TSH Level as a Risk Factor for Thyroid Malignancy in Euthyroid Nodules

Abdulaziz K Alaraifi
Division of Otolaryngology-Head and Neck Surgery, Department of Surgery, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia

Mohammed Alessa
Department of Otolaryngology-Head and Neck Surgery, College of Medicine, King Saud University, Riyadh, Saudi Arabia

Leen O Hijazi
Division of Otolaryngology-Head and Neck Surgery, Department of Surgery, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia https://orcid.org/0000-0002-3911-617X

Areej M Alayed
College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

Abdulaziz A Alsalem (a.alsalem@mail.com)
Division of Otolaryngology-Head and Neck Surgery, Department of Surgery, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia https://orcid.org/0000-0002-2196-1287

Research Article

Keywords: Thyroid cancer, TSH, Thyroid nodule, Euthyroid nodule, Bethesda

Posted Date: October 11th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2136397/v1

Abstract

Objective

With the increased prevalence of incidental thyroid cancer, determining the predictors of thyroid malignancy has become a source of debate. This study aimed to determine the impact of Thyroid Stimulating Hormone (TSH) levels on thyroid cancer incidence in euthyroid nodules.

Methods

A retrospective study included 421 patients who underwent thyroidectomy at a tertiary hospital between 2016 and 2020. Patients' demographics, history of cancer, preoperative workup, and final histology reports were obtained. The study sample was divided into two groups based on the final histopathology (benign vs. malignant). The two groups were compared using the appropriate statistical tests to determine the predictors of thyroid cancer in euthyroid nodules.

Results

TSH level was significantly higher in malignant nodules compared to benign nodules (1.94 vs. 1.62, p = 0.002). It was 1.54 times more likely for thyroid nodules to be malignant when TSH levels were higher (p = 0.038). Meanwhile, larger nodules (> 4 cm) were significantly more prevalent in benign nodules (43.1%) than in malignant nodules (21.1%). Larger nodules decreased the possibility of thyroid cancer by 24% (OR = 0.760, p-value 0.004).

Conclusion

High TSH levels in euthyroid nodules were significantly correlated with the risk of thyroid malignancy. In addition, as Bethesda category proceeded toward malignancy, TSH levels increased. High TSH levels and small nodule sizes can be used as additional parameters in predicting thyroid cancer in euthyroid nodules.

Introduction

Thyroid nodules are common in clinical practice; however, their incidence varies according to the diagnostic methods (1). Epidemiological studies have shown a 2–6% prevalence on physical examination, 19–68% using high-resolution ultrasound, and 36–50% in autopsy series (1, 2). The incidence rate of thyroid cancer is rising with the increased detection rates of non-palpable thyroid nodules (2). The risk factors for thyroid malignancy in thyroid nodules include age (> 70 years), male gender, radiation exposure, family history, compressive symptoms, cervical lymphadenopathy, rapid growth, and fixed-hard nodules (3).

With the increased rate of incidental thyroid cancer, finding the best available diagnostic method has been a subject of debate. Fine Needle Aspiration (FNA) using the Bethesda System for Reporting Thyroid Cytopathology has been the initial diagnostic method of choice for the past two decades (4). However, FNA has its limitations, being nondiagnostic and inconclusive in 20–25% of cases, necessitating further evaluation (5). Laboratory and molecular markers have also been reported to be of prognostic and predictive value. Thyroid Stimulating Hormone (TSH) has been evaluated as a predictor of malignancy in thyroid nodules, showing that a higher serum concentration of TSH is associated with an increased risk of thyroid cancer (6–10).

Although there are multiple studies on the association between TSH level and thyroid malignancy, studies investigating this relationship in euthyroid nodules are limited. Therefore, this study aims to determine the influence of TSH levels on the incidence of thyroid cancer in euthyroid patients.

Methods

Study design and subjects

A retrospective study included all patients who underwent hemithyroidectomy or total thyroidectomy at King Abdulaziz Medical City in Riyadh, Saudi Arabia (SA), from 2016 to 2020. The indications for thyroidectomy were based on the American Thyroid Association Management (ATA) Guidelines (2015) (1). Patients with hypothyroidism, hyperthyroidism, history of radioactive iodine treatment or thyroid medication use were excluded from the study. A total of 421 patients met our criteria and were included in the study.

