biopsy, "*Pak J Med Science*, vol. 27, No. 4., pp. 870-873, 2011.

[5] A. M. Moon, G. J. Webb, C. Aloman, M. J. Armstrong, T. Cargill, R. Dhanasekaran, J. Genescà, U. S. Gill, T. W. James, and P. D. Jones, "High mortality rates for SARS-CoV-2 infection in

patients with pre-existing chronic liver disease and cirrhosis: preliminary results from an international registry," *Journal of hepatology*, vol. 73, no.3, pp. 705-708, 2020.

[6] T. Arshad, P. Golabi, L. Henry, and Z. M. Younossi, "Epidemiology of non-alcoholic fatty liver disease in North America," *Current Pharmaceutical Design*, vol. 26, no.10, pp. 993-997, 2020.

[7] S. Dam-Larsen, M. Franzmann, I. Andersen, P. Christoffersen, L. Jensen, T. Sørensen, U. Becker, and F. Bendtsen, "Long term prognosis of fatty liver: risk of chronic liver disease and death," *Gut*, vol. 53, no.5, pp. 750-755, 2004.

[8] S. M. F. Karim, M. R. Rahman, S. Shermin, and R. Sultana, "Correlation between aminotransferase ratio (AST/ALT) and other biochemical parameters in chronic liver disease of viral origin," *Delta Medical College Journal*, vol. 3, no.1, pp. 13-17, 2015.

[9] R. H. Nafal, H. S. Al-Warid, and H. J. Al-Sultan, "Seroprevalence of Toxoplasmosis in patients with chronic liver disease in Baghdad," *Iraqi Journal of Science*, vol. 60, no.8, pp. 1667-1672, 2019.

[10] J. H. Murtadha, I. Hashim, and A. Razzaq, "Study of Liver Function and Lipid Profile Changes in Iraqi Cirrhotic patients," *Research Journal of Pharmacy and Technology*, vol. 13, no.4, pp. 1839-1842, 2020.

[11] S. A. Al-Jowary, "Determination of the Liver Enzymes Level and Kidney Functions in Pregnant Women in the Second Trimester of Pregnancy at Different Age Groups," *Iraqi Journal of Science*, vol. 58, no. 44, pp. 1802-1807, 2017.

[12] G. Ray and P. M. Bhargav, "A study of hormonal abnormalities in chronic liver disease," *J Assoc Physicians India*, vol. 67, no. 44, pp. 47-52, 2019.

[13] K. S. Bura, C. Lord, S. Marshall, A. McDaniel, G. Thomas, M. Warrier, J. Zhang, M. A. Davis, J. K. Sawyer, and R. Shah, "Intestinal SR-BI does not impact cholesterol absorption or transintestinal cholesterol efflux in mice," *Journal of lipid research*, vol. 54, no.6, pp. 1567-1577, 2013.

[14] W. Högler, U. Baumann, and D. Kelly, "Endocrine and bone metabolic complications in chronic liver disease and after liver transplantation in children," *Journal of pediatric gastroenterology and nutrition*, vol. 54, no. 3, pp. 313-321, 2012.

[15] X. Zhang, H. Zhao, J. Horney, N. Johnson, F. Saad, K. S. Haider, A. Haider, and X. Xu, "Testosterone deficiency, long-term testosterone therapy, and inflammation," *Journal of Cardiovascular Pharmacology and Therapeutics*, vol. 26, no.6, pp. 638-647, 2021.

[16] M. Sinclair, M. Grossmann, P. J. Gow, and P. W. Angus, "Testosterone in men with advanced liver disease: abnormalities and implications," *Journal of gastroenterology and hepatology*, vol. 30, no.2, pp. 244-251, 2015.

[17] M. Sarkar, L. B. VanWagner, J. G. Terry, J. J. Carr, M. Rinella, P. J. Schreiner, C. E. Lewis, N. Terrault, and C. A. R. D. in Young, "Sex Hormone–Binding Globulin Levels in Young Men Are Associated with Nonalcoholic Fatty Liver Disease in Midlife," *The American journal of gastroenterology*, vol. 114, no.5, pp. 758, 2019.

[18] P. E. Marik, S. M. Pastores, D. Annane, G. U. Meduri, C. L. Sprung, W. Arlt, D. Keh, J. Briegel, A. Beishuizen, and I. Dimopoulou, "Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine," *Critical care medicine*, vol. 36, no.6, pp. 1937-1949, 2008.

