International Journal of General Medicine

Dovepress
Taylor & Francis Group

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ORIGINAL RESEARCH

Stimulated Thyrotropin (TSH) Levels Were Inversely Correlated with Age

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Purpose: Serum Thyrotropin (TSH) levels in the elderly have been reported to be inconsistent in different studies. One of the difficulties in determining the effect of aging on TSH levels is that TSH levels are influenced by various factors, including thyroid-related factors. Therefore, this study aimed to assess the effect of aging on TSH levels while controlling for thyroid factors.

Patients and Methods: This study included a total of 343 subjects, who underwent thyroidectomy, levothyroxine (LT4) supplementation and withdraw. All participants were divided into young(18–44year old), middle(45–59year old), and old age(>60year old) groups based on their age. The clinical data of the subjects were reviewed, and analyzed based on their age.

Results: With LT4 supplementation, there was no difference in free triiodothyronine (FT3), free thyroxine (FT4), and TSH levels among the three age groups. However, after approximately 4 weeks of LT4 withdrawal, the TSH levels of the three groups showed significant differences. The median stimulated TSH levels were 100, 83.1, and 64.6 mIU/L in the young, middle, and old age groups, respectively ($P<0.01$). Moreover, the percentages of subjects, with TSH levels higher than 100 mIU/L, were 63.2%, 33.1%, and 12.9% ($P<0.01$) in the young, middle, and old age groups, respectively. Spearman correlation analysis ($R=-0.42$, $P<0.01$) and partial correlation analysis ($R=-0.44$, $P<0.01$) revealed an inverse correlation between age and TSH levels after LT4 withdrawal.

Conclusion: Aging plays an important role in TSH regulation. Age was inversely related to the stimulated TSH levels. The effect of senescence on TSH levels, as well as the underlying regulatory mechanisms, warrant further investigation.

Keywords: aging, senescence, pituitary, thyroid

Introduction

TSH, a hormone synthesized and secreted by the pituitary gland, regulates the proliferation of thyroid cells, and stimulates the thyroid gland to produce thyroxine (T4). However, studies have reported that the TSH receptor (TSHR) is not only present in the thyroid but also in many other organs, including the brain, liver, heart, and adipose tissue.[1–5] Indeed, TSH plays a crucial role in regulating various extra-thyroid physiological and pathological processes, including lipid metabolism, cognitive function, and atherosclerosis.[6,7] Moreover, abnormal TSH levels, whether elevated (subclinical hypothyroidism) or decreased (subclinical hyperthyroidism), have been associated with various diseases.[7] Higher TSH levels are associated with cardiovascular disease, dyslipidemia, cognitive decline, dementia, and Type 2 diabetes mellitus.[8] On the other hand, lower TSH levels are related to cardiovascular disease, osteoporosis, fractures, dementia, and cognitive dysfunction.[9] It is worth noting that these diseases are often associated with aging. Therefore, understanding the changes in TSH levels during aging can provide valuable insights into the prevention and treatment of these TSH-related diseases.

The relationship between aging and TSH levels is a topic of ongoing debate in conflicting studies. The TSH levels of the elderly have been reported to be increased, decreased, or unchanged.[10–13] These discrepancies can be attributed to

Received: 9 October 2024
Accepted: 21 December 2024
Published: 27 December 2024

various factors, including differences in study populations, study designs, and the complexity of the hypothalamus-pituitary gland-thyroid (HPT) axis.

As part of the HPT axis coordination, TSH is feedback-suppressed by T4 and Triiodothyronine (T3) from the thyroid gland, and is stimulated by thyrotropin-releasing hormone (TRH) from the hypothalamus. This intricate HPT axis coordination maintains normal thyroid function. Therefore, changes in serum TSH concentration during the aging process may not solely reflect alterations in TSH synthesis or secretion from the pituitary gland, but also the adaptation of the HPT axis to aging. It is challenging to determine whether there is a single modifying factor or if each organ within the axis adjusts independently during the aging process. While TRH remains relatively stable during the aging process,[14] the pituitary and thyroid play critical roles in the HPT axis adjustment to aging. Researchers and clinicians have primarily focused on the aging thyroid, and considered that the changed physiological thyroid function contributes to the variation in TSH levels during aging. However, these views have not been systematically verified. The direct effect of aging on TSH levels is still not fully understood. This drives us to explore the effect of age on TSH levels while controlling for thyroid factors.

