ORIGINAL ARTICLE
Endocrinology, Nutrition & Metabolism

JKMS

https://doi.org/10.3346/jkms.2017.32.10.1626 • J Korean Med Sci 2017; 32: 1626-1632

The Relationship between Subclinical Thyroid Disease and Cardiovascular Disease Risk Score in Koreans

Hee Joong Lim,[1] Seong Hee Ahn,[2] Seongbin Hong,[2] and Young Ju Suh[3]

[1]Department of Medicine, Inha University College of Medicine, Incheon, Korea; [2]Department of Internal Medicine, Inha University College of Medicine, Incheon, Korea; [3]Department of Biomedical Sciences, Inha University College of Medicine, Incheon, Korea

Received: 19 April 2017
Accepted: 15 July 2017

Address for Correspondence:
Young Ju Suh, PhD
Department of Biomedical Sciences, Inha University College of Medicine, 27 Inhang-ro, Jung-gu, Incheon 22332, Republic of Korea
E-mail: ysuh@inha.ac.kr

Funding: This work was supported by the Inha University Research Grant (grant No. 55954).

Subclinical hyperthyroidism and subclinical hypothyroidism are characterized by abnormal thyroid stimulating hormone (TSH) with normal free thyroxine. Subclinical thyroid diseases, to date, have received less attention compared with other thyroid diseases since they are asymptomatic. This study aimed to verify the association between subclinical thyroid diseases and cardiovascular diseases (CVDs) risk score in the Korean population. This was a population-based cohort study using data collected from 3,722 subjects (aged ≥ 30 years) during the 6th Korea National Health and Nutrition Examination Survey (KNHANES VI; 2013–2015). Gender-specific Framingham risk scores were calculated to identify the association between subclinical thyroid diseases and 10-year CVD risk score. Complex survey, with consideration of sampling weight, was analyzed using generalized linear models after stratification by gender. The TSH reference range was between 0.61 and 6.91 mIU/L in this study. TSH showed a positive association with the 10-year CVD risk score only in the female population (P = 0.001). There were significant differences in the least squares means of 10-year CVD risk score by the effect of subclinical hypothyroidism compared with euthyroidism (normal group) in females, after adjusting for body mass index, white blood cell, and urine iodine (P = 0.006 and Bonferroni corrected P = 0.012). In conclusion, subclinical hypothyroidism is associated with increased 10-year CVD risk score in the female Korean population aged 30 years or more. Therefore, we recommend to clinically checkup major CVD risk factors in female patients with subclinical hypothyroidism aged 30 years or more.

Keywords: Subclinical Hyperthyroidism; Subclinical Hypothyroidism; Thyroid Stimulating Hormone; Cardiovascular Diseases; Korean; Framingham Risk Score

INTRODUCTION

Subclinical thyroid disease is comprised of subclinical hyperthyroidism and subclinical hypothyroidism, which are characterized by abnormal thyroid stimulating hormone (TSH) with normal free thyroxine. Although subclinical thyroid diseases are common in middle-aged and elderly individuals (1), they receive less attention compared with other overt thyroid diseases due to their asymptomatic clinical characteristic. However, several studies have demonstrated that subclinical thyroid diseases are associated with increased risk of cardiovascular disease (CVD) (2). For subclinical hyperthyroidism, several large prospective cohort studies showed an increased risk of coronary heart disease mortality, incident atrial fibrillation, and heart failure in patients with serum TSH levels < 0.1 mIU/L (2). For subclinical hypothyroidism, previous studies demonstrated the association between hypercholesterolemia and atherosclerosis, which can elevate the risk of CVD (3). Moreover, in a recent meta-analysis, subclinical hypothyroidism was shown to actually be correlated with increased risk of CVD and mortality (4). Therefore, concerns about screening and treatment to prevent CVD have also been magnified in patients with subclinical hypothyroidism (5).

