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# Benefits of Levothyroxine Replacement Therapy in Subclinical Hypothyroidism Egyptian Patients with Chronic Hepatic Encephalopathy

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ORIGINAL ARTICLE

# Benefits of Levothyroxine Replacement Therapy in Subclinical Hypothyroidism Egyptian Patients with Chronic Hepatic Encephalopathy

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Abstract

*Background:* ***Subclinical hypothyroidism (SCH) is a condition marked by increased concentrations of thyroid-stimulating hormone (TSH) in the bloodstream, along with normal thyroxine (T4) and triiodothyronine (T3) concentrations.***

*Aims and objectives:* ***To assess the benefits of levothyroxine replacement treatment in SCH cases with chronic hepatic encephalopathy (HE),***

*Patients and methods:* ***This comparative research was performed on 50 Egyptian cases aged 18–65 with SCH and chronic HE, separated into two groups: Group I: 25 cases did not receiveLT4 replacement therapy, and Group II: 25 patients received LT4 replacement therapy chosen from the outpatient clinic of & admitted to the Internal Medicine department of Sayed Galal Hospital Al-Azhar University from May 2023 to November 2023.***

*Results:* ***Regarding liver function tests following six months, there was a statistically significant variance among Group I and Group II as regards aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT). Regarding thyroid function tests and lipid profile following six months, there was statistically significant variance among groups I and II with regard to TSH and HE grade and a highly statistically significant distinction with regard to ammonia and triglycerides (TGs). Regarding the Child-Pugh score and hepatic encephalopathy frequency following six months, there was a statistically significant distinction between groups I and II.***

*Conclusion:* ***SCH can trigger HE in cirrhotic individuals, which can lead to hyperammonemia and/or worsen ammonia brain toxicity. Thus, it is important to assess for hypothyroidism in patients with cirrhosis and refractory HE, especially when considering aggressive therapies.***

*Keywords:* SCH; HE; Levothyroxine

## 1. Introduction

Although the liver is commonly perceived as an organ unaffected by hormones, a complex correlation is present between the thyroid gland and the liver in both healthy and diseased states. This intricate interaction is essential for maintaining homeostasis at both locations. [1]

The liver is also a primary participant in the transport and metabolism of thyroid hormones. It also contributes to their activation and deactivation via deiodinase activity. The primary thyroid hormone-transport proteins , transthyretin (TTR) , thyroxine-binding globulin (TBG), and albumin, which supply a pool of rapidly exchangeable circulating thyroid hormone, are synthesized in the liver. During a single passage, the liver extracts 5–10 percent of plasma thyroxine, thereby influencing T4 plasma levels. Liver dysfunction may thus significantly influence the bioavailability of thyroid hormones. [2,3]

A condition known as hepatic encephalopathy (HE) causes brain dysfunction that arises from liver insufficiency and portosystemic shunting. Spanning a broad range of clinical manifestations involving altered consciousness, coma, and mild neuropsychological symptoms, HE is commonly accompanied by changes in behaviour, motor tone, and consciousness. [4,5,6]

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Subclinical hypothyroidism (SCH) is shown by normal levels of T4 and triiodothyronine (T3) in the blood. High levels of serum thyroid-stimulating hormone mark SCH. [7,8]

Because hypothyroidism exhibits similar clinical symptoms, including attention and memory disturbances, HE is considered a differential diagnosis. Concerning whether hypothyroidism precipitates or coexists with HE, nevertheless, little is known. [9]

Hypothyroidism can trigger HE in people with cirrhosis by causing hyperammonemia and worsening ammonia-induced brain damage. Therefore, it is crucial to assess hypothyroidism in patients with cirrhosis and refractory HE before initiating levothyroxine (LT4) replacement medication, especially if they are contemplating harsh therapies. [10,11]

The objective of this research was to assess the benefits of levothyroxine replacement therapy in SCH cases with chronic hepatic encephalopathy (HE).

## 2. Patients and methods

We conducted this comparative research on 50 Egyptian cases with SCH and chronic HE, aged 18–65. We divided them into two groups: Group I: Twenty-five cases did not receive LT4 replacement therapy, and Group II: Twenty-five patients received LT4 replacement therapy. We selected the study participants from the outpatient clinic and admitted them to the Internal Medicine department of Sayed Galal Hospital, Al-Azhar University, between May 2023 and November 2023.

