Original Research Article

Can high normal TSH level predispose to hypercholesterolemia?

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Abstract

Background: Thyroid hormone plays an important role in carbohydrate, protein, and lipid and electrolyte metabolism. Studies have demonstrated the association of hypothyroidism with dyslipidaemia. However the impact of high normal TSH on lipid profile is lacking. Also, thyroid hormone is known to influence glomerular filtration rate, and renal electrolyte handling. So, this study compared TSH levels in normal ranges with fasting lipid profile and electrolytes.
Objectives: To measure and compare the levels of serum TSH, fasting lipid profile and electrolytes in euthyroid individuals with normal TSH and to correlate serum TSH with lipid profile and electrolytes across different age groups in both sexes.
Materials and methods: After obtaining ethical clearance, 2 ml of fasting venous blood sample was drawn from 200 subjects (males=100, females=100) aged between 20-75years who consented to participate. Serum was used for estimation of TSH, lipid profile and electrolytes. TSH was measured by 4th generation Immunoassay in Cobas 6000 e601 autoanalyzer (Roche). The lipid profile and electrolytes were assayed in Cobas 6000 c501 autoanalyzer (Roche).
Results: Serum TSH values showed significant positive correlation with total cholesterol (p=<0.001), triglycerides (p=<0.001) and LDL cholesterol (p=<0.001), but did not show any significant correlation with HDL cholesterol. Also serum TSH showed significant negative correlation with sodium (r=-0.185, p=0.048) and potassium (r=-0.205, p=0.028) levels.
Conclusion: TSH and thyroid status can influence lipid and electrolyte metabolism. High normal TSH level may predispose to hypercholesterolemia and hypertriglyceridemia. High normal TSH patients can have lower serum electrolytes.

Key words

Hypercholesterolemia, Hypertriglyceridemia, High normal TSH, Electrolytes, Euthyroid.

Introduction

Thyroid hormone is a central regulator of body hemodynamics, thermoregulation and metabolism [1-4]. Hypothyroidism is one of the common metabolic disorders in the general population and it is thought to affect around 6–10% of women which may rise up to 25% in women over the age of 65 years [5]. Men are also affected, but less frequently. Hypothyroidism often leads to secondary dyslipidaemia [6]. Thyroid hormone plays an important role in carbohydrate, protein, and lipid and electrolyte metabolism. In recent years, studies have demonstrated that even within the normal range, serum TSH can influence cholesterol, low density lipoprotein, triglycerides and high density lipoprotein metabolism [7]. Even though, existing evidence indicates that decreased thyroid function can lead to reduced activity of HMG CoA reductase, total cholesterol and LDL-C (low density lipoprotein cholesterol) are found to be increased in patients with hypothyroidism [8]. This may be due to decreased LDL receptors activity resulting in decreased catabolism of LDL or a decreased lipoprotein lipase activity resulting in a decreased clearance of triglyceride rich lipoproteins [9]. Therefore, hypothyroid patients may also present with elevated triglyceride levels. Also, Thyroid hormone is known to influence glomerular filtration and renal electrolyte handling [10]. Thyroid hormones are necessary for growth and development of the kidney and for the maintenance of water and electrolyte homeostasis. On the other hand, kidney is involved in the metabolism and elimination of Thyroid hormones indicating a close interplay between them in regulating each other's function.

Hence, the goal of this study evaluated the association between serum TSH levels in normal range with lipid profile and electrolytes in euthyroid individuals.

Materials and methods

Approval was obtained from institutional Ethics Committee Kasturba Hospital Manipal for this study. Two hundred individuals aged between 20-75years who consented to participate were enrolled in this study. But only 142 subjects were taken as study subjects and the rest were excluded.

Inclusion criteria: Both males and females of age group 20-75 years.

Exclusion criteria*:* Individuals aged less than 20 years and more than 75 years. Also individuals suffering from renal, hepatic, bone disorders, thyroid disorders, diabetes mellitus, and subjects on long term medications which might affect thyroid assay, lipid profile and electrolytes were excluded. Fasting serum samples were used for biochemical estimations. TSH was measured by Immunoassay in Cobas 6000 e601 autoanalyzer (Roche). The lipid profile and electrolytes were assayed in Cobas 6000 c501 autoanalyzer.

Based on serum TSH levels study subjects were grouped as follows:

Group - 1: 0.3-1.5 µIU/mL
Group - 2: 1.5-3 µIU/mL
Group - 3: 3-5 µIU/mL

Also to assess the influence of TSH levels on lipid profile and electrolytes across different age groups, the study subjects were sub grouped as follows:

Group A: 20-40 years
Group B: 40-60 years
Group C: >60 years

Data analysis was done using SPSS version 16.0. One way ANOVA was used for intergroup comparisons. All parameters were correlated with TSH levels. P value <0.05 considered to be significant.

Results

Demographic profile of study subjects was as per **Table – 1**. Comparison of serum lipid profile between the groups was as per **Table – 2**. Correlation of lipid profile with serum TSH was as per **Table – 3**. Comparison of serum TSH and serum lipid profile among different age groups was as per **Table – 4**. Correlation of TSH with lipid profile in males was as per **Table – 5**. Correlation of TSH with lipid profile in females was as per **Table – 6**. Correlation between serum TSH and electrolytes of whole group was as per **Table – 7**.

Table - 1: Demographic profile of study subjects.

Groups	Mean Age in years	Male : Female
1 (n=40)	44.22±15.84	25:15
2 (n= 54)	43.37±13.77	28:26
3 (n=48)	45.37±14.56	30:18

Table - 2: Comparison of serum lipid profile between the groups.

Lipid profiles	Group 1	Group 2	Group 3
TC	165.2±35.43	187.1±41.8*	205.7±36.7**
TG	107.30±47.7	138.14±75.9	135.2±37.85
HDL-C	46.97±17.45	45.87±13.36	46.08±13.73
LDL-C	99.35±31.18	113.6±35.2#	132.7±33.3##

TC = Total Cholesterol (mg/dL), TG = Triglycerides (mg/dL), HDL-C = High Density Lipoprotein Cholesterol (mg/dL), LDL-C = Low Density Lipoprotein Cholesterol (mg/dL)

*TC significant between group 1 & 2(p=0.02)
**TC significant between group 1 & 3(p<0.001)
#LDL-C significant between group 1 & 3(p<0.001)
##LDL-C significant between group 2 & 3(p=0.01)

Table - 3: Correlation of lipid profile with serum TSH.

Lipid profiles	r value	p value*
Total cholesterol	0.46	<0.001*
Triglycerides	0.25	<0.001*
HDL-C	0.038	0.59 NS
LDL-C	0.407	<0.001*
Ratio	0.038	0.59 NS

NS - Not significant, * Pearson's correlation

Discussion

We observed a significant correlation between TSH levels and lipid profile suggesting that individuals with high normal TSH can be predisposed to hypercholesterolemia and hypertriglyceridemia (**Table – 2, 3, Figure – 1 to 4**). When serum TSH and serum lipid profile was compared in different age groups, all the lipid profile parameters showed significant correlation between the groups (**Table – 4**). Only TG showed a positive correlation in males (**Table - 5, Figure – 5**) whereas in females there was no statistically significant correlation of serum TSH with lipid profile (**Table – 6**) when compared between the sexes.

Subjects with higher normal TSH (TSH 3-5μIU/mL) had significantly higher levels of total cholesterol, LDL-C as compared that of low normal TSH subjects respectively indicating a

strong influence of thyroid hormones on lipid metbolism. We also correlated serum electrolytes with TSH which showed statistically significant negative correlation **(Table - 7, Figure – 6, 7**).

Table - 4: Comparison of serum TSH and serum lipid profile among different age groups.

	Group A (n=58)	**Group B (n=75)**	**Group C (n=20)**
Age (years)	20-40	40-60	>60
Mean age (mean±SD)	30.9±5.7	49.7±6.1	65.6±3.8
TSH (µIU/ml)	2.5±1.0	3.11±1.9*	3.35±1.7**
TC	188±45.8	203.8±41.0$^{\#}$	186.9±39.2$^{\#\#}$
TG	133.2±47.2	146.7±52.8	115±43.3$^{\#\#\#}$
HDL-C	44±14.9	48.4±13.0$^{\$}$	51.7±15.7$^{\$\$}$
LDL-C	119±37.8	125.9±37.4	111.8±30.6$^{\%}$

TC = Total Cholesterol (mg/dL), TG = Triglycerides (mg/dL), HDL-C = High Density Lipoprotein Cholesterol (mg/dL), LDL-C = Low Density Lipoprotein Cholesterol (mg/dL)

TC significant between group **I**& **II** (p=0.02)
##TC significant between group **II**&**III** (p=0.05)
###TG significant between group **II**&**III** (p=0.02)
$HDL-C significant between group **I**&**II** (p=0.03)
$$HDL-C significant between group **I**& **III** (p=0.02)
%LDL-C significant between group **II**&**III** (p=0.05)

Table - 5: Correlation of TSH with lipid profile in males.

	r value	**p value**
Total Cholesterol	0.206	0.092 **NS**
Triglycerides	0.294	0.015 *****
HDL-C	-0.061	0.621 **NS**
LDL-C	0.11	0.37 **NS**

Only triglyceride was stastiscally postiviely correlated with TSH levels in males.

Table - 6: Correlation of TSH with lipid profile in females.

	r value	**p value**
Total Cholesterol	0.022	0.84 NS
Triglycerides	0.077	0.505 NS
HDL-C	-0.076	0.514 NS
LDL-C	0.033	0.77 NS

There was no statistically significant correlation of TSH with lipid profile in females

Table - 7: Correlation between serum TSH and electrolytes of whole group.

Electrolytes	**r value**	**p value**
Sodium	-0.185	0.048 *
Potassium	-0.205	0.028 *

**** significant***

Figure - 1: Correlation between serum TSH (µIU/mL) and total cholesterol (mg/dL).

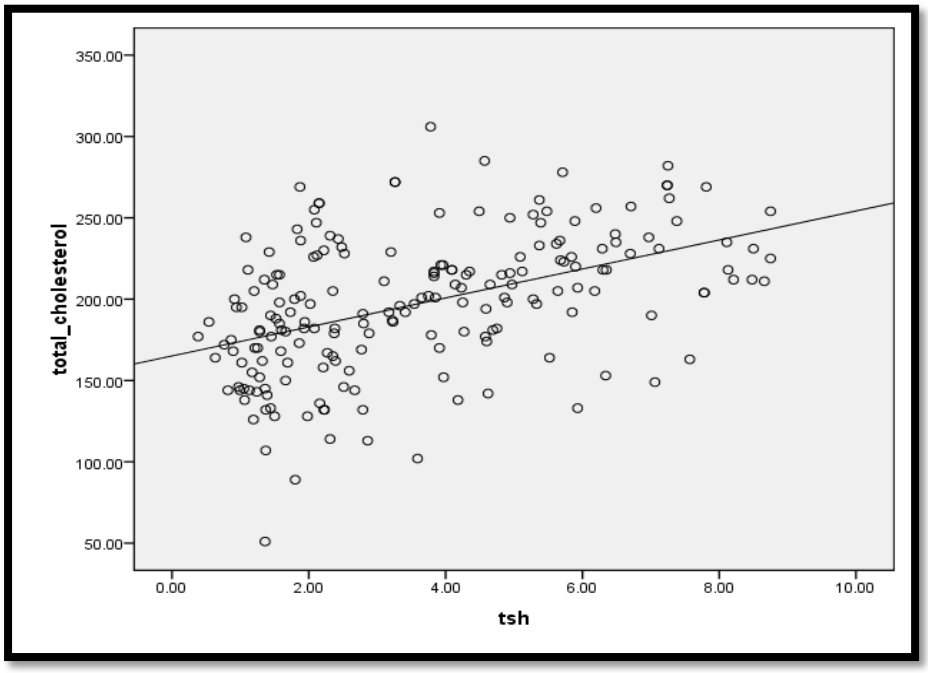
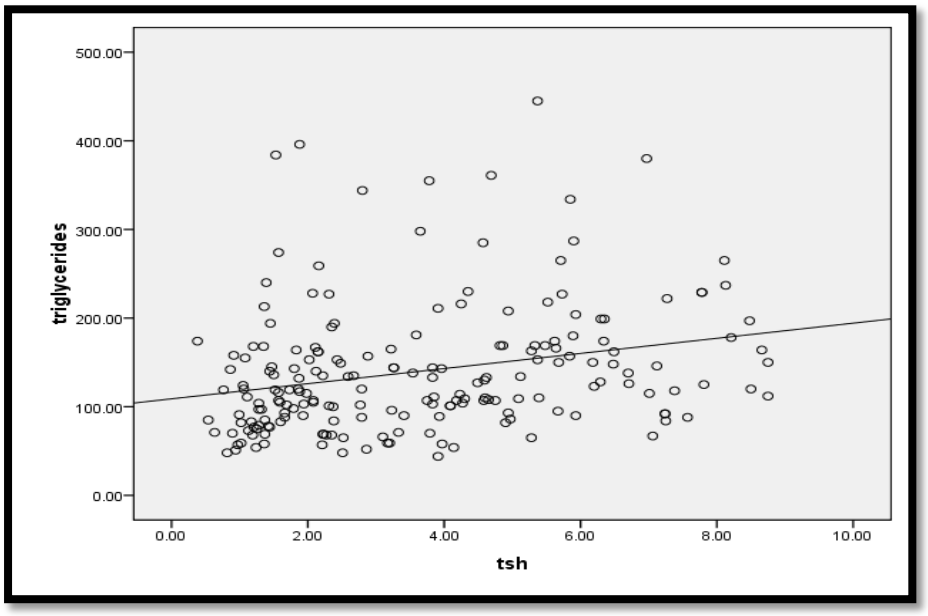


Figure - 2: Correlation between serum TSH (µIU/mL) and triglycerides (mg/dL).



Studies conducted in euthyroid subjects of Korea [11], Latin American [12], and Spanish [13] individuals have shown a significant increase in serum TC, TG and LDL-C levels with TSH levels. Similar result was obtained in the HUNT study performed in Norway [14]. In a large cohort study on euthyroid Indian women [15] suggested that TSH in the upper limits of reference range was associated with increased serum TC. But an Austrian study of 4856 participants with normal thyroid function [16] was contradictory to our study, as it showed no

increase in lipid status with increasing TSH levels within the normal range indicating a possible influence of genetic and ethnic variations among these subjects.

Figure - 3: Correlation between serum TSH (µIU/mL) and LDL-C (mg/dL).

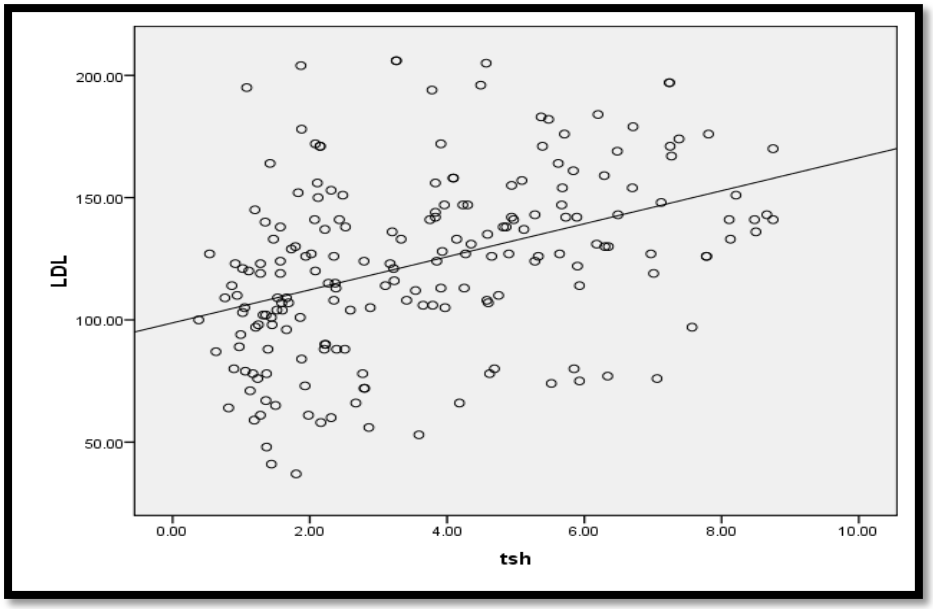
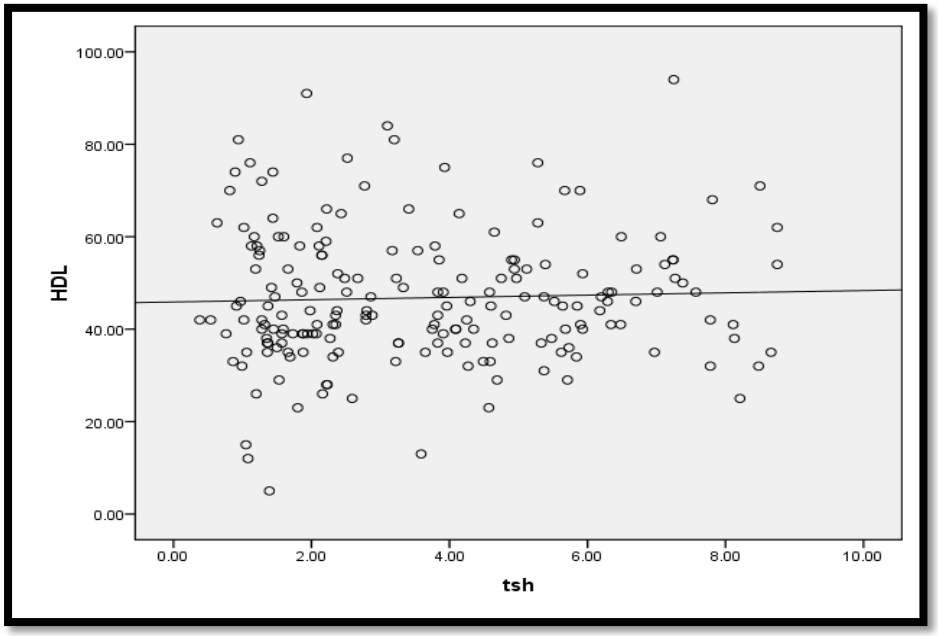


Figure - 4: Correlation between serum TSH (µIU/mL) and HDL-C (mg/dL).



Studies have shown that the TSH receptors were expressed in a variety of extra thyroidal tissues, including the liver, skin, kidney, white and brown adipose tissues [17] suggesting possible extra thyroidal roles of TSH. This can be further substantiated by studies showing positive correlations between TSH level and waist circumference, body mass index and blood

pressure [18-20]. Zhang, et al. [21] have demonstrated that liver cells express TSH receptor protein and that TSH upregulates the expression of HMG CoA reductase (a rate limiting enzyme in cholesterol biosynthesis) [22].

Figure - 5: Correlation between serum TSH (µIU/mL) and triglycerides (mg/dL) in males.

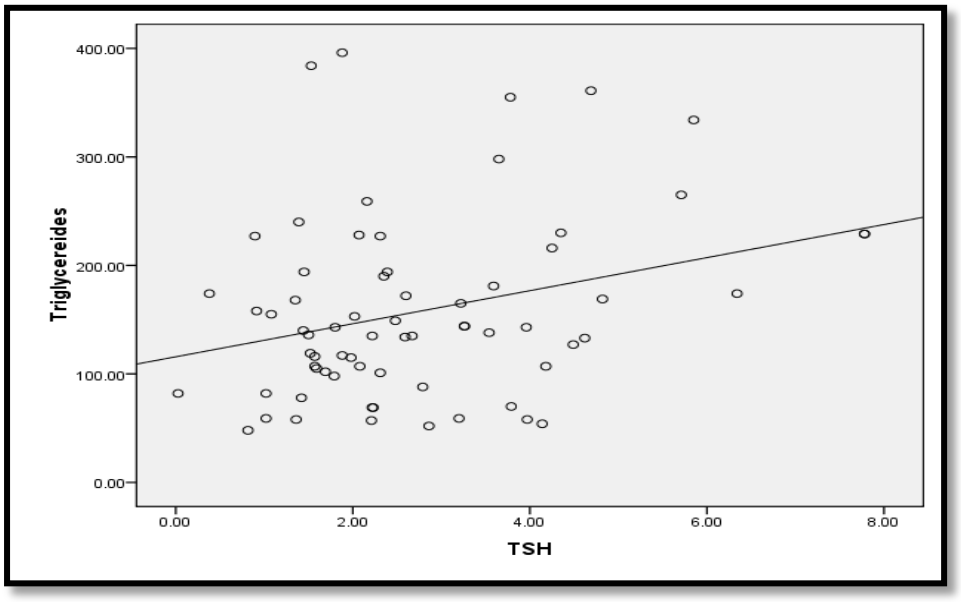
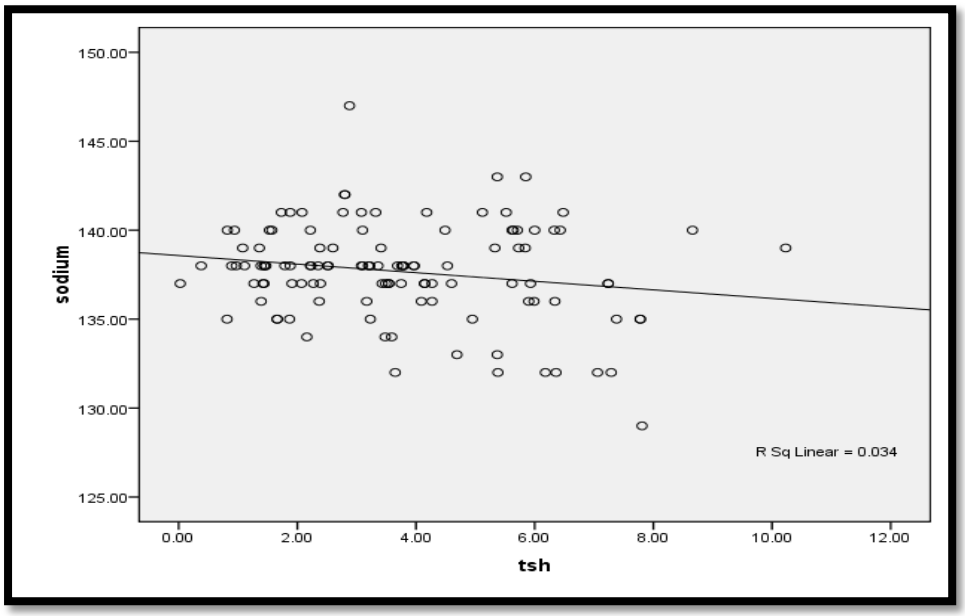


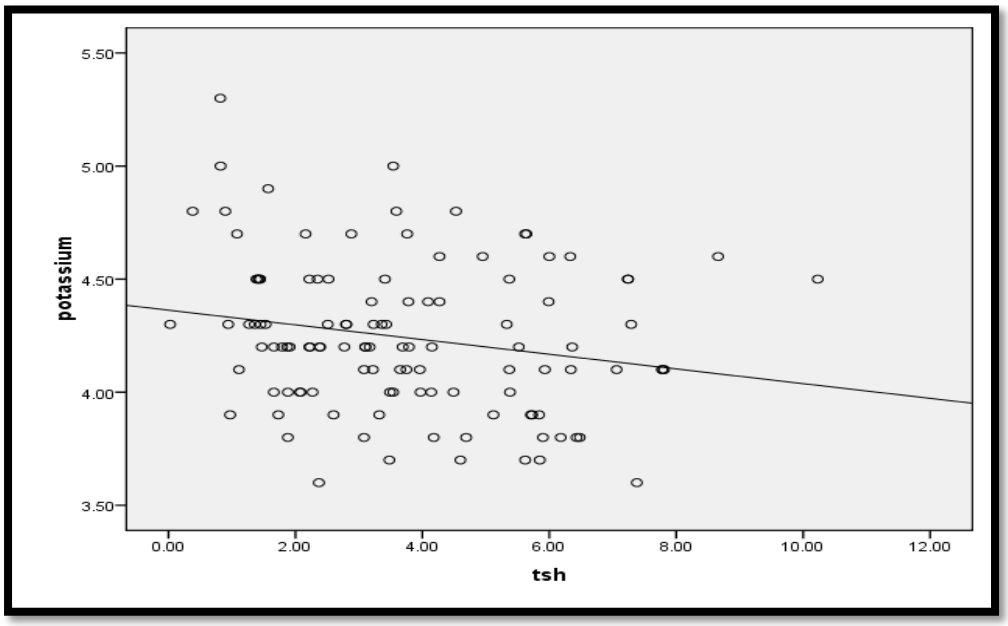
Figure - 6: Correlation between serum TSH (µIU/mL) and serum sodium (mEq/L) levels.



Our data showed that subjects with relatively high normal TSH levels were more likely to have hypercholesterolemia and hypertriglyceridemia. Therefore, according to these results, even within the clinically normal range, subjects with high TSH levels might be prone to dyslipidaemia. The electrolyte status has an influence on renal haemodynamics, glomerular filtration, as well as the renin angiotensin aldosterone system and renal electrolyte handling [23]. Thyroid

dysfunction has a remarkable effect on glomerular and tubular functions of kidney and therefore on electrolyte and water homeostasis. Some studies show that hypothyroidism is accompanied by hyponatremia and a decrease in glomerular filtration [24]. Hyponatremia observed in severe hypothyroidism and myxoedema, has been attributed to enhanced renal water retention mediated by vasopressin [27].

Figure - 7: Correlation between serum TSH(µIU/mL) and serum potassium (mEq/L) levels.



This study also showed a significant negative correlation of TSH with sodium and potassium levels suggesting a possible role for TSH in maintenance of electrolyte balance. Although the weak correlation may suggest that correlation between electrolyte disturbances and thyroid function could be seen in severe cases of hypothyroidism. As electrolyte disorders are common among hospitalised patients, little more attention may have to be given for electrolytes if they are suffering from thyroid disorders [25-26].

Conclusion

High normal TSH levels may predispose to hypercholesterolemia and hypertriglyceridemia. Association of high-normal TSH levels with dyslipidemia may indicate that thyroid hormones can influence lipid metabolism in many ways including receptor uptake and metabolism of lipoproteins, cholesterol and lipoprotein synthesis, activation/inactivation of lipoprotein lipase etc. TSH and thyroid status can influence lipid and electrolyte metabolism. High normal TSH patients can have lower serum electrolytes. People with high normal Serum TSH levels may require a close monitoring of lipid profiles and electrolytes.

Limitations

As most studies show significant associations of TSH with lipid profiles and electrolytes, it implies a need for a detailed study to understand the exact mechanism of this influence and their clinical implications.

References

1. Unnikrishnan AG, Menon UV. Thyroid disorders in India: An epidemiological perspective. Indian journal of endocrinology and metabolism, 2011; 15(Suppl2): S78.

2. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Archives of internal medicine, 2000; 160(4): 526-34.
3. Murgod R, Soans G. Changes in electrolyte and lipid profile in hypothyroidism. Life Science Bio Chemistry, 2012; 2(3): 185-94.
4. Kaur J, Ahemad N, Gupta A. Changes in the electrolyte profile of patient having hypothyroidism. Journal of Medical Science and Clinical Research, 2014; 2(4): 633-37.
5. Abdel-Razzak M. Effect of age and sex on thyroid function tests. Establishment of norms for the Egyptian population. Developments in radioimmunoassay and related procedures, 1991; 26: 353.
6. Lu L, Wang B, Shan Z, Jiang F, Teng X, Chen Y, Lai Y, Wang J, Xue H, Wang S, Li C. The correlation between thyrotropin and dyslipidemia in a population-based study. Journal of Korean medical science, 2011; 26(2): 243-9.
7. Åsvold BO, Vatten LJ, Nilsen TI, Bjøro T. The association between TSH within the reference range and serum lipid concentrations in a population-based study. The HUNT Study. European Journal of Endocrinology, 2007; 156(2): 181-6.
8. Mariani LH, Berns JS. The renal manifestations of thyroid disease. Journal of the American Society of Nephrology, 2012; 23(1): 22-6.
9. Nikkilä EA, Kekki M. Plasma triglyceride metabolism in thyroid disease. Journal of Clinical Investigation, 1972; 51(8): 2103.
10. Duntas LH. Thyroid disease and lipids. Thyroid, 2002; 12(4): 287-93.
11. Jung CH, Sung KC, Shin HS, Rhee EJ, Lee WY, Kim BS, Kang JH, Kim H, Kim SW, Lee MH, Park JR. Thyroid dysfunction and their relation to cardiovascular risk factors such as lipid profile, hsCRP, and waist hip ratio in Korea. The Korean journal of internal medicine, 2003; 18(3): 146-53.
12. Diehl LA, Garcia V, Bonnema SJ, Hegedüs L, Albino CC, Graf H. Management of the nontoxic multinodular goiter in Latin America: comparison with North America and Europe, an electronic survey. The Journal of Clinical Endocrinology & Metabolism, 2005; 90(1): 117-23.
13. Fernández-Real JM, López-Bermejo A, Castro A, Casamitjana R, Ricart W. Thyroid function is intrinsically linked to insulin sensitivity and endothelium-dependent vasodilation in healthy euthyroid subjects. The Journal of Clinical Endocrinology & Metabolism, 2006; 91(9): 3337-43.
14. Iqbal A, Jorde R, Figenschau Y. Serum lipid levels in relation to serum thyroid-stimulating hormone and the effect of thyroxine treatment on serum lipid levels in subjects with subclinical hypothyroidism: the Tromsø Study. Journal of internal medicine, 2006; 260(1): 53-61.
15. Boggio A, Muzio F, Fiscella M, Sommariva D, Branchi A. Is thyroid-stimulating hormone within the normal reference range a risk factor for atherosclerosis in women? Internal and emergency medicine, 2014; 9(1): 51-7.
16. Hueston WJ, Pearson WS. Subclinical hypothyroidism and the risk of hypercholesterolemia. The Annals of Family Medicine, 2004; 2(4): 351-5.
17. Williams GR. Extrathyroidal expression of TSH receptor. In Annales d'endocrinologie, 2011; 72(2): 68-73.
18. De Pergola G, Ciampolillo A, Paolotti S, Trerotoli P, Giorgino R. Free triiodothyronine and thyroid stimulating hormone are directly associated with waist circumference, independently of insulin resistance, metabolic parameters and blood pressure in overweight and obese women. Clinical endocrinology, 2007; 67(2): 265-9.

19. Knudsen N, Laurberg P, Rasmussen LB, Bülow I, Perrild H, Ovesen L, Jørgensen T. 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, 2005; 90(7): 4019-24.
20. Iqbal A, Figenschau Y, Jorde R. Blood pressure in relation to serum thyrotropin: the Tromsø study. Journal of human hypertension, 2006; 20(12): 932-6.
21. Zhang W, Tian LM, Han Y, Ma HY, Wang LC, Guo J, Gao L, Zhao JJ. Presence of thyrotropin receptor in hepatocytes: not a case of illegitimate transcription. Journal of cellular and molecular medicine, 2009; 13(11-12): 4636-42.
22. Tian L, Song Y, Xing M, Zhang W, Ning G, Li X, Yu C, Qin C, Liu J, Tian X, Sun X. A novel role for thyroid-stimulating hormone: Up-regulation of hepatic 3-hydroxy-3-methyl-glutaryl-coenzyme a reductase expression through the cyclic adenosine monophosphate/protein kinase A/cyclic adenosine monophosphate–responsive element binding protein pathway. Hepatology, 2010; 52(4): 1401-9.
23. Adrogué, Horacio J., Nicolaos E. Madias. Hyponatremia. New England Journal of Medicine, 2000; 342(21): 1581-1589.
24. Iglesias P, Diez JJ. Thyroid dysfunction and kidney disease. European journal of endocrinology, 2009; 160(4): 503-15.
25. Darmon M, Timsit JF, Francais A, Nguile-Makao M, Adrie C, Cohen Y, Garrouste-Orgeas M, Goldgran-Toledano D, Dumenil AS, Jamali S, Cheval C. Association between hypernatraemia acquired in the ICU and mortality: a cohort study. Nephrology Dialysis Transplantation, 2010 Feb 17:gfq067.
26. Mariani LH, Berns JS. The renal manifestations of thyroid disease. Journal of the American Society of Nephrology, 2012; 23(1): 22-6.
27. Iwasaki Y, Oiso Y, Yamauchi K, Takatsuki K, Kondo K, Hasegawa H, Tomita A. Osmoregulation of Plasma Vasopressin in Myxedema. The Journal of Clinical Endocrinology & Metabolism, 1990; 70(2): 534-9.