The biochemical reference range for defining subclinical thyroid diseases is dependent on the serum TSH levels, which can be affected by multiple factors, such as age, gender, smoking, body mass index (BMI), iodine intake, and thyroid autoantibodies (6,7). A recent Korean study with subjects between the age 20 and 79 years using institutional routine health check-up data demonstrated that the serum TSH levels in a Korean reference population were higher (0.73–7.06 mIU/L) than those reported in other countries (0.4–4.2 mIU/L) (8). Relevant research using the data of the Korea National Health and Nutrition Examination Survey (KNHANES) VI also showed similar results regarding the serum TSH levels (0.62–6.68 mIU/L) in a Korean reference population who were 10 years or more (9). Therefore, there is a possibility that the relationship between subclinical thyroid diseases and CVD risk may show a different characteristic compared with previous results usually conducted in Western countries.

pISSN 1011-8934
eISSN 1598-6357

The Framingham risk score has been renowned as a 10-year CVD risk score model that most reliably predicts CVD events and mortality in the next 10 years with subjects of baseline examinations free of CVD, who were 30 years or more (10-12). The predictors used in the risk model are age, gender, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure (SBP), treatment status of hypertension or diabetes, and smoking status (12), which we can easily obtain from large population-based data. Nevertheless, there have been a few studies investigating the relationship between subclinical thyroid diseases and the 10-year CVD risk score to date.

Therefore, the objectives of this study were to verify the association between subclinical thyroid diseases and 10-year CVD risk score in the Korean population who are 30 years or more, and to establish a new TSH reference range extracted from KNHANES VI data.

MATERIALS AND METHODS

Study participants

This study was performed using the data obtained from the KNHANES VI study (2013 to 2015), a cross-sectional and nationally representative survey conducted on non-institutionalized individuals by the Division of Chronic Disease Surveillance, Korea Centers for Disease Control and Prevention. The KNHANES data is obtained from 3,840 individuals, randomly chosen from 192 regions in Korea, on an annual basis, using a stratified, multistage sampling procedure. The survey was comprised of a health interview, a health examination, and a nutrition survey. The data were collected via household interviews and standardized physical examinations were conducted at mobile examination centers. Treatment status was defined as patients currently taking antihypertensive medications. Subjects were classified as having diabetes mellitus if their fasting plasma glucose was ≥ 126 mg/dL or they reported actively using an oral hypoglycemic agent or insulin on the health survey. Patients currently taking oral hypoglycemic agents or insulin were defined as treatment status of diabetes. The KNHANES database is publicly available at the KNHANES website (available at http://knhanes.cdc.go.kr/knhanes/eng). Following the criteria based on the Framingham Heart Study data, subjects without prevalent CVD who were 30 to 74 years of age were included in this study (12). Stroke, myocardial infarction, and angina pectoris were defined as CVD in the KNHANES data. Pregnant women were excluded from the reference population, since it is possible for physiologic changes to affect thyroid function. Finally, we included a reference population of 3,722 subjects (1,922 males and 1,800 females) with no history of thyroid disease, no history of taking medications that could affect thyroid function, no family history of thyroid disease, negative anti-thyroid peroxidase antibody (TPOAb) results (less than 35 IU/mL), and serum-free T4 (fT4) levels in the reference range (0.80 to 1.80 ng/dL).

Data extraction

The TSH reference range was defined to be between 2.5th and 97.5th percentile of the reference population. Subclinical thyroid disease groups were categorized into three groups; subclinical hyperthyroidism, euthyroidism that is normal, and subclinical hypothyroidism, by cutoff of TSH. The reference population with a TSH range of below the 2.5th percentile was defined as subclinical hyperthyroidism and those of above the 97.5th percentile as subclinical hypothyroidism

We used a gender-specific algorithm enabling physicians to identify candidates with high-risk atherosclerotic CVD events using measurements readily available at the clinic or at the office. In accordance with the gender-specific 10-year CVD risk score prediction formula (12), we calculated the risk scores of subjects based on their age, gender, total cholesterol, HDL cholesterol, SBP, treatment status of hypertension, and diabetes, as well as smoking status for males and females, respectively.

Biochemical measurements

Blood samples were collected from the antecubital vein of each participant after overnight fasting to obtain the levels of serum TSH, fT4, TPOAb, total cholesterol, HDL cholesterol, and white blood cell (WBC) counts. After separation of the serum within 30 minutes, the sample was transferred to the testing facility. The samples were processed, transported to the Central Testing Institute located in Seoul, and analyzed within 24 hours. The levels of serum TSH, fT4, and TPOAb were analyzed using an electrochemiluminescence immunoassay within the first 24 hours (Roche Diagnostics, Mannheim, Germany). TSH was measured using an E-TSH kit (Roche Diagnostics), for which the reference range was 0.35 to 5.50 mIU/L. The fT4 was measured using an E-Free T4 kit (Roche Diagnostics). The fT4 reference range was 0.89 to 1.76 ng/mL. TPOAb was measured using an E-Anti-TPO kit (Roche Diagnostics). The normal range for TPOAb in humans is < 34.0 IU/mL. The reported results of TSH, fT4, and TPOAb levels met the specifications regarding accuracy, general chemistry, special immunology, and ligand of the quality control and quality assurance guidelines set forth by the College of American Pathologist. The levels of total and HDL cholesterols were measured using the homogenous enzymatic colorimetric method (Hitachi Automatic Analyzer 7600-210; Hitachi, Tokyo, Japan). WBC counts were collected using a flow cytometry via a semiconductor laser (XE-2100D and XN-9000; Sysmex, Kobe, Japan). Blood pressure was measured three times at 30 second intervals after a minimum of 5 minute of rest in a seated position, and recorded as an average value of the second and third measurements. Hypertension was defined as SBP above 140 mmHg or diastolic blood pressure (DBP) above 90 mmHg. Urine iodine (UIod) concentrations were measured