[19] T. Vasu, J. Stewart, R. Cavallazzi, A. Hirani, and P. Marik, "Hepatoadrenal Syndrome: Prevalence and Factors Predicting Adrenal Insufficiency in Critically Ill Patients with Liver Disease," in *A41. CLINICAL TRIALS IN ICU*: American Thoracic Society, 2009, p. A1588.

[20] A. Risso, C. Alessandria, C. Elia, L. Mezzabotta, A. Andrealli, M. Spandre, A. Morgando, A. Marzano, and M. Rizzetto,"OC-30 Adrenal dysfunction in nonseptic cirrhotic patients with ascites: Impact on survival," *Digestive and Liver Disease*, vol. no.43, pp. S74-S75, 2011.

[21] G. Fede, L. Spadaro, T. Tomaselli, G. Privitera, S. Piro, A. M. Rabuazzo, A. Sigalas, E. Xirouchakis, J. O'Beirne, and M. Garcovich,"Assessment of adrenocortical reserve in stable patients with cirrhosis," *Journal of hepatology*, vol. 54, no.2, pp. 243-250, 2011.

[22] C. Gluud, "Serum testosterone concentrations in men with alcoholic cirrhosis: background for variation," *Metabolism*, vol. 36, no.4, pp. 373-378, 1987.

[23] D. Van Thiel, S. Kumar, J. Gavaler and R. Tarter, "Effect of liver transplantation on the hypothalamic-pituitary-gonadal axis of chronic alcoholic men with advanced liver disease," *Alcoholism: Clinical and Experimental Research*, vol. 14, no.3, pp. 478-481, 1990.

[24] M. Sinclair, M. Grossmann, R. Hoermann, P. W. Angus, and P. J. Gow, "Testosterone therapy increases muscle mass in men with cirrhosis and low testosterone: a randomised controlled trial," *Journal of hepatology*, vol. 65, no.5, pp. 906-913, 2016.

[25] M. Grossmann, R. Hoermann, L. Gani, I. Chan, A. Cheung, P. J. Gow, A. Li, J. D. Zajac, and P. Angus, "Low testosterone levels as an independent predictor of mortality in men with chronic liver disease," *Clinical endocrinology*, vol. 77, no.2, pp. 323-328, 2012.

[26] D. Schwinge, A. Carambia, A. Quaas, T. Krech, C. Wegscheid, G. Tiegs, I. Prinz, A. W. Lohse, J. Herkel, and C. Schramm, "Testosterone suppresses hepatic inflammation by the downregulation of IL-17, CXCL-9, and CXCL-10 in a mouse model of experimental acute cholangitis," *The Journal of Immunology*, vol. 194, no.6, pp. 2522-2530, 2015.

[27] B. Als-Nielsen, W. Chen, C. Gluud, and L. L. Kjaergard, "Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events." *Jama*, vol. 290, no.7, pp. 921-928, 2003.

[28] E. Karagianni, C. Papazachos, D. Panagiotopoulos, P. Suhadolc, A. Vuan, and G. Panza, "Shear velocity structure in the Aegean area obtained by inversion of Rayleigh waves," *Geophysical Journal International*, vol. 160, no.1, pp. 127-143, 2005.

[29] S. K. Jha and S. Kannan, "Serum prolactin in patients with liver disease in comparison with healthy adults: A preliminary cross-sectional study," *International Journal of Applied and Basic Medical Research*, vol. 6, no.1, pp. 8, 2016.

[30] Z. Huang, Q. Yao, J. Zhu, Y. He, Y. Chen, F. Wu, and T. Hua, "Efficacy and safety of trans jugular intrahepatic portosystemic shunt (TIPS) created using covered stents of different diameters: A systematic review and meta-analysis," *Diagnostic and Interventional Imaging*, vol. 102, no.5, pp. 279-285, 2021.

[31] S. Taki, T. Sato, K. Ogasawara, T. Fukuda, M. Sato, S. Hida, G. Suzuki, M. Mitsuyama, E.-H. Shin, and S. Kojima, "Multistage regulation of Th1-type immune responses by the transcription factor IRF-1," *Immunity*, vol. 6, no.6, pp. 673-679, 1997.

[32] M. Kawaguchi, M. Takahashi, T. Hata, Y. Kashima, F. Usui, H. Morimoto, A. Izawa, Y. Takahashi, J. Masumoto, and J. Koyama, "Inflammasome activation of cardiac fibroblasts is essential for myocardial ischemia/reperfusion injury," *Circulation*, vol. 123, no.6, pp. 594-604, 2011.

[33] A. Eshraghian and A. H. Jahromi, "Non-alcoholic fatty liver disease and thyroid dysfunction: a systematic review," World journal of gastroenterology: WJG, vol. 20, no.25, pp. 8102, 2014.

