

Association between thyroid cysts and chronic kidney disease (CKD) by systolic hypertension status among the general Japanese population: a cross-sectional study

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Abstract

Our previous study revealed that thyroid cysts might have a beneficial effect on thyroid hormone activation. Subclinical hypothyroidism is reportedly associated with chronic kidney disease (CKD). Since systolic hypertension is associated with hyperthyroidism and thyroid cysts are associated with systolic hypertension, the presence of thyroid cysts could be inversely associated with CKD, especially in patients with systolic hypertension. Such an association could indicate that thyroid cysts have a beneficial effect on thyroid hormone activation. To investigate systolic hypertension status-specific associations between thyroid cysts and CKD, a cross-sectional study with 1,750 individuals aged 40–74 years who participated in annual health check-ups was conducted. Independent of thyroid hormone levels (free triiodothyronine (T3) and thyroid-stimulating hormone (TSH)), the presence of thyroid cysts was significantly inversely associated with CKD in subjects with systolic hypertension, but not in subjects without systolic hypertension. The adjusted odd ratios and 95% confidence intervals were 0.52 (0.28, 0.98) for subjects with systolic hypertension and 1.11 (0.82, 1.50) for subjects without systolic hypertension. Thyroid cysts might affect CKD in a beneficial manner. Systolic hypertension could act as an effect modifier on the association between thyroid cysts and CKD. These findings could help clarify thyroid-related mechanisms of CKD development.

1. Introduction

Although thyroid cysts are regarded as clinically insignificant in general clinical practice, the normal range of anti-thyroid peroxidase antibodies (TPO-Abs), a known cause of autoimmune thyroiditis, was revealed to be inversely associated with thyroid cysts among the general euthyroid population [1]. This study indicates that the absence of thyroid cysts could be associated with the presence of latent thyroid damage.

Our previous study revealed a significant positive association between thyroid cysts and systolic hypertension [2]. Since hyperthyroidism is a known cause of isolated systolic hypertension [3], participants with thyroid cysts might have comparative higher levels of thyroid hormone activity than individuals without thyroid cysts.

In addition, subclinical hypothyroidism is reported to be associated with chronic kidney disease (CKD) [4]. Thyroid hormone increases the number of circulating endothelial progenitor cells [5, 6] that might confer renal protection [7]. Therefore, the presence of thyroid cysts might have the beneficial effect of preventing renal dysfunction. Furthermore, hypertension in CKD is predominantly systolic [8–10], which is positively associated with thyroid cysts [2].

These studies indicate that the presence of thyroid cysts could be inversely associated with CKD, especially among individuals with systolic hypertension, as a indicator of high levels of thyroid hormone activity.

Therefore, we hypothesized that the presence of thyroid cysts is inversely associated with CKD among patients with systolic hypertension. To evaluate this hypothesis, we conducted a cross-sectional study of 1,750 Japanese individuals aged 40–74 years who participated in annual health check-ups in 2014.

2. Material And Methods

2.1. Participants

This study involved Japanese individuals in the general population aged 40–74 years who underwent an annual medical check-up in Saza town in western Japan during 2014.

Subjects without blood pressure data ($n = 1$), thyroid function data (free triiodothyronine [T3] and thyroid stimulating hormone [TSH]) ($n = 20$), and body mass index data (BMI) ($n = 1$) were excluded. To avoid the influence of chronic diseases, subjects with low BMI ($< 18 \text{ kg/m}^2$) ($n = 111$) were also excluded. The remaining 1,750 subjects with a mean age of 60.7 years (standard deviation (SD): 9.1; range: 40–74) were included in the study.

To ensure that participants understood the objective of the study, written consent forms in Japanese were made available. Informed consent was obtained from all study participants. This study was approved by the Ethics Committee of Nagasaki University Graduate School of Biomedical Sciences (project registration number 14051404-13). All procedures involving human participants were performed in accordance with the ethical standards of the institution research committee and with the 1964 Helsinki Declaration and its later amendments for comparable ethical standards.