Inclusion criteria: both sexes, age from 18 to 65, cases with Subclinical hypothyroidism (TSH more than five mU/L & normal free thyroxine (FT4), and chronic liver disease (CLD) with HE (West Haven Criteria).

Exclusion criteria: patients with overt hypothyroidism, age more than 65, and CLD without HE.

Ethics and patient consent: Every patient's consent was obtained, and all procedures conformed to the guidelines set forth by the ethical committee at Al-Azhar University.

Methods:

The two groups were exposed to thorough history taking with special emphasis on age, sex, autoimmune hepatitis, viral hepatitis, nonalcoholic fatty liver disease (NAFLD), hypothyroidism, chronic illness, family history of liver diseases (Hemochromatosis and Wilson), history of any specific treatment has been started, and clinical examination with special emphasis on stigmata of CLD (Ascites, Jaundice, Ecchymosis, Spider Naevi, HE).

Thyroid Profile: Following observing at least 10 hours of fasting, venous blood samples were collected from 8:00 to 10:00 a.m. The chemiluminescence methods of Cobas E601 (Roche, Basel, Switzerland) were utilized to measure the levels of serum-free triiodothyronine (FT3), FT4, and TSH. The reference levels for these methods were as follows: FT4 (0.70–1.70 ng/dl), TSH (0.35–5 uIU/ml), and FT3.

Ammonia level: The patient should be calm when having blood drawn into a 4 mL Ethylenediamine Tetraacetic Acid (EDTA) tube and sent on ICE by an adult, as venipuncture difficulties can lead to a spurious rise in ammonia levels. Transporting the sample to the laboratory on ice necessitates its separation within 15 minutes of collection and prompt analysis. It is of utmost importance to maintain blood samples at a low temperature following collection, as ammonia concentrations autonomously rise in standing blood and plasma. This increase has been predominantly. The primary cause of this increase is the production and discharge of ammonia from erythrocytes, along with the deamination of amino acids, specifically glutamine. Whole blood plasma ammonia concentrations maintained at 4 oC remain stable for less than one hour. Plasma ammonia concentrations remain stable at 4 C for 4 hours following prompt separation from blood and for 24 hours when frozen at -20 C (19–82 ug/dl). [12]

Imaging: The presence of cirrhosis in the liver is distinguished by alterations in volume distribution, widened porta hepatis and fissures, regenerative nodules, and an enlargement of the caudate lateral segments of the left and right lobes, respectively. In advanced cirrhosis, secondary findings associated with portal hypertension may manifest, such as fatty infiltration in the mesentery and omentum, varices, and ascites; gastrointestinal tract wall thickening because of venous congestion; and arteriovenous or arterioportal shunts within the liver; the liver may also exhibit a diminutive and nodular appearance. Cirrhosis is diagnosed on the basis of surface nodularity, increased echogenicity, and the presence of irregular zones. People predominantly observe right lobe atrophy, while caudate or left lobe hypertrophy is more prevalent. Enlarged spectral regions and constriction of the hepatic vein Doppler waves distinguish Cirrhosis.[13] Attenuation occurs in the phasic oscillations of hepatic venous flow. The hepatic vein's normal physicality indicates a pressure shift in the right atrium during the cardiac cycle. In liver cirrhosis, the phasicity of the hepatic vein is decreased because of decreased liver flexibility and narrowed venous segments generated by nearby regenerating nodules. Bypass collateral veins appear to cause changes in the direction of blood flow away from the liver and result in a decrease in the diameter of the portal vein to lower than one centimetre. At first, the portal vein exhibits a dilation of almost 1.4 cm. A big arteriovenous shunt or arterioportal

shunt lowers the hepatic artery's resistance. Without it, the artery would have a high resistive index. [14]

## 3. Results

Table 1 shows that the mean age among group I was 48.5± 17.2 and 47.9± 19.2 among group II. There wasn't statistically significant distinction among both groups regarding age. According to gender, there were 72% men and 28% women in group I, while there were 60% men & 40% women in group II, with no statistically significant distinction among both groups regarding gender. (Table 1)

