Hyperinsulinemia and thyroid peroxidase antibody in Chinese patients with papillary thyroid cancer

Xiaoyan Guo¹⁾*, Xinyan Chen²⁾*, Ce Zhang³⁾, Jiahuan Zhang¹⁾ and Chunyu Zhang¹⁾

¹⁾ Department of Geriatrics, the Second Affiliated Hospital of Dalian Medical University, Dalian 116023, China

²⁾ Department of Osteoporosis, Affiliated Zhongshan Hospital of Dalian University, Dalian 116001, China

³⁾ Department of Pharmacy, the Second Affiliated Hospital of Dalian Medical University, Dalian 116023, China

Abstract. This study aimed to investigate if hyperinsulinemia and/or insulin resistance was correlated with the occurrence of papillary thyroid cancer (PTC) in a group of Chinese patients. 258 inpatients were included in the study. According to the postoperative pathology results, all subjects were divided into PTC ($n = 153$) and control groups (with benign thyroid nodules, $n = 105$). Body mass index (BMI), fasting glucose, fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), thyroid-stimulating hormone (TSH), FT4, FT3, thyroid peroxidase antibody (TPOAb), thyroglobulin antibody (TGAb), serum uric acid (UA), and lipid levels. Fasting insulin levels, HOMA-IR values, TPOAb levels, serum TSH levels, and serum uric acid levels in the PTC group were higher than those in the control group ($p < 0.05$). However, no significant differences in age, gender, BMI, history of hypertension, and the levels of fasting plasma glucose, FT3, FT4, TGAb, total cholesterol, triglyceride, low-density lipoprotein, and high-density lipoprotein were observed between the two groups ($p > 0.05$). After the multiple logistic regression analysis, the occurrence of PTC was positively associated with fasting insulin (odds ratio [OR] = 1.048, 95% confidence interval [CI]: 1.003–1.096, $p = 0.037$) and TPOAb levels (OR = 1.001, 95% CI: 1.000–1.002, $p = 0.032$). Moreover, TPOAb level was positively correlated with vague margin ($r = 0.126$, $p = 0.045$) and negatively correlated with homogeneous echo ($r = -0.179$, $p = 0.004$). However, fasting insulin levels were not correlated with pathological characteristics of PTC. Hyperinsulinemia and higher TPOAb levels might be the risk factors of PTC, but not disease severity in Chinese patients.

Key words: Hyperinsulinemia, Insulin resistance, Papillary thyroid cancer, Risk factor, Thyroid peroxidase antibody

AS THE MOST COMMON ENDOCRINE MALIGNANCY, the incidence of thyroid cancer in the past few years is higher than that of any other malignant tumor [1, 2]. Differentiated thyroid cancer accounted for approximately 90% of all thyroid cancers, and papillary thyroid cancer (PTC) was the most common type of well-differentiated thyroid cancer (75%) [3, 4]. Epidemiological and clinical data that suggested unknown factors might cause the increasing incidence of thyroid cancer [5, 6]. Insulin resistance and hyperglycemia are considered to be important risk factors of several types of cancer, such as colorectal, endometrial, lung, breast cancer, prostatic, and endometrial cancers [7–11]. Patients with insulin resistance also have a higher prevalence of thyroid nodules and bigger thyroid glands. A small cross-

sectional study reported that increased prevalence of insulin resistance was present in patients with differentiated thyroid carcinomas [12]. A study from Sahin *et al.* showed PTC patients are more insulin resistant [13]. Recently, Bae *et al.* also demonstrated that hyperinsulinemia and/or insulin resistance may be associated with the development of PTC in Korean women [14]. In contrast, a study suggested that no difference in insulin resistance or insulin levels between thyroid cancer and benign thyroid nodules [15]. Although previous studies investigated the relationship between hyperinsulinemia or insulin resistance and thyroid cancer, the results were controversial. Therefore, further explorations on relationship between hyperinsulinemia and thyroid cancer are still needed.

Herein, we aimed to study the correlation between hyperinsulinemia and insulin resistance with the development of PTC by comparing the differences between PTC and benign thyroid nodules in a group of Chinese patients. In addition, associations between fasting insulin and TPOAb levels with pathological characteristics of PTC were assessed in this cohort.

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Correspondence to: Chunyu Zhang, Department of Geriatrics, the Second Affiliated Hospital of Dalian Medical University, No. 467 Zhongshan Road, Shahekou District, Dalian 116023, China.
E-mail: 17709876116@163.com

*These are co-first authors and contributed equally to this work.