2.2. Data Collection and Laboratory Measurements

A trained interviewer obtained information on history of medication use. Body weight and height were measured with an automatic body composition analyzer (BF-220; Tanita, Tokyo, Japan) and BMI (kg/m^2) was calculated. Blood pressure [systolic blood pressure (SBP) and diastolic blood pressure (DBP)] was recorded at rest. Systolic hypertension was defined as $\text{SBP} \geq 140 \text{ mmHg}$.

A fasting blood sample was collected. TSH and free T3 were measured using standard procedures at the LSI Medience Corporation (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 cyst in the thyroid with a maximum diameter $\geq 2.0 \text{ mm}$ and no solid component was defined as a thyroid cyst for this study.

Serum creatinine was measured using standard laboratory procedures at SRL, Inc. (Tokyo, Japan). Glomerular filtration rate (GFR) was estimated using an established method recently proposed by a working group of the Japanese Chronic Kidney Disease Initiative [11]. The adapted equation was: $\text{GFR} (\text{mL/min}/1.73 \text{ m}^2) = 194 \times (\text{serum creatinine (enzyme method)})^{-1.094} \times (\text{age})^{-0.287} \times (0.739 \text{ for women})$. CKD was defined as $\text{GFR} < 60 \text{ mL/min}/1.73 \text{ m}^2$.

2.3. Statistical Analysis

Characteristics of the study population were expressed as means \pm SD except for gender, anti-hypertensive medication use, and TSH. Gender and anti-hypertensive medication use were expressed as proportions. Since TSH values had a skewed distribution, they were expressed as the median [interquartile range].

Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for systolic hypertension and thyroid cysts. We also evaluated systolic hypertension status-specific associations between CKD and thyroid cysts.

Three models were generated. Model 1 adjusted for only sex and age (Model 1). Model 2 further included potential confounding factors directly associated with thyroid function, namely TSH (μ IU/mL) and free T3 (pg/mL). Model 3 adjusted for variables in Model 2 plus potential confounding factors directly associated with systolic hypertension: anti-hypertensive medication use (yes/no).

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

Table 1. Characteristics of the study population (n=1,750)

Men, %	37.3
Age, years	60.7 \pm 9.1
TSH, μ IU/mL (0.39–4.01)	1.60 [1.09, 2.37]*
Free T3, pg/mL (2.1–4.1)	3.2 \pm 0.3
SBP, mmHg	125 \pm 16
DBP, mmHg	74 \pm 10
Anti-hypertensive medication use, %	31.0
Values are means \pm standard deviation unless otherwise indicated. The normal range is given in parentheses. *Median [interquartile range]. TSH, thyroid stimulating hormone; free T3, free triiodothyronine; SBP, systolic blood pressure; DBP, diastolic blood pressure.	

3. Results

Characteristics of study population are shown in Table 1.

Table 2 shows the associations between systolic hypertension and thyroid cysts. In the sex- and age-adjusted model (Model 1), thyroid cysts were significantly associated with systolic hypertension. This association remained unchanged even after further adjustment for thyroid function (free T3 and TSH)

(Model 2). However, after further adjustment for anti-hypertensive medication use (Model 3), the association was not statistically significant, even though the essentially same association was observed.

Table 2. Association between thyroid cysts and systolic hypertension

	Thyroid cyst		p
	(-)	(+)	
No. of participants	1188	562	
Systolic hypertension, n (%)	188 (15.8)	118 (21.0)	
Model 1	Ref	1.32 (1.01, 1.72)	0.042
Model 2	Ref	1.31 (1.00, 1.71)	0.048
Model 3	Ref	1.30 (1.00, 1.70)	0.054
Ref: Reference. Model 1: adjusted only for sex and age. Model 2: adjusted further for thyroid function (free T3 and TSH). Model 3: adjusted for variables in Model 2 and anti-hypertensive medication use.			

Systolic hypertension status-specific associations between thyroid cysts and CKD are shown in Table 3. No significant associations were observed for subjects without systolic hypertension. For subjects with systolic hypertension, thyroid cysts were significantly inversely associated with CKD. The associations were unchanged even after further adjustment for thyroid function and anti-hypertensive medication use. Furthermore, an investigation into the effect of the association between thyroid cyst and systolic hypertension status on CKD revealed significant interactions.