*Table 1. Comparison among Group I & Group II concerning age and gender.*

| VARIABLES | GROUP I | GROUP II | TEST VALUE | P VALUE |
|---|---|---|---|---|
| AGE<br>MEAN± SD | 48.5± 17.2 | 47.9± 19.2 | 0.251 | 0.802[1] |
| GENDER<br>MALE N (%)<br>FEMALE N (%) | 18 (72%)<br>7 (28%) | 15 (60%)<br>10 (40%) | 3.264 | 0.085[2] |

P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

Table 2 showed that there wasn't statistically significant variance among Group I & Group II concerning liver function tests at baseline (AST, ALT, T. Bill, D.Bill, Alb, ALP, GGT, INR and PT)

*Table 2. Comparison among Group I & Group II concerning Liver function tests at baseline*

| | Baseline | Group I | Group II | Test-value | P-value | Sig. |
|---|---|---|---|---|---|---|
| | | No.=25 | No.=25 | | | |
| AST | Median(IQR) | 38 (27-52) | 43 (29-58) | -0.563‡ | 0.573 | NS |
| | Range | 15 - 69 | 17 - 210 | | | |
| ALT | Median(IQR) | 43 (35-57) | 47 (37-57) | -1.023‡ | 0.311 | NS |
| | Range | 19 - 78 | 26 - 102 | | | |
| T.Bill | Median(IQR) | 0.9 (0.6-1) | 0.9 (0.6-1.2) | -0.264‡ | 0.792 | NS |
| | Range | 0.4 - 1.3 | 0.4 - 2.3 | | | |
| D.Bill | Median(IQR) | 0.4 (0.4-0.6) | 0.5 (0.4-0.7) | -0.738‡ | 0.461 | NS |
| | Range | 0.2 - 0.9 | 0.2 - 1.8 | | | |
| ALb | Mean±SD | 3.17 ± 0.33 | 3.01 ± 0.31 | 1.791• | 0.080 | NS |
| | Range | 2.5 - 3.8 | 2.4 - 3.5 | | | |
| ALP | Mean±SD | 107.4 ± 32.42 | 110.64 ± 29.11 | -0.372• | 0.712 | NS |
| | Range | 33 - 160 | 54 - 203 | | | |
| GGT | Median(IQR) | 49 (46-65) | 53 (47-59) | -0.165‡ | 0.869 | NS |
| | Range | 25 - 120 | 34 - 99 | | | |
| INR | Mean±SD | 1.21 ± 0.37 | 1.09 ± 0.2 | 1.417• | 0.163 | NS |
| | Range | 0.8 - 2.3 | 0.8 - 1.4 | | | |
| PT | Mean±SD | 13.16 ± 1.21 | 12.92 ± 0.81 | 0.822• | 0.415 | NS |
| | Range | 12 - 17 | 12 - 14 | | | |

Independent t-test; ‡: Mann-Whitney test

Table 3 showed that there wasn't statistically significant variance among Group I and Group II concerning thyroid function tests, lipid profile, ammonia level, and HE grade at baseline.

*Table 3. Comparison among Group I & Group II regarding thyroid function tests, lipid profile, Ammonia level and HE Grade*

| | Baseline | Group I | Group II | Test-value | P-value | Sig. |
|---|---|---|---|---|---|---|
| | | No.=25 | No.=25 | | | |
| TSH | Mean±SD | 9.19 ± 2.99 | 9.2 ± 2.23 | -0.021• | 0.983 | NS |
| | Range | 5.8 - 18 | 5.7 - 13.4 | | | |
| FT3 | Mean±SD | 2.97 ± 0.92 | 3.13 ± 1.15 | -0.543• | 0.590 | NS |
| | Range | 1.5 - 4.3 | 0.9 - 4.7 | | | |
| FT4 | Mean±SD | 1.26 ± 0.35 | 1.16 ± 0.37 | 1.014• | 0.316 | NS |
| | Range | 0.7 - 1.7 | 0.7 - 1.7 | | | |
| Ammonia | Median(IQR) | 153 (100-190) | 110 (96-205) | -1.116‡ | 0.264 | NS |
| | Range | 66 - 400 | 75 - 410 | | | |
| TGs | Mean±SD | 119.36 ± 40.49 | 112.56 ± 29.71 | 0.677• | 0.502 | NS |
| | Range | 53 - 220 | 55 - 190 | | | |
| Cholesterol | Mean±SD | 179.28 ± 65.64 | 163.84 ± 51.04 | 0.928• | 0.358 | NS |
| | Range | 67 - 310 | 67 - 260 | | | |
| HE Grade | Grade 1 | 11 (44%) | 10 (40.0%) | 4.518* | 0.104 | NS |
| | Grade 2 | 11(44%) | 6 (24.0%) | | | |
| | Grade 3 | 3 (12%) | 9 (36.0%) | | | |

Table 4 showed that regarding liver function tests following 6 months, there was a statistically significant variance among Group I & Group II as regard AST, ALT, T. Bill, D. Bill, Alb, and GGT, a highly statistically significant variance as regard INR and PT, and no statistically significant difference as regard ALP.

