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A RETROSPECTIVE STUDY IN LEBANON. THYROID-STIMULATING HORMONE AND ITS POSSIBLE ASSOCIATION WITH SERUM LIPIDS.

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ABSTRACT

Thyroid gland diseases are a public health problem worldwide**.** Many disorders result from the imbalance in the regulation of thyroid hormones, these ranges from a small goiter to life threatening diseases, like thyroid cancer. Until these days, the relationship between thyroid stimulating hormone and hyperlipidemia remained a topic of debate. The aim of this study is to examine the influence of gender and age on the association between serum TSH and lipid profile among a population in Beirut. The present study includes the results derived from analyzing TSH and serum lipids levels of 776 individuals including 567 females and 209 males aged between 5 and 80 years. This was achieved by collecting data from different laboratory databases over an 8-year period from 2009 till 2016. Our results showed a significant association between gender and TSH levels where f females have a significant higher risk than males. Moreover, the risk of hypothyroidism increases with age in both genders with the highest prevalence rate was found in the females between 41 and 50 years old and the males between 51 and 60 years. Furthermore, TSH was associated with hypertriglyceridemia and high serum low-density lipoprotein-cholesterol in all patients studied. However, no significant relationship was observed between high TSH and hyperlipidemia in male subjects considered alone. Concerning female cases, a significant association was observed between high TSH and high triglyceride levels only. Further

understanding requires additional population-based studies to better assess and compare different results.

KEYWORDS:

INTRODUCTION

The world faces a burden of thyroid disease that has reached epidemic proportions *(Zhaowei Meng, 2015).* An estimated 200 million individuals worldwide have various kinds of thyroid dysfunctions, with over 50 percent remained undiagnosed. Thyroid disease is one of the silent epidemics of our time and as with many of today's illness, the increased incidence of thyroid disease can be linked to an overburden of toxins due to pollution, through air, water and food, and the most common cause of thyroid disorders is iodine deficiency and literature shows that almost one third of the world's population lives in the area of iodine deficiency *(Zimmermann, 2009).*

The most important regulator of thyroid hormone secretion is TSH, also known as thyrotropin, which is secreted from the anterior pituitary gland. Almost every step of thyroid hormone synthesis and secretion is stimulated by TSH. TSH stimulates the process of iodide trapping and each step in T4 and T3 synthesis *(Denise Kirsten, 2000).* It also stimulates the endocytosis of the colloid, the breaking apart of the thyroglobulin into the two thyroid hormones and the ultimate release of T_4 and T_3 into the circulation (Berne R,1998). In addition to enhancing thyroid hormone secretion, TSH is also responsible for maintaining the structural integrity of the thyroid gland.

Thyroid hormones are recognized as catabolic hormones and they regulate various processes of metabolism, their most obvious and well-known action is an increase in basal energy expenditure obtained by acting on protein, carbohydrate and lipid metabolism. With specific regard to lipid metabolism, thyroid hormones affect synthesis, mobilization and degradation of lipids, although degradation is influenced more than synthesis *(Pucci E., 2000).* Imbalance in the regulation of these hormones can cause many disorders *(Ratni, 2015).* The association between thyroid function and lipid status has recently become a popular area of research. Several studies have shown that TSH is associated with changes in lipid metabolism and increased cardiovascular risks too.

Therefore, the aim of this study was to determine the impact of gender and age on the relationship between TSH and lipid profile among a population in Beirut.

METHODS

Population study

The present retrospective study was performed by collecting data of 776 patients from different laboratory databases in Beirut, over a period of 8 years from 2009 till 2016. This data retrieval was approved by the laboratory assistants. Furthermore, the population studied comprised individuals between 5 and 80 years who have had their TSH and serum lipids (cholesterol, triglycerides, LDL and HDL) tested.

Statistical Analysis

The statistical analyses were performed by using GraphPad (Prism5). Normality of the data distribution was checked by the Kolmogorov-Smirnov test. The *Chi-Square* test (X^2 test) of Independence is used to determine if there is a significant relationship between two categorical variables. Pearson r test is used to test the significant correlation between two continuous variables. P-Values < 0.05 were considered as significant.

RESULTS

Association between TSH level and gender.

A significant association was found between gender and TSH level (Pvalue=0.0425). The females have a significant 1.7 times higher risk to have high TSH level than males (odds ratio=1.715; 95% confidence interval 1.013 to 2.902) (figure 1).

Association between TSH level and age.

The results showed a significant association between age and TSH level for all patients (Pvalue=0.0104). The results showed that the risk of suffering high TSH levels increases with age for both genders. In males, the highest number of patients with high TSH was those between 51 and 60 years, and then the number decreases gradually above this age. Concerning females, the risk of increased TSH concentration is the highest between the ages 41 and 50 years which is around menopause (figure 2).

Association between TSH and serum lipids

Outcomes examined were serum cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride levels in those who had hypothyroidism and

in euthyroid controls, where hypothyroidism is defined as an elevated concentration of TSH (n=102) and euthyroid controls included participants with a TSH in a normal range (n =674).

There was a significant association between TSH and triglycerides levels (Pvalue =0.0008). The patients with high triglyceride level have a significant 2 times higher risk to have high TSH level than patients with normal triglyceride level (odds ratio 2.036; 95% confidence interval 1.333.098) (figure 3). No significant association was found between TSH and cholesterol levels (Pvalue= 0.914). (figure 3).

However, a significant association was observed between TSH levels and LDL (p=0.0311) in all patients. The patients with high LDL level have a significant 1.8 times higher risk to have high TSH level than patients with normal triglyceride level (odds ratio 1.849; 95% confidence interval 1.050 to 3.257). (figure 3).

Considering female cases alone, a significant association was observed only between TSH and triglycerides (p=0.0007) (table 1; figure 4). An opposite result was detected when analyzing male cases, where no significant association was observed with any type of serum lipids studied (table 1; figure 5).

A very weak significant positive correlation was found between TSH level and HDL and LDL in all patients (Pvalue= 0.0118 and 0.0059 respectively) (table 2).

However, in males a moderate significant positive correlation was found between TSH level and cholesterol (Pvalue= 0.0001) and LDL and (Pvalue= 0.0005) (table 2). We didn't find any correlation between TSH and these parameters in females.

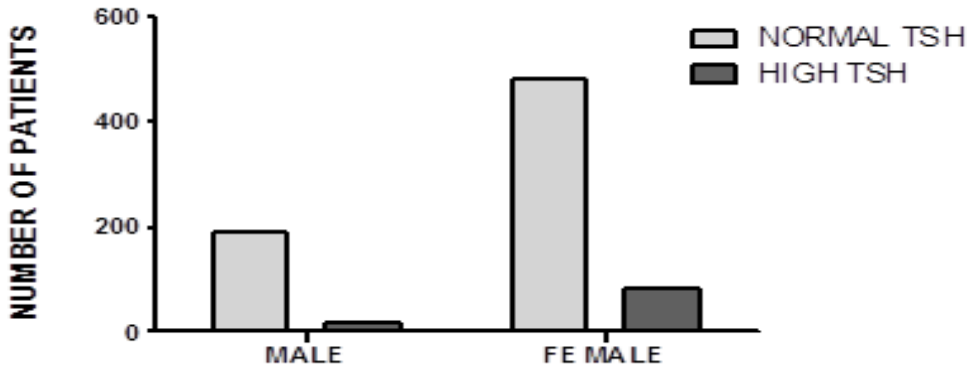

Figure 1: Distribution of all patients according to the TSH level and gender. TSH, thyroid-stimulating hormone. Pvalue =0.0425.

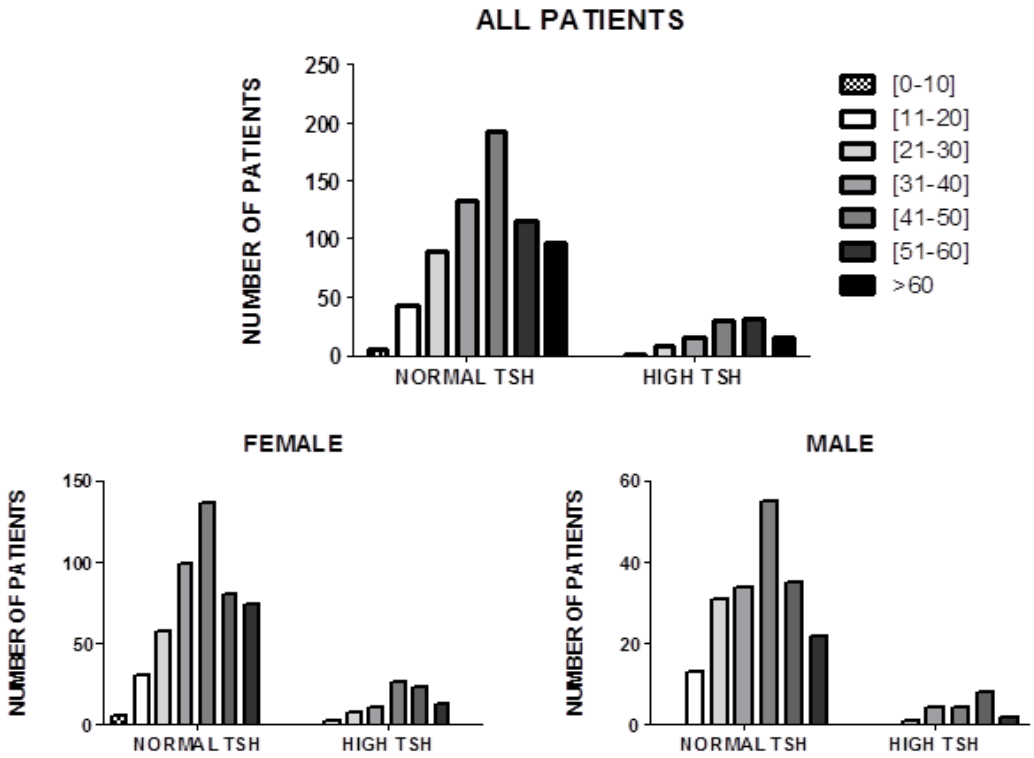

Figure 2: Distribution of patients in both gender according to the TSH level and age. TSH, thyroid-stimulating hormone.

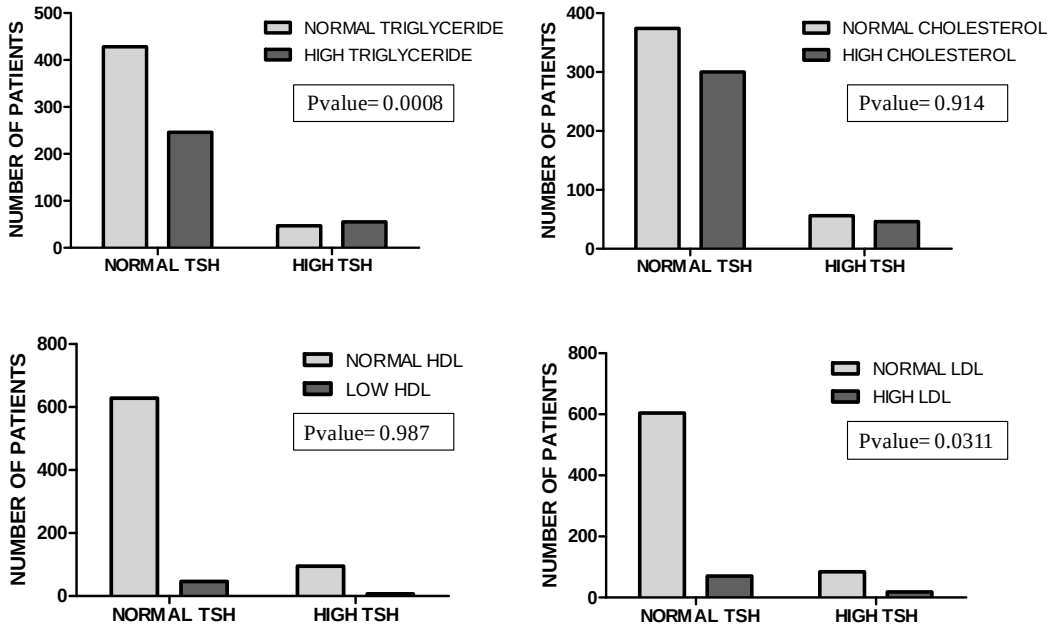

Figure 3: Distribution of all patients according to the TSH and and serum lipids. TSH, thyroid-stimulating hormone; LDL, low-density lipoprotein; HDL, high-density lipoprotein. Significant at Pvalue<0.05.

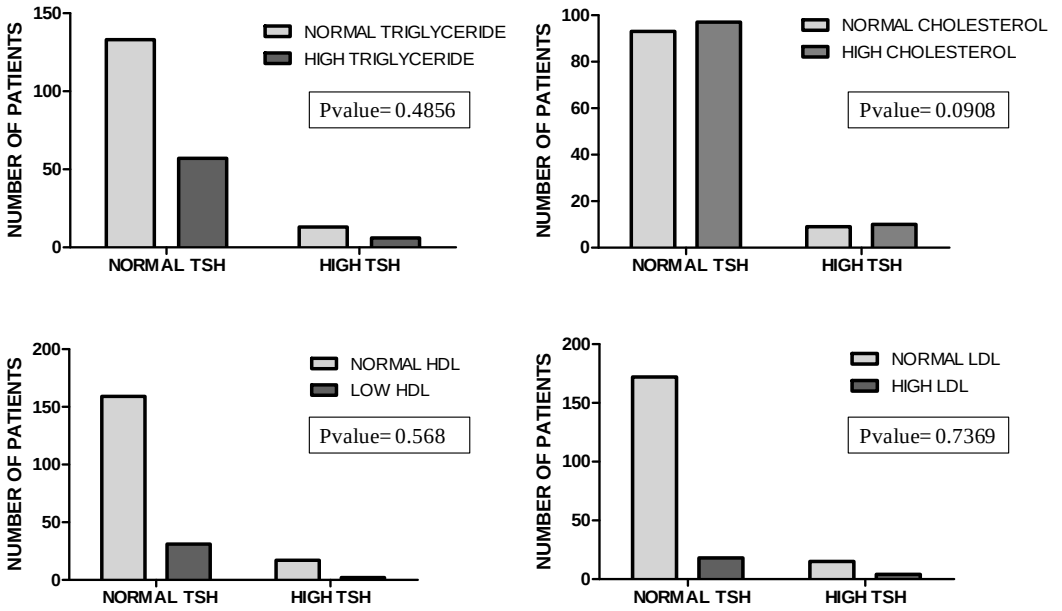

Figure 4: Distribution of males according to the TSH and and serum lipids. TSH, thyroid-stimulating hormone; TC, LDL, low-density lipoprotein; HDL, high-density lipoprotein. Significant at Pvalue<0.05.

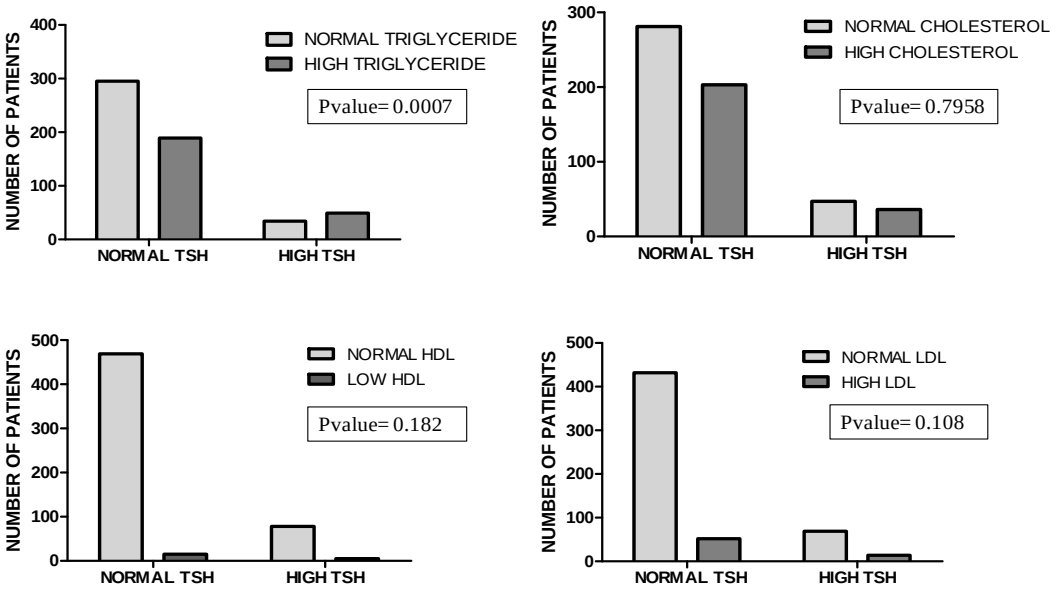

Figure 5: Distribution of females according to the TSH and and serum lipids. TSH, thyroid-stimulating hormone; LDL, low-density lipoprotein; HDL, high-density lipoprotein. Significant at Pvalue<0.05.

Table 1. Distribution of both genders according to the TSH and and serum lipids.				
Gender	TC	TG	LDL	HDL
Male (n=209)				
TSH	0.7369	0.4856	0.0908	0.5691
Female (n=567)				
TSH	0.7958	0.0007	0.1080	0.1820

TSH, thyroid-stimulating hormone; TC, total cholesterol; TG, triglycerides, LDL, low-density lipoprotein; HDL, high-density lipoprotein. Significant at Pvalue<0.05.

Table 2: Correlation between TSH level and the other paremeters						
	Parameter	**Age**	**Triglyceride**	**Cholesterol**	**HDL**	**LDL**
All patients	Pearson r	0.03853	0.06945	0.06961	0.09030	0.09877
	95% CI	-0.03196 to 0.1086	-0.0009486 to 0.1392	-0.0007896 to 0.1393	0.02003 to 0.1597	0.02858 to 0.1680
	P value	0.2838	0.0531	0.0526	**0.0118**	**0.0059**
Females	Pearson r	0.03628	0.08846	-0.009498	0.07028	0.04513
		-0.04622 to 0.1183	0.006147 to 0.1696	-0.09179 to 0.07292	-0.01216 to 0.1518	-0.03738 to 0.1270
	P value	0.3885	**0.0352**	0.8215	0.0946	0.2834
Males	Pearson r	0.04230	0.04349	0.2594	0.1318	0.2384
	95% CI	-0.09399 to 0.1770	-0.09280 to 0.1782	0.1282 to 0.3817	-0.003981 to 0.2629	0.1061 to 0.3624
	P value	0.5431	0.5318	**0.0001**	0.0571	**0.0005**

DISCUSSION

Hypothyroidism is a condition in which the thyroid gland is unable to make adequate amounts of thyroid hormone to meet the requirements of peripheral tissues. It can be primary hypothyroidism, characterized by failure of the thyroid gland itself; a fall in serum concentrations of thyroid hormone causes an increased secretion and elevation of serum thyroid-stimulating hormone (TSH) concentrations. Decreased thyroidal secretion of thyroid hormone can also be caused by insufficient stimulation of a structurally normal gland due to diminished TSH release from the pituitary, which is termed secondary hypothyroidism, or consequent to inadequate thyrotropin-releasing hormone (TRH) release from the hypothalamus also known as tertiary hypothyroidism. The term subclinical hypothyroidism is used to define that grade of primary hypothyroidism in which there is an elevated TSH concentration in the presence of normal serum free thyroxine (T4) and triiodothyronine (T3) concentrations. The prevalence of Subclinical Hypothyroidism in the general population is estimated at 4.3% - 9%. Subclinical Hypothyroidism may progress to overt hypothyroidism in approximately 2–5% of cases annually. The population in the present study comprised patients having high serum levels of TSH that could be due to overt or subclinical hypothyroidism, for this reason both possibilities are going to be considered. According to

the American Thyroid Association (ATA), women are five to eight times more likely than men to have thyroid problems and these statistics are in concord with the above-reported data, where the prevalence of hypothyroidism in female cases studied was 17.14%, approximately two times higher than that in males 9.04%.

Thyroid hormones and TSH have different effects on lipid metabolism. Thyroid hormones affect serum lipid levels by increasing the elimination of neutral sterols and bile acids, and by reducing the absorption of cholesterol in the intestines. Two animal studies have revealed that thyroid hormones can stimulate the hepatic LDL-C receptor and increase the removal of LDL-C from the circulation *(Ness GC, 1990;Boone LR, 2011).* Boone *et al (Boone LR, 2011)* revealed that thyroid hormones enhanced the cholesterol-accepting capacity of serum via the ABCA1 transporter. Furthermore, Ness *et al (Ness GC, 1990)* demonstrated that the hypocholesterolemic effect of thyroid hormone resulted from the expression of the hepatic cholesterol 7 α hydroxylase gene. Tan *et al (Tan KC, 1998)* suggested that thyroid hormones could increase the activity of hepatic lipase and thereby reduce serum total cholesterol (TC) levels. As previously mentioned, thyroid hormones also induce the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is the first step in cholesterol biosynthesis. Although decreased thyroid function is thus accompanied by reduced activity of HMG-CoA reductase, several studies have shown that TC and LDL-C levels are increased in patients with overt hypothyroidism. Moreover, Hypothyroid patients have increased lipoprotein (a), a lipoprotein rich in cholesterol that differs from LDL as it contains an additional protein, apolipoprotein (a). Similar to LDL, a Lp(a) particle also contains one molecule of apolipoprotein B. Lp(a) levels are associated with increased cardiovascular disease (CVD) risk.

However, elevation of serum TC and LDL-C has also been observed in patients with subclinical hypothyroidism. In addition, some studies have shown that subclinical hypothyroidism dyslipidemia may also be accompanied by increased TGs and decreased HDL-C levels. Thus, the development of hyperlipidemia in subclinical hypothyroidism cannot be explained only by the role of thyroid hormones. This means that elevated TSH also plays a role in the development of hypercholesterolemia in hypothyroidism, but by having a different effect on the metabolism of lipids.

In addition to thyroid cells, TSH receptors are also expressed in many extrathyroidal tissues, including the liver *(Tian L, 2010; Xu C, 2012).* TSH binds to the TSH receptor on

hepatocytes and stimulates the cyclic adenosine monophosphate/protein kinase A/cyclic adenosine monophosphate-responsive element binding protein(cAMP/PKA/CREB) signaling system. In this way, TSH upregulates the expression of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase, a rate-limiting enzyme in cholesterol synthesis, which can modulate lipoprotein metabolism and facilitate cholesterol uptake by the liver *(Tian L, 2010; Xu C, 2012; Wang F, 2012)*. Two cross-sectional studies discovered that TSH levels were associated with serum lipid profiles independent of thyroid hormones *(Xu C, 2012; Wang F, 2012)*. Furthermore, Wang *et al (Wang F, 2012)* observed that TSH levels induced a significant direct effect on TC levels. Xu *et al (Xu C, 2012)* quantitatively demonstrated that each 1 μIU/ml increase in the TSH level tended to elevate the TC level by 0.016 mmol/l. A study also revealed that TSH receptor could also play an important role in adipocyte differentiation and adipogenesis, resulting in obesity in mice and increasing BMI in humans *(Lu S, 2012).* TSH could stimulate lipolysis in cultured adipocytes and elevate serum-free fatty acid levels in vivo *(Gagnon A, 2010).*

The present study revealed significant positive correlation between TSH level and HDL and LDL levels. Furthermore, the risk of developing dyslipidemia due to high TSH level was identified as gender-related where females had a higher risk than males. Therefore, the results of the present study indicate that sex hormones may be an important contributor to this phenomenon. Tognini *et al (Tognini S, 2012)* also found that gender substantially influenced the association between thyroid status and serum lipid levels.

Regarding the mechanism of different sex hormones' effects on lipid metabolism, testosterone and estradiol have different roles. First, lipoprotein lipase (LPL) and hepatic lipase (HL) are the major lipolytic enzymes of the lipoprotein metabolism. These enzymes remove TG from the bloodstream and decrease the serum chylomicron levels. Androgens stimulate HL activity; however, estrogens inhibit the HL and LPL activities. Secondly, testosterone increases lipolysis by stimulating β-adrenergic activity. Thirdly, testosterone upregulates genes responsible for HDL-C catabolism and increases the activity of both hepatic lipase and scavenger receptor BI (SR-BI). Furthermore, SR-BI increases the uptake of lipids into hepatocytes and enhances cholesterol efflux from peripheral cells). Finally, estrogen is capable of increasing cholesterol and LDL-C levels and these metabolic effects appear to be mediated by estrogen receptor α.

Clinically, low levels of testosterone and high levels of estrogen are associated with unfavorable lipid levels. Several meta-analyses with the topic of the changes in lipoprotein profiles resulting from exogenous testosterone administration have been conducted. For instance, Whitsel *et al (Whitsel EA, 2001)* performed such a meta-analysis by analyzing 19 studies, and demonstrated that the intramuscular administration of testosterone esters to hypogonadal males was associated with a dosage-dependent reduction of TC and LDL-C levels. By contrast, considering estrogen, Wranicz *et al (Wranicz JK, 2005)* revealed a significantly positive correlation between estradiol levels and serum TC, TG and LDL-C levels. Ott *et al (Ott, 2011)* performed a study to explore the change of serum lipid levels of transsexuals after cross-gender therapy and significant increases of TC, TG and HDL-C were identified in male to female transsexuals. Another study demonstrated that the estradiol concentration in males had a significant negative correlation with HDL-C concentration and a significant positive correlation with the TG level.

Besides gender, age should also be taken as a crucial factor for TSH-related dyslipidemia. Results of the current study showed that the risk of hypothyroidism is directly related to age, where the prevalence of high TSH levels increases as the age of the patient increases. In addition to that, different studies have revealed that aging is generally associated with deterioration of serum lipid profile. It is further recognized that women have less risk of atherosclerotic cardiovascular disease compared with men up until midlife (age 50–60), after which the gap begins to narrow and hyperlipidemia in women even surpass those in men. Therefore, after menopause and beyond, lipid profile of women undergoes unfavorable changes, becoming worse than men.

CONCLUSION

In conclusion, we found that there is an association between serum TSH levels and the levels of cholesterol, triglycerides and LDL and the incidence of hyperlipidemia. Moreover, these associations were found to be stronger with increasing age. Furthermore, females showed more detrimental effects of high TSH on hyperlipidemia than males. The present study had both strengths and weaknesses. The importance of the study was that it focused on the correlation between TSH and serum lipid profiles which have become a major topic in the recent years. However, due to the higher prevalence of hypothyroidism in females than that in males, the number of males in the present study was relatively small. Another limitation of this study was lacking information concerning the lifestyle of the patients, such as eating

habits or smoking, and whether the patients are receiving lipid-lowering drugs and other treatments or not. All this may affect the accuracy of the results. Finally, further investigation is required to determine their exact cause-effect relationship and to discover if a short-term increase of serum lipids during hypothyroidism will increase the risk of cardiovascular diseases.

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