Body mass index (BMI) is associated with serum thyroid-stimulating hormone (TSH) level in infertile women: a cross-sectional study

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Abstract. Studies suggest that there is a relationship between body mass index (BMI) and thyroid-stimulating hormone (TSH) levels. But conflicting evidence exists regarding the relationship between the two variables. Moreover, thyroid function is closely related to female fertility and has certain effects on infertility. Therefore, the present study will explore the relationship between BMI and TSH levels in patients with infertility in our center. We retrospectively analyzed relevant indicators of 2,789 in Tubal Factor Infertility patients undergoing assisted reproduction technology from January 2016 to December 2018 in our center in order to analyze the relationship between BMI and serum TSH level. The medical histories of patients were reviewed. The relationship between BMI and TSH was assessed using smooth curve fitting and multivariate regression model. The smoothing curve fitting between BMI and TSH exhibited a non-linear relationship, and the resulting curve exhibited a two-stage change and a breakpoint. By multivariate piecewise linear regression, we found that the TSH level was increased with the increase of BMI when the BMI was greater than 25.3 kg/m² (β = 0.06, 95% CI 0.02, 0.01; p = 0.0028). In contrast, the TSH level was decreased with the increase of BMI when the BMI was less than 25.3 kg/m² (β = -0.02, 95% CI -0.05, 0.00; p = 0.0573). Collectively, our study described a non-linear relationship between BMI and TSH level in infertile patients after adjustment of potential confounders. However, such causal relationship between BMI and TSH in infertile women still needs to be further clarified in future investigations.

Key words: Infertility, Thyroid stimulating hormone, Body mass index, Obesity

THE PREVALENCE of overweight and obesity is high and increasing, which has become a major public health concern globally [1, 2]. As a systemic disease, obesity can pose a series of comorbidities and affect functions of multiple organs, including thyroid function [3-5]. Some studies have revealed a positive relationship between serum thyroid-stimulating hormone (TSH) and body mass index (BMI), suggesting that changes in body weight are related to thyroid dysfunction [6-9]. However, several studies have found conflicting results regarding BMI and TSH levels in obese patients, for example, some research results show a negative relationship between BMI and TSH levels, while others suggest that there is no significant relationship between the two [10-12]. In this sense, there is still controversy about the relationship between BMI and TSH level. Moreover, thyroid function is closely related to female fertility and has certain effects on infertility. Therefore, in the present study, we reviewed the medical histories of infertile patients at a single center in China and investigated the relationship between BMI and TSH level in this population.

Materials and Methods

Study population

The study group consisted of 4,655 infertile patients, who underwent intrauterine insemination (IUI), in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) cycles from January 2016 to December 2018 at the Center for Reproductive Medicine, Affiliated Hospital of Jining Medical University, Jining, Shandong, China. The subjects were included according to the criteria as follows: Tubal Factor Infertility patients, patients ≤40 years old, patients with normal thyroid function (TSH <
mIU/L, FT4 9–25 pmol/L, FT3 2.1–5.4 pmol/L), or subclinical hypothyroidism (TSH < 4.5 mIU/L, FT4 9–25 pmol/L, FT3 2.1–5.4 pmol/L). The exclusion criteria were as follows: patients with diseases, such as heart disease, severe hepatic or renal diseases, severe gastrointestinal diseases, malignant tumor, hypertension, diabetes mellitus, or mental illness; and subjects with thyroid disease (such as Hashimoto’s thyroiditis, hypothyroidism, hyperthyroidism, thyroid neoplasm), pituitary neoplasms, hyperprolactinemia, polycystic ovary syndrome (PCOS) [13], diminished ovarian reserve, endometriosis and ovarian endometrioma. Finally, a total of 2,789 eligible patients were enrolled in the present study.

**Data collection**

Relevant indicators for the first examination were collected for these patients. The medical histories of patients were reviewed, including the parameters as follows: Age (year), Anti-Müllerian hormone (AMH) (ng/mL), BMI (kg/m²), TSH (mIU/L), Duration of infertility (year), Follicle-stimulating hormone (FSH) (mIU/mL), Luteinizing hormone (LH) (mIU/mL), LH/FSH ratio, Total testosterone (T) (ng/mL), Prolactin (PRL) (ng/mL), Antral follicle count (AFC), and Type of infertility. Generally, for patient convenience, serum levels of these hormones were measured at 2–4 days of the menstrual cycle. If the patient had amenorrhea for more than 3 months, the examination was performed during any day of the menstrual cycle. The study was approved by the Human Ethics Committee of the Affiliated Hospital of Jining Medical University.

