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Original Article

Association of TSH Levels in the Therapeutically Neglected Range of 6.5–8 mIU/L with Significant Changes in Liver and Kidney Function: A Retrospective Study of the Kashmiri Population

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Abstract

Background: The thyroid gland secretes hormones crucial for growth, differentiation, regulation of metabolic processes, and homeostasis. In response to underactivity of this gland, the pituitary secretes thyrotropin, also known as the thyroid-stimulating hormone (TSH). Medication for thyroid hypofunction is usually started when TSH levels exceed 10 mIU/L. However, we hypothesize that TSH levels much below this therapeutic threshold level may herald significant renal and hepatic dysfunction. The present study was thus conducted to assess liver and kidney function parameters in cases having TSH in the subclinical range with particular focus on the therapeutically neglected (6.5–8 mIU/L) range.

Methods: Hospital laboratory archives of 297 adults with laboratory evidence of hypothyroidism, that is, TSH > 6.5 mIU/L, were retrieved and compared with data obtained from 430 euthyroid hospital controls, that is, TSH < 2.5 mIU/L, also from the same period. The thyroid profile and clinical chemistry analyses were performed on Beckman Coulter's UniCel DxI 800 and AU 5800, respectively. SPSS version 20 was used to analyze the results.

Results: Significant differences in triiodothyronine (T3), thyroxine (T4), TSH, urea, creatinine, total bilirubin, total protein (TP), and liver enzymes were observed between cases with TSH > 6.5 mIU/L and controls ($P < 0.05$). There was also a significant difference in T4, TSH, urea, creatinine, total bilirubin, albumin and aspartate aminotransferase (AST) among cases with TSH in the range of 6.5–8 mIU/L when compared with controls ($P < 0.05$). A correlation of T3 with TSH, urea, and creatinine was seen ($P < 0.05$). No correlations between TSH and other clinical chemistry parameters could be observed. However, in the 6.5–8 mIU/L subgroup, correlation of TSH was seen with TP and albumin only.

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Conclusion: Authors found that, as a rule, subtle renal and hepatic dysfunction were established in cases with TSH levels <8 mIU/L, which was below the typical "therapeutic cut-off" of 10 mIU/L. Accordingly, we advocate against incautiousness and suggest regular monitoring, especially in the 6.5–8 mIU/L range.

Keywords: subclinical hypothyroidism, liver function test, kidney function test, thyroid-stimulating hormone

1. Introduction

Thyroid hormones (THs), namely Thyroxine (T4) and 3, 5,3I L-tri-iodothyronine (T3), secreted by the thyroid gland following synthesis from the amino acid tyrosine in the thyroid follicles act as the "master regulators," exerting a profound influence on almost every cell of the body by "canonical" and "non-canonical" mechanisms [1]. THs are crucial for regulating protein, carbohydrate, and fat metabolism. They are essential for the general processes of metabolism, development and growth, which they accomplish through various genomic as well as non-genomic routes. Of particular importance is the action of THs on the liver, where they actively modulate glucose, cholesterol, and fatty acid metabolism and stimulate de-novo lipogenesis. These hepatic actions have a bearing on basal energy expenditure, thermogenesis, and metabolic homeostasis [2]. THs act on kidneys where they regulate the renal hemodynamics by direct mechanisms and by modulating ion transport in the glomerular and tubular cells. THs also affect the organs above by influencing the cardiac output.

Hypothyroidism adversely affects cardiac contractility, myocardial oxygen consumption, vascular resistance, blood pressure, and electrophysiological conduction. As THs have genomic effects, any reduction in their concentrations result in decline of translational products involved in myocardial contractility, endothelial vasodilation, and renin synthesis. Response to β-adrenergic stimulus is also downgraded. This has a profound impact on the renal milieu [3].

Certain studies have hinted at histological changes in hypothyroidism. Several observational studies have shown that elevated thyroid-stimulating hormone (TSH) levels are significantly associated with the development of non-alcoholic fatty liver disease (NAFLD). This can be partly explained by the steatogenic changes induced by an underactive thyroid. Modulation of signal transduction pathways, impairment in lipid metabolism, increased de-novo lipogenesis, and upregulation of reactive oxygen

species (ROS) and inflammatory cytokines can all be triggered by disturbances in thyroid function [4].