Materials and Methods

Subjects

Our study was performed at the Second Affiliated Hospital of Dalian Medical University between March 2016 and August 2016. Clinical data of 363 inpatients at the thyroid surgery department were retrospectively collected. Individuals with the following characteristics were excluded from the study: those with a history of other cancer except thyroid cancer ($n = 3$), diabetes mellitus ($n = 28$), other types of thyroid cancer (*i.e.*, follicular, medullary, or anaplastic; $n = 7$), history of thyroidectomy ($n = 14$), previous thyroid medication therapy at any time ($n = 4$), the subjects who only had cytology from ultrasound-guided fine-needle aspiration biopsies, not surgery ($n = 31$), severe liver insufficiency (Child-Pugh score 10 to 15) and severe renal insufficiency (estimated glomerular filtration rate $<30 \text{ mL/min} \times 1.73 \text{ m}^2$) ($n = 10$), or those who reject operation ($n = 8$). No one has a history of neck ionizing I^{131} therapy. Ultimately, 258 subjects who underwent thyroidectomy with postoperative pathology were included in this study. The patients were divided into PTC ($n = 153$) and control groups (with benign thyroid nodules, $n = 105$) based on the postoperative pathological results. The study was approved by the local institutional ethics committee of the Second Affiliated Hospital in Dalian Medical University.

Anthropometric measurements

Body weights (kg) and heights (cm) were measured without shoes and/or cap before surgery. Body mass index (BMI) was expressed as weight per height squared (kg/m^2). The anthropometric measurements were performed in triplicate.

Biochemical evaluations

Blood samples were collected between 8:00 and 9:00 in the morning, with the patients fasting for at least 8 h preoperatively. Serum samples obtained after centrifuge were stored at -80°C to prepare for assaying. Then, fasting insulin was assayed in our clinical laboratory and was determined using chemiluminescence with antibody-coated tubes (ADVIA Centaur XP, chemiluminescence analyzer, Siemens, USA). The cutoff value of $>15 \text{ IU/mL}$ was used to define hyperinsulinemia. Fasting plasma glucose level was measured using the glucose oxidase method (ADVIA 2400, automatic biochemical analyzer, Siemens, USA). The homeostasis model assessment of insulin resistance (HOMA-IR) level, an indicator of insulin resistance, was calculated with the formula fasting serum insulin (IU/mL) $\times$ fasting plasma glucose (mmol/L)/22.5 [16]. A HOMA-IR index ≥ 2.5

denoted insulin resistance [16]. Free T4, free T3, thyroid-stimulating hormone (TSH), thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TGAb) levels were measured using chemiluminescence (ADVIA CentaurXP, chemiluminescence analyzer, Siemens, USA). Serum total cholesterol, triglyceride, and serum uric acid were measured using enzyme colorimetric method. Low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were measured using direct method. The levels of serum uric acid, cholesterol, triglyceride, LDL-C, and HDL-C were determined using the ADVIA 2400 automatic biochemical analyzer (Siemens, USA). The above biochemical evaluations were performed in triplicate.

Statistical analysis

Data were analyzed using SPSS software (Statistical Package for the Social Sciences, version 22.0). The measurement data are presented as means $\pm$ standard deviations (SDs) for continuous variable. Categorical variables are interpreted by frequency tables.

An independent sample *t*-test was used to compare distributed variables. On the other hand, the Mann-Whitney U-rank sum test was used for non-normally distributed variables. The Chi-square test was employed to analyze categorical variables when appropriate. *P*-values <0.05 were considered statistically significant. Logistic regression models were utilized to estimate odds ratios (ORs; 95% confidence intervals [CIs]) to define the associations among fasting insulin, HOMA-IR, TSH and TPOAb with the prevalence of PTC. Additionally, a multivariate logistic regression analysis was performed to evaluate the associations of fasting insulin, HOMA-IR, TSH and TPOAb with the prevalence of PTC after adjusting for other three variables. To ensure that there were no collinearity problems, we implemented a collinearity diagnostic procedure, the variance inflation factor (VIF), to ensure low correlation (VIF lower than 10) between the variables in the multiple regression model. It was showed no collinearity among fasting insulin, HOMA-IR, TSH and TPOAb.

Results

Clinical and metabolic characteristics of PTC and control groups

Clinical and laboratory characteristics of PTC and control groups are shown in Table 1. No significant difference in age, BMI, gender, fasting plasma glucose levels, serum FT3 levels, serum FT4 levels, TGAb levels, total cholesterol levels, triglyceride levels, LDL levels, HDL levels, and history of hypertension (systolic pressure $\geq 140 \text{ mmHg}$ or diastolic pressure $\geq 90 \text{ mmHg}$) was