**Measurement of serum specimen**

The blood sample was usually collected at 2–4 days of the menstrual cycle for patient convenience. TSH results of the first test were analyzed rather than the results after clinical intervention. Serum TSH levels were determined by UniCel DxI800 analyzer (Beckman Coulter Diagnostics, America) based on the principle of paramagnetic microparticle chemiluminescent immunoassay (CLIA). Serum AMH levels were measured by Diagnostic Kit for the Quantitative Detection of Anti-Mullerian hormone (ELISA). The determination of other hormones was also carried out based on the principle of CLIA.

**Statistical analysis**

Data were analyzed with the use of the statistical packages R (The R Foundation; http://www.r-project.org; version 3.4.3) and Empower (R) (www.empowerstats.com, X&Y solutions, inc. Boston, Massachusetts). The continuous variables were expressed as the means ± standard deviations, and the categorical data were expressed as a number (percentage). The relationship between BMI and TSH level was investigated using smooth curve fitting after adjustment of potential confounders. A univariate analysis was used to determine the significance of the association between BMI and TSH as well as the other variables. Finally, a multivariate regression model was further applied to examine the independent association of BMI and TSH level. Statistical significance was indicated by as a two-sided *p* < 0.05.

**Results**

**Baseline characteristics of all participants**

Table 1 shows the baseline characteristics of all participants. A total of 2,789 infertile patients with a mean age of 31.64 ± 4.48 years were enrolled in the present study. The mean BMI of the patients was 22.98 ± 3.35 kg/m². The mean duration of infertility was 2.73 ± 2.28 years. The mean level of TSH was 2.15 ± 1.11 mIU/L. The mean AFC and AMH levels were 14.67 ± 7.17 and 4.57 ± 3.12 ng/mL, respectively. There were 905 (32.45%) patients with primary infertility, while the majority of the patients (1,884, 67.55%) were of secondary infertility.

**Univariate analysis**

Univariate linear regression analysis was performed to determine the relationships between clinical parameters and TSH level. Table 2 shows that there was no signifi-
cant association between BMI and TSH for the unadjusted model ($p > 0.05$). Moreover, no significant association was observed between TSH level and type of infertility, duration of infertility, AFC, FSH, LH and LH/FSH ratio ($p > 0.05$). On the contrary, there was a significant negative relationship between the age and TSH level ($p = 0.0032$), and a significant positive association existed between the TSH level and PRL or T ($p < 0.01$).

**Independent relationship between BMI and TSH by multivariate piecewise linear regression**

We selected these confounders on the basis of their associations with the outcomes of interest or a change in effect estimate of more than 10%. Table 3 shows that covariates that needed to be adjusted were screened out. Fig. 1 reveals that smooth curve fitting was performed after adjustment of possible confounding factors, including Age, FSH, LH, LH/FSH, PRL, T, AFC, AMH and Infertility duration. BMI of patients exhibited a non-linear relationship with TSH level, and the resulting curve exhibited a two-stage change and a breakpoint. When the BMI was greater than the breakpoint, there was a positive relationship between BMI and TSH level. However, if the value was less than the breakpoint, there was an inverse relationship between BMI and TSH level. Table 4 shows that the threshold effect was further analyzed based on curve fitting, and the data indicated that the inflection point of the BMI was 25.3 kg/m$^2$. Specifically, the TSH level was decreased with the increase of BMI when the BMI was less than 25.3 kg/m$^2$ ($\beta = 0.02$, 95% CI $-0.05$, 0.00; $p = 0.0573$). But this independent relationship was not significant. In contrast, the TSH level displayed an increasing trend significantly with the increase of BMI when the BMI was greater than 25.3 kg/m$^2$ ($\beta = 0.06$, 95% CI 0.02, 0.01; $p = 0.0028$).

**Discussion**

In the present study, we observed that there was a non-linear relationship between BMI and TSH level in infertile patients, and the BMI turning point was 25.3 kg/m$^2$. There was a negative relationship between BMI and TSH when the BMI <25.3 kg/m$^2$, but this relationship was not significant. However, there was a significant positive relationship between BMI and TSH after the BMI reached the inflection point.