Hypothyroidism and hyperthyroidism indicate underactivity and overactivity of the thyroid gland, respectively [5]. Subclinical hypothyroidism (SCH) is a laboratory diagnosis wherein TSH levels are higher than normal, while levels of T3 and T4 remain in the normal range.

Hypothyroidism is the most prevalent among thyroid disorders in South Asia and especially so in the northern Himalayan states of India, where iodine deficiency has been a historical concern. Coastal Indian cities have a lower prevalence of hypothyroidism (both SCH and overt) than northern inland territories. In fact, a north Indian study suggested that the prevalence of SCH could be as high as 19.3% [6].

Of late, questions on thyroid gland underactivity have been arising, primarily whether cases of TH values falling marginally outside of normal limits should be pharmacologically addressed, or is overprescription of T4 for the treatment of these "laboratory derangements" a genuine concern in that, are we treating the lab reports or the patient themselves?[7]. SCH is usually characterized by laboratory evidence of increased TSH (5–10 mIU/L or more) along with average T4 values. Older studies did not provide sufficient evidence for the benefits of treatment at TSH values of 4.5–10 mIU/L [8]. In fact, treatment was only recommended for TSH values higher than the threshold value of 10 mIU/L [9]. A comprehensive perusal of recent studies shows that levothyroxine is generally prescribed only in manifest hypothyroidism. Therapy for SCH is usually discouraged unless TSH values exceed 10 mIU/L [10]. However, there is a possibility that undue focus on the 10 mIU/L threshold may potentially leave out many who are otherwise worthy of the medication. Specific ailments, such as psychiatric disorders [11], unexplained infertility [12], and metabolic syndrome may have a thyroid basis. Pathological alterations in crucial analytes as seen in hyperinsulinemia, insulin resistance, dyslipidemia, hypercoagulability, cardiovascular status (as gauged by elevated hsCRP), and hyperuricemia are often closely related to thyroid function. These alterations may manifest themselves even at TSH levels <10 mIU/L [13]. In many such cases, despite mid- to high-normal TSH values, subtle thyroid dysfunction is evident beyond doubt. Evidently, there is a possibility of the setting in of indiscreet biochemical changes which may benefit from early therapy. All these questions lend more weight to the concept of individualized assessment of thyroid function status [5]. Some persons may not have any (obvious) symptoms, and clues obtained from measuring biochemical parameters despite borderline TH measurements may herald a less than assuring prognosis. In

such persons, therapy initiation at high-normal to moderately raised TSH levels may provide both tangible and intangible benefits.

1.1. Renal effects of thyroid hypofunction

The thyroid influences both the kidney and liver (Figure 2). Bulur *et al.* observed that T4 therapy in previously hypothyroid patients caused renal function to improve significantly as the raised creatinine and TSH levels normalized. They also attributed the raised creatinine levels in hypothyroidism to a reduction in GFR and renal plasma flow. This was in turn due to a "hypodynamic state" of the circulatory system in addition to the lack of TH-induced inotropic and chronotropic stimulus. Creatinine was thus not cleared from the circulation in such individuals with the same vigor as seen in euthyroid individuals [14]. Either that or actual effects on glomerular physiology or both may be the reason for creatinine elevation. Animal studies on hypothyroid rats showed histological evidence of a reduction in glomerular capillary density, which indicated a pro-angiogenic role for THs [15]. These hormones may also be instrumental in increasing vascularity. In addition, they exert an activatory effect on the renin–angiotensin system (RAS), both with and without the involvement of the sympathetic nervous system. In a study by Ichihara *et al.*, T3 was found to increase renin secretion and renin mRNA in juxtaglomerular cell cultures by calcium-dependent and independent mechanisms [16]. Certain indirect (endocrine/paracrine) effects mediated via signal proteins like vascular endothelial growth factor (VEGF) and insulin-like growth factor type 1 (IGF-1) are also contributory to the renal effects seen in SCH [17].