*Table 4. Comparison among Group I & Group II as regard Liver function tests after 6 months*

| | After 6 months | Group I | Group II | Test-value | P-value | Sig. |
|---|---|---|---|---|---|---|
| | | No.=25 | No.=25 | | | |
| AST | Median (IQR) | 40 (30-60) | 27 (25 - 38) | -2.508‡ | 0.012 | S |
| | Range | 15 - 220 | 17 – 94 | | | |
| ALT | Median (IQR) | 44 (35-70) | 35 (36 - 48) | -2.355‡ | 0.019 | S |
| | Range | 19 - 310 | 26 – 92 | | | |
| T.Bill | Median (IQR) | 1 (0.6-1.2) | 0.7 (0.4 - 0.9) | -2.580‡ | 0.010 | S |
| | Range | 0.4 - 9.6 | 0.4 – 1.2 | | | |
| D.Bill | Median (IQR) | 0.5 (0.4-0.8) | 0.4 (0.3 - 0.5) | -2.357‡ | 0.018 | S |
| | Range | 0.2 - 5.6 | 0.2 – 0.8 | | | |
| ALb | Mean± SD | 3.01 ± 0.31 | 3.23 ± 0.37 | -2.251• | 0.029 | S |
| | Range | 2.4 - 3.5 | 2.5 - 3.8 | | | |
| ALP | Mean± SD | 129.56 ± 64.71 | 104.76 ± 19.69 | 1.833• | 0.073 | NS |
| | Range | 33 - 370 | 54 - 158 | | | |
| GGT | Median (IQR) | 60 (48-97) | 49 (46-57) | -2.487‡ | 0.013 | S |
| | Range | 25 - 200 | 33 - 66 | | | |
| INR | Mean± SD | 1.43 ± 0.44 | 0.99 ± 0.18 | 4.650• | 0.000 | HS |
| | Range | 0.8 - 2.3 | 0.8 - 1.4 | | | |
| PT | Mean± SD | 13.64 ± 1.35 | 12.48 ± 0.65 | 3.867• | 0.000 | HS |
| | Range | 12 - 17 | 12 - 14 | | | |

Table 5 showed that regarding thyroid function tests, lipid profile, ammonia level, & HE grades following 6 months, There was statistically significant variance among Group I & Group II as regard TSH and HE grade, a highly statistically significant variance as regard ammonia, TGs, and cholesterol, and no statistically significant difference as regard FT3

and FT4.

*Table 5. Comparison among Group I & Group II concerning Thyroid Function tests & lipid profile after 6 months.*

| After 6 months | | Group I No.=25 | Group II No.=25 | Test-value | P-value | Sig. |
|---|---|---|---|---|---|---|
| TSH | Mean±SD | 9.20 ± 2.23↓↓ | 7.66 ± 1.93 | 2.612 • | 0.012 | S |
| | Range | 5.7 - 13.4 | 5.8 – 13.4 | | | |
| FT3 | Mean±SD | 2.97 ± 0.92 | 3.13 ± 1.15 | - 0.543 • | 0.590 | NS |
| | Range | 1.5 - 4.3 | 0.9 - 4.7 | | | |
| FT4 | Mean±SD | 1.26 ± 0.35 | 1.16 ± 0.37 | 1.014 • | 0.316 | NS |
| | Range | 0.7 - 1.7 | 0.7 - 1.7 | | | |
| Ammonia | Median(IQR) | 210 (140-287) | 97 (85-110) | - 4.177 ‡ | 0.000 | HS |
| | Range | 66 - 420 | 75 – 230 | | | |
| TGs | Mean±SD | 164.76 ± 65.5 | 106.28 ± 23.36 | 4.205 • | 0.000 | HS |
| | Range | 87 - 310 | 55 - 150 | | | |
| Cholesterol | Mean±SD | 223.12 ± 107.81 | 147.64 ± 44.38 | 3.237 • | 0.002 | HS |
| | Range | 67 - 480 | 67 - 240 | | | |
| HE Grade | Grade 1 | 7 (28.0%) | 11 (44.0%) | 8.435 * | 0.015 | S |
| | Grade 2 | 7 (28.0%) | 12 (48.0%) | | | |
| | Grade 3 | 11 (44.0%) | 2 (8%) | | | |