Materials and Methods

patient

In this retrospective study, a total of 343 patients after thyroidectomy were included. Due to differentiated thyroid cancer (DTC), the patients underwent thyroidectomy, TSH suppression therapy (levothyroxine supplementation, LT4 supplementation), radioactive iodide (RAI) therapy in Shandong Provincial Hospital from October 2021 to January 2023. Additionally, the preparation for RAI includes TSH stimulation (levothyroxine withdrawal, LT4 withdrawal), and a low iodine diet[15,16] (Figure1). These treatments allowed for the study of changes in TSH levels by controlling for thyroid factors.

Patients with the following conditions were excluded: (1) patients with pituitary diseases; (2) patients with neuropsychiatric disorders, renal disease, and other conditions affecting thyroid function; (3) females who were pregnant or had taken hormonal medication within the past one year. (4) patients who lacked sufficient follow-up information.

The subjects were divided into three groups based on age: young, middle, and old age group. The cutoff points chosen for these groups were 45 years and 60 years.

The recorded data included the subjects' medical history and laboratory test results. Medical history included age, gender, height, body weight, blood pressure, and cancer situation (number and maximum diameter of DTC). Baseline laboratory tests included FT3, FT4, TSH, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine,

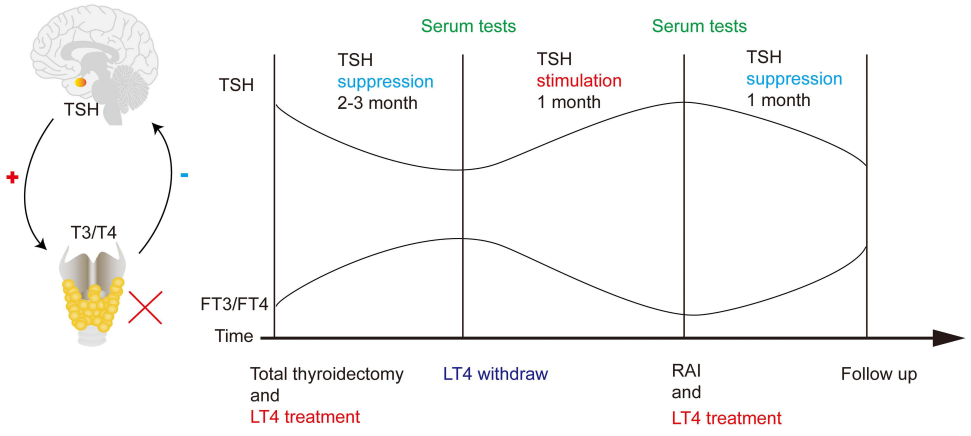

Figure 1 The treatment process of DTC patients.
Notes: In China, the patients with DTC usually underwent thyroidectomy, TSH suppression therapy (LT4 treatment), RAI therapy and TSH suppression therapy sequentially. Additionally, the preparation for RAI included TSH stimulation (LT4 withdrawal) and a low iodine diet. In this process, we monitored the changes of serum TSH and thyroid hormone (FT3 and FT4) levels.
Abbreviations: DTC, differentiated thyroid cancer; LT4, levothyroxine; RAI, radioactive iodide; TSH, Thyrotropin; FT3, free triiodothyronine; FT4, free thyroxine.

glycemia, and uric acid. Body mass index (BMI) is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m^2). Glomerular filtration rate (GFR) is calculated using the MDRD formulas.[17,18]

Laboratory Examination

The thyroid hormones of the subjects were detected before and after T4 withdrawal separately. The hormone assessment of thyroid function, including FT3, FT4, and TSH, was performed using Chemiluminescent methods (Cobas E601, Roche, Basel, Switzerland).

When subjects admitted to hospital for radioactive iodide (RAI) therapy, Other clinical data were reviewed and assessed after T4 withdrawal. Thyroglobulin (Tg) and Tg antibody (TgAb) were determined by ADVIA Centaur XP (Siemens, Germany). Urinary iodine was assessed by colorimetry method (AU 5800, Beckman, California, USA). Biochemical markers (ALT, AST, Creatinine, Glycemia, uric acid) were assessed by the ARCHITECT ci16200 Integrated System (Abbott, Illinois, USA).