1.2. Hepatic effects of thyroid hypofunction

Historically, the liver has always been an indispensable organ for medical research. It is probably the most influenced by the thyroid. Preliminary studies on rat liver and kidneys during the early second world war period revealed that the administration of T_4 and TSH had definitive effects on tissue respiration and organ weight, with the former hormone consistently elevating the oxygen consumption rates (QO_2) as compared to the latter [18]. The effect of TH perturbations on liver function was demonstrated in another study during the cold war period, utilizing electrophoresis. The said study showed alterations in serum protein patterns in thyroid disorders, with hypothyroid patients exhibiting lower albumin levels and elevated β globulin fractions. Treatment with T4, however, tended to reduce levels of both these fractions [19]. A seminal work

on biochemical changes underlying cellular differentiation during T_3-induced metamorphosis in tadpoles observed a significant increase in specific activities of liver nucleic acids and proteins when administered the TH. The Liver RNA: DNA ratio also increased indicating active transcription triggered by T_3 [20]. The same year, while studying the effect of T_3 on the growth of the liver in thyroidectomized rats, an Indian researcher, Jamshed Tata, observed accelerated incorporation of amino acids into nuclear protein. He also reported an increased turnover of basic nuclear proteins [21]. An early animal experiment to assess the role of THs on hepatic metabolism revealed an increased efficiency in lactate utilization in hypothyroid rats administered T_3. The sensitivity to glucagon improved and gluconeogenesis was also found to be markedly enhanced. The gluconeogenic enzyme pyruvate carboxylase appeared to be highly responsive to T_3. The latter hormonewas also effective in reducing urea formation. Redox equilibrium of the perfused hypothyroid liver, which showed a more reduced state, possibly due to underutilization of NADH in gluconeogenesis, was normalized by the administration of T_3[22].

In the early 1970s, the pioneer of TH action, J.H. Oppenheimer, identified high-affinity receptors for T_3 in nuclei of rat liver and kidney [23]. In one of the earliest reviews on TH action, he mentioned that the interaction of T_3 (and to a much lesser extent T4) with the receptors resulted in significant modulation of gene activity. Enzymes vital to carbohydrate and lipid metabolism, such as α-glycerophosphate dehydrogenase and malic enzyme, were particularly affected by T_3(by that time, they were already being used as resourceful indices for studying the hormone's effects in rat liver). The rat liver tissue had a high binding capacity and a larger number of binding sites per nucleus compared to several other organs [24]. The liver affects circulating TH concentrations as well. Carrier proteins that bind T4 and transport it to different targets in the body are synthesized and degraded by the liver. Only 0.04% of T4 circulates freely. Most of it is complexed with TH carrier proteins like thyroxine-binding globulin (TBG), thyroxine-binding pre-albumin (TBPA), albumin, and other plasma proteins. The hepatocyte thus represents a central control point. Peripheral deiodination is also accomplished by deiodinases which synthesized in the liver. The liver–thyroid relationship is thus a two-way interaction [25].

The purpose of this study was to assess derangements in routine liver and kidney biochemical parameters in subclinical and overt hypothyroidism with respect to controls. Special attention was paid to the analysis of such derangements in the therapeutically neglected TSH range of 6.5–8 mIU/L. We also attempted to determine the correlation between T3, T4, TSH levels and these parameters.

2. Materials and Methods

2.1. Study population

Hospital laboratory archives of adult OPD patients visiting SKIMS (Sher-i-Kashmir Institute of medical sciences) Medical College and Hospital, Srinagar, Jammu & Kashmir, India between January 2017 and March 2021 were accessed and scanned for all records with laboratory evidence of hypothyroidism, that is, TSH > 6.5 mIU/L (including mild/significant SCH and OH). After several rounds of exclusion, records of 297 adults (78 males [26.26%] and 219 females [73.74%]) were retrieved and compared with data obtained from 430 euthyroid hospital controls, that is, TSH < 2.5 mIU/L (57 males [13.26%] and 373 females [86.74%]), also from the same period.

2.2. Inclusion and exclusion criteria

Adults of either sex were included. Those with a history of thyroid surgery or use of T4, amiodarone, or lithium were excluded. We also excluded all records with TSH levels between 2.51 and 6.49 mIU/L or <0.5 mIU/L for both cases and controls. The scheme of enrollment of data is given in Figure 1.

2.3. Data collection methodology

The authors' laboratory currently uses a reference range for TSH of 0.45 to 6.0 mIU/L. Thus, 4997 lab archives with adequate quality control (QC) results were retrospectively scanned, and data of all individuals with TSH levels > 6.5 mIU/L were considered. After exclusion, it was narrowed down to 297 records. These included routine LFT (n = 281) and KFT (n = 297) records. Cases were divided into two groups for statistical analysis. The first group had TSH in the "therapeutically neglected" range of 6.5–8 mIU/L (n = 44 for LFT and n = 48 for KFT), while the second group had TSH in the "therapeutically important" range of >8 mIU/L (n = 237 for LFT and n = 249 for KFT). Hospital controls were used, also from the lab archive database, wherein data having TSH in the range of 0.5–2.5 mIU/L (n = 430) were selected.