Data Collection:

The patients' electronic records were reviewed using the hospital's health care information system. The data collection flowsheet included patients' demographics (i.e., age, gender, height, and weight), history of cancer, thyroid function tests, FNA finding, nodule size, and final histopathology.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS®) version 25. Categorical data were summarized and reported as frequencies and proportions, while continuous variables were summarized and reported as means and standard deviations (SD). The study sample was divided into two groups based on final histopathology (benign vs. malignant). Categorical and continuous variables were compared using chi-square test and independent T-test, respectively. All the variables were included in a multivariable logistic regression model to determine the predictors of thyroid malignancy in euthyroid nodules. A p-value of < 0.05 was declared as statistically significant.

Ethics And Permissions

The institutional review board (IRB) of King Abdullah International Medical Research Center (KAIMRC) approved the study (KIMARC, NRC21R/364/09).

Results

The study included 421 patients with thyroid nodules. The mean age of our patients was 45.93 (±14.3) years old, and females represented most of our sample (80.3%). The mean TSH level was 1.84 (±1.0) mIU/L, and almost two-thirds of the patient had a TSH level less than 2 mIU/L (63.9%). Final surgical histopathology showed benign pathology in one-third of the cases (32.5%) and malignant in almost two-thirds of the patients (67.5%). Table 1 demonstrates the demographic and clinical characteristics of all patients.

The mean TSH level was significantly higher in malignant thyroid nodules compared to benign nodules (1.94 vs. 1.62, p-value 0.002). TSH level (>2 mIU/L) was significantly more common in malignant thyroid nodules (39.4%) than in benign nodules (29.2%), p-value (0.040). Large nodules (≥ 4 cm) were more common in benign nodules (43.1%) than in malignant nodules (21.1%), p-value (0.000). Moreover, the mean nodule size and mean BMI were significantly larger in patients with benign thyroid nodules than in malignant nodules (3.88 vs. 2.74, p-value 0.000) and (31.65 vs. 30.33, p-value 0.043), respectively. Table 2 demonstrates the differences between benign and malignant thyroid nodules.

Table 3 illustrates the predictors of thyroid cancer in euthyroid patients in multivariable regression analysis. A higher TSH level increased the likelihood of malignancy in thyroid nodules by 1.54 times (p-value 0.038). Moreover, larger nodules decreased the possibility of thyroid cancer by 24% (OR=0.760, p-value 0.004). Age, gender, BMI, history of cancer, and free thyroxine (FT4) level were not associated with the final histopathology of thyroid nodules in multivariable regression analysis.

Table 4 and figure 1 demonstrate the relationship between the TSH level and the Bethesda system category. TSH level was significantly correlated with the Bethesda system category (p-value 0.001). It showed that the higher the Bethesda category, the higher the TSH level.

Table 1: Demographic and clinical characteristics of all study cohorts

Variables	Statistics (n = 421)
Age (Mean ± SD)	45.93 (±14.3)
Age (N%)	
1. < 55 years	294 (69.8%)
2. ≥ 55 years	127 (30.2%)
Gender (N%)	
1. Male	83 (19.7%)
2. Female	338 (80.3%)
BMI (Mean ± SD)	30.76 (±6.3)
Personal history of cancer (N%)	
1. Yes	33 (7.8%)
2. No	388 (92.2%)
TSH (Mean ± SD)	1.84 (±1.0)
TSH (N%)	
1. ≤ 2 mIU/L	269 (63.9%)
2. > 2 mIU/L	152 (36.1%)
FT4 (Mean ± SD)	12.51 (±1.5)
Nodule size (Mean ± SD)	3.11 (±2.0)
Nodule size (N%)	
1. < 4 cm	302 (71.7%)
2. ≥ 4 cm	119 (28.3%)
Final histopathology (N%)	
1. Benign	137 (32.5%)
2. Malignant	284 (67.5%)

Table 2: Description of selected characteristics of benign and malignant thyroid nodules

