Sex-Dependent Association between Weight Change and Thyroid Dysfunction: Population-Level Analysis Using the Korean National Health and Nutrition Examination Survey

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Keywords

Thyroid dysfunction · Hyperthyroidism · Hypothyroidism ·
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Abstract

Background: Although body weight change (BWC) is a common manifestation of thyroid dysfunction, solid evidence for whether to perform or on whom to perform thyroid function test in subjects complaining of BWC is lacking. **Objective:** To evaluate the association between thyroid dysfunction and BWC using a nationwide survey. **Method:** Data was obtained from the Korea National Health and Nutrition Examination Survey VI 2013–2015 and 5,456 subjects without previous thyroid disease were included. Serum thyroid-stimulating hormone (TSH), free T4, and self-reported BWC during the previous year were used for the evaluation. Weight loss or gain was defined as weight change of at least 3 kg. **Results:** In total, 1,017 men (37.3%) and 1,175 women (43.0%) reported BWCs during the previous year. The overall weighted prevalence of thyroid dysfunction was not significantly associated with the extent of BWC in men ($p = 0.705$) or wom-

en ($p = 0.094$). However, when the impact of TSH levels on weight change was separately evaluated for weight gain and loss after adjusting for age and body mass index in each sex, weight loss in women was significantly associated with TSH levels (hazard ratio 0.64, 95% CI 0.47–0.85, $p = 0.03$). No association of thyroid dysfunction was observed for weight gain in women ($p = 0.23$) or any changes in men ($p = 0.875$ in weight gain, $p = 0.923$ in weight loss). **Conclusions:** This study highlights the necessity of performing thyroid function testing in women who complain of weight loss, but such testing may be less vital in women with weight gain or men with any changes in weight.

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Introduction

The incidence of body weight change (BWC) in patients with overt thyroid dysfunction exceeds 50%, representing one of the most common symptoms [1, 2]. Overt hyperthyroidism (OHyper) is frequently associated with weight loss, and conversely, overt hypothy-

roidism (OHypo) with weight gain [3, 4]. Previous studies reported that some patients with hyperthyroidism gained weight after adequate treatment [5], whereas hypothyroidism was linked to modest weight loss following thyroid hormone replacement therapy [6]. However, these findings are not universally true; about 2–12% of patients with hyperthyroidism describe weight gain at presentation [2, 7–9], suggesting that the tendency of weight change due to thyroid dysfunction is not consistent. Clinicians face difficulties when deciding whether patients complaining of weight gain or loss of various degrees require thyroid function testing. This may be mainly because the incidence of thyroid dysfunction in patients with BWC is not clearly addressed in previous studies. Thus, clear evidence regarding the indication for evaluating thyroid function status in patients with BWC is necessary. To address this issue, we examined the prevalence of 5 categories of thyroid function status according to the extent of self-reported BWC in each sex in a large population-level cohort. Furthermore, we aimed to evaluate whether thyroid function has an independent role in BWC after adjusting for major confounding factors such as age and body mass index (BMI).

Materials and Methods

Study Design and Population

In the study, data was obtained from the Korea National Health and Nutrition Examination Survey (KNHANES) VI, a nationwide, cross-sectional survey conducted by the Korea Centers for Disease Control and Prevention from 2013 to 2015 to provide national health, diet, and nutrition data representing the civilian, non-institutionalized Korean population. Research participants were selected using two-stage stratified cluster sampling of the population and housing census data. The data was collected via household interviews and standardized physical examinations. The KNHANES database is available publicly (<http://knhanes.cdc.go.kr/knhanes/eng>).

The study included 2,724 men and 2,732 women aged ≥ 19 years without previous thyroid disease or receiving any thyroid-related medication (Fig. 1). All the included subjects underwent thyroid function testing. Participants aged < 19 years were excluded from the analysis to obtain reliable data on the history of changes in body weight. Informed consent was obtained from each participant prior to performing the survey, and secondary anonymized data were used in the analyses. The study protocol was approved by the Institutional Review Board of Asan Medical Center, Seoul, Korea.