The range of detection of the analytics measured was as follows: FT3(0.6–50pmol/l); FT4(0.5–100pmol/l); TSH (0.005–100uIU/mL); Tg(0.1–1000ng/mL); TgAb(10–4000IU/mL); ALT(3–500u/l); Creatinine(30–2000umol/l); Glycemia(0.6–45mmol/l); uric acid(89–1785umol/l).

Statistical Analysis

The statistical analysis was conducted using SPSS (version 21th). To assess the normality of the data, the Kolmogorov–Smirnov test and Q-Q diagram were employed. Continuous variables, that were found to be non-normally distributed, were presented as median with interquartile range. While, normally distributed variables were expressed as mean ± standard deviation (SD). If the data met the assumptions of normal distribution and homogeneity of variance, the difference among the three groups was tested using ANOVA. Otherwise, the Kruskal–Wallis test was used. Spearman rank correlation was utilized to estimate the correlation between age and TSH levels after T4 withdrawal. Partial correlation analysis was used to measure the relationship between age and TSH levels after withdrawal whilst controlling for the effect of potential interfering factors, including gender, systolic pressures (SPs), diastolic pressures (DPs). $P < 0.05$ was considered as statistically significant.

Results

Clinical Characteristics

In this study, the subjects consisted of 228 females (66.5%) and 115 males (33.5%). The age of study population was 45.8 ±13.3yr, and followed a normal distribution. Then, the subjects were divided into three groups: young, middle, and old age group. The cutoff points chosen for these groups were 45 years and 60 years.

The baseline characteristics of the cohort were presented in Table1. There were no significant differences in gender ratio, BMI, ALT, AST, glycemia, uric acid, creatinine, GFR, and cancer situation (number and maximum diameter of DTC) among the three groups. While, the differences were observed in systolic pressure (SPs), diastolic pressure (DPs), GFR, and glycemia, which was in line with other studies.[18–20]

TSH Levels After LT4 Withdrawal Showed Significant Difference Among the Young, Middle and Old Age Groups

Before LT4 withdrawal, there were no differences in FT3, FT4 and TSH levels among the three groups (Table2). However, after approximately four weeks of LT4 withdrawal, the original levels of FT3 and FT4 in the body decreased. Without the presence of self-thyroid and exogenous T4 supplementation, the feedback suppression of TSH was reduced. As a result, the pituitary TSH reserve was maximally stimulated.

As stimulated TSH levels were higher than measured maximum, and FT4 levels were lower than detected minimum in part of patients in this study. Kruskal–Wallis test, a nonparametric test, was used to examine the difference in TSH levels and FT4 concentrations among the three groups. The median stimulated TSH levels were found to be 100 mIU/L in the young age group, 83.1 mIU/L in the middle age group, and 64.6 mIU/L in the old age group. The difference

Table 1 Baseline Characteristics of Patients

	Young age (<45y)	Middle age (45–59y)	Old age (>60y)	P value
N	164	117	62	–
Gender (female %)	64	69.2	67.7	0.64
BMI	25.6±4.4	26.4±3.5	26.4±3.2	0.21
SPs (mmHg)	118.2±14.8*	130.5±18.4	130.8±17.7	<0.01
DPs (mmHg)	78.8±11.4*	83.2±11.5	82.9±8.6	<0.01
ALT (U/L)	38.4±34.6	38.3±26.5	37±22.7	0.95
AST (U/L)	37.8±27.9	39.2±20.7	37.5±15.8	0.85
Glycemia (mmol/L)	5.0±1.3*	5.5±1.3	5.6±1.7	<0.01
Uric acid (umol/L)	346.9±119	328.9±97	328.8±105.5	0.31
Creatinine (umol/L)	74.5±17.9	75.5±21.7	74.3±17.7	0.90
GFR	101.3±17.1*	89.4±14.9	87.9±16.4	<0.01
DTC number	2.1±1.4	2.2±1.4	2.1±1.4	0.82
DTC max diameter (cm)	1.5±0.9	1.4±0.9	1.2±0.8	0.22

Note: The *standard for significant difference with the other two groups.