2.4. Protocol and procedure

All retrospective records we obtained were of patients who, as per routine protocol, were advised to report for sampling after an overnight fast. A single blood draw was used to

obtain a 4–6 mL venous blood sample and divided into two aliquots immediately post phlebotomy. One aliquot was sent to the biochemistry laboratory, and another aliquot was sent to the immunology section, which performs the thyroid panel. Immediately after receipt of the aliquots, centrifugation for 5 min at 3000 g was performed. Serum was subsequently separated. While the biochemistry aliquots were immediately processed and analyzed after a brief (15–30 min) delay to allow for data entry, the thyroid panel aliquot was subject to a moderate (30–60 min) delay for sufficient batch size to form and then processed. Generally, the average turnaround time (TAT; from sample registration to report authentication) of biochemistry samples is in the 60–120 min range, while thyroid panel TAT averages around 120–180 min. Different technical staff performed the analyses of each aliquot and results were automatically uploaded on the hospital LAN (local area network).

2.5. Measurement of T3, T4, and TSH

T3, T4, and TSH (3^{rd} gen) levels were estimated on Beckman Coulter's UniCel DxI 800 Access Immunoassay System. This analyzer utilizes chemiluminescent detection and magnetic particle-separation technology. Reference intervals provided by the manufacturer were TSH 0.45–5.33 mIU/L for TSH, 0.87–1.78 ng/ml for T3, and 6.09–12.23 µg/dl for T4. The sensitivities of TSH, T3, and T4 were 0.01 mIU/L, 0.1 ng/mL, and 0.50 µg/dL, respectively.

2.6. Measurement of biochemical parameters

The biochemical parameters, namely urea, creatinine, total bilirubin, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) were examined on Beckman Coulter's AU5800 clinical chemistry system. This analyzer is based on the principles of spectrophotometry and potentiometry.

2.7. Quality control

Apart from stringent daily maintenance and calibration protocols, internal controls for clinical chemistry and immunoassay parameters provided by Bio-rad® laboratories were run at least twice daily. Any nonconformity or errors reported were investigated and root cause analysis performed. Outliers or results exceeding linearity were subject to repeat

testing with suitable dilution. The intraassay coefficients of variation (CV) for T3, T4, and TSH were <10%. The clinical chemistry parameters also had acceptable CVs (Table 1).

2.8. Statistical analysis

The recorded data were compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean ± SD, and categorical variables were summarized as frequencies and percentages. The Student's independent *t*-test was employed for comparing continuous variables. Karl Pearson's correlation coefficient was applied to determine the correlation of TSH, T3 and T4 with various parameters among study cases. A *P*-value of < 0.05 was considered statistically significant. All *P*-values were two-tailed.

3. Results

In the present study, on comparison of liver and kidney function parameters, it was found that the total bilirubin, total protein, globulin, liver enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP), urea and creatinine were significantly elevated in the cases which had TSH > 6.5 mIU/L when compared to the controls (Table 2). The same effect was seen when comparing the group with TSH > 8 mIU/L to controls (Table 3). Albumin levels were not statistically different in the cases vis-à-vis controls. Globulin levels were higher nonetheless, and this resulted in lower A/G ratios in the cases. However, on comparing cases with TSH levels in the 6.5–8 mIU/L range to controls, we found that the total protein, ALT and ALP ceased to show a statistically significant difference. At the same time, albumin and the other LFT and KFT parameters remained significantly elevated (Table 4). Thus, the rise in urea, creatinine, total bilirubin, albumin, globulin, and AST appears to have established itself in this "therapeutically neglected" range, even though T3 and T4 levels, despite being significantly lower, were still mainly in the normal to low normal range. No significant correlations were found between TSH/T4 and any biochemical parameter. Nonetheless, we did find a significant correlation between serum T3 and urea, creatinine ($P =< 0.001$), and a moderately significant correlation between serum T3 and ALP ($P = 0.059$). Interestingly, when we limited the analysis to TSH in the range of 6.5–10, we found a significant correlation between TSH on the one hand and total protein ($P = 0.004$), albumin ($P = 0.013$) on the other. Urea levels also showed a

moderate correlation in this TSH range ($P = 0.086$) (Table 5). Thus, the fluctuations in TSH levels observed in individuals within this range may be accompanied by corresponding changes in the above parameters.