Variables	Benign (n = 137)	Malignant (n = 284)	P-value
Age (Mean ± SD)	45.24 (±13.4)	46.27 (±14.64)	0.489
Age (N%)			0.451
1. < 55 years	99 (72.3%)	195 (68.7%)	
2. ≥ 55 years	38 (27.7%)	89 (31.3%)	
Gender (N%)			0.796
1. Male	28 (20.4%)	55 (19.4%)	
2. Female	109 (79.6%)	229 (80.6%)	
BMI (Mean ± SD)	31.65 (±6.04)	30.33 (±6.33)	0.043*
Personal history of cancer (N%)			0.148
1. Yes	7 (5.1%)	26 (9.2%)	
2. No	130 (94.9%)	258 (90.8%)	
TSH (Mean ± SD)	1.62 (±1.0)	1.94 (±1.0)	0.002*
TSH (N%)			0.040*
1. ≤ 2 mIU/L	97 (70.8%)	172 (60.6%)	
2. > 2 mIU/L	40 (29.2%)	112 (39.4%)	
FT4 (Mean ± SD)	12.62 (±1.55)	12.45 (±1.51)	0.300
Nodule size (Mean ± SD)	3.88 (±1.83)	2.74 (±1.91)	0.000*
Nodule size (N%)			0.000*
1. < 4 cm	78 (56.9%)	224 (78.9%)	
2. ≥ 4 cm	59 (43.1%)	60 (21.1%)	

* Significant at p<0.05 level.

Table 3: Predictors of thyroid cancer in euthyroid patients in logistic regression analysis

Variable	Odd Ratio	P-value	95% LCI	95% UCI
TSH level	1.544	0.038*	1.024	2.329
Nodule size	0.760	0.004*	0.630	0.918
BMI	0.967	0.083	0.931	1.004
FT4	0.890	0.109	0.771	1.026
Older age	1.004	0.754	0.978	1.031
Male gender	1.058	0.844	0.604	1.852

* Significant at p<0.05 level.

Table 4: Mean TSH levels in different Bethesda system categories (II-VI)

Variable	II (n = 128)	III (n = 79)	IV (n = 38)	V (n = 53)	VI (n = 123)	P-value
TSH (Mean ± SD)	1.57 (±0.93)	1.77 (±0.95)	1.91 (±1.1)	2.01 (±0.99)	2.07 (±1.0)	0.001*

Discussion

Thyroid nodules are common clinical findings, with a prevalence reaching 70%. Most thyroid nodules are benign, while the incidence of malignancy is around 5% (11). Multiple clinical, pathological, laboratory and radiological factors were proposed to differentiate benign from malignant nodules; however, the reported predictors are inconclusive.

TSH is a major regulator of thyroid function. Multiple studies have evaluated it as a predictor of malignancy in thyroid nodules with conflicting results (6–10, 12). Most studies showed that a higher serum concentration of TSH is associated with an increased risk of thyroid cancer. However, studies investigating this relationship in euthyroid nodules are limited (13). In the present study, the TSH level was higher in malignant euthyroid nodules compared to benign euthyroid nodules. TSH levels within the higher end of the reference range increased the likelihood of thyroid malignancy by 1.54 times. Baser et al. evaluated 1433 patients who underwent thyroidectomy and reported that malignant thyroid nodules had elevated TSH levels compared to the benign group ($p < 0.001$) (13). The TSH level threshold above which the risk of thyroid malignancy increases was 1 mIU/L (14). Conflicting these studies, Castro et al. reported that serum TSH level was not associated with increased malignancy risk among 327 thyroid lesions suspicious for follicular neoplasm or Hürthle cell neoplasms (12). Singh et al. found no association between Hashimoto's thyroiditis, which has high TSH levels, and the incidence of malignancy in a meta-analysis conducted in 1999 (15). Moreover, Holm et al. found that patients with uncontrolled hypothyroidism had no increased risk of thyroid malignancy after two decades of follow-up (16).