Body Weight Change

Participants were required to complete a questionnaire regarding BWC over the previous year. Weight loss or gain was defined

Fig. 1. Description of study subjects. TSH, thyroid-stimulating hormone.

by a weight change of at least 3 kg, whereas lower levels of weight loss were categorized as minimal changes. Weight gain and loss were further classified as (a) ≥ 6 kg or (b) at least 3 kg but < 6 kg when evaluating the prevalence of thyroid dysfunction according to BWC. Data on BMI was also collected from each participant and was used for adjustment.

Thyroid Function Test and Definition of Thyroid Dysfunction

From 2013 to 2015 in KNHANES VI, thyroid function testing has been conducted in one third of all subjects, approximately 2,400 persons aged ≥ 10 years annually and the sum of 3 years represents the entire population of Korea. The population was selected by stratified subsampling considering the number of inhabitants in each year.

Serum thyroid-stimulating hormone (TSH) was measured by electrochemiluminescence immunoassay (E-TSH kit, Roche Diagnostics, Mannheim, Germany), and the TSH reference interval was determined to be between the 2.5th and 97.5th percentile of the serum TSH levels of the reference population, as previously reported [10]. Serum fT4 was also measured using electrochemiluminescence immunoassay (E-Free T4 kit, Roche Diagnostics, Mannheim, Germany), and the reference range was 0.89–1.76 ng/mL.

Levels of serum TSH and free T4 (fT4) as measures of thyroid function were used to categorize the study subjects into 5 groups according to their thyroid function status as follows: (1) OHypo, fT4 < 0.89 ng/dL and TSH > 6.8 mIU/L; (2) subclinical hypothyroidism, normal fT4 and TSH > 6.8 mIU/L; (3) euthyroid, normal fT4 and TSH; (4) subclinical hyperthyroidism, normal fT4 and TSH < 0.6 mIU/L; and (5) OHyper, fT4 > 1.76 ng/dL and TSH < 0.6 mIU/L.

Statistical Analysis

R version 3.4.0 software and the R libraries survey, RODBC, and Cairo were used for data analysis (R Foundation for Statistical Computing, Vienna, Austria; available at <http://www.R-project.org>). All statistical calculations were calculated using sample

Table 1. Baseline characteristics of the study population

	Total (n = 5,456)	Male (n = 2,724)	Female (n = 2,732)	p value
Age, years, median (IQR)	44 (32–57)	44 (32–57)	43 (31–56)	0.027
BMI, kg/m ²	23.5 (21.3–25.9)	24.1 (22.1–26.4)	22.8 (20.6–25.1)	<0.001
Thyroid function status				0.001
OHypo	35 (0.6)	10 (0.4)	25 (1.2)	
SCHypo	157 (2.9)	60 (2.1)	97 (3.8)	
Euthyroid	5,128 (94.0)	2,590 (95.0)	2,538 (92.1)	
SCHyper	118 (2.1)	59 (2.3)	59 (2.4)	
OHyper	18 (0.3)	5 (0.1)	13 (0.4)	
Body weight change				<0.001
≥6 kg weight loss	206 (3.8)	120 (4.5)	86 (2.7)	
≥3 and <6 kg weight loss	603 (11.1)	304 (10.9)	299 (10.5)	
Minimal change	3,264 (59.8)	1,707 (62.6)	1,557 (58.0)	
≥3 and <6 kg weight gain	1,000 (18.3)	402 (14.9)	598 (21.9)	
≥6 kg weight gain	383 (7.0)	191 (7.1)	192 (6.9)	

Figures in parentheses are percentages. IQR, interquartile range; OHypo, overt hypothyroidism; SCHypo, subclinical hypothyroidism; SCHyper, subclinical hyperthyroidism; OHyper, overt hyperthyroidism.

weights assigned to sample participants by the KNHANES. The sample weights were constructed to attain unbiased estimates representing the entire Korean population, with consideration for its stratified multistage probability sampling design of each survey year. Weighted sample values were used in the analysis to represent the Korean population. TSH levels were logarithmically transformed to normalize the distribution. Continuous variables are presented as medians with interquartile ranges (IQRs), and categorical variables are presented as frequencies with weighted percentages. The chi-square test was used to compare the prevalence of thyroid dysfunction according to changes in body weight. Differences with $p < 0.05$ were regarded as statistically significant.