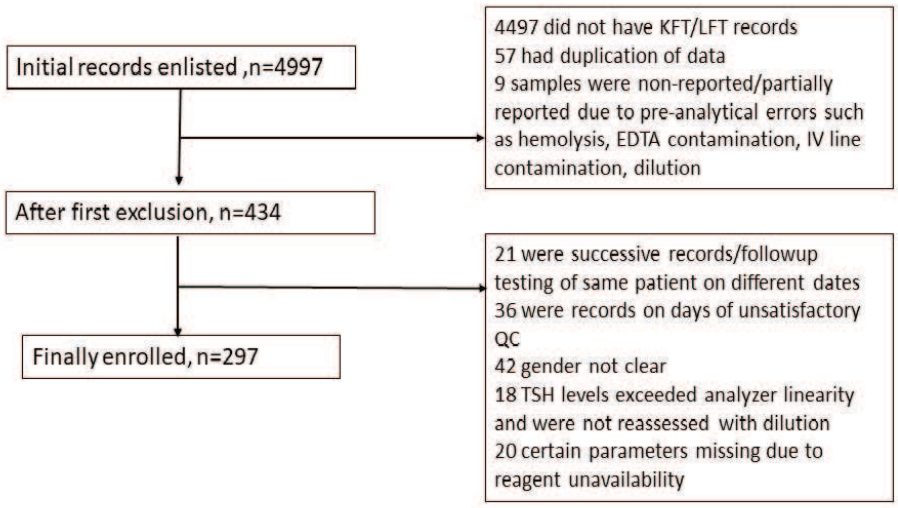

Figure 1: Scheme of data enrollment.

TABLE 1: Assay specifications of hepatic and renal parameters.

Analyte	Method	Reference range	Sensitivity	Intra-assay CV
Urea	Adaptation of the enzymatic method utilizing glutamate-dehydrogenase (GLDH)	17–43 mg/dL	5 mg/dL	≤5%
Creatinine	Kinetic modification of the Jaffe procedure	0.6–1.3 mg/dL	0.2 mg/dL	≤3%
Total bilirubin	3,5-dichlorophenyldiazonium tetrafluoroborate (DPD) modification of Diazo method	0.3–1.0 mg/dL	0.01 mg/dL	≤3%
Total protein	Weichselbaum modification of biuret	6.4–8.9 g/dL	3 g/dL	≤3%
Albumin	Modification of Doumas and Rodkey Bromocresol green method	3.5–5.7 g/dL	1.5 g/dL	≤3%
AST	Modification of the International Federation of Clinical Chemistry (IFCC) method	13–39 U/L	3 U/L	≤10%
ALT	Wroblewski and LaDue modification of the International Federation of Clinical Chemistry (IFCC) method	7–52 U/L	3 U/L	≤10%
ALP	Bowers and McComb method	30–120 U/L	5 U/L	≤10%

4. Discussion

We found substantial derangements in almost all of the recorded kidney and liver function parameters in those with TSH > 6.5 mIU/L. Most of these derangements