This result was not completely consistent with the findings of previous clinical studies. A previous study has supported that BMI is positively associated with the serum TSH level among euthyroid adults [14]. However, a recent review has shown that there is a positive association between serum TSH level and measures of adiposity in only 11 out of 17 study based on clinical samples. Such discrepancy might be attributed to other factors, such as thyroid disease, pathological obesity, smoking or gender [7, 15-18]. On contrary, a recent study has found that there is a negative relationship between BMI and TSH in patients with thyroid cancer [19]. However, this

| Table 2 | Factors correlated to TSH by a univariate analysis |
|---------|-------------------------------------------------|
|         | $\beta$   | (95% CI) | $p$ value |
| Age (year) | $-0.02$ | $(-0.03, -0.01)$ | $0.0032$ |
| BMI (kg/m$^2$) | $0.00$ | $(-0.01, 0.02)$ | $0.7216$ |
| Infertility duration (year) | $-0.01$ | $(-0.03, 0.01)$ | $0.3069$ |
| AMH (ng/mL) | $-0.01$ | $(-0.02, 0.01)$ | $0.2107$ |
| AFC (number) | $-0.00$ | $(-0.01, 0.01)$ | $0.6478$ |
| FSH (mIU/mL) | $-0.01$ | $(-0.02, 0.01)$ | $0.5468$ |
| LH (mIU/mL) | $0.00$ | $(-0.00, 0.01)$ | $0.3573$ |
| LH/FSH ratio | $0.04$ | $(-0.02, 0.10)$ | $0.2330$ |
| PRL (ng/mL) | $0.03$ | $(0.02, 0.03)$ | $<0.0001$ |
| T (ng/mL) | $0.20$ | $(0.17, 0.23)$ | $<0.0001$ |

Type of infertility

|            | $\beta$     | (95% CI) | $p$ value |
|-------------|--------------|----------|-----------|
| Primary infertility | 0       | 0       | 0         |
| Secondary infertility | $-0.07$ | $(-0.17, 0.03)$ | $0.1912$ |

Abbreviations: AMH, Antimüllerian hormone; BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; LH/FSH ratio, ratio of LH to FSH; T, total testosterone; PRL, prolactin; AMH, Antimüllerian hormone; AFC, antral follicle count.

$P < 0.05$ is considered to be statistically significant.
is only the accidental discovery of the researchers, while no detailed analysis has been performed.

Interestingly, no previous study has found a non-linear relationship between BMI and TSH level in infertile patients. This discrepancy might be attributed to the different study populations. The other explanation could be that previous studies have not analyzed whether different levels of BMI affect the relationship between BMI and TSH.

In previous studies, age, sex and smoking are the adjusted variables, which have been proved to affect the relationship between BMI and TSH. In our study, we enrolled infertile women ≤40 years old and excluded the patients with thyroid disease other than subclinical hypothyroidism. In addition, we also adjusted the patient’s age and other hormone levels, and a non-linear relationship was still observed between BMI and TSH. It was worth mentioning that in our study, there was a positive relationship between BMI and TSH level only when BMI ≥25.3 kg/m². Therefore, we thought about whether weight loss can reduce TSH. After consulting the relevant literature, we found that bariatric surgery has been proved to be the most effective treatment for patients with severe obesity [20, 21]. Some studies have proved that bariatric surgery can reduce the TSH level [22-24]. A research has suggested that a mass of adipocytokines (such as leptin) from adipose tissue have a stimulatory impact on thyroid activity, thereby leading to increased TSH secretion. Therefore, weight loss can result in a decline in the TSH level [25, 26]. These studies have suggested a relationship between BMI and TSH level. A research has proposed that TSH may directly stimulate the differentiation of preadipocytes to induce adipogenesis [27]. In recent years, some studies have also considered that the relationship between BMI and TSH may be explained by neuroendocrine regulation of TSH in the hypothalamic-pituitary-thyroid axis by leptin [28].