Results

Baseline Characteristics of the Study Subjects

The baseline characteristics of the study subjects are summarized in Table 1. The median subject age and BMI were 44 years (IQR 32–57) and 23.5 kg/m² (IQR 21.3–25.9), respectively. Both age and BMI were significantly lower in women than that in men ($p = 0.027$ and $p < 0.001$, respectively). Overall, 94% of the study subjects were euthyroid, whereas the remaining 6% had thyroid dysfunction as follows: OHypo, 0.6%; subclinical hypothyroidism, 2.9%; subclinical hyperthyroidism, 2.1%; and OHyper, 0.3%.

Thyroid dysfunction was significantly more common in women than in men (7.1 vs. 4.9%, $p = 0.001$). Similarly, BWCs were also more frequent in women (43.0 vs. 37.3%,

$p < 0.001$). Therefore, further analysis was separately conducted in each sex.

Prevalence of Thyroid Dysfunction According to BWC

The weighted prevalence of thyroid dysfunction in each category of BWC is summarized in Table 2 and briefly schematized in online supplementary Figure 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000499961), with the data illustrating that most study subjects were euthyroid regardless of the changes in body weight. There was statistically no significant association between the overall prevalence of thyroid dysfunction and BWC both in men ($p = 0.705$) and women ($p = 0.094$).

Association between BWC and Thyroid Dysfunction by Sex

In further analysis, the impact of TSH levels (log-transformed) on weight change was separately evaluated by weight gain and loss as a categorical variable using univariate/multivariate analysis. Age and BMI were used as adjustment factors since both men and women aged <55 years or had BMI ≥23 kg/m² had significantly more changes in body weight than their counterparts, indicating that relatively younger and heavier participants have more frequent BWCs (online suppl. Table 1). Table 3 reveals no significant influence of TSH on both weight gain (hazard ratio [HR] 1.03, 95% CI 0.73–1.45, $p = 0.875$) and loss (HR

Table 2. Prevalence of thyroid dysfunction according to body weight change

Sex	Thyroid function status	Weight loss		Minimal change <3 kg	Weight gain		<i>p</i> value
		≥6 kg	≥3 and <6 kg		≥3 and <6 kg	≥6 kg	
Male	Study subjects	120	304	1,707	402	191	0.705
	OHypo	1 (1.0)	0 (0)	7 (0.5)	2 (0.4)	0 (0)	
	SCHypo	3 (2.4)	6 (2.2)	38 (2.2)	11 (2.3)	2 (0.8)	
	Euthyroid	115 (96.1)	290 (95.0)	1,621 (94.7)	383 (96.1)	181 (95.0)	
	SCHyper	1 (0.5)	8 (2.8)	37 (2.5)	5 (1.1)	8 (4.2)	
	OHyper	0 (0)	0 (0)	4 (0.2)	1 (0.1)	0 (0)	
Female	Study subjects	86	299	1,557	598	192	0.094
	OHypo	0 (0)	1 (0.1)	17 (1.6)	5 (0.7)	2 (1.0)	
	SCHypo	2 (2.8)	7 (2.5)	67 (4.7)	20 (3.1)	1 (1.3)	
	Euthyroid	82 (94.7)	281 (93.1)	1,439 (91.2)	557 (93.8)	179 (92.4)	
	SCHyper	1 (1.4)	6 (2.9)	28 (2.1)	15 (2.3)	9 (4.7)	
	OHyper	1 (1.0)	4 (1.3)	6 (0.4)	1 (0.1)	1 (0.5)	

Figures in parentheses are percentages. OHypo, overt hypothyroidism; SCHypo, subclinical hypothyroidism; SCHyper, subclinical hyperthyroidism; OHyper, overt hyperthyroidism.