It is unclear whether higher TSH levels increase the malignant potential of the thyroid nodules or whether the malignant nodules produce higher levels of TSH. It is suggested that TSH modulates the thyroid cell function, growth, and expression of specific proteins after binding to its receptors of the follicular cells. This leads to the continuous stimulation and proliferation of the thyroid nodules by high TSH levels, which results in cellular alternations and modulation of thyroidal gene expression (17, 18). Animal experiments on mice and golden hamsters showed that TSH stimulation is associated with thyroid malignancy, as overstimulation of TSH leads to hyperplasia and, eventually, thyroid cancer (6). Moreover, this hypothesis is supported by the fact that patients with well-differentiated thyroid cancer benefit from TSH suppressive treatment with levothyroxine as it decreases disease progression, recurrence rates, and cancer-related mortality (19). On the other hand, recent genetic studies aimed to search for sequence variants that link TSH with thyroid malignancy. Two variants, located on 9q22.33 and 14q13.3, were associated with thyroid cancer; both have also been associated with low serum TSH (20). Moreover, an

inverse relationship between TSH receptor mRNA and cancer progression was documented by Shi et al (21).

TSH level was measured for each Bethesda category separately in the present study. TSH level was significantly correlated with the Bethesda system category. The higher the Bethesda category, the higher the TSH level was, and the highest levels were found in the malignant categories (V-VI). Similarly, Baser et al. reported that TSH levels increased gradually as the Bethesda category did, rising from Bethesda category II to VI (13).

Malignant thyroid nodules are smaller in size than benign in the present study. Moreover, our study showed the large nodule size (> 4cm) decreased the possibility of thyroid cancer by 24%. Our findings correlate with Castro et al. and Baser et al., who reported that smaller nodules were more frequently seen in patients with malignancy (12, 13). On the other hand, Sahin et al. and Chung et al. found no association between the size of the thyroid nodule and its malignant potential (22, 23).

In addition to TSH, low FT4 levels were reported as an independent predictor of thyroid malignancy in the literature (24). Our study had no significant association between FT4 levels and thyroid malignancy. Extremes of age and the male gender were also reported to increase the risk of thyroid malignancy (3). However, we did not find a significant correlation between age and gender with thyroid malignancy. A meta-analysis conducted by Zhao et al. found that obesity is significantly associated with an increased risk of thyroid cancer (25). In our study, the univariate analysis showed a significant association between high BMI and the risk of thyroid malignancy; however, the multivariate analysis did not support this finding.

Our study has a few limitations, such as being a retrospective single-center study which may limit its generalizability. Moreover, it only included patients who underwent thyroidectomies. Patients with Bethesda categories I-III who did not have other indications for surgical intervention were not included in the study. However, this is the first study to evaluate the association between TSH levels and thyroid malignancy in SA.

Conclusion

High TSH levels in euthyroid nodules were significantly associated with the risk of thyroid malignancy. In addition, as Bethesda category proceeded toward malignancy, TSH levels increased. High TSH levels and small nodule sizes can be used as additional parameters in predicting thyroid cancer in euthyroid nodules.

Declarations

Ethical considerations The study was approved by the Institutional Review Board of King Abdullah International Medical Research Center (KAIMRC), Riyadh, Saudi Arabia [Date of approval 12 September

2021, approval number NRC21R/364/09]. Due to the retrospective nature of the study and the use of anonymized patient data, the requirement for informed consent was waived.

