

# Subclinical hypothyroidism and hypertension in relation to thyroid cysts: A cross-sectional study

Souichiroh OZASA<sup>1</sup>, Shin-Ya KAWASHIRI<sup>2,3</sup>, Yuko NOGUCHI<sup>2</sup>, Yasuhiro NAGATA<sup>2,3</sup>, Takahiro MAEDA<sup>1,3</sup>, Naomi HAYASHIDA<sup>3,4</sup>, Yuji SHIMIZU<sup>1,5</sup>

<sup>1</sup> Department of General Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

<sup>2</sup> Department of Community Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

<sup>3</sup> Leading medical research core unit, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

<sup>4</sup> Division of Promotion of Collaborative Research on Radiation and Environment Health Effects, Atomic Bomb Disease Institute, Nagasaki University, Nagasaki, Japan

<sup>5</sup> Department of Cardiovascular Disease Prevention, Osaka Center for Cancer and Cardiovascular Disease Prevention, Osaka, Japan

Subclinical hypothyroidism is a condition characterized by a normal range of thyroid hormone [triiodothyronine (T<sub>3</sub>) and thyroxine (T<sub>4</sub>)] but with an elevated level of thyroid stimulating hormone (TSH). It is also reported to be associated with hypertension. Since thyroid cysts could have a beneficial effect on the activation of thyroid hormone as reported in our previous study, their presence could influence the association between subclinical hypothyroidism and hypertension. To clarify those associations, a cross-sectional study of 1,724 Japanese within normal range of thyroid hormone (i.e., normal range of free T<sub>3</sub> and free T<sub>4</sub>), aged 40-74 years, who participated in an annual health checkup in 2014 was conducted. Among the study population, 98 were diagnosed as having subclinical hypothyroidism. For participants without a thyroid cyst, hypertension had a significant positive association with subclinical hypothyroidism, while for participants with a thyroid cyst, even though the power could not reach a significant value, an inverse tendency between hypertension and subclinical hypothyroidism was observed. The adjusted odd ratios (ORs) and 95% confidence intervals (CIs) were 1.91 (1.08, 3.37) for participants without thyroid cysts and 0.63 (0.26, 1.55) for participants with thyroid cysts, respectively. The status of thyroid cysts could act as a determining factor in the association between subclinical hypothyroidism and hypertension among participants within normal range of thyroid hormone.

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**Key words:** subclinical hypothyroidism; thyroid-stimulating hormone; thyroid hormone; thyroid cyst

## Introduction

Previously, subclinical hypothyroidism but not subclinical hyperthyroidism was reported to be associated with hypertension [1].

In addition, an inverse association between thyroid cysts and the anti-thyroid peroxidase antibody (TPO-Ab) was reported in our previous cross-sectional study with a euthyroid population

[2]. Since TPO-Ab is known to cause autoimmune thyroiditis, this inverse association between thyroid cysts and TPO-Ab might indicate that the absence of thyroid cysts is related to latent thyroid damage. In other words, thyroid cysts could possess a beneficial effect on activation of thyroid hormone. Therefore, the presence of thyroid cysts could reduce the influence of hypothyroidism.

These studies speculate that hypertension is positively

**Address correspondence:** Yuji Shimizu, MD, PhD., Department of Community Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki-shi, Sakamoto 1-12-4, Nagasaki 852-8523, Japan  
Tel.: +81-95-819-7578, Fax: +81-95-819-7189, E-mail: shimizu@osaka-ganjin.jp

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associated with subclinical hypothyroidism only among subjects without thyroid cysts.

To clarify those associations, we conducted a cross-sectional study of 1,724 euthyroid Japanese aged 40-74 years, who participated in an annual health checkup in 2014.

## Materials and Methods

### 1. Study population

The methods used in the present risk survey including thyroid function also have been described elsewhere [2].

Written consent forms were made available to ensure that participants understood the objective of the study, and informed consent was obtained. This study was approved by the Ethics Committee of Nagasaki University Graduate School of Biomedical Sciences (project registration number 14051404).

The study population comprised 1,883 Japanese people between the ages of 40 and 74 years from Saza town in the western part of Japan who underwent an annual medical check-up in 2014, as recommended by the Japanese government.

To avoid the influence of thyroid disease, subjects with a history of thyroid disease ( $n=60$ ); a loss in one of any thyroid function data including TSH, free  $T_3$ , and free  $T_4$  ( $n=17$ ); or with an abnormal free  $T_3$  (normal range: 2.1-4.1 pg/mL) range or with an abnormal free  $T_4$  (normal range: 1.0-1.7 ng/dL) range were excluded ( $n=77$ ).

Additionally, subjects without body mass index (BMI) data ( $n=1$ ) or blood pressure data ( $n=1$ ) were excluded. Furthermore, subjects without preference data (smoking status and drinking status) ( $n=3$ ) were excluded.

The remaining subjects, comprising 1,724 individuals with a mean age of 60.5 years (standard deviation (SD): 9.1; range 40-74) were enrolled in the study.

### 2. Data collection and Laboratory Measurements

A trained interviewer obtained information on clinical characteristics such as history of thyroid disease, glucose-lowering medication use and status of preference. Bodyweight and height were measured with an automatic body composition analyzer (BF-220; Tanita, Tokyo, Japan) and BMI ( $\text{kg}/\text{m}^2$ ) was calculated. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded at rest.

A fasting blood sample was collected. TSH, free  $T_3$  and free  $T_4$  were measured by standard procedures at the LSI Medience Corporation (Tokyo, Japan). Normal ranges for free  $T_3$  (2.1-4.1 pg/mL), free  $T_4$  (1.0-1.7 ng/dL), and TSH (0.39-4.01  $\mu\text{IU}/\text{mL}$ ) based on this method were reported

[3]. Hemoglobin A1c (HbA1c), triglycerides (TG), and high-density lipoprotein cholesterol (HDLc) were also measured using standard procedures at SRL, Inc. (Tokyo, Japan).

Thyroid cysts were detected by experienced technicians using a LOGIQ Book XP with a 10-MHz transducer (GE Healthcare, Milwaukee, WI, USA). A thyroid cyst (maximum diameter  $\geq 2.0$  mm) without a solid component was defined as a thyroid cyst for this study.

Participants with serum concentration of TSH  $> 4.01$   $\mu\text{IU}/\text{mL}$  were defined as having subclinical hypothyroidism.

Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg and/or anti-hypertensive medication use.

Overweight was defined as BMI  $\geq 25.0$   $\text{kg}/\text{m}^2$ , Hypertriglyceridemia as TG  $\geq 150$  mg/dL, low HDLc as HDLc  $< 40$  mg/dL, and High HbA1c as HbA1c  $\geq 6.5\%$ .

### 3. Statistical analysis

Characteristics of the study population by status of thyroid cysts were analyzed. Continuous values were expressed as mean  $\pm$  standard deviation (SD) except for TSH. Since TSH showed a skewed distribution, the characteristics of this study population were expressed as median [the first quartile, the third quartile]. Significant differences by status of thyroid cysts were evaluated using analysis of variance (ANOVA).

Logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to determine the association between subclinical hypothyroidism and hypertension. Three adjustment models were used. The first model was adjusted only for sex and age (model 1); the second model (model 2) further included the potential confounding factor that is directly associated with thyroid function, namely free  $T_3$ . The last model (model 3) was further adjusted for potential confounding factors that were indirectly associated with thyroid function and hypertension; those were overweight (BMI  $\geq 25$   $\text{kg}/\text{m}^2$ ), smoking status (never, former, current), drinking status (non, often, daily), hypertriglyceridemia (TG  $\geq 150$  mg/dL), low HDLc (HDLc  $< 40$  mg/dL), and high HbA1c (HbA1c  $\geq 6.5\%$ ).

We also evaluated the association between subclinical hypothyroidism and hypertension stratified by status of thyroid cysts.

For sensitivity analysis, we also evaluated the sex-specific association between subclinical hypothyroidism and hypertension by status of thyroid cysts by using an age-adjusted model.

All statistical analyses were performed with the SAS system for Windows (version 9.4: SAS Inc., Cary, NC, USA). Values of  $p < 0.05$  were regarded as statistically significant.

## Results

Among the study population, 564 were diagnosed as having thyroid cysts. Among those participants with thyroid cyst, only one case shows maximum diameter  $\geq 10.0$ mm.

### 1. Characteristics of the study population by status of thyroid cysts

The characteristics of the study population by status of thyroid cysts are shown in Table 1. Compared to participants without thyroid cysts, participants with thyroid cysts showed significantly higher values of age, hypertension and blood pressure (both of systolic and diastolic) while significantly lower prevalence of men and high HbA1c.

### 2. Association between subclinical hypothyroidism and hypertension

ORs and 95% CIs of subclinical hypothyroidism in relation to hypertension are shown in Table 2. Even though the statistical power could not reach a significant value, a positive tendency between subclinical hypothyroidism and hypertension was observed.

### 3. Association between subclinical hypothyroidism and hypertension stratified by status of thyroid cysts

Table 3 shows a thyroid cyst status-specific association between subclinical hypothyroidism and hypertension. We found a significant positive association between subclinical hypothyroidism and hypertension only for participants without

**Table 1.** Characteristics of study population

	Thyroid cysts		p
	(-)	(+)	
No. at risk	1160	564	
Men, %	40.7	29.4	<0.001
Age, year	59.8 $\pm$ 9.4	62.0 $\pm$ 8.2	<0.001
TSH, (0.39-4.01) <sup>*2</sup> $\mu$ IU/mL	1.57 [1.10, 2.29] <sup>*1</sup>	1.60 [1.07, 2.33] <sup>*1</sup>	0.850 <sup>*2</sup>
free T <sub>3</sub> , (2.1-4.1) <sup>*2</sup> pg/mL	3.2 $\pm$ 0.3	3.2 $\pm$ 0.3	0.054
free T <sub>4</sub> , (1.0-1.7) <sup>*2</sup> ng/dL	1.3 $\pm$ 0.2	1.2 $\pm$ 0.2	0.107
Overweight (BMI $\geq 25.0$ kg/m <sup>2</sup> )	24.6	20.6	0.065
Current smoker, %	14.7	11.5	0.068
Daily drinker, %	40.9	39.2	0.506
Hypertension, %	37.4	44.7	0.004
SBP, mmHg	124 $\pm$ 17	126 $\pm$ 17	0.005
DBP, mmHg	73 $\pm$ 11	74 $\pm$ 10	0.045
Anti-hypertensive medication, %	28.7	33.0	0.070
Hypertriglyceridemia (TG $\geq 150$ mg/dL), %	16.0	14.2	0.319
Low HDL-cholesterol (HDLc < 40mg/dL), %	5.7	6.0	0.778
High HbA1c (HbA1c $\geq 6.5$ %), %	8.2	5.0	0.015

TSH; thyroid stimulating hormone, free T<sub>3</sub>; free triiodothyronine, free T<sub>4</sub>; free thyroxine, BMI; body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, TG; triglycerides, HDLc; high density lipoprotein cholesterol. Values are mean  $\pm$  standard deviation. \*1: Values are median [the first quartile, third quartile]. \*2: Normal range of measurements.

**Table 2.** Odds ratios (ORs) and 95% confidence intervals (CIs) for subclinical hypothyroidism in relation to hypertension

	Hypertension		p
	(-)	(+)	
No. at risk	1038	686	
No. of case (%)	48 (4.6)	50 (7.3)	
Model 1	1	1.55 (0.99, 2.41)	0.055
Model 2	1	1.55 (0.99, 2.42)	0.054
Model 3	1	1.36 (0.85, 2.16)	0.200

Model 1: adjusted for sex and age. Model 2: + free T<sub>3</sub>. Model 3: + over weight (BMI  $\geq 25$ kg/m<sup>2</sup>), smoking status (never, former, current), drinking status (non, often, daily), hypertriglyceridemia (TG  $\geq 150$ mg/dL), low HDL-cholesterol (HDLc < 40mg/dL), high HbA1c (HbA1c  $\geq 6.5$ %).

**Table 3.** Odds ratios (ORs) and 95% confidence intervals (CIs) for subclinical hypothyroidism in relation to hypertension stratified by thyroid cysts

	Thyroid cysts						Interaction
	(-)			(+)			
	Hypertension		p	Hypertension		p	
	(-)	(+)		(-)	(+)		
No. at risk	726	434		312	252		
No. of case (%)	30 (4.1)	39(9.0)		18 (5.8)	11 (4.4)		
Model 1	1	2.34 (1.35, 4.04)	0.002	1	0.64 (0.29, 1.44)	0.282	0.017
Model 2	1	2.34 (1.35, 4.07)	0.002	1	0.64 (0.29, 1.45)	0.288	0.019
Model 3	1	1.91 (1.08, 3.37)	0.028	1	0.63 (0.26, 1.55)	0.316	0.023

Model 1: adjusted for sex and age. Model 2: + free T<sub>3</sub>. Model 3: + over weight (BMI≥25kg/m<sup>2</sup>), smoking status (never, former, current), drinking status (non, often, daily), hypertriglyceridemia (TG ≥150mg/dL), low HDL-cholesterol (HDLc<40mg/dL), high HbA1c (HbA1c≥6.5%).

thyroid cysts. For participants with thyroid cysts, even though the power could not reach a significant value, an inverse tendency between subclinical hypothyroidism and hypertension was observed. This association remained unchanged, even after further adjustment for thyroid hormone (free T<sub>3</sub>) and thyroid hormone-related factors. Investigations of the associations between hypertension and the status of thyroid cysts on subclinical hypothyroidism revealed a significant interaction.

#### 4. Sex-specific associations between subclinical hypothyroidism and hypertension by status of thyroid cysts.

For sensitivity analysis, we also made sex-specific analysis by using age-adjusted model and found essentially the same associations. Among men, the ORs and 95% CIs of subclinical hypothyroidism for participants without thyroid cysts (n=472) was 1.97 (0.86, 4.55) and for participants with a thyroid cyst (n=166) was 0.72 (0.21, 2.53), respectively. Among women, the corresponding values were (n=688) 2.61 (1.29, 5.30) and (n=398) 0.59 (0.20, 1.74), respectively.

## Discussion

The major findings of the present study are that for participants without a thyroid cyst, hypertension is significantly positively associated with subclinical hypothyroidism, while for participants with a thyroid cyst, even though the power could not reach a significant value, an inverse tendency between hypertension and subclinical hypothyroidism is observed.

A previous meta-analysis study reported significant positive associations between subclinical hypothyroidism and blood pressure (both of systolic and diastolic) [1]. This study is partly compatible with the present study, which showed that even though the power could not reach a significant value, a

positive tendency between subclinical hypertension and hypertension was observed. In the present study, we found further evidence that hypertension is significantly positively associated with subclinical hypothyroidism only for participants without thyroid cysts. However, the mechanisms underlying those associations were not yet clarified.

Subclinical hypothyroidism is characterized by elevated levels of TSH but the concentrations of thyroid hormones (free T<sub>3</sub> and free T<sub>4</sub>) are normal. Since TSH stimulates thyroid hormone synthesis, participants with subclinical hypothyroidism could have been inefficient at synthesizing thyroid hormones.

Thyroglobulin, which plays an important role in synthesizing and transporting thyroid hormone (free T<sub>3</sub> and free T<sub>4</sub>) [4], is revealed to be rich in the fluid of thyroid cysts [5]. Therefore, thyroid cysts might pool thyroglobulin, which could have a beneficial effect on activating thyroid hormone.

A previous study with school-aged children reported that the number of thyroid cysts increase with progression of age [6]. School years are a crucial period of growth, and thyroid hormone is important for physical development [7]. Therefore, to activate thyroid hormone effectively, the number of thyroid cysts could be increased among those participants who need higher activity of thyroid hormone.

In contrast, decreasing thyroid function may have a beneficial effect on longevity [8]. Therefore, aging is the process that reduces the demand on thyroid activity. Since thyroid cysts might pool thyroglobulin [5], the prevalence of thyroid cysts could be increased with aging by indicating expanding capacity of pooling thyroglobulin. In the present study, participants with thyroid cysts were shown to be significantly older than participants without thyroid cysts.

TPO-Ab causes autoimmune thyroid diseases such as Hashimoto's thyroiditis [9]. Since thyroid peroxidase, which is inhibited by TPO-Ab, takes an important role in synthesizing

thyroid hormone [10], euthyroid participants with a higher titer of TPO-Ab might have inefficient production of thyroid hormones because of latent damage to the thyroid. Also, in our previous study with a euthyroid population, TPO-Ab was revealed to be inversely associated with thyroid cysts, possibly indicating latent damage to thyroid that could be related to inefficient production of thyroid hormones [2]. In other words, the absence of thyroid cysts might be associated with latent thyroid damage that is related to inefficient thyroid hormone synthesis.

Therefore, the positive association between hypertension and subclinical hypothyroidisms could be limited to euthyroid participants with latent damage that is related to inefficient thyroid hormone synthesis.

In the present study, participants with thyroid cysts showed a significantly higher prevalence of hypertension compared to those without thyroid cysts. Even though subclinical hypothyroidism but not subclinical hyperthyroidism has been shown to be associated with hypertension [1], both hypothyroidism and hyperthyroidism have been reported to be positively associated with hypertension [11,12,13]. In addition, participants with thyroid cysts were, on average, older than those without thyroid cysts. Furthermore, the absence of thyroid cysts may indicate latent thyroid damage [2]. Since thyroid function demands decline with age [8], the higher prevalence of hypertension in participants with thyroid cysts may be caused by a comparatively higher activity of thyroid hormone; the exact opposite condition to subclinical hypothyroidism. Therefore, in the present study, although the statistical power could not reach significance, an inverse tendency between hypertension and subclinical hypothyroidism was observed in participants with thyroid cysts. To clarify those associations, further investigation on this topic is necessary.

Even further investigation is necessary, and the status of thyroid cysts could be an efficient tool to evaluate latent thyroid damage, which relates to efficiency of thyroid hormone production in daily clinical practice by using a non-invasive medical technique. Furthermore, the fact that the status of thyroid cysts could determine the association between subclinical hypothyroidism and hypertension also could be an effective tool to making efficient strategy to prevent hypertension. These are clinical perspectives of the present study.

The potential limitations of this study do warrant consideration. First, we evaluated the existence of a thyroid cyst on the parameters of whether or not it was present. However, the number and size of a given cyst could be an important factor. Further investigation with this data is necessary. Due to the limited amount of blood samples, we could not evaluate the

influence of anti-thyroglobulin antibodies, which may act as a strong confounding factor. Further investigation with data of the anti-thyroglobulin antibody is necessary. Severe inflammatory disease, liver disease, and pregnancy could be associated with thyroid function and might have influenced our results, which we could not verify as we have no data for these factors. Nevertheless, the main findings of the study were unchanged even after further adjustment for free  $T_3$ . Also, this was a cross-sectional study where a causal relationship could not be established.

## Conclusion

For participants without thyroid cyst, hypertension is significantly positively associated with subclinical hypothyroidism but not for participants with thyroid cyst. The status of thyroid cyst could act as a determinant factor in the association between hypertension and subclinical hypothyroidism.

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## Availability of data and material

The datasets generated during and/or analyzed during the current study are not publicly available due to ethical consideration but are available from the corresponding author on reasonable request.

## Consent for publication

Not applicable

## Competing interests

The authors declare that they have no conflict of interest.

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