### Table 3  Screening of covariates

| Covariate                | Basic model | Complete model | Selected |
|--------------------------|-------------|----------------|----------|
| Age (year)               | 0.0019      | 0.0055         | Yes      |
| Type of infertility      | 0.0020      | 0.0055         | No       |
| Infertility duration (year) | 0.0021*   | 0.0052         | Yes      |
| FSH (mIU/mL)             | 0.0013*     | 0.0065*        | Yes      |
| LH (mIU/mL)              | 0.0024*     | 0.0056         | Yes      |
| LH/FSH ratio             | 0.0021*     | 0.0056         | Yes      |
| PRL (ng/mL)              | 0.0066*     | 0.0014*        | Yes      |
| T (ng/mL)                | 0.0017*     | 0.0056         | Yes      |
| AMH (ng/mL)              | 0.0013*     | 0.0065*        | Yes      |
| AFC (number)             | 0.0023*     | 0.0054         | Yes      |

* Indicates a change of more than 10% compared to the initial regression coefficient.

### Table 4  The independent relationship between BMI on TSH by multivariate piecewise linear regression

| Inflection point of BMI | β (95% CI) | p value |
|-------------------------|------------|---------|
| <25.3                   | -0.02 (-0.05, 0.00) | 0.0573  |
| ≥25.3                   | 0.06 (0.02, 0.10)  | 0.0028  |

Abbreviations: BMI, body mass index; TSH, thyroid-stimulating hormone. Adjustment variables: Age; FSH, follicle-stimulating hormone; LH, luteinizing hormone; LH/FSH ratio, ratio of LH to FSH; T, total testosterone; PRL, prolactin; AFC, antral follicle count; AMH, Anti-müllerian hormone.

P < 0.05 is considered to be statistically significant.
relationship between BMI and TSH was not significant when the BMI <25.3 kg/m², just showing a downward trend in smooth curve fitting. Therefore, further research is required to confirm our findings whether there was a negative relationship between BMI and TSH in infertile patients with BMI <25.3 kg/m².

From another perspective, hypothyroidism may be the initial event, with a reduction in basal metabolic expenditure, resulting in a positive energy balance associated with weight gain, and a higher weight gain is directly related to the degree of hypothyroidism [29, 30]. In summary, the relation between BMI (or weight) and thyroid function is complex, which involves multiple levels of interaction. Thence, further controlled longitudinal studies are needed to better understand the mechanisms underlying the relationship between BMI and TSH.

The large number of studied subjects is the advantage of our study. However, our study also has several limitations. Firstly, this study was a retrospective study. Secondly, we did not evaluate more obesity-related indicators, such as waist circumference, waist-to-hip ratio.

Conclusions

Collectively, we, in the present study, described a non-linear relationship between BMI and TSH level in infertile patients after adjustment of potential confounders. The TSH level was increased with the increase of BMI when the BMI was greater than 25.3 kg/m². However, such causal relationship between BMI and TSH still needs to be further validated.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

References

1. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, et al. (2014) Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the global burden of disease study 2013. Lancet 384: 766–781.

2. NCD Risk Factor Collaboration (NCD-RisC) (2016) Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 387: 1377–1396.

3. Michalaki MA, Vagenakis AG, Leonardou AS, Argentou MN, Habeos IG, et al. (2006) Thyroid function in humans with morbid obesity. Thyroid 16: 73–78.

4. Inge TH, Courcoulas AP, Jenkins TM, Michalisky MP, Helmarth MA, et al. (2016) Weight loss and health status 3 years after bariatric surgery in adolescents. N Engl J Med 374: 113–123.

5. Jankovic D, Wolf P, Anderwald CH, Winhofer Y, Promintzer-Schifferl M, et al. (2012) Prevalence of endocrine disorders in morbidly obese patients and the effects of bariatric surgery on endocrine and metabolic parameters. Obes Surg 22: 62–69.

6. Ambrosi B, Masserini B, Iorio L, Delneo A, Malavazos AE, et al. (2010) Relationship of thyroid function with body mass index and insulin-resistance in euthyroid obese subjects. J Endocrinol Invest 33: 640–643.

7. Marwaha RK, Tandon N, Garg MK, Ganie MA, Narang A, et al. (2013) Impact of body mass index on thyroid functions in Indian children. Clin Endocrinol (Oxf) 79: 424–428.

8. de Moura Souza A, Sichieri R (2011) Association between serum TSH concentration within the normal range and adiposity. Eur J Endocrinol 165: 11–15.