Table 3. Association between body weight change and TSH levels

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Male				
Weight gain				
Log TSH	1.04 (0.75–1.44)	0.804	1.03 (0.73–1.45)	0.875
Age <55	3.10 (2.30–4.18)	<0.001	3.28 (2.43–4.42)	<0.001
BMI ≥23	2.90 (2.27–3.70)	<0.001	3.04 (2.38–3.88)	<0.001
Weight loss				
Log TSH	1.02 (0.65–1.59)	0.943	1.02 (0.65–1.60)	0.923
Age <55	1.09 (0.84–1.41)	0.521	1.08 (0.83–1.40)	0.563
BMI <23	1.50 (1.22–1.86)	<0.001	1.50 (1.21–1.86)	<0.001
Female				
Weight gain				
Log TSH	0.84 (0.65–1.08)	0.172	0.85 (0.65–1.15)	0.23
Age <55	2.20 (1.72–2.80)	<0.001	2.85 (2.22–3.65)	<0.001
BMI ≥23	2.28 (1.85–2.81)	<0.001	2.83 (2.28–3.50)	<0.001
Weight loss				
Log TSH	0.62 (0.47–0.84)	0.002	0.64 (0.47–0.85)	0.003
Age <55	1.31 (0.97–1.75)	0.075	1.25 (0.92–1.70)	0.148
BMI <23	1.17 (0.90–1.53)	0.234	1.12 (0.85–1.47)	0.417

BMI, body mass index; TSH, thyroid-stimulating hormone.

1.02, 95% CI 0.65–1.60, $p = 0.923$) in men. However, in women, TSH was independently associated with weight loss after adjusting for age and BMI (HR 0.64, 95% CI 0.47–0.85, $p = 0.003$) but not weight gain (HR 0.85, 95% CI 0.65–1.15, $p = 0.23$).

Discussion

Weight change is a frequent complaint of patients with thyroid dysfunction. Zulewski et al. [1] examined the classical signs and symptoms of hypothyroidism, and weight increase was reported by 54% of patients with OHypo. Similarly, Boelaert et al. [2] evaluated the prevalence of symptoms of overt thyrotoxicosis, and weight loss was the most commonly reported symptom with an incidence of 60.7%. Although data on baseline BMI or the degree of weight change were lacking in the 2 aforementioned studies, it is conceivable that weight loss or gain is closely associated with thyroid dysfunction. This is attributable to the role of thyroid hormones in body weight regulation, which occurs mainly by modulating resting energy expenditure [11] with influences on thermogenesis and leptin levels [12]. In line with this finding, many studies demonstrated that serum TSH concentrations are elevated in obese adults [13–16], as well as the reverse in patients with anorexia nervosa [14, 17, 18], although there is no definite indication for thyroid hormone treatment to control body weight at present.

Compared to several large observational studies on BWC according to thyroid dysfunction, few studies have addressed the prevalence of thyroid dysfunction according to BWC. Therefore, there is no clear evidence regarding when to assess thyroid function status in subjects complaining of BWC. Additionally, various factors such as caloric intake [19], smoking and alcohol habits [20],

physical activity [20, 21], inflammation [22], genetic factors [23], and metabolic factors [24] contribute to weight status in a complex manner. This heterogeneity in BWC makes it challenging for clinicians to determine whether BWC resulted solely from thyroid dysfunction. These circumstances highlight the need to systematically evaluate the prevalence of thyroid dysfunction according to the degree of BWC in large patient cohorts. To the best of our knowledge, no previous studies addressed this issue. Our nationwide cohort study of 5,456 subjects revealed that most subjects with BWC were in a euthyroid state rather than exhibiting thyroid dysfunction. There was no statistically significant association between weighted prevalence of thyroid dysfunction and BWC in each sex.

However, when the impact of TSH levels on BWC was evaluated separately for each sex after adjustment for major confounding factors via multivariate analysis, there was a significant positive association between TSH levels and weight loss in women. TSH levels were not significantly associated with weight gain in women or any weight changes in men. This finding of sex-dependent association is in agreement with previous studies [25, 26], probably because of differences in body composition between the sexes, but further studies are required to validate this finding.

One of the strengths of this study is the availability of large population-level data from sex-pooled analyses of the prevalence of thyroid dysfunction according to the extent of BWC. Our finding of a significant association between TSH levels and weight loss in women may provide clear evidence for clinicians to perform thyroid function

testing. One major limitation of our study is that data on BWC relied on self-report, which may lower the accuracy or cause response bias. Also, the criteria of 3 and 6 kg for the BWC are arbitrarily chosen and used by KNHANES. Further studies with objective measurement of BWC are necessary to validate our findings. In addition, because this is a cross-sectional study that used data from a single point, the observed association does not necessarily reflect a causal relationship. We were not able to evaluate other potential causes or medications that may impact on BWC individually from this KNHANES data.

In summary, weight loss in women was significantly related to thyroid dysfunction, whereas no association of thyroid dysfunction was observed for weight gain in women or any changes in men. This result provides evidence regarding the need for thyroid function testing in women who complain of weight loss, but testing may be less vital for women with weight gain or men with any changes in weight.

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Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

References

- 1 Zulewski H, Müller B, Exer P, Miserez AR, Staub JJ. Estimation of tissue hypothyroidism by a new clinical score: evaluation of patients with various grades of hypothyroidism and controls. *J Clin Endocrinol Metab*. 1997 Mar; 82(3):771–6.
- 2 Boelaert K, Torlinska B, Holder RL, Franklyn JA. Older subjects with hyperthyroidism present with a paucity of symptoms and signs: a large cross-sectional study. *J Clin Endocrinol Metab*. 2010 Jun;95(6): 2715–26.
- 3 Hoogwerf BJ, Nuttall FQ. Long-term weight regulation in treated hyperthyroid and hypothyroid subjects. *Am J Med*. 1984 Jun;76(6): 963–70.
- 4 Baron DN. Hypothyroidism; its aetiology and relation to hypometabolism, hypercholesterolaemia, and increase in body-weight. *Lancet*. 1956 Aug;271(6937):277–81.
- 5 Dale J, Daykin J, Holder R, Sheppard MC, Franklyn JA. Weight gain following treatment of hyperthyroidism. *Clin Endocrinol (Oxf)*. 2001 Aug;55(2):233–9.
- 6 Tzotzas T, Krassas GE, Konstantinidis T, Bougoulia M. Changes in lipoprotein(a) levels in overt and subclinical hypothyroidism before and during treatment. *Thyroid*. 2000 Sep; 10(9):803–8.
- 7 Gurney C, Hall R, Harper M, Owen SG, Roth M, Smart GA. Newcastle thyrotoxicosis index. *Lancet*. 1970 Dec;2(7686):1275–8.
- 8 Nordyke RA, Gilbert FI Jr, Harada AS. Graves' disease. Influence of age on clinical findings. *Arch Intern Med*. 1988 Mar;148(3): 626–31.
- 9 Williams RH. Thiouracil treatment of thyrotoxicosis; the results of prolonged treatment. *J Clin Endocrinol Metab*. 1946 Jan;6(1):1–22.
- 10 Kim WG, Kim WB, Woo G, Kim H, Cho Y, Kim TY, et al. Thyroid stimulating hormone reference range and prevalence of thyroid dysfunction in the Korean population: Korea national health and nutrition examination survey 2013 to 2015. *Endocrinol Metab (Seoul)*. 2017 Mar;32(1):106–14.
- 11 Danforth E Jr, Burger A. The role of thyroid hormones in the control of energy expenditure. *Clin Endocrinol Metab*. 1984 Nov;13(3): 581–95.
- 12 Santini F, Marzullo P, Rotondi M, Ceccarini G, Pagano L, Ippolito S, et al. Mechanisms in endocrinology: the crosstalk between thyroid gland and adipose tissue: signal integration in health and disease. *Eur J Endocrinol*. 2014 Oct;171(4):R137–52.
- 13 Nyren A, Jorde R, Sundsfjord J. Serum TSH is positively associated with BMI. *Int J Obes*. 2006 Jan;30(1):100–5.

- 14 Reinehr T, Isa A, de Sousa G, Dieffenbach R, Andler W. Thyroid hormones and their relation to weight status. *Horm Res.* 2008;70(1): 51–7.
- 15 Reinehr T. Obesity and thyroid function. *Mol Cell Endocrinol.* 2010 Mar;316(2):165–71.
- 16 Rotondi M, Leporati P, La Manna A, Pirali B, Mondello T, Fonte R, et al. Raised serum TSH levels in patients with morbid obesity: is it enough to diagnose subclinical hypothyroidism? *Eur J Endocrinol.* 2009 Mar;160(3):403–8.
- 17 Haas V, Onur S, Paul T, Nutzinger DO, Bösych-Westphal A, Hauer M, et al. Leptin and body weight regulation in patients with anorexia nervosa before and during weight recovery. *Am J Clin Nutr.* 2005 Apr;81(4):889–96.
- 18 Onur S, Haas V, Bösych-Westphal A, Hauer M, Paul T, Nutzinger D, et al. L-tri-iodothyronine is a major determinant of resting energy expenditure in underweight patients with anorexia nervosa and during weight gain. *Eur J Endocrinol.* 2005 Feb;152(2):179–84.
- 19 Tataranni PA, Harper IT, Snitker S, Del Parigi A, Vozarova B, Bunt J, et al. Body weight gain in free-living Pima Indians: effect of energy intake vs expenditure. *Int J Obes Relat Metab Disord.* 2003 Dec;27(12):1578–83.
- 20 Rissanen AM, Heliövaara M, Knekt P, Reunanen A, Aromaa A. Determinants of weight gain and overweight in adult Finns. *Eur J Clin Nutr.* 1991 Sep;45(9):419–30.
- 21 Zurlo F, Ferraro RT, Fontvielle AM, Rising R, Bogardus C, Ravussin E. Spontaneous physical activity and obesity: cross-sectional and longitudinal studies in Pima Indians. *Am J Physiol.* 1992 Aug;263(2 Pt 1):E296–300.
- 22 Engström G, Hedblad B, Stavenow L, Lind P, Janzon L, Lindgärde F. Inflammation-sensitive plasma proteins are associated with future weight gain. *Diabetes.* 2003 Aug;52(8): 2097–101.
- 23 Snyder EE, Walts B, Pérusse L, Chagnon YC, Weisnagel SJ, Rankinen T, et al. The human obesity gene map: the 2003 update. *Obes Res.* 2004 Mar;12(3):369–439.
- 24 Ravussin E, Lillioja S, Knowler WC, Christin L, Freymond D, Abbott WG, et al. Reduced rate of energy expenditure as a risk factor for body-weight gain. *N Engl J Med.* 1988 Feb; 318(8):467–72.
- 25 Gopinath B, Liew G, Flood VM, Wang JJ, Kifle A, Leeder SR, et al. The association between weight gain and thyroid function in an older population. *Arch Intern Med.* 2008 Nov;168(20):2283–4.
- 26 Friedrich N, Roszkopf D, Brabant G, Völzke H, Nauck M, Wallaschofski H. 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.* 2010 Apr;118(4):266–73.