Table 1 Clinical and metabolic characteristics of PTC group and control group

Variables	Control group (<i>n</i> = 105)	PTC group (<i>n</i> = 153)	<i>p</i> -value
Age (year)	48.42 ± 11.85	45.67 ± 11.61	0.065
Gender (female/male, <i>n</i>)	80/25	116/37	0.945
BMI (kg/m ²)	24.57 ± 3.50	25.13 ± 3.94	0.243
FPG (mmol/L)	5.45 ± 1.05	5.41 ± 0.75	0.717
Fasting insulin (uU/mL)	7.82 ± 5.88	10.00 ± 8.14	0.019
HOMA-IR	1.94 ± 1.81	2.46 ± 2.09	0.042
TSH (uIU/mL)	1.40 (0.78, 2.09)	1.82 (1.17, 2.67)	0.005
FT3 (pmol/L)	4.78 ± 0.70	4.86 ± 0.71	0.082
FT4 (pmol/L)	15.39 ± 2.05	15.54 ± 2.66	0.149
TPOAb (U/mL)	28.0 (9.29, 489.64)	31.3 (10.05, 1,301.00)	0.015
TGAb (U/mL)	25.6 (10.5, 501.00)	28.8 (12.30, 393.31)	0.511
Total cholesterol (mmol/L)	4.82 ± 0.77	4.83 ± 0.73	0.893
Triglyceride (mmol/L)	1.52 ± 0.92	1.53 ± 0.92	0.929
LDL (mmol/L)	2.59 ± 0.61	2.60 ± 0.58	0.924
HDL (mmol/L)	1.29 ± 0.25	1.27 ± 0.32	0.616
Serum uric acid (umol/L)	287.42 ± 76.89	307.78 ± 83.94	0.049
Hypertension (<i>n</i> , %)	13 (12.4%)	26 (17.0%)	0.310

PTC, papillary thyroid cancer; BMI, body mass index; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; TGAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2 Logistic regression analysis showing the associations of fasting insulin, HOMA-IR, TSH and TPOAb with the prevalence of PTC

	Univariate analysis		Multivariate analysis	
	OR	95%CI (<i>p</i> value)	OR	95%CI (<i>p</i> value)
Fasting insulin (uU/mL)	0.951	0.909–0.994 (0.027)	1.048	1.003–1.096 (0.037)
HOMA-IR	0.859	0.736–1.004 (0.056)	1.535	0.832–2.832 (0.171)
TSH (uIU/mL)	1.016	0.958–1.078 (0.593)	1.054	0.972–1.142 (0.202)
TPOAb (U/mL)	0.999	0.998–1.000 (0.018)	1.001	1.000–1.002 (0.032)

observed between the PTC and control groups ($p > 0.05$). Fasting insulin levels, HOMA-IR values, TPOAb levels, serum TSH levels, and serum uric acid levels in the PTC group were significantly higher than those in the control group ($p < 0.05$).

Logistic regression analysis on clinical and metabolic characteristics between the two groups

In unadjusted logistic regression models, higher fasting insulin, HOMA-IR and TPOAb were strongly correlated with the occurrence of PTC (Table 2). As univariate analysis only considered the influence of single factor on PTC without considering the influence between factors, further multivariate analysis was performed.

In the multiple logistic regression analysis, PTC was associated with fasting insulin and TPOAb levels positively. The adjusted ORs (95% CI) for subjects were 1.048 (95% CI: 1.003–1.096, $p = 0.037$) for fasting insulin levels and 1.001 (95% CI: 1.000–1.002, $p = 0.032$) for TPOAb (Table 2). However, there was no correlation between insulin level and TPO Ab titer ($r = 0.067$, $p = 0.54$).

Associations between fasting insulin and TPOAb levels with pathological characteristics of PTC

The pathology reports for PTC patients were reviewed to determine the severity of cancer as evidenced by the microcalcification (53 cases), streak-like calcifications

Table 3 Associations among fasting insulin and TPOAb levels with pathological characteristics of PTC

Pathological characteristics	Fasting insulin		TPOAb	
	<i>r</i> value	<i>p</i> value	<i>r</i> value	<i>p</i> value
Microcalcification	−0.12	0.871	0.033	0.600
Streak-like calcifications	0.095	0.201	0.099	0.117
Coarse calcification	−0.082	0.268	−0.086	0.171
Single nodule	0.05	0.501	−0.036	0.571
Multiple nodules	−0.065	0.381	0.033	0.602
Vague margin	0.066	0.37	0.126	0.045
Nodule with a longitudinal/transverse ratio of >1	−0.091	0.215	0.051	0.417
Blood flow	−0.027	0.718	0.023	0.715
Homogeneous echo	0.016	0.833	−0.179	0.004
Lymph node metastasis	0.069	0.1352	0.036	0.615
Tumor distant metastasis	−0.101	0.176	0.110	0.124

(54 cases), coarse calcification (33 cases), single nodule (60 cases), multiple nodules (198 cases), vague margin (119 cases), nodule with a longitudinal/transverse ratio of >1 (65 cases), blood flow (224 cases), homogeneous echo (66 cases), lymph node metastasis (71 cases), and tumor distant metastasis (2 cases). As shown in Table 3, single nodule, multiple nodules, nodule with a longitudinal/transverse ratio of >1, microcalcification, streak-like calcifications, coarse calcification, vague margin, blood flow, homogeneous echo, lymph node metastasis, and tumor distant metastasis were not significantly associated with fasting insulin level. However, TPOAb level was positively correlated with vague margin ($r = 0.126$, $p = 0.045$) and negatively correlated with homogeneous echo ($r = -0.179$, $p = 0.004$).