9. Ruminska M, Witkowska-Sedek E, Majcher A, Pyrzak B (2016) Thyroid function in obese children and adolescents and its association with anthropometric and metabolic parameters. Adv Exp Med Biol 912: 33–41.

10. Bjergved L, Jorgensen T, Perrild H, Laurberg P, Krejbjer A, et al. (2014) Thyroid function and body weight: a community-based longitudinal study. Plos One 9: e93515.

11. Svare A, Nilsen TI, Bjoro T, Asvold BO, Langhammer A (2011) Serum TSH related to measures of body mass: longitudinal data from the HUNT Study, Norway. Clin Endocrinol (Oxf) 74: 769–775.

12. Handelsman RS, Alvarez AL, Picado O, Farra JC, Lew JI (2019) Inverse relationship of BMI to TSH and risk of papillary thyroid cancer in surgical patients. J Surg Res 244: 96–101.

13. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 81: 19–25.

14. Kitahara CM, Platz EA, Ladenson PW, Mondul AM, Menke A, et al. (2012) Body fatness and markers of thyroid function among U.S. men and women. Plos One 7: e34979.

15. Asvold BO, Bjoro T, Vatten LJ (2009) Association of serum TSH with high body mass differs between smokers and never-smokers. J Clin Endocrinol Metab 94: 5023–5027.
16. Knudsen N, Laurberg P, Rasmussen LB, Bulow I, Perrild H, et al. (2013) Small differences in thyroid function may be important for obesity in the population. J Clin Endocrinol Metab 90: 4019–4024.

17. Friedrich N, Rosskopf D, Brabant G, Volzke H, Nauck M, et al. (2010) Associations of anthropometric parameters with serum TSH, prolactin, IGF-I, and testosterone levels: results of the study of health in Pomerania (SHIP). Exp Clin Endocrinol Diabetes 118: 266–273.

18. Nyrnes A, Jorde R, Sundsfjord J (2006) Serum TSH is positively associated with BMI. Int J Obes (Lond) 30: 100–105.

19. Handelsman RS, Alvarez AL, Picado O, Farra JC, Lew JJ (2019) Inverse relationship of BMI to TSH and risk of papillary thyroid cancer in surgical patients. J Surg Res 244: 96–101.

20. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, et al. (2017) Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. N Engl J Med 376: 641–651.

21. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, et al. (2015) Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. Lancet 386: 964–973.

22. Lips MA, Pijl H, van Klinken JB, de Groot GH, Janssen IM, et al. (2013) Roux-en-Y gastric bypass and calorie restriction induce comparable time-dependent effects on thyroid hormone function tests in obese female subjects. Eur J Endocrinol 169: 339–347.

23. Abu-Ghanem Y, Inbar R, Tyomkin V, Kent I, Berkovich L, et al. (2015) Effect of sleeve gastrectomy on thyroid hormone levels. Obes Surg 25: 452–456.

24. Witkowska-Sedek E, Kucharska A, Ruminska M, Pyrzak B (2017) Thyroid dysfunction in obese and overweight children. Endokrynol Pol 68: 54–60.

25. Kok P, Roelfsema F, Langendonk JG, Frolich M, Burggraaf J, et al. (2005) High circulating thyrotropin levels in obese women are reduced after body weight loss induced by caloric restriction. J Clin Endocrinol Metab 90: 4659–4663.

26. Kozlowska L, Rosolowska-Huszcz D (2004) Leptin, thyrotropin, and thyroid hormones in obese/overweight women before and after two levels of energy deficit. Endocrine 24: 147–153.

27. Sorisky A, Bell A, Gagnon A (2000) TSH receptor in adipose cells. Horm Metab Res 32: 468–474.

28. Marcello MA, Cunha LL, Batista FA, Ward LS (2014) Obesity and thyroid cancer. Endocr Relat Cancer 21: T255–T271.

29. Garcia-Solis P, Garcia OP, Hernandez-Puga G, Sanchez-Tusie AA, Saenz-Luna CE, et al. (2018) Thyroid hormones and obesity: a known but poorly understood relationship. Endokrynol Pol 69: 292–303.

30. Park HK, Ahima RS (2015) Physiology of leptin: energy homeostasis, neuroendocrine function and metabolism. Metabolism 64: 24–34.