Table 3. Associations between chronic kidney disease (CKD) and thyroid cysts by systolic hypertension status

	Systolic hypertension						
	(-)			(+)			
	Thyroid cyst		p	Thyroid cyst		p	Interaction
	(-)	(+)	(-)	(+)			
No. of participants	1000	444		188	118		
CKD, n (%)	163 (16.3)	89 (20.0)		47 (25.0)	18 (15.3)		
Model 1	Ref	1.08 (0.80, 1.46)	0.608	Ref	0.52 (0.28, 0.97)	0.038	0.033
Model 2	Ref	1.11 (0.83, 1.50)	0.483	Ref	0.52 (0.28, 0.97)	0.041	0.026
Model 3	Ref	1.11 (0.82, 1.50)	0.513	Ref	0.52 (0.28, 0.98)	0.044	0.031

Ref: Reference. Model 1: adjusted only for sex and age. Model 2: adjusted further for thyroid function (free T3 and TSH). Model 3: adjusted for variables in Model 2 and anti-hypertensive medication use.

4. Discussion

The major finding of the present study is a significant inverse association between thyroid cysts and CKD in subjects with systolic hypertension, even though no significant associations were observed in subjects without systolic hypertension. Because a previous study reported noticeable increases in thyroglobulin concentrations of thyroid cyst fluid [12] and thyroglobulin plays a crucial role in thyroid hormone synthesis [13], the presence of thyroid cysts could affect the levels of thyroid hormone activity [1, 14, 15].

In addition, hyperthyroidism is the most frequent secondary cause of isolated systolic hypertension [3]. We previously reported that thyroid cysts are positively associated with systolic hypertension but not with diastolic hypertension [2].

These studies indicate that the presence of thyroid cysts could reflect higher levels of thyroid hormone activity associated with systolic hypertension. In the present study, we found a significant positive association between thyroid cysts and systolic hypertension. The presence of thyroid cysts could indicate comparative higher levels of thyroid hormone activity, especially in subjects with systolic hypertension.

Since subclinical hypothyroidism is reportedly associated with reduced GFR [16] and CKD [4], thyroid cysts could be inversely associated with CKD, indicating higher levels of thyroid hormone activity among subjects with systolic hypertension. In the present study, we found a significant inverse association between thyroid cysts and CKD among subjects with systolic hypertension even after adjustment for thyroid function (TSH and free T3).

The absence of thyroid cysts might act as an indicator of latent thyroid damage related to inefficient thyroid hormone synthesis. However, actual plasma concentrations of TSH and free T3 were not associated with the presence of thyroid cysts [1, 14, 15]. To clarify this mechanism, further investigation that accounts for thyroid hormone synthesis is necessary.

Potential limitations of this study warrant consideration. First, we evaluated the presence or absence of thyroid cysts. However, the number and size of thyroid cysts could be important factors. 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 might act as a strong confounding factor. Further investigation with data on anti-thyroglobulin antibodies is necessary. In addition, this was a cross-sectional study through which a causal relationship could not be established.

5. Conclusion

In conclusion, the presence of thyroid cysts is inversely associated with CKD in subjects with systolic hypertension, but not in subjects without systolic hypertension. These findings could help clarify thyroid-related mechanisms of CKD development.

Declarations

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Author's contribution

YS designed the study, performed the statistical analyses, interpreted the data, and drafted and revised the manuscript. YS, SY.K, YuN, SN, TM and NH assisted with the study design, were involved in data collection, and checked the manuscript. SN participated in the study concept and checked the manuscript. TM and NH were the general coordinator and designed the study.

Competing interests

The authors declare that they have no conflict of interest.

Availability of data and materials

We cannot publicly provide individual data due to participant privacy, according to ethical guidelines in Japan. Additionally, the informed consent was obtained does not include a provision for publicity sharing data. Qualifying researchers may apply to access a minimal dataset by contacting Prof Naomi Hayashida, Principal Investigator, Division of Promotion of Collaborative Research on Radiation and Environment Health Effects, Atomic Bomb Disease Institute, Nagasaki University, Nagasaki, Japan at naomin@nagasaki-u.ac.jp. Or, please contact the office of data management at ritouken@vc.fctv-net.jp. Information for where data request is also available at <https://www.genken.nagasaki-u.ac.jp/dscr/message/> and <http://www.med.nagasaki-u.ac.jp/cm/>.

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