Discussion

In the last 20 years, the incidence of differentiated thyroid cancer, especially PTC, has continuously and dramatically increased [2, 17]. Some studies believed that the major cause of this increasing incidence was the result of enhanced detection of early stage tumors [17]. Others argued that a true increase was also occurring and the causes of this increase were unknown [1, 2]. Some risk factors that might contribute to thyroid cancers were iodine intake status (low for follicular thyroid cancer), female, neck radiation, hereditary conditions, previous thyroid disease, and radioactive fallout from nuclear accidents [3, 18]. However, several recent studies attempted to identify the relationship of metabolic syndrome with the development of thyroid cancer [13, 19].

Hyperinsulinemia is considered to be a factor in the relationship between insulin resistance and cancer. It

appears that hyperinsulinemia is secondary to obesity-induced insulin resistance. Rezzonico *et al.* [20] found that hyperinsulinemia could directly induce thyroid proliferation, which resulted in larger thyroid volume and the formation of thyroid nodules. A recent study from Bae *et al.* found that hyperinsulinemia was strongly associated with the risk of PTC and the multifocality of this disease [13]. In our study, we revealed that hyperinsulinemia was associated with the occurrence of PTC. These findings in our study were in accordance with previous studies [13, 20], further demonstrating that hyperinsulinemia might be the risk factor of PTC.

Hyperinsulinemia and insulin resistance are tightly linked each other. HOMA-IR, the mathematical product of fasting glucose and insulin, was independently associated with cancer mortality [21]. A previous literature showed patients with insulin resistance had larger thyroid volume and higher risk for formation of thyroid nodules [22]. Rezzonico *et al.* found that 20 patients with thyroid cancer exhibited increased HOMA-IR value than the control subjects [12]. Sahin *et al.* [14] showed that HOMA-IR value was high in patients with PTC in an iodine sufficient area. Recently, a study enrolled 735 Korean women showed that a higher HOMA-IR was significantly associated with the occurrence of PTC [13]. In contrast, Balkan *et al.* [15] did not find any difference in HOMA-IR index between differentiated thyroid cancer and benign thyroid nodules. The inconsistency of these results may be due to different pathological diagnosis. Some pathologic results were based on fine-needle aspiration cytology, which may deviate from the lesion in the lump, and some pathological results were based on tissues obtained after thyroidectomy. In our study, all patients underwent pathological analysis after thyroidec-

tomy and we found that HOMA-IR value in the PTC group was significantly higher than that in the control group, however, HOMA-IR lost its statistical significance in multivariate model. It was reported that HOMA-IR can accurately describe insulin resistance in normal glucose tolerance population, while it should be cautious to use HOMA-IR in diabetic patients with abnormal glucose regulation, especially those with poor blood glucose control [23]. In our study, the number of undiagnosed diabetes in the included subjects is not clear, which may be a factor lead to no statistical differences on the association between HOMA-IR and PTC.

TPOAb and TGAb were produced by the thyroid gland. As a type of autoimmune thyroid disease, Hashimoto's thyroiditis had higher TGAb and TPOAb levels, which might promote the occurrence and development of thyroid cancer [19]. Higher TGAb and TPOAb levels might contribute to the development of thyroid cancer [24]. Previous studies showed that TGAb was a predictor for thyroid cancer, but not TPOAb [25, 26]. A study on palpable thyroid nodules found that TPOAb was associated with an increased risk of malignancy; however, this association was lost after adjusting for TSH [27]. Our study showed that higher TPOAb levels were a risk factor of PTC. Cipollini *et al.* [28] also reported that the occurrence of differentiated thyroid carcinoma was associated with TPOAb genetic variants. The mutation status of TPOAb gene was not analyzed in the present study. Whether stratified analysis of the mutation status of TPOAb gene will lead to different conclusions regarding the TPOAb role in PTC still needs further study.

TSH was an important hormone to promote the growth of thyroid cells and thyroid hormone synthesis. Boelaert *et al.* [27] reported that serum TSH concentration could be a predictor of malignancy in thyroid nodules through the fine-needle aspiration. A meta-analysis of 28 studies showed that the proportion of thyroid cancer in patients with thyroid nodules with decreased serum TSH levels was lower than those with normal or elevated serum TSH levels [29]. Recently, Tam *et al.* showed an association between serum TSH and aggressive variants of PTC regardless of autoