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RESEARCH ARTICLE

SERUM TSH AND 25(OH) D IN SAUDI THYROID CANCER PATIENTS: A RETROSPECTIVE, CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Thyroid cancer (TC) is the most common endocrine malignancy in the world. Previous studies that link the levels of thyroid-stimulating hormone (TSH) and 25-hydroxyvitamin D (25(OH) D) to TC have been relatively inconsistent. Our goal is to assess alterations in serum levels of TSH and 25(OH)D between TC patients and non-toxic goiter patients and to examine the association between TSH and 25(OH) D levels in Saudi patients. **Methods:** A retrospective analysis of serum hormone fluctuations in primary TC (n= 162) and non-toxic goiter (n=98) cases. **Results:** TSH was significantly higher in TC patients than in non-toxic goiter patients ($P<0.05$). When gender was taken into consideration, the difference in females remained significant but was eliminated in males. Conversely, there was an insignificant difference in 25(OH) D between the two groups ($P>0.05$). Spearman rank correlation analysis demonstrated a statistically insignificant association between TSH and 25(OH) D ($r=0.011$), TSH and ($r=0.005$), or 25 (OH)D and body mass index BMI ($r=0.159$) in TC patients. **Conclusion:** TSH level is associated with TC in female Saudi patients, independent of 25(OH) D or obesity.

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INTRODUCTION

Thyroid cancer (TC) is the most common endocrine malignancy in the world with a rapidly increased incidence rate over the past 30 years (Olson *et al*., 2019; Davies, 2010; Vaccarella *et al*., 2016). On a global scale, TC is the seventh and fourteenth most common cancer in females and males, respectively (Goodarzi *et al*., 2016). In Saudi Arabia, TC represents the second most common cancer in females and among the ten most commonly diagnosed tumors in males (Al-Eid, 2015). Although factors underlying disease progression are still unclear, increased age, female gender, exposure to ionizing radiation, obesity, history of benign thyroid disease, and a family history of TC are established risk factors (Wartofsky, 2010; Imaizumi, 2006; Preston-Martin *et al*., 2003; Iribarren *et al*., 2001; Kitahara, 2011). Thyroid-stimulating hormone (TSH) constitutes a growth factor for thyrocytes and controls thyroid functions. Production and secretion of thyroid hormones, triiodothyronine (T3) and thyroxine (T4), are regulated by TSH (McLeod, 2014). Blood concentrations of T3 and T4 inversely regulate the release of TSH, produced from the pituitary gland, through a negative feedback loop. Previous studies that link TSH levels to TC have been relatively inconsistent. For example, high TSH levels were associated with an increased TC risk in a meta-analysis of 22 studies (McLeod, 2012), and with papillary TC, the most common form of the tumor, in an animal model (Franco, 2011). On the other hand, it has recently been found that an increased risk of papillary TC is associated with low TSH levels among women and with high TSH levels among men (Huang, 2017). Vitamin D is a family of fat-soluble compounds mainly synthesized in the skin in response to sun exposure, or obtained from the diet.

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These compounds are responsible for regulation of intestinal absorption of calcium, magnesium, and phosphates, and regulation of cell signaling involving cell cycle, angiogenesis, and tissue invasion (Chakraborti, 2011). 25-hydroxyvitamin D (25(OH)D) is the major vitamin D form present in blood and is frequently measured to assess and monitor vitamin D status in individuals. The relationship between vitamin D deficiency and breast cancer, colon cancer, and prostate cancer has previously been examined (Deeb, 2007). However, its association with TC remains ill-defined. While previous studies reported that low levels of serum vitamin D are significantly associated with TC (Stepien *et al*., 2010; Roskies, 2012; Şahin, 2013; Heidari *et al*., 2017), other studies failed to reciprocate the same results (Jonklaas, 2013; Choi *et al*., 2017; Laney *et al*., 2010; Kachui *et al*., 2017). The aim of the current study, thus, is to examine the association of serum levels of TSH and 25 (OH) D with TC in Saudi patients. We hypothesize that there are significant differences in the levels of TSH and 25 (OH) D between TC patients as compared to non-toxic goiter patients. Additional analyses seek to determine whether the levels of TSH and 25 (OH) Dare significantly correlated, and whether they are influenced by obesity.

METHODS

Study Subjects and Design: This retrospective, cross-sectional study was approved by the institutional review board (IRB) at King Abdullah International Medical Research Center (KAIMRC) and included a total of 260 patients who were diagnosed with primary TC (*n*=162) or with non-toxic goiter (*n*= 98) during the period of January, 2015 to December, 2017 at King Abdul-Aziz Medical City (KAMC) in Riyadh, Saudi Arabia. Patients with TC were excluded if they did not have TSH and/or25(OH)D levels available, or if they had a history of thyroid-related autoimmune disease such as Hashimoto's thyroiditis and Graves' disease.TC patients, who underwent thyroidectomy and did have pre-operative TSH and/or 25(OH)D levels available, were also excluded. Likewise, patients with non-toxic goiter were excluded if they did not have TSH and/or 25(OH)D levels available or if they were pregnant. Some patients had both TSH and 25(OH)D levels measured, while others only had either. Figure 1shows the inclusion and exclusion criteria implemented in the current study.

Data collection: Clinical and demographic data collected from patients' medical records included TSH, 25(OH)D, lipid profile, glucose, body mass index (BMI), age, and gender.

Statistical analysis: Data from each group were expressed as median with 95% confidence interval (CI). Mann-Whitney test was used to test differences among TC patients and non-toxic goiter patients. In addition, Spearman rank correlation was used to test the correlation between two variables. Statistical analyses were performed using Graph Pad Prism software, and differences were considered significant when $P < 0.05$.

RESULTS AND DISCUSSION

The current study reveals a significant difference in circulating TSH levels in TC patients compared to those with non-toxic goiter (Figure 2A). When gender was taken into consideration, the difference in females remained significant (Figure 2B) but was abolished in males (Figure 2C). Our study also showed no correlation between serum 25(OH) D levels and TC (Figure 3) or between serum levels of 25(OH) D and TSH (Figure 4), independent of gender. Moreover, we examined the effect of BMI on both hormones, and, similarly, no statistically significant correlation between BMI and TSH or 25(OH)D levels could be found (Figure 5). These findings corroborate previous studies reporting a positive association between increased TSH serum levels and TC (McLeod, 2012; Franco, 2011). Along those lines, lowering TSH levels is an effective therapeutic approach that yields prolonged survival in TC patients (Jonklaas *et al*., 2006). This highlights the positive role of TSH in driving TC progression, an effect also mirrored in other types of cancers (Moeller *et al*., 2013). Gender disparity is observed in multiple types of cancers, including lung, thyroid, and liver (Cerfolio, 2006; Ortega, 2004), and TC is 2.9 times more common in females than in males (Rahbari, 2010).

Table 1. Baseline characteristics of TCpatients (*n*=124) and non-toxic goiter patients (*n*=74). Data are represented as mean ± standard deviation or percentage.

Characteristic	Non-toxic goiter	Thyroid cancer
Age	57 ± 16	51 ± 17
Gender	F: 84%	F: 74%
	M: 16%	M: 26%
BMI	32 ± 7	30 ± 7
Diabetics	32%	34%
Total cholesterol	4.3±1.2	4.4±1.7
Triglycerides	1.4 ± 0.8	1.7 ± 0.9

It remains elusive, however, what the genetic or molecular determinants of this predisposition are. Studies on estrogen signaling, somatic mutations in *BRAF*, and neurotrophin receptor-tyrosine kinase (NTRK) have so far failed to explain the gender disparity observed in TC (Rahbari, 2010; Lee, 2007; Liu, 2006; Tuttle, 2008; Moses, 2010). Interestingly, differences among men and women are specific to the histopathological subtype of TC. While aggressive types are evenly distributed in both genders, follicular TC and papillary TC are more commonly seen in females (Rahbari, 2010). On the other hand, men tend to have poorer prognosis than women (Kilfoy, 2009; Gilliland, 1997). Marital status and ethnicity have also been found to be predictors of TC survival (Gilliland, 1997). Recently, Huang *et al.* identified a positive association between risk of papillary TC in women and total triiodothyroinine (TT_3), a hormone under the influence of TSH (Huang, 2017). This suggests an augmented response by thyroid tissue to TSH in females compared to males, which may explain, at least in part, the significantly increased TSH levels in TC women reported in the current study.

The association between obesity and TC has previously been investigated. In a recent study, while an inverse relationship between TC risk and BMI was found, average TSH level was significantly lower as BMI increased (Handelsman *et al*., 2019). An earlier study reported that risk for papillary TC was inversely associated with levels of TSH within the normal range, irrespective of gender (Huang, 2017). This is in contrast to investigations linking higher TSH with increased BMI (Knudsen, 2005; Iacobellis, 2005), a view that has recently been challenged (Rios-Prego, 2019), and further corroborated by the current study. Consequently, management of TC patients is not apparently influenced by body weight, a factor that similarly does not seem to predispose for TC. Although the major role of vitamin D is regulating bone health and mineral homeostasis, its impact on cardiovascular, immune, and malignant disease, has recently ignited the interest of many investigators (Kim, 2017).

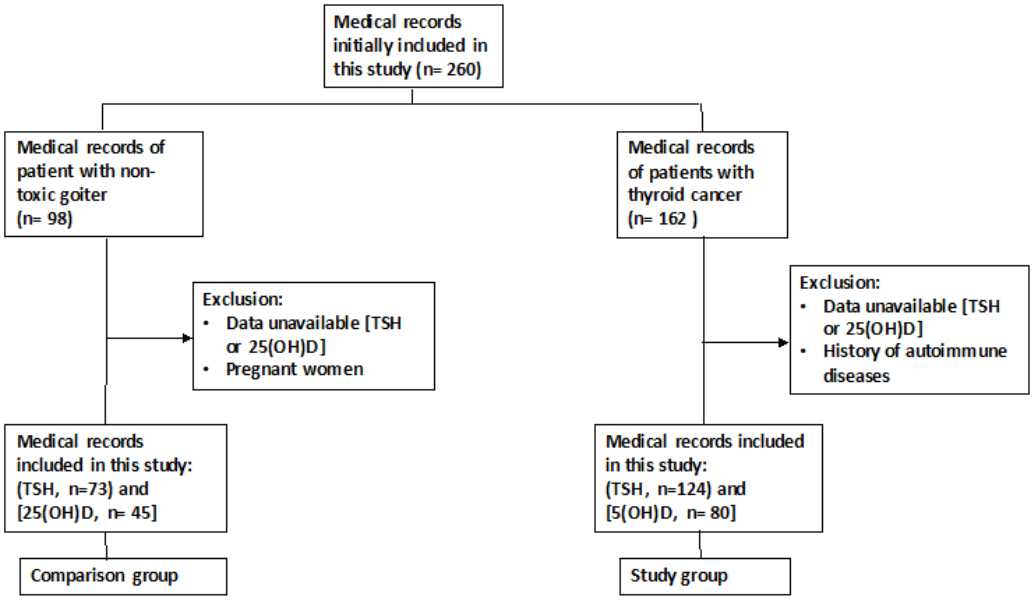

Figure 1. Inclusion and exclusion criteria. Flowchart showing selection procedure in both study and comparison groups

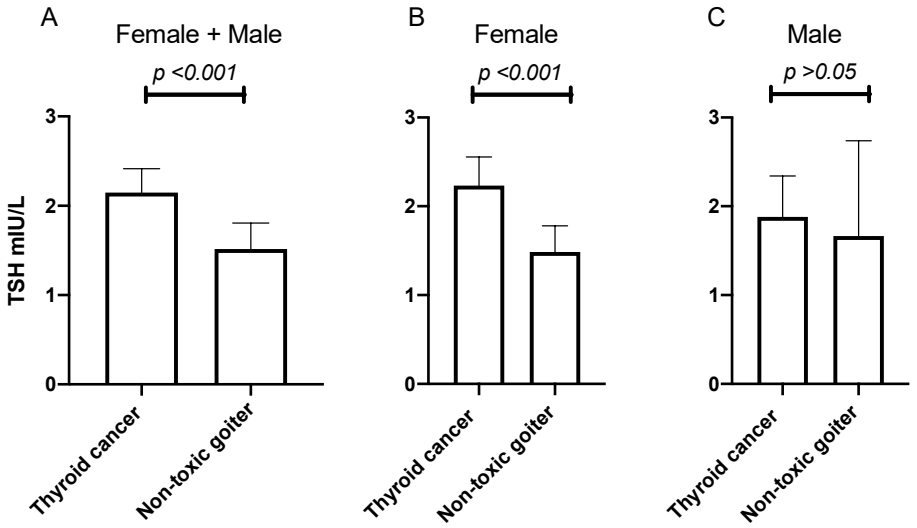

Figure 2. TSH levels in TC patients. Differences in TSH levels between TC and non-toxic goiter patients in both males and females(A), females only (B), and males only (C)

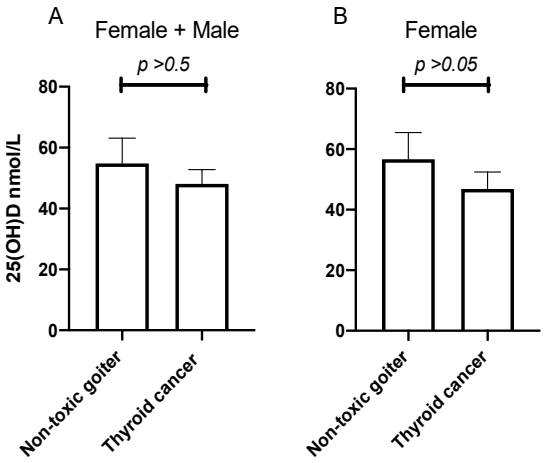

Figure 3. 25(OH)D in TC patients. Comparative analysis of 25(OH)D levels in TC and non-toxic goiter patients in both males and females(A) and in females(B). Mann-Whitney test was used to examine the statistical significance of TSH levels between the two groups of patients

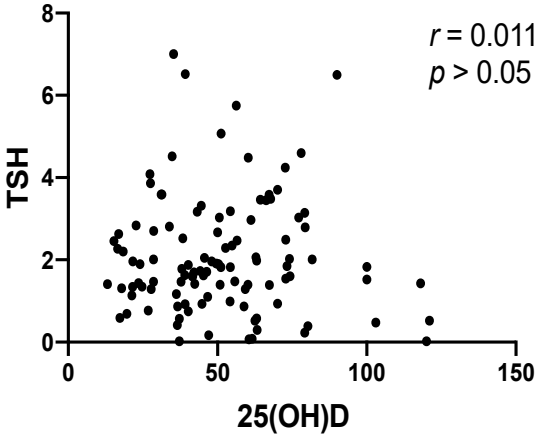

Figure 4. TSH and 25(OH) D serum levels are unrelated. Spearman correlation analysis showing insignificant correlation between the levels of TSH and 25(OH)D in patients with thyroid disorders

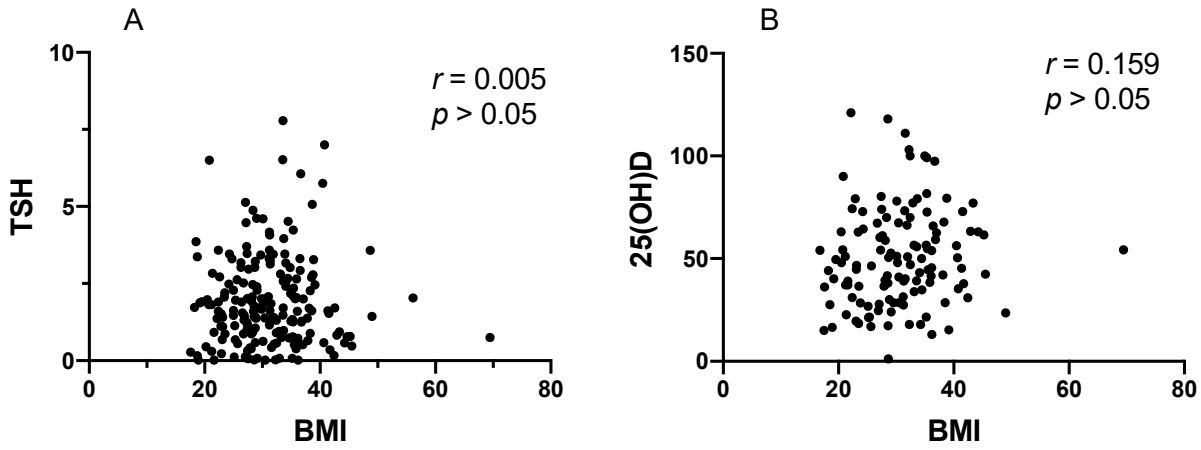

Figure *5.* **TSH, 25(OH)D, and BMI are unrelated. Spearman correlation analysis showing insignificant correlation neither between TSH and BMI (A) nor between 25(OH)D and BMI (B) in patients with thyroid disorders**

Although our data show no positive correlation between serum 25(OH)D levels and TC, impaired vitamin D signaling has previously been shown to promote TC growth (Muscogiuri, 2015; Kmiec, 2015), as the hormone modulates signal transduction cascades involved in cellular survival, growth, and proliferation (Kim, 2017). In spite of this, several clinical investigations found no association between serum 25(OH)D and TC staging or prognosi. Furthermore, serum 25(OH)D does not seem to segregate benign and malignant thyroid tumors (Danilovic, 2016). Notably, the expression of vitamin D receptor (VDR) is differentially modulated in malignant thyroid tissue (Khadzkou, 2006), suggesting it may represent an attractive target for further investigation. Likewise, polymorphisms in *VDR* have also been studied, with one report finding a positive association with TC and another failing to do so (Danilovic, 2016). It must be stressed that conflicting results observed in population-based studies, are influenced by many factors. Individual variation among study participants, circadian rhythm and seasonal changes in blood chemistry, different analysis procedures and diagnostic methods, are among the most common. With the increasing global incidence of TC (Rahbari, 2010), future efforts should focus on identifying molecular determinants of TC predisposition, diagnosis, and prognosis in Saudi patients. A genomic approach to reveal novel mutations relevant to TC is also warranted.

Conflict of interest: The authors declare they have no conflict of interest relevant to this manuscript.

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