Table 2 Thyroid Function of Patients Before LT4 Withdraw

	Young age (<45y)	Middle age (45–59y)	Old age (>60y)	P value
N	164	117	62	–
FT3 (pmol/L)	4.4±0.8	4.3±0.9	4.5±0.9	0.61
FT4 (pmol/L)	14.8±3.5	14.6±3.7	15±3.5	0.85
TSH (mIU/L)	1.5±3.3	1.0±2.1	1.3±5.0	0.48

between each group was significant (P<0.01, Table3). These data suggested that stimulated TSH levels decrease with aging. The FT4 concentrations in most subjects (327 out of 343) was lower than the minimum detectable level. We did not observe a significant difference in FT4 levels among the three age groups. Similarly, FT3 levels also did not show a significant difference in these subjects.

Next, we classified the values of serum TSH levels into two categories depending on whether were in the detected range. Using chi-square tests, we found a significant difference in the proportion of subjects whose TSH values were higher than the maximum detectable range among the three age groups. The percentages of subjects with elevated TSH levels were 63.2% in the young age group, 33.1% in the middle age group, and 12.9% in the old age group. The

Table 3 Thyroid Function of Patients After LT4 Withdraw

	Young age (<45y)	Middle age (45–59y)	Old age (>60y)	P value
N	164	117	62	–
FT3 (pmol/L)	1.7±0.4	1.8±0.4	4.5±21.5	0.08
FT4 < Min (%)	95.7	93.2	98.4	0.28
TSH >Max (%)	63.2*	33.1*	12.9*	<0.01
Tg (ng/mL)	25.7±73.2	30.7±80.8	27.5±90.8	0.87
TgAb (IU/mL)	106±290.2	61.8±274.4	145.4±532.5	0.28
Urinary iodine (ug/L)	214.1±63.8	214±48.1	202.5±59.4	0.37
T4 Withdraw time (day)	26.6±4.7	27.7±4.5	27.3±4.7	0.13

Note: The * standard for significant difference with the other two groups.

Table 4 The Spearman Correlation Between Age and TSH After LT4 Withdraw

	N	Spearman correlation coefficient	P value
Total	343	−0.42	<0.01
Female	228	−0.39	<0.01
Male	115	−0.52	<0.01

difference between each group was also significant (P<0.01, Table3). These findings suggested a potential correlation between stimulated TSH levels and age.

Other factors affecting TSH regulation were also analyzed in this study (Table3). Tg is a glycoprotein produced by thyroid follicular epithelial cells or DTC cells. It plays an important role in the synthesis and storage of thyroid hormones. Tg antibody (TgAb) levels were found to be elevated in 20–30% of DTC patients and could interfere with Tg determination. Therefore, Tg and TgAb levels are often used to assess residual thyroid gland function or DTC recurrence in patients who have undergone thyroidectomy. In this study, no significant differences were observed in Tg and TgAb levels among the three age groups, suggesting that the residual thyroid function was similar in all subjects. Iodine, which is an essential component of thyroid hormone, can affect TSH secretion and the occurrence of DTC. Urinary iodine, which reflects the iodine level in the body, also showed no significant differences among the three age groups. Moreover, the duration of LT4 withdrawal was similar among the subjects, and did not appear to influence the TSH response to LT4 withdrawal. These findings collectively supported that age independently affects TSH concentration.

The Inverse Correlation Between Age and TSH Levels After LT4 Withdrawal

Spearman rank correlation was utilized to estimate the correlation between age and TSH levels after T4 withdrawal (R= −0.42, P<0.01). This data suggested that older subjects are more likely to show lower TSH levels compared to their counterparts after T4 withdrawal (Table4). Both male and female showed the same correlation. Additionally, we also used the partial correlation analysis to consider other potential interfering factors such as gender, SPs, DPs, DTC number, DTC diameter, Tg, TgAb, T4 withdrawal time, urinary iodine, ALT, AST, glycemia, uric acid, creatinine, and GFR. After precluding these potential interfering factors, partial correlation analysis confirmed the correlation between age and TSH after T4 withdrawal (R=−0.44, P<0.01).

Discussion

In the present study, we focused on understanding the impact of age on TSH regulation in patients after thyroidectomy. Without self-thyroid and exogenous T4 supplementation, TSH cells in pituitary almost lost feedback suppression. As a result, the TSH levels increased maximally. Our findings revealed an inverse correlation between age and TSH levels after LT4 withdrawal. Older subjects were more likely to exhibit lower TSH levels compared to their younger counterparts. These data suggested that the aging process may lead to alterations in TSH regulation. Interestingly, the inverse correlation between age and TSH levels was consistent across both male and female subjects. This indicated that age-related changes in TSH regulation are not influenced by gender.

Moreover, there were some data supporting our report. Older individuals exhibited reduced TSH responsiveness to TRH administration,[12,21] diminished nocturnal TSH surge,[22] and altered circadian pattern of TSH secretion.[10,22] These findings supported the notion that the changes in TSH regulation with aging are part of a broader age-related alteration in HPT-axis function. The exact mechanisms underlying the age-related changes in TSH regulation are still unclear and require further investigation. It is possible that age-related changes in the hypothalamus-pituitary-thyroid axis, as well as alterations in the hormone metabolism and sensitivity, contribute to the observed differences in TSH levels. Overall, our study highlights that age is an important factor in the interpretation of TSH levels.

This study provided valuable insights into the impact of aging on TSH regulation and shed light on its clinical implications. The stimulated TSH levels were significantly lower in the elderly compared to those in the younger

individuals. Consistently, many other studies found that age is an important factor in TSH regulation[10,12] and TSH-related disorders.[13,14] Together, the findings suggested that we should pay more attention to the role of age in TSH-related diseases. Additionally, we also provided clinical evidences supporting personalized treatment approaches for DTC patients. It suggested that the responsiveness of TSH cells to thyroid hormones changes is likely to be reduced with age. Our study also implied that older subjects might need a longer period of T4 cease for RAI treatment.

However, it is worth noting that epidemiological research on the relationship between TSH levels and age has not reached a consensus.[11,13,23] These discrepancies highlight the complexity of TSH regulation and its shift during the aging process. The heterogeneity of the studies, including factors such as gender, age, race, BMI, and iodine intake, may contribute to the divergent results. Furthermore, it is important to note that the elderly population exhibits significant inter-individual variability in TSH levels,[14] thereby adding to the complexity of understanding TSH regulation in aging. The interplay between these factors may contribute to the variability in TSH levels observed in different studies. Further research is needed to elucidate the mechanisms underlying the relationship between age and TSH regulation.

To harmonize these outcomes and focus on the correlation between age and TSH levels, a new studying model was required. In our research, we selected subjects who were preparing for RAI treatment after thyroidectomy. By controlling thyroid hormone feedback suppression, we were able to effectively examine the relationship between age and TSH levels. The subjects of this study were patients with DTC, who usually needed sequential therapies including thyroidectomy, exogenous T4 replacement, RAI, and/or observation. Because DTC cells retained the TSH-dependent growth pattern of thyroid follicular cells, T4 supplementation was needed to suppress TSH after surge. In addition, increased TSH improved the sodium/ iodide symporter (NIS) function of residual thyroid follicular epithelial cells and DTC cells, thereby increased the uptake of 131-indione and the effect of RAI.[24] So, the preparation for RAI usually required LT4 withdrawal and low iodine diet in China.[25] The supplementation and withdrawal of LT4 induced different TSH situation. The model of our study was suitable in the researches on the TSH regulation. Besides, the inappropriate iodine uptake is associated with higher DTC prevalence[26] and abnormal TSH levels.[27] The subjects in this study were mainly from Shandong province, eastern of China, where the iodine intake of the population was appropriate. So, the surveys in other areas would be required to evaluate the correlation between TSH levels and age. However, it's important to note that these results are specific to the population studied in this research. Further studies may be needed to confirm these findings and explore the underlying mechanisms.

Alterations in the neuroendocrine system might be the potential mechanism explaining the changed TSH levels with aging. It is crucial to acknowledge that there are many neuroendocrine factors that interact with and influence the HPT axis. For instance, dopamine, an inhibitory neurotransmitter, can directly decrease serum TSH levels and reduce its response to TRH administration.[21] Leptin, a hormone involved in regulating energy balance, also plays a crucial role in TSH rhythms. Leptin and TSH exhibit similar secretion patterns, and their rhythms are coupled. In patients with a loss of the leptin gene, the TSH rhythm disappears.[28] Somatostatin can suppress TSH release through its receptors (SST2 and SST5) expressed on TSH cells.[27] It would be interesting to further explore the changes in these factors in our study subjects. Although there are many other factors that modulate and interact with the HPT axis, thyroid feedback suppression remains the main mechanism regulating TSH. Our study's model sheds light on the relationship between age and TSH levels by controlling thyroid feedback suppression, providing a powerful method for researching the HPT axis.

It is interesting to note that there has been attention given to the relationship between TSH levels and longevity. Some studies have reported that higher TSH levels are often associated with extended longevity in humans and certain animals.[29,30] However, the exact contribution of higher TSH concentration to exceptional longevity remains unclear, and further research is needed to understand the interaction between age and TSH levels.

Conclusions

In conclusion, our study sheds light on the effect of aging on TSH levels. By controlling for thyroid feedback suppression, we demonstrated an inverse correlation between age and stimulated TSH levels. These findings have implications for clinical practice. We highlight that age should be taken into consideration when interpreting TSH levels and designing personalized treatment strategies for patients with thyroid-related diseases.

Acknowledgments

This study was approved by the biomedical research ethical committee of the Shandong Provincial Hospital Affiliated to Shandong First Medical University (No.SWYX2023-331). As the retrospective study only involves clinical data from hospital database but not uses human samples, the written informed consent from the participants is waived. Meantime, the data is anonymized and maintained with confidentiality to protect the privacy of the participants. This study complies with the Declaration of Helsinki.

Funding

This work was supported by the Shandong Provincial Natural Science Foundation (ZR2022MH121) and Shandong Provincial Medical Health Science and Technology Development Plan (202003061399).

Disclosure

The authors declare that they have no conflicts of interest in this work.

References

1. Drvota V, Janson A, Norman C, et al. Evidence for the presence of functional thyrotropin receptor in cardiac muscle. *Biochem Biophys Res Commun*. 1995;211(2):426–431. doi:10.1006/bbrc.1995.1831
2. Lu S, Guan Q, Liu Y, et al. Role of extrathyroidal TSHR expression in adipocyte differentiation and its association with obesity. *Lipids Health Dis*. 2012;11:17. doi:10.1186/1476-511X-11-17
3. Luan S, Bi W, Shi S, et al. Thyrotropin receptor signaling deficiency impairs spatial learning and memory in mice. *J Endocrinol*. 2020;246 (1):41–55. doi:10.1530/JOE-20-0026
4. Yan F, Wang Q, Lu M, et al. Thyrotropin increases hepatic triglyceride content through upregulation of SREBP-1c activity. *J Hepatol*. 2014;61 (6):1358–1364. doi:10.1016/j.jhep.2014.06.037
5. Zeng S, Hu H, Li Z, et al. Local TSH/TSHR signaling promotes CD8 + T cell exhaustion and immune evasion in colorectal carcinoma. *Cancer Commun*. 2024;44:1287–1310. doi:10.1002/cac2.12605
6. Floriani C, Gencer B, Collet TH, Rodondi N. Subclinical thyroid dysfunction and cardiovascular diseases: 2016 update. *Eur Heart J*. 2018;39 (7):503–507. doi:10.1093/eurheartj/ehx050
7. Hashimoto K. Update on subclinical thyroid dysfunction. *Endocr J*. 2022;69(7):725–738. doi:10.1507/endocrj.EJ22-0182
8. Jansen HI, Boelen A, Heijboer AC, Bruinstroop E, Fliers E. Hypothyroidism: the difficulty in attributing symptoms to their underlying cause. *Front Endocrinol*. 2023;14:1130661. doi:10.3389/fendo.2023.1130661
9. Kim HJ, McLeod DSA. Subclinical Hyperthyroidism and Cardiovascular Disease. *Thyroid*. 2024;34:1335–1345. doi:10.1089/thy.2024.0291
10. Barreca T, Franceschini R, Messina V, Bottaro L, Rolandi E. 24-hour thyroid-stimulating hormone secretory pattern in elderly men. *Gerontology*. 1985;31(2):119–123. doi:10.1159/000212690
11. d'Herbomez M, Jarrige V, Darte C. Reference intervals for serum thyrotropin (TSH) and free thyroxine (FT4) in adults using the Access Immunoassay System. *Clin Chem Lab Med*. 2005;43(1):102–105. doi:10.1515/CCLM.2005.017
12. van Coevorden A, Laurent E, Decoster C, et al. Decreased basal and stimulated thyrotropin secretion in healthy elderly men. *J Clin Endocrinol Metab*. 1989;69(1):177–185. doi:10.1210/jcem-69-1-177
13. Liu Y, Shan Z, Endocrine Metabolic Diseases Group of the Chinese Geriatrics S, Thyroid Group of the Chinese Society of Endocrinology CMA. Expert consensus on diagnosis and treatment for elderly with thyroid diseases in China (2021). *Aging Med*. 2021;4(2):70–92. doi:10.1002/agm2.12165
14. Duntas LH. Aging and the hypothalamic-pituitary-thyroid axis. *Vitam Horm*. 2021;115:1–14.
15. Palot Manzil FF, Kaur H. Radioactive Iodine for Thyroid Malignancies. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2024.
16. Nguyen NC, Anigati EM, Desai NB, Oz OK. Radioactive Iodine Therapy in Differentiated Thyroid Cancer: an Update on Dose Recommendations and Risk of Secondary Primary Malignancies. *Semin Nucl Med*. 2024;54(4):488–496. doi:10.1053/j.semnuclmed.2024.05.002
17. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Modi Diet Renal Disease Study Group Ann Intern Med*. 130(6):461–470.
18. Muzaale A, Khan A, Glassock RJ, Tantisattamoa E, Ahdoot RS, Al Ammary F. Kidney function assessment in the geriatric population. *Curr Opin Nephrol Hypertens*. 2024;33(2):267–271. doi:10.1097/MNH.0000000000000955
19. Singh JN, Nguyen T, Kerndt CC, Dhamoon AS. Physiology, Blood Pressure Age Related Changes. 2023 Aug 28. in:*StatPearls [Internet]*: Treasure Island (FL); StatPearls Publishing; 2024.
20. Yu JX, Hussein A, Mah L, Jean Chen J. The associations among glycemic control, heart variability, and autonomic brain function in healthy individuals: age- and sex-related differences. *Neurobiol Aging*. 2024;142:41–51. doi:10.1016/j.neurobiolaging.2024.05.007
21. Chakraborti S, Chakraborti T, Mandal M, Das S, Batabyal SK. Hypothalamic-pituitary-thyroid axis status of humans during development of ageing process. *Clin Chim Acta*. 1999;288(1–2):137–145. doi:10.1016/S0009-8981(99)00061-3
22. Greenspan SL, Klibanski A, Rowe JW, Elahi D. Age-related alterations in pulsatile secretion of TSH: role of dopaminergic regulation. *Am J Physiol*. 1991;260(3 Pt 1):E486–491. doi:10.1152/ajpendo.1991.260.3.E486
23. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): national Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002;87(2):489–499. doi:10.1210/jcem.87.2.8182
24. Pacini F, Fuhrer D, Elisei R, et al. ETA Consensus Statement: what are the indications for post-surgical radioiodine therapy in differentiated thyroid cancer? *Eur Thyroid J*. 2022;11(1). doi:10.1530/ETJ-21-0046

25. CM AN. Guidelines for the 131-I treatment of differentiated thyroid cancer (2021). *Chin J Nuclear Medi Molecular Im*. 2021;04:218–241.
26. Zhai X, Zhang L, Chen L, et al. An Age-Specific Serum Thyrotropin Reference Range for the Diagnosis of Thyroid Diseases in Older Adults: a Cross-Sectional Survey in China. *Thyroid*. 2018;28(12):1571–1579. doi:10.1089/thy.2017.0715
27. Roelfsema F, Veldhuis JD. Thyrotropin secretion patterns in health and disease. *Endocr Rev*. 2013;34(5):619–657.
28. Mantzoros CS, Ozata M, Negrao AB, et al. Synchronicity of frequently sampled thyrotropin (TSH) and leptin concentrations in healthy adults and leptin-deficient subjects: evidence for possible partial TSH regulation by leptin in humans. *J Clin Endocrinol Metab*. 2001;86(7):3284–3291. doi:10.1210/jcem.86.7.7644
29. Jansen SW, Roelfsema F, van der Spoel E, et al. Familial Longevity Is Associated With Higher TSH Secretion and Strong TSH-fT3 Relationship. *J Clin Endocrinol Metab*. 2015;100(10):3806–3813. doi:10.1210/jc.2015-2624
30. Arosio B, Monti D, Mari D, et al. Thyroid hormones and frailty in persons experiencing extreme longevity. *Exp Gerontol*. 2020;138:111000. doi:10.1016/j.exger.2020.111000