Table 6 showed a high statistically significant variance among Group I & Group II as regards the child-pugh score and hepatic encephalopathy frequency after 6 months and no statistically significant variance among Group I & Group II as regard the child-pugh grade after 6 months. Additionally, there wasn't statistically significant variance among Group I & Group II in terms of Child-Pugh grade, Child-Pugh score, and the frequency of hepatic encephalopathy at baseline.

*Table 6. Comparison among Group I & Group II regarding child-Pugh score and hepatic encephalopathy frequency at baseline and after 6 months among the studied patients*

| | | GROUP I No. = 25 | GROUP II No. = 25 | TEST VALUE | P-VALUE | SIG. |
|---|---|---|---|---|---|---|
| BASELINE | | | | | | |
| CHILD-PUGH GRADE | B | 22 (88.0%) | 18 (72.0%) | 2.000* | 0.157 | NS |
| | C | 3 (12.0%) | 7 (28.0%) | | | |
| CHILD-PUGH SCORE | Median (IQR) | 9 (8 – 9) | 9 (8 – 10) | -1.336≠ | 0.182 | NS |
| | Range | 7 – 10 | 8 – 11 | | | |
| HEPATIC ENCEPHALOPATHY FREQUENCY | Median (IQR) | 8 (7 – 8) | 8 (8 – 9) | -1.250≠ | 0.211 | NS |
| | Range | 5 – 11 | 5 – 12 | | | |
| AFTER 6 MONTHS | | | | | | |
| CHILD-PUGH GRADE | B | 18 (72.0%) | 23 (92.0%) | 3.388* | 0.066 | NS |
| | C | 7 (28.0%) | 2 (8.0%) | | | |
| CHILD-PUGH SCORE | Median (IQR) | 9 (9 – 10) | 8 (7 – 8) | -4.321≠ | 0.000 | HS |
| | Range | 7 – 12 | 7 – 11 | | | |
| HEPATIC ENCEPHALOPATHY FREQUENCY | Median (IQR) | 9 (8 – 9) | 7 (6 – 8) | -3.947≠ | 0.000 | HS |
| | Range | 6 – 11 | 5 – 10 | | | |

## 4. Discussion

Regarding the main characteristics of the enrolled patients, our results revealed that the mean age among Group I was 48.5± 17.2 and 47.9± 19.2 among Group II. There wasn't a statistically significant distinction among both groups regarding age. According to gender, 72% of the patients were men and 28% women in Group I, while 60% of the patients were men and 40% women in Group II. There wasn't a statistically significant variance among both groups regarding gender.

Regarding liver enzyme levels among the two studied groups, our study showed a significant (p-value = 0.012) decrease in the mean AST level. When comparing Group II to Group I and also the significant (p-value = 0.019) decreased ALT level in Group II when contrasted with Group I, those results were after six months of starting LT4 replacement therapy.

In agreement with our results, Liu et al.[11] This study utilized an open label, randomized, controlled design to evaluate the advantages of LT4 replacement treatment in individuals with SCH and chronic liver disease. There were 363 individuals in all, with 33 having substantial SCH and 330 having moderate SCH. As for liver enzymes, there wasn't a distinction in blood AST or alanine aminotransferase levels among the sub-LT4 Group and the subcontrol group at the start of the study (p > 0.05 for all). The patients with mild Subclinical hypothyroidism were split into two groups: the mild SCH-LT4 group, which had 181 patients who received LT4, and the mild SCH-control Group, which had 149 patients who did not receive any treatment.