from the random spot urine samples (first morning urine, if possible) of the study populations via an inductively coupled plasma mass spectrometry devise (ICP-MS; Perkin Elmer ICP-MS, Waltham, MA, USA). UIod concentrations were measured using an Iodine standard (Inorganic Venture, Christiansburg, VA, USA).

Statistical analysis

The value of CVD risk score was log-transformed due to non-normality. All statistical analyses were performed after stratification by gender, since the CVD risk score was a gender-specific value. The weighted results were estimated using survey sample weight variables for the associations between health interview and health examination. The association between clinical variables and log 10-year CVD risk score was identified using simple and multiple linear regression analyses for the complex survey. We estimated the least squares means (LS means) of log 10-year CVD risk score for the effect according to the subclinical thyroid disease group compared with the euthyroidism group in the generalized linear model, after adjusting for BMI, WBC, and UIod. The LS means specify the predicted marginal mean over the balanced population. We also tested differences of the LS means of log 10-year CVD risk score using pairwise Wald χ^2 test with Bonferroni correction for multiple comparisons. Statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). A *P* value of less than 0.05 was considered to be statistically significant (two-tailed).

RESULTS

TSH reference range of the study population

The distribution of TSH level is shown in Table 1. In this study population, the TSH reference range was defined as being between 0.61 (2.5th percentile) to 6.91 mIU/L (97.5th percentile). The TSH reference range in males (0.60–6.37 mIU/L) tended to be lower than that in females (0.65–7.38 mIU/L). A population with less than 0.61 mIU/L of TSH was considered to have subclinical hyperthyroidism, those in between 0.61 to 6.91 mIU/L to have euthyroidism, and those with greater than 6.91 mIU/L to have subclinical hypothyroidism.

Baseline characteristics of the study population

The clinical characteristics of 1,922 males and 1,800 females are

Table 1. Distribution of TSH in the study population

Gender	Mean ± SD	TSH levels (mIU/L) by percentile				
		2.5th	25th	50th	75th	97.5th
Male (n = 1,922)	2.340 ± 1.648	0.60	1.40	2.03	2.92	6.37
Female (n = 1,800)	2.760 ± 1.804	0.65	1.60	2.32	3.43	7.38
Total (n = 3,722)	2.560 ± 1.735	0.61	1.49	2.17	3.16	6.91

TSH = thyroid stimulating hormone, SD = standard deviation.

Table 2. Baseline characteristics of study population

Characteristics	Male				Female				Total
	Subclinical hyperthyroidism (n = 50)	Euthyroidism (n = 1,840)	Subclinical hypothyroidism (n = 32)	Total (n = 1,922)	Subclinical hyperthyroidism (n = 40)	Euthyroidism (n = 1,700)	Subclinical hypothyroidism (n = 60)	Total (n = 1,800)	(n = 3,722)
Age, yr	51.00 ± 12.02	49.24 ± 11.70	51.09 ± 11.04	49.32 ± 11.70	50.53 ± 12.29	49.96 ± 11.65	52.15 ± 9.75	49.11 ± 11.62	49.21 ± 11.66
Total cholesterol, mg/dL	193.34 ± 33.20	191.58 ± 33.94	191.97 ± 31.59	191.61 ± 33.87	186.50 ± 33.22	192.74 ± 35.84	197.43 ± 27.45	192.76 ± 35.54	192.18 ± 34.69
HDL cholesterol, mg/dL	47.58 ± 11.15	47.40 ± 11.23	48.22 ± 10.48	47.42 ± 11.21	51.56 ± 11.43	53.65 ± 11.68	52.13 ± 10.79	53.55 ± 11.65	50.40 ± 11.83
SBP, mmHg	121.14 ± 14.96	120.18 ± 15.08	122.94 ± 16.71	120.25 ± 15.10	112.85 ± 12.95	115.10 ± 16.85	116.92 ± 15.91	115.11 ± 16.74	117.76 ± 16.12
BP treatment	10 (20.0)	310 (16.8)	9 (28.1)	329 (17.1)	7 (17.5)	246 (14.5)	7 (11.7)	260 (14.4)	589 (15.8)
Smoking	29 (58.0)	788 (42.8)	6 (18.8)	823 (42.8)	2 (5.0)	101 (5.9)	2 (3.3)	105 (5.8)	928 (24.9)
Diabetes	3 (6.0)	147 (8.0)	4 (12.5)	154 (8.0)	3 (7.5)	104 (6.1)	3 (5.0)	110 (6.1)	264 (7.1)
10-year CVD risk score*	17.08 ± 15.69	12.60 ± 11.58	12.75 ± 11.75	12.75 ± 11.75	4.65 ± 4.76	5.14 ± 6.07	5.49 ± 4.25	5.14 ± 5.99	9.07 ± 10.16
BMI, kg/m^2	25.02 ± 3.15	24.46 ± 3.25	24.43 ± 2.57	24.47 ± 3.24	23.25 ± 2.73	23.57 ± 3.43	24.19 ± 3.92	23.58 ± 3.43	24.04 ± 3.36
WBC, Thous/uL	7.04 ± 1.94	6.69 ± 1.83	6.20 ± 1.45	6.69 ± 1.83	5.90 ± 2.07	5.86 ± 1.56	5.69 ± 1.40	5.86 ± 1.57	6.28 ± 1.76
UIod, μg/L	3,508.58 ± 20,851.57	709.34 ± 1,540.56	1,559.59 ± 2,126.91	795.50 ± 3,689.29	1,157.19 ± 2,449.09	847.30 ± 2,628.40	1,426.95 ± 2,254.11	873.55 ± 2,614.03	832.05 ± 3,230.39

Data are shown as mean ± standard deviation or number (%).
HDL = high-density lipoprotein, SBP = systolic blood pressure, BP = blood pressure, CVD = cardiovascular disease, BMI = body mass index, WBC = white blood cell, UIod = urine iodine.
*The 10-year CVD risk score was calculated based on each subject's age, gender, total cholesterol, HDL cholesterol, SBP, treatment status of hypertension or diabetes, and smoking status according to the gender-specific CVD risk prediction formula (12).

https://doi.org/10.3346/jkms.2017.32.10.1626

shown in Table 2. There were 90 subjects (50 males and 40 females) considered to have subclinical hyperthyroidism, 3,540 subjects (1,840 males and 1,700 females) to have euthyroidism, and 92 subjects (32 males and 60 females) to have subclinical hypothyroidism. The mean age (± standard deviation) for males (49.32 ± 11.70 years) was similar to that for females (49.11 ± 11.62 years). HDL cholesterol level seemed high in females (53.55 ± 11.65) compared with males (47.42 ± 11.21), which was also the case for each subgroup of study population (i.e., subclinical hyperthyroidism, euthyroidism, and subclinical hypothyroidism). The cigarette smoking rate was much higher in males (42.8%) than in females (5.8%). There was a difference in the 10-year CVD risk score between the two genders. The 10-year CVD risk score in males seemed higher (12.75 ± 11.75) than that in females (5.14 ± 5.99), which was also found in each subgroup of subclinical hyperthyroidism, euthyroidism, and subclinical hypothyroidism. The distributions of the other factors were similar between males and females.

Association between TSH and 10-year CVD risk score by gender

Since the 10-year CVD risk score was different based on gender, we examined the association between TSH (log-transformed) and 10-year CVD risk score separately for each gender (Tables 3 and 4). TSH showed a significantly positive association with 10-year CVD risk score, after adjusting for confounding factors (such as BMI, WBC, and Ulod) in females (P = 0.008), but not in males (P = 0.792). BMI was statistically significant in each gender. WBC was significantly associated with the 10-year CVD risk score, after adjusting for confounding factors, in males only (P < 0.001). UIod showed no significance in both genders.

Table 3. Association* between TSH and 10-year CVD risk score† (male population)

Variables	Simple			Multiple		
	β (Exp [β]‡)	SE	*P* value	β (Exp [β]‡)	SE	*P* value
log(TSH)	0.002 (1.002)	0.040	0.965	−0.010 (0.990)	0.039	0.792
BMI	0.027 (1.027)	0.008	< 0.001	0.022 (1.022)	0.008	0.004
WBC	0.060 (1.062)	0.139	< 0.001	0.053 (1.054)	0.013	< 0.001
Ulod	1.2E-6 (1.000)	1.5E-6	0.417	1.7E-6 (1.000)	1.37E-6	0.188

TSH = thyroid stimulating hormone, CVD = cardiovascular diseases, SE = standard error, BMI = body mass index, WBC = white blood cell, Ulod = urine iodine.
*Simple and multiple linear regression model were executed for the complex survey in males. †Log-transformed 10-year CVD risk score was regressed due to non-normality on residuals. ‡Exponentially transformed β coefficient in the fitted model.

Association between subclinical thyroid diseases and 10-year CVD risk by gender

Following the results of Tables 3 and 4, we explored which group of subclinical thyroid diseases significantly conferred a risk of increased 10-year CVD risk score after stratification by gender (Fig. 1). Adjusted means of log 10-year CVD risk score by group of subclinical thyroid diseases tended to be higher in males than those in females. Significant differences were identified between groups in females (overall P = 0.021), but not in males (overall P = 0.650). In particular, there was a significant difference in the LS means of 10-year CVD risk score by the effect of subclinical hypothyroidism group compared with euthyroidism (normal group) in females, after adjusting for BMI, WBC, and UIod (P = 0.006 and Bonferroni corrected P = 0.012). However, there was no significance between subclinical hyperthyroidism and euthyroidism group in females (P = 0.877).

Association between TSH and components of 10-year CVD risk score

To explain the reason of a positive association between TSH and 10-year CVD risk, we performed correlation analyses between TSH (log-transformed) and the components of 10-year CVD risk score in the Framingham formula for males and fe-

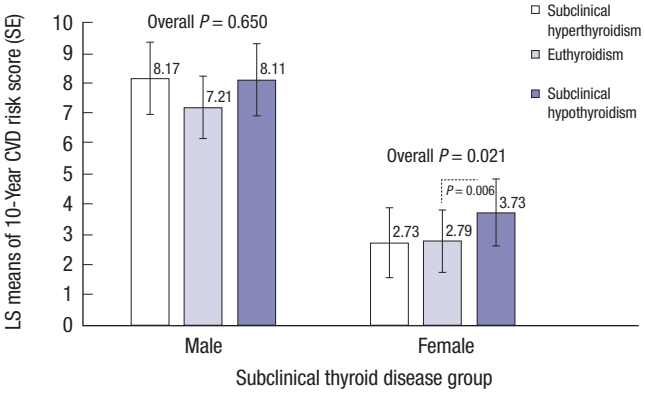

Fig. 1. The effect of subclinical thyroid diseases on 10-year CVD risk by gender.
CVD = cardiovascular diseases, SE = standard error, LS mean = least squares mean.

Table 4. Association* between TSH and 10-year CVD risk score† (female population)

Variables	Simple			Multiple		
	β (Exp [β]‡)	SE	*P* value	β (Exp [β]‡)	SE	*P* value
log(TSH)	0.102 (1.107)	0.036	0.005	0.089 (1.093)	0.033	0.008
BMI	0.108 (1.114)	0.008	< 0.001	0.109 (1.115)	0.009	< 0.001
WBC	0.072 (1.075)	0.016	< 0.001	0.009 (1.009)	0.016	0.583
Ulod	−6.93E-6 (1.000)	7.02E-6	0.323	−4.856E-6 (1.000)	5.335E-6	0.363

TSH = thyroid stimulating hormone, CVD = cardiovascular diseases, SE = standard error, BMI = body mass index, WBC = white blood cell, Ulod = urine iodine.
*Simple and multiple linear regression model were executed for the complex survey in females. †Log-transformed 10-year CVD risk score was regressed due to non-normality on residuals. ‡Exponentially transformed β coefficient in the fitted model.

males, respectively. Among the components of age, gender, total cholesterol, HDL cholesterol, SBP, treatment status of hypertension or diabetes, and smoking status, smoking was correlated with increased log (TSH) both in males (correlation coefficient ρ = 0.183; standard error [SE] = 0.032; $P < 0.001$) and in females (ρ = 0.204; SE = 0.072; $P = 0.005$). In females, age (ρ = 0.003; SE = 0.001), total cholesterol and SBP (ρ = 0.002; SE = 0.001) were also positively correlated with log (TSH) ($P < 0.05$).

DISCUSSION

In this study, the TSH reference range was defined to be 0.61–6.91 mIU/L based on the TSH distribution data of 3,722 subjects included in KNHANES VI. The association between subclinical thyroid disease and CVD risk has not been established and remained controversial. Several studies indicated increased CVD risk for those with subclinical thyroid disease. From prospective cohort studies, subclinical hypothyroidism was associated with increased risk of CVD events and CVD mortality (13). Subclinical hyperthyroidism was also relevant with increased risks of total CVD mortality and incidences of atrial fibrillation (14,15). Whereas, another study including a total of 344 subclinical hypothyroidism and 2,624 euthyroid participants aged over 40 years showed that additional assessments of serum TSH levels provided little incremental benefits for the prediction of CVD risk (16). However, these studies usually applied a common TSH reference range without considering the factors that may affect serum TSH levels, such as age and race. In this context, our study firstly showed the association of TSH and 10-year CVD risk score with the applicability of a new TSH reference range that is appropriate for representing the Korean population who are 30 years or more.

Since thyroid hormone, such as triiodothyronine, controls the inotropic and lusitropic properties of myocardium, cardiac growth, and myocardial contractility, hypothyroidism causes a low cardiac output with decreased heart rate and stroke volume (17,18). Vascular function is also deteriorated even in mild thyroid hormone deficiency (19). Moreover, hypothyroidism is accompanied by the hypercoagulable state, increased blood viscosity, and high plasma concentration of total homocysteine. Since these cardiovascular deteriorations may also be relevant with subclinical hypothyroidism (20-22), a careful prediction of CVD risk or CVD events, in addition to creating an appropriate indication for treatment in these patients, is important. Moreover, the increased risk of coronary heart disease and mortality was even reported in young patients affected by subclinical hypothyroidism with serum TSH levels > 10 mIU/L (13,23). In the same context, the 2013 European Thyroid Association (ETA) guideline recommended a levothyroxine replacement therapy for patients aged less than 65–70 years with serum TSH > 10 mIU/L (24-26), despite being asymptomatic. Moreover, in these patients, treatment should also be considered when the serum TSH levels are below 10 mIU/L, if these patients have any evidence of heart disease.

We demonstrated that there was a positive, significant association between TSH and 10-year CVD risk score in Korean females, but not in Korean males. Moreover, the 10-year CVD risk score was also significantly higher in females of the subclinical hypothyroidism group than in euthyroid females. Our additional correlation analyses between TSH and the components of 10-year CVD risk score in the Framingham formula showed that age, total cholesterol and SBP may affect increased TSH among the components of 10-year CVD risk score in females. In agreement with our findings, higher cholesterol level has been reported to be associated with higher TSH levels in females (27). Anagnostis et al. (27) demonstrated that atherogenic lipid profiles (high low-density lipoprotein [LDL] and low HDL) were associated with a risk of high TSH in females, even though a more atherogenic lipid profile was generally shown in males than females. The study of Meng et al. (28) verified that males who suffered from hyperlipidemia showed a protective effect of low TSH, while females in hyperlipidemia showed a risk of high TSH. In the 11-year follow-up of the Nord-Trøndelag health study (HUNT) (29), higher SBP and DBP were associated with higher TSH in females, which was consistent with our findings of this study. Furthermore, biochemical abnormalities and physiological changes may explain the increased risk of CVD in females with subclinical hypothyroidism.

This study has several strengths. First, it is the first nationwide epidemiological study investigating the association between subclinical thyroid disease and Framingham risk score in Koreans. We used a new TSH reference range that is appropriate for representing the Korean population who are 30 years or more. Second, this research can suggest a treatment like levothyroxine for females with subclinical hypothyroidism. In Korea, the study of subclinical thyroid disease has a tendency of little interest because it shows rare symptoms, and the recent recommendations regarding this disease have not been widely adopted. Although more clinical trials regarding this issue should be performed in the future studies, this study can be a milestone for subclinical thyroid disease.

However, there are also some limitations to consider. First, we were unable to confirm a causal relationship between TSH and 10-year CVD risk score due to the cross-sectional nature of the study. Second, we could not consider other factors that may have affected the TSH levels, such as high-sensitivity C-reactive protein (hs-CRP), other autoimmune antibodies, pregnancy or 24-hour iodine intake amount (30-36). In particular, there are several results regarding the correlation between hs-CRP concentration and subclinical hypothyroidism. Hs-CRP can be regarded as a contributing factor. We suggest future studies regarding the subclinical thyroid disease and hs-CRP. Lastly, spot

 https://doi.org/10.3346/jkms.2017.32.10.1626

UIod concentration data might have some possible observation bias due to a daily variability in iodine intake. A 24-hour urine sample data or UIod to creatinine ratio in random single voided urine can be more reliable. We were unable to use urine creatinine due to the high missing rate of our data.

To summarize, TSH showed a statistical significance with the 10-year CVD risk in Korean females. Moreover, subclinical hypothyroidism was associated with increased 10-year CVD risk in comparison with euthyroidism in Korean female population aged more than 30 years. Therefore, we recommend to clinically checkup major CVD risk factors in female patients aged more than 30 years with subclinical hypothyroidism.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conceptualization: Lim HJ, Suh YJ. Investigation: Lim HJ, Suh YJ. Writing - original draft: Lim HJ, Suh YJ. Writing - review & editing: Ahn SH, Hong S, Suh YJ.

ORCID

Hee Joong Lim https://orcid.org/0000-0002-9931-6472
Seong Hee Ahn https://orcid.org/0000-0003-2558-2118
Seongbin Hong https://orcid.org/0000-0002-8189-395X
Young Ju Suh https://orcid.org/0000-0002-6816-8067

REFERENCES

1. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med* 2000; 160: 526-34.
2. Biondi B, Bartalena L, Cooper DS, Hegedüs L, Laurberg P, Kahaly GJ. The 2015 European Thyroid Association guidelines on diagnosis and treatment of endogenous subclinical hyperthyroidism. *Eur Thyroid J* 2015; 4: 149-63.
3. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. *Ann Intern Med* 2000; 132: 270-8.
4. Ochs N, Auer R, Bauer DC, Nanchen D, Gussekloo J, Cornuz J, Rodondi N. Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. *Ann Intern Med* 2008; 148: 832-45.
5. Hueston WJ, Pearson WS. Subclinical hypothyroidism and the risk of hypercholesterolemia. *Ann Fam Med* 2004; 2: 351-5.
6. Leung AM, Braverman LE. Consequences of excess iodine. *Nat Rev Endocrinol* 2014; 10: 136-42.
7. Nyrnes A, Jorde R, Sundsfjord J. Serum TSH is positively associated with BMI. *Int J Obes (Lond)* 2006; 30: 100-5.
8. Kim M, Kim TY, Kim SH, Lee Y, Park SY, Kim HD, Kwon H, Choi YM, Jang EK, Jeon MJ, et al. Reference interval for thyrotropin in a ultrasonography screened Korean population. *Korean J Intern Med* 2015; 30: 335-44.
9. Kim WG, Kim WB, Woo G, Kim H, Cho Y, Kim TY, Kim SW, Shin MH, Park JW, Park HL, 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* 2017; 32: 106-14.
10. Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, Folsom AR, Hirsch AT, Dramaix M, deBacker G, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA* 2008; 300: 197-208.
11. Widmer RJ, Collins NM, Collins CS, West CP, Lerman LO, Lerman A. Digital health interventions for the prevention of cardiovascular disease: a systematic review and meta-analysis. *Mayo Clin Proc* 2015; 90: 469-80.
12. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008; 117: 743-53.
13. Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP, Asvold BO, Iervasi G, Imaizumi M, Collet TH, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA* 2010; 304: 1365-74.
14. Collet TH, Gussekloo J, Bauer DC, den Elzen WP, Cappola AR, Balmer P, Iervasi G, Åsvold BO, Sgarbi JA, Völzke H, et al. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. *Arch Intern Med* 2012; 172: 799-809.
15. Auer J, Scheibner P, Mische T, Langsteger W, Eber O, Eber B. Subclinical hyperthyroidism as a risk factor for atrial fibrillation. *Am Heart J* 2001; 142: 838-42.
16. Kim TH, Choi HS, Bae JC, Moon JH, Kim HK, Choi SH, Lim S, Park DJ, Park KS, Jang HC, et al. Subclinical hypothyroidism in addition to common risk scores for prediction of cardiovascular disease: a 10-year community-based cohort study. *Eur J Endocrinol* 2014; 171: 649-57.
17. Fazio S, Palmieri EA, Lombardi G, Biondi B. Effects of thyroid hormone on the cardiovascular system. *Recent Prog Horm Res* 2004; 59: 31-50.
18. Klein I, Danzi S. Thyroid disease and the heart. *Circulation* 2007; 116: 1725-35.
19. Ripoli A, Pingitore A, Favilli B, Bottoni A, Turchi S, Osman NF, De Marchi D, Lombardi M, L'Abbate A, Iervasi G. Does subclinical hypothyroidism affect cardiac pump performance? Evidence from a magnetic resonance imaging study. *J Am Coll Cardiol* 2005; 45: 439-45.
20. Chadarevian R, Bruckert E, Ankri A, Beucler I, Giral P, Turpin G. Relationship between thyroid hormones and plasma D-dimer levels. *Thromb Haemost* 1998; 79: 99-103.
21. Költringer P, Eber O, Wakonig P, Klima G, Lind P. Hypothyroidism and the influence on human blood rheology. *J Endocrinol Invest* 1988; 11: 267-72.
22. Nedrebø BG, Ericsson UB, Nygård O, Refsum H, Ueland PM, Aakvaag A, Aanderud S, Lien EA. Plasma total homocysteine levels in hyperthyroid and hypothyroid patients. *Metabolism* 1998; 47: 89-93.
23. Razvi S, Shakoor A, Vanderpump M, Weaver JU, Pearce SH. The influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease: a meta analysis. *J Clin Endocrinol Metab* 2008; 93: 2998-3007.
24. Helfand M; U.S. Preventive Services Task Force. Screening for subclinical thyroid dysfunction in nonpregnant adults: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2004; 140:

128-41.
25. Pearce SH, Brabant G, Duntas LH, Monzani F, Peeters RP, Razvi S, Wemeau JL. 2013 ETA guideline: management of subclinical hypothyroidism. *Eur Thyroid J* 2013; 2: 215-28.
26. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 2004; 291: 228-38.
27. Anagnostis P, Stevenson JC, Crook D, Johnston DG, Godsland IF. Effects of menopause, gender and age on lipids and high-density lipoprotein cholesterol subfractions. *Maturitas* 2015; 81: 62-8.
28. Meng Z, Liu M, Zhang Q, Liu L, Song K, Tan J, Jia Q, Zhang G, Wang R, He Y, et al. Gender and age impact on the association between thyroid-stimulating hormone and serum lipids. *Medicine (Baltimore)* 2015; 94: e2186.
29. Asvold BO, Bjøro T, Vatten LJ. Associations of TSH levels within the reference range with future blood pressure and lipid concentrations: 11-year follow-up of the HUNT study. *Eur J Endocrinol* 2013; 169: 73-82.
30. Allan WC, Haddow JE, Palomaki GE, Williams JR, Mitchell ML, Hermos RJ, Faix JD, Klein RZ. Maternal thyroid deficiency and pregnancy complications: implications for population screening. *J Med Screen* 2000; 7: 127-30.
31. Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, Cunningham FG. Subclinical hypothyroidism and pregnancy outcomes. *Obstet Gynecol* 2005; 105: 239-45.
32. Tudela CM, Casey BM, McIntire DD, Cunningham FG. Relationship of subclinical thyroid disease to the incidence of gestational diabetes. *Obstet Gynecol* 2012; 119: 983-8.
33. Tuzcu A, Bahceci M, Gokalp D, Tuzun Y, Gunes K. Subclinical hypothyroidism may be associated with elevated high-sensitive c-reactive protein (low grade inflammation) and fasting hyperinsulinemia. *Endocr J* 2005; 52: 89-94.
34. Wilson KL, Casey BM, McIntire DD, Halvorson LM, Cunningham FG. Subclinical thyroid disease and the incidence of hypertension in pregnancy. *Obstet Gynecol* 2012; 119: 315-20.
35. Yu YT, Ho CT, Hsu HS, Li CI, Davidson LE, Liu CS, Li TC, Shih CM, Lin CC, Lin WY. Subclinical hypothyroidism is associated with elevated high-sensitive C-reactive protein among adult Taiwanese. *Endocrine* 2013; 44: 716-22.
36. Kim HS, Kim BJ, Oh S, Lee DY, Hwang KR, Jeon HW, Lee SM. Gestational age-specific cut-off values are needed for diagnosis of subclinical hypothyroidism in early pregnancy. *J Korean Med Sci* 2015; 30: 1308-12.

 https://doi.org/10.3346/jkms.2017.32.10.1626