Acknowledgements

None

Conflict of Interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1–133.
2. Yoon DY, Chang SK, Choi CS, Yun EJ, Seo YL, Nam ES, et al. The prevalence and significance of incidental thyroid nodules identified on computed tomography. J Comput Assist Tomogr. 2008;32(5):810–5.
3. Boelaert K. The association between serum TSH concentration and thyroid cancer. Endocr Relat Cancer. 2009;16(4):1065–72.
4. Yazici P, Mihmanli M, Bozkurt E, Ozturk FY, Uludag M. Which is the best predictor of thyroid cancer: thyrotropin, thyroglobulin or their ratio? Hormones (Athens). 2016;15(2):256–63.
5. Chow LS, Gharib H, Goellner JR, van Heerden JA. Nondiagnostic thyroid fine-needle aspiration cytology: management dilemmas. Thyroid. 2001;11(12):1147–51.
6. Fiore E, Vitti P. Serum TSH and risk of papillary thyroid cancer in nodular thyroid disease. J Clin Endocrinol Metab. 2012;97(4):1134–45.
7. Haymart MR, Repplinger DJ, Leverson GE, Elson DF, Sippel RS, Jaume JC, et al. Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. J Clin Endocrinol Metab. 2008;93(3):809–14.
8. Kim HK, Yoon JH, Kim SJ, Cho JS, Kweon SS, Kang HC. Higher TSH level is a risk factor for differentiated thyroid cancer. Clin Endocrinol (Oxf). 2013;78(3):472–7.
9. Zafon C, Obiols G, Mesa J. Preoperative TSH level and risk of thyroid cancer in patients with nodular thyroid disease: nodule size contribution. Endocrinol Nutr. 2015;62(1):24–8.
10. Shi RL, Liao T, Qu N, Liang F, Chen JY, Ji QH. The Usefulness of Preoperative Thyroid-Stimulating Hormone for Predicting Differentiated Thyroid Microcarcinoma. Otolaryngol Head Neck Surg. 2016;154(2):256–62.

11. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973–2002. JAMA. 2006;295(18):2164–7.
12. Castro MR, Espiritu RP, Bahn RS, Henry MR, Gharib H, Caraballo PJ, et al. Predictors of malignancy in patients with cytologically suspicious thyroid nodules. Thyroid. 2011;21(11):1191–8.
13. Baser H, Topaloglu O, Tam AA, Evranos B, Alkan A, Sungu N, et al. Higher TSH can be used as an additional risk factor in prediction of malignancy in euthyroid thyroid nodules evaluated by cytology based on Bethesda system. Endocrine. 2016;53(2):520–9.
14. Adhami M, Michail P, Rao A, Bhatt CR, Grodski S, Serpell JW, et al. Anti-Thyroid Antibodies and TSH as Potential Markers of Thyroid Carcinoma and Aggressive Behavior in Patients with Indeterminate Fine-Needle Aspiration Cytology. World J Surg. 2020;44(2):363–70.
15. Singh B, Shaha AR, Trivedi H, Carew JF, Poluri A, Shah JP. Coexistent Hashimoto's thyroiditis with papillary thyroid carcinoma: impact on presentation, management, and outcome. Surgery. 1999;126(6):1070–6; discussion 6–7.
16. Holm LE, Blomgren H, Lowhagen T. Cancer risks in patients with chronic lymphocytic thyroiditis. N Engl J Med. 1985;312(10):601–4.
17. Ledent C, Parmentier M, Maenhaut C, Taton M, Pirson I, Lamy F, et al. The TSH cyclic AMP cascade in the control of thyroid cell proliferation: the story of a concept. Thyroidology. 1991;3(3):97–101.
18. Kimura T, Van Keymeulen A, Golstein J, Fusco A, Dumont JE, Roger PP. Regulation of thyroid cell proliferation by TSH and other factors: a critical evaluation of in vitro models. Endocr Rev. 2001;22(5):631–56.
19. Biondi B, Filetti S, Schlumberger M. Thyroid-hormone therapy and thyroid cancer: a reassessment. Nat Clin Pract Endocrinol Metab. 2005;1(1):32–40.
20. Gudmundsson J, Sulem P, Gudbjartsson DF, Jonasson JG, Masson G, He H, et al. Discovery of common variants associated with low TSH levels and thyroid cancer risk. Nat Genet. 2012;44(3):319–22.
21. Shi Y, Zou M, Farid N. Expression of thyrotropin receptor gene in thyroid carcinoma is associated with good prognosis. Clin Endocrinol (Oxf). 1993;39:269–74.
22. Sahin M, Gursoy A, Tutuncu NB, Guvener DN. Prevalence and prediction of malignancy in cytologically indeterminate thyroid nodules. Clin Endocrinol (Oxf). 2006;65(4):514–8.
23. Chung SR, Baek JH, Choi YJ, Sung TY, Song DE, Kim TY, et al. The relationship of thyroid nodule size on malignancy risk according to histological type of thyroid cancer. Acta Radiol. 2020;61(5):620–8.
24. Gul K, Ozdemir D, Dirikoc A, Oguz A, Tuzun D, Baser H, et al. Are endogenously lower serum thyroid hormones new predictors for thyroid malignancy in addition to higher serum thyrotropin? Endocrine. 2010;37(2):253–60.
25. Zhao ZG, Guo XG, Ba CX, Wang W, Yang YY, Wang J, et al. Overweight, obesity and thyroid cancer risk: a meta-analysis of cohort studies. J Int Med Res. 2012;40(6):2041–50.