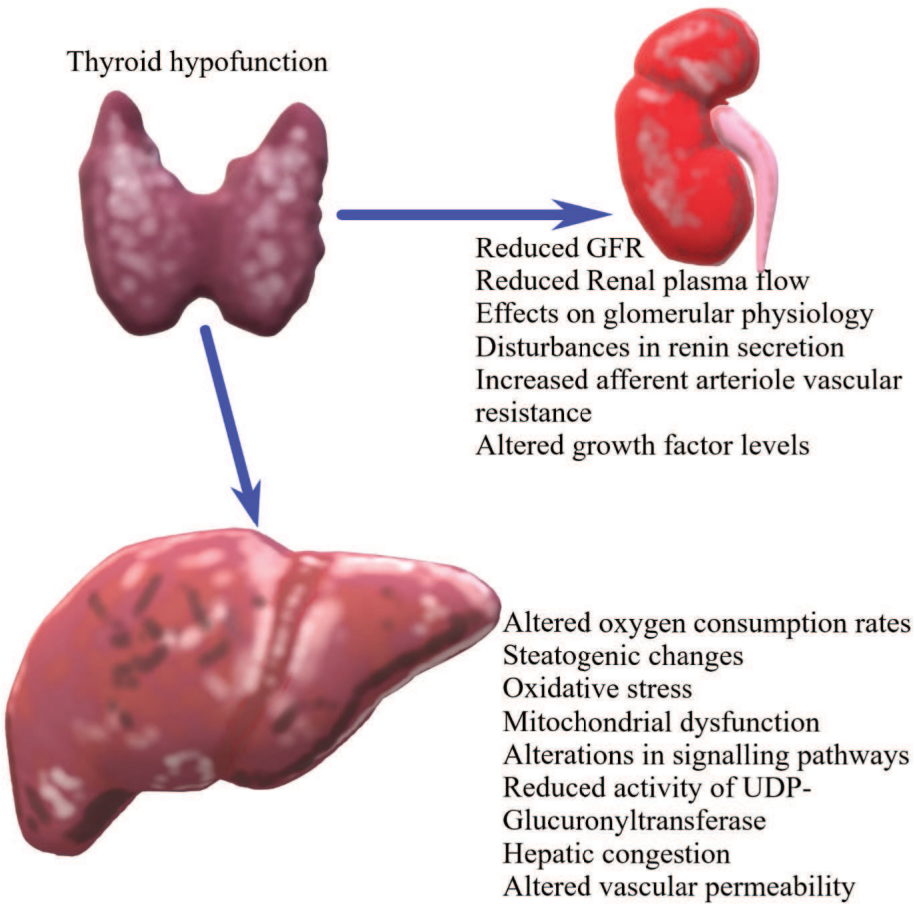

Figure 2: Underlying mechanisms for the effects of thyroid hypofunction on the liver and kidney.

were evident even at TSH levels <8 mIU/L. We could also establish a significant negative correlation between Tri-iodothyronine levels and the renal function markers. Liver function indicators such as total bilirubin, albumin, globulin, some of the liver enzymes, as well as kidney function parameters were affected even in the narrow TSH range of 6.5–8 mIU/L. In the 6.5–10 mIU/L range, the presence of significant correlations between TSH levels and total protein, albumin, and urea were evident. Thus, TSH levels far below the conventional "therapeutic boundary" of 10 mIU/L were often associated with laboratory evidence of incipient organ impairment.

Our findings compare with the Indian study by Arora *et al.*, who reported significantly higher levels of creatinine (albeit not exceeding the reference range) in hypothyroid subjects compared to euthyroid controls ($P < 0.001$) and also with another Indian study by Yadav *et al.* which observed significantly raised serum ALT, ALP, and total protein levels in SCH subjects (TSH 6–9.9 mIU/L) [26, 27]. A third Indian study by Saini *et al.* demonstrated higher urea and creatinine levels in SCH and OH patients than controls

Table 2: Comparison of LFT parameters in cases and controls.

Parameter	Cases (TSH > 6.5) (n = 281)		Controls (TSH < 2.5) (n = 425)		P-value
	Mean	SD	Mean	SD	
T3	1.20	0.53	1.41	0.35	<0.001*
T4	8.41	2.31	10.09	1.95	<0.001*
TSH	16.73	39.58	1.70	0.51	<0.001*
Total bilirubin	0.74	0.43	0.59	0.28	<0.001*
TP	7.65	0.72	7.44	0.52	<0.001*
Albumin	4.09	0.59	4.08	0.50	0.822
Globulin	3.57	0.56	3.371	0.39	<0.001*
A/G ratio	1.17	0.26	1.23	0.21	0.002*
AST	37.22	25.90	30.95	15.78	<0.001*
ALT	37.03	36.53	31.57	24.17	0.017*
ALP	124.62	55.52	115.25	65.73	0.035*
Comparison of KFT parameters in cases and controls					
Parameter	**Cases (TSH > 6.5) (n = 297)**		**Controls (TSH < 2.5) (n = 430)**		**P-value**
	Mean	**SD**	**Mean**	**SD**	
Urea	26.45	11.04	19.71	8.55	<0.001*
Creatinine	0.74	0.39	0.51	0.19	<0.001*

Table 3: Comparison of LFT parameters in cases with TSH > 8 and controls.