[34] Y. Wu, S. You, H. Zang, H. Liu, Y. Mao, P. Mao, B. Zhu, J. Xu, G. Xie, and J. Guo, "Usefulness of serum thyroid-stimulation hormone (TSH) as a prognostic indicator for acute-on-chronic liver failure," Annals of Hepatology, vol. 14, no.2, pp. 218-224, 2015.

[35] A. Antonelli, C. Ferri, A. Pampana, P. Fallahi, C. Nesti, M. Pasquini, S. Marchi, and E. Ferrannini,"Thyroid disorders in chronic hepatitis C," *The American journal of medicine*, vol. 117, no.1, pp. 10-13, 2004.

[36] A. Antonelli, C. Ferri, P. Fallahi, A. Pampana, S. M. Ferrari, F. Goglia, and E. Ferrannini, "Hepatitis C virus infection: evidence for an association with type 2 diabetes," *Diabetes care*, vol. 28, no.10, pp. 2548-2550, 2005.

[37] X.-c. Liu, G.-d. He, K. Lo, Y.-q. Huang, and Y.-q. Feng, "The triglyceride-glucose index, an insulin resistance marker, was non-linear associated with all-cause and cardiovascular mortality in the general population," *Frontiers in cardiovascular medicine*, vol. 7, no.10, pp. 628109, 2021.

[38] A. Yadav, S. Arora, V. Saini, M. K. Arora, R. Singh, and J. Bhattacharjee, "Influence of thyroid hormones on biochemical parameters of liver function: a case-control study in North Indian population," *Internet Journal of Medical Update-EJOURNAL*, vol. 8, no.1, pp. 2013.

[39] P. Punekar, A. K. Sharma, and A. Jain, "A study of thyroid dysfunction in cirrhosis of liver and correlation with severity of liver disease," *Indian journal of endocrinology and metabolism*, vol. 22, no.5, pp. 645, 2018.

[40] N. Knudsen, P. Laurberg, L. B. Rasmussen, I. Bulow, H. Perrild, L. Ovesen, and T. Jørgensen, "Small differences in thyroid function may be important for body mass index and the occurrence

of obesity in the population," *The Journal of Clinical Endocrinology & Metabolism*, vol. 90, no.7, pp. 4019-4024, 2005.

[41] A. P. Delitala, G. Fanciulli, M. Maioli, and G. Delitala,"Subclinical hypothyroidism, lipid metabolism and cardiovascular disease," *European journal of internal medicine*, vol. 38, no.5, pp. 17-24, 2017.

[42] Y. Chen, C. Zhu, Y. Chen, N. Wang, Q. Li, B. Han, L. Zhao, C. Chen, H. Zhai, and L. Zhang, "Are thyroid autoimmune diseases associated with cardiometabolic risks in a population with normal thyroid-stimulating hormone?" *Mediators of Inflammation*, vol. 22, no.5, pp. 645-668, 2018.

[43] R. S. Mani, M. A. Amin, X. Li, S. Kalyana-Sundaram, B. A. Veeneman, L. Wang, A. Ghosh, A. Aslam, S. G. Ramanand, and B. J. Rabquer, "Inflammation-induced oxidative stress mediates gene fusion formation in prostate cancer," *Cell reports*, vol. 17, no.10, pp. 2620-2631, 2016.

[44] F. Gao, "Variation tendency of coagulation parameters in different hypothyroidism stages," *Acta Endocrinologica (Bucharest)*, vol. 12, no.4, pp. 450, 2016.

[45] J. R. Carvalho and M. V. Machado, "New insights about albumin and liver disease," *Annals of Hepatology*, vol. 17, no.4, pp. 547-560, 2018.

[46] H. L. Weng, Y. Liu, J. L. Chen, T. Huang, L. J. Xu, P. Godoy, J. H. Hu, C. Zhou, F. Stickel, and A. Marx, "The etiology of liver damage imparts cytokines transforming growth factor β1 or interleukin-13 as driving forces in fibrogenesis," *Hepatology*, vol. 50, no.1, pp. 230-243, 2009.

[47] S. Dooley and P. Ten Dijke,"TGF-β in progression of liver disease," *Cell and tissue research*, vol. 347, no.1, pp. 245-256, 2012.

[48] T. Liu, X. Wang, M. A. Karsdal, D. J. Leeming, and F. Genovese, "Molecular serum markers of liver fibrosis," *Biomarker insights*, vol. 7, no. 6, pp. 105-117, 2012.