Figures

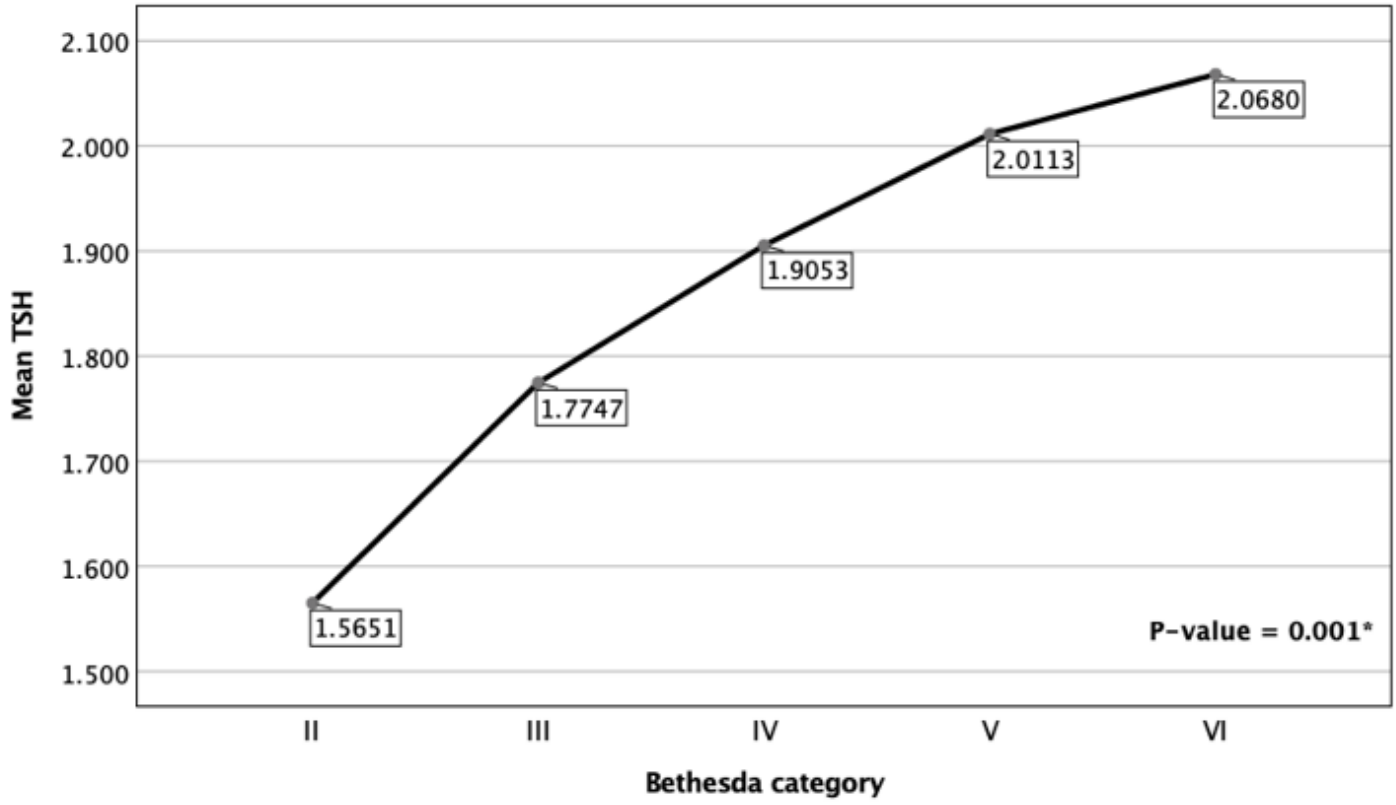

Figure 1

Mean TSH levels in different Bethesda system categories (II-VI)