Regarding hyperbilirubinemia among the two studied groups, our study showed statistically significant decreased T. bilirubin levels (p-value = 0.010) and D. bilirubin levels (p-value = 0.018) in Group II when contrasted with Group I. Those results were after six months of starting LT4 replacement therapy. Regarding cholestasis among the two studied groups, our study showed a statistically significant (p-value = 0.013) decreased GGT level in Group II. When comparing Group I, there is no statistically significant distinction (p-value =0.073) between the studied groups (Group I and Group II) regarding ALP; those results were after six months of starting LT4 replacement therapy.

In agreement with our results, Shatla and Faisal[15] revealed that the mean serum concentrations of GGT, total, and direct bilirubin decreased significantly throughout the twelve months of LT4 replacement therapy (p < 0.001), nevertheless not ALP (p = 0.073).

Our study revealed that, regarding serum albumin level, there was a statistically significant (p-value = 0.029) increased albumin level in Group II when compared to Group I after six months of starting LT4 replacement treatment.

As opposed to our findings, Bruinstroop et al.[16] a multicenter, single-arm study designed to assess the benefits of LT4 treatment in cases with

type 2 DM & CLD with 30 patients enrolled in it, revealed a non-significant change in serum albumin level over six months of observation under treatment with LT4 with a P-value of 0.804.

Our research revealed, regarding coagulopathy, a highly statistically significant (p-value = 0.000) decreased INR level in Group II when contrasted with Group I and a highly statistically significant (p-value = 0.000) decreased PT level in Group II when compared to Group I after six months of starting LT4 replacement therapy.

Our results were supported by a case report documented by Díaz-Fontenla et al.[17] which revealed an improvement in serum INR level over one year from 1.18 to 1.14.

Our study revealed that after six months, there was a greatly statistically significant (p-value = 0.000) decrease in TGs and cholesterol levels in Group II compared to Group I.

Consistent with our study, Liu et al.[11] in relation to serum lipids, individuals who received treatment with LT4 exhibited a more significant reduction in serum TC in comparison to those who did not receive treatment. While serum TG and HDL-C did not significantly suffer from LT4, serum LDL-C and non-HDL-C displayed a similar decline trend.

Our study revealed that, regarding thyroid function tests, there was a statistically significant (p-value = 0.012) decreased TSH level in Group II compared with Group I after six months.

In support of our study, Díaz-Fontenla et al.[17] revealed an improvement in TSH levels from 69.86 to 2.66 mIU/l.

However, in comparison between the two groups after six months, there is no statistically significant difference among the studied groups (Group I & Group II) with regard to FT3 (p-value =0.590) & FT4 (p-value = 0.316).

Liu et al.[11] attained Thyroid Function Normalization: In comparison to the baseline level, the TSH level decreased significantly, and the FT4 level elevated significantly ($p < 0.05$ for all of these variables). Serum FT4 levels remained constant in the mild Subclinical hypothyroidism -control group for the duration of the investigation. Despite a gradual decline towards the conclusion of the research, the serum TSH level in the mild Subclinical hypothyroidism -control group remained above the established normal range of 0.27–4.2 mIU/L. No significant change in serum FT3 was observed in any of the groups over the course of the research.

Our study revealed that in comparison between the two groups after six months, there was a highly statistically significant (p-value = 0.000) decreased ammonia level in Group II. When comparing to Group I, Díaz-Fontenla et al.[17] revealed an improvement in serum ammonia levels over one year from 62 mol/L to 23 mol/L.

Our study revealed that, after six months, statistically significant (p-value = 0.015) improved HE grades in Group II were observed compared with Group I. There was also an improvement in the Child-Pugh score and a decrease in the frequency of hepatic encephalopathy in Group II in the 6-month follow-up period after administration of LT4 replacement therapy.

Our results have been supported by Díaz-Fontenla et al.[17] who revealed a dramatic improvement in hepatic encephalopathy grades and frequency after proper control of elevated TSH in hypothyroid patients with HE.

Limitations: This research was limited by a small sample size, a small geographical scale, and a short period of follow-up.

### *4. Conclusion*

Our study showed that chronic liver illness is associated with a higher incidence of SCH. Cirrhotic patients may develop HE as a result of hyperammonemia induced by SCH and/or an increase in ammonia brain toxicity. Cases with cirrhosis and refractory HE should, therefore, be assessed for hypothyroidism, especially when aggressive treatment options are being considered.

## Disclosure

The authors have no financial interest to declare in relation to the content of this article.

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All authors have a substantial contribution to the article

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## Conflicts of interest

There are no conflicts of interest.

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