Parameter	Cases (n = 237)		Controls (TSH < 2.5) (n = 425)		P-value
	Mean	SD	Mean	SD	
T3	1.18	0.51	1.41	0.35	<0.001*
T4	8.37	2.41	10.09	1.95	<0.001*
TSH	18.39	42.69	1.70	0.51	<0.001*
Total bilirubin	0.72	0.42	0.59	0.28	<0.001*
TP	7.68	0.72	7.44	0.52	<0.001*
Albumin	4.13	0.60	4.08	0.50	0.311
Globulin	3.57	0.583	3.371	0.39	< .001*
A/G ratio	1.11	0.2	1.23	0.21	0.02*
AST	37.21	23.49	30.95	15.78	<0.001*
ALT	38.16	38.34	31.57	24.17	0.007*
ALP	126.89	58.24	115.25	65.73	0.023*
Comparison of KFT parameters in cases with >8 mIU/L and controls					
Parameter	**Cases (TSH > 8) (n = 249)**		**Controls (TSH < 2.5) (n = 430)**		**P-value**
	Mean	**SD**	**Mean**	**SD**	
Urea	27.16	11.35	19.71	8.55	<0.001*
Creatinine	0.75	0.41	0.51	0.19	<0.001*

[17]. Arora *et al.*, however, reported no significant differences in urea levels of cases and controls. They reported a positive correlation between serum TSH on the one

Table 4: Comparison of LFT parameters in cases with TSH 6.5–8 mIU/L and controls.

Parameter	Cases (n = 44)		Controls (TSH < 2.5 mIU/L) (n = 425)		P-value
	Mean	SD	Mean	SD	
T3	1.32	0.60	1.41	0.35	0.211
T4	8.63	1.64	10.09	1.95	<0.001*
TSH	7.25	0.48	1.70	0.51	<0.001*
Total bilirubin	0.85	0.49	0.59	0.28	<0.001*
TP	7.46	0.71	7.44	0.52	0.803
Albumin	3.90	0.49	4.08	0.50	0.022*
Globulin	3.55	0.46	3.371	0.39	.00588*
A/G ratio	1.11	0.2	1.23	0.21	0.00416*
AST	37.28	36.84	30.95	15.78	0.035*
ALT	30.83	23.67	31.57	24.17	0.847
ALP	111.76	34.26	115.25	65.73	0.735
Comparison of KFT parameters in cases with TSH 6.5–8 mIU/L and controls					
Parameter	**Cases (n = 49)**		**Controls (TSH < 2.5 mIU/L) (n = 430)**		**P-value**
	Mean	**SD**	**Mean**	**SD**	
Urea	22.72	8.38	19.71	8.55	0.022*
Creatinine	0.70	0.27	0.51	0.19	<0.001*

Table 5: Correlation of TSH with various parameters among study cases for TSH values 6.5–10 mIU/L.

Parameter	Pearson correlation	P-value
T3	0.352	<0.001*
T4	–0.382	<0.001*
Urea	0.142	0.084
Creatinine	0.041	0.619
Total bilirubin	–0.095	0.295
Total protein	0.242	0.004*
Albumin	0.212	0.013*
Globulin	0.017	0.842
AST	–0.003	0.972
ALT	0.107	0.213
ALP	0.128	0.137

hand and serum ALT, AST, total protein, and albumin on the other, and a negative correlation between serum T4 and the latter four parameters. Yadav *et al.* found a positive correlation between TSH and the liver enzymes, AST and ALP. Saini *et al.* also reported a negative correlation between TSH with urea. However, as seen in the results, our study could not replicate the correlation results of the three Indian studies in cases with TSH > 6.5 mIU/L. One scholar confirmed our findings of higher bilirubin levels

in SCH subjects. He additionally reported lower albumin levels, a finding which we observed in subjects with TSH in the 6.5–8 mIU/L range [28].

Our observation is that kidney function is affected in SCH and OH, as typified in direct measurements such as creatinine and indirect measurements such as estimated glomerular filtration rate (eGFR). We found support for our findings in a study by Schairer *et al.*, who studied a cohort of chronic kidney disease (CKD) patients post-transplantation, concluding that positive changes in TSH (ΔTSH) were associated with decrease in (eGFR) (to the tune of 1.34 mL/min for every 1 μIU/mL increase in TSH) [29]. Another study by Shin *et al.* focusing on CKD patients with SCH found that TSH reduction secondary to TH replacement therapy was helpful in preventing the deterioration of renal function [30].

Tsuda *et al.* reported drastic glomerular hemodynamic effects of hypothyroidism, even in the high-normal TSH range. TSH was found to have a significant positive correlation with afferent arteriole vascular resistance and a significant negative correlation with renal plasma flow (RPF), renal blood flow (RBF), and GFR. This may have arisen due to the direct action of TSH on its specific receptors in the kidneys. Thus, the effects of compromised thyroid function would lead to suppressed renal function [31].

Recent studies such as that of Kim *et al.* found that lower thyroid function was associated with higher prevalence and risk of nonalcoholic steatohepatitis (NASH) and fibrosis. They found histological evidence of extensive hepatic steatosis showing significant hepatocyte “balloon degeneration” and fibrosis. High- and high-normal TSH levels were closely related to NASH and NASH-related advanced fibrosis. This could be explained by the increasing propensity for development of insulin resistance and other metabolic disturbances brought about by dyslipidemia and obesity in hypothyroid individuals. Insulin resistance has been shown to improve with TH therapy. Other mechanisms of thyroid hypofunction-induced hepatic damage are oxidative stress, mitochondrial dysfunction, and altered TH signaling in hepatocyte fibrogenesis [32]. TSH on binding to receptors on hepatocytes has been found to upregulate sterol regulatory element-binding protein-1c (SREBP-1c) activity. This may induce steatogenic changes [4]. Our findings of higher bilirubin and liver enzymes in subjects with TSH > 8 mIU/L would be secondary to the above changes. The findings of elevated bilirubin, low albumin, high globulin, and high AST in the TSH range of 6.5–8 mIU/L suggest that thyroid dysfunction in this range of TSH profoundly induces impairment in lipid metabolism. This in turn results in steatogenic changes by the various mechanisms discussed previously, thus precipitating and/or potentiating hepatic injury [28]. In some cases, cholestatic jaundice coincident with hypothyroidism has been ascribed to the impairment in bilirubin and

bile excretion, which is secondary to the hepatic injury. The enzyme activity of UDP-glucuronyl transferase may also be reduced, thus hampering bilirubin excretion. Diminution in bile flow also results from an increased membrane cholesterol–phospholipid ratio and the consequent reduction in fluidity. Membrane transporters may thus be affected [25]. Consequently bilirubin levels rise in hypothyroidism. AST may rise due to a combination of myopathies and hepatic injury. Hypothyroidism is an inflammatory state, possibly elevating liver enzyme levels and increasing total proteins, mostly the inflammatory globulins, which could partially explain our findings of raised globulin levels in all the cases with TSH > 6.5 mIU/L [26]. A significant positive correlation between TSH and total proteins, albumin in the 6.5–8 mIU/L range suggests that hepatic damage may have already started in this range. Putative mechanisms of this damage are hepatic congestion secondary to hypothyroidism-induced cardiac compromise and augmented state of vascular endothelial permeability, in addition to the changes mentioned above [33].

5. Conclusion

We suggest physicians exercise caution in cases having TSH in the range of 6.5–8 mIU/L without apparent signs and symptoms. The results of our study strongly emphasize that alterations possibly involving steatogenic changes in the liver, and insidious decrements in kidney function, among myriad other processes discussed above, establish themselves in this range, and a treatment initiation threshold of 8 or 10 mIU/L TSH may be incautious. A new diagnostic scoring system, which takes into account TSH levels for evaluating steatogenic liver changes must be envisaged [4]. Thyroid hypofunction may precipitate/worsen kidney disease, especially in hospitalized patients [17]. In cases of established liver injury, hypothyroidism should not be ruled out as a significant causative factor [33]. It is thus imperative to perform regular liver and kidney function tests for all patients, even for TSH levels <8 mIU/L. Also, the possibility of TH analogues in reversing hypothyroidism-induced fatty change (as well as other indiscreet biochemical changes) at this range of 6.5–8 mIU/L may be considered and further researched [34]. The direct positive correlation of TSH with total protein and albumin in this range suggests that efforts to reduce TSH levels even in this therapeutically neglected range may have tangible benefits.

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Ethical Consideration

Ethical clearance for the study was obtained from the institutional ethical committee of SKIMS medical college, Bemina, Srinagar, J&K, India.

Competing Interests

None declared.

Availability of Data and Material

All data and materials associated with this study are available through the corresponding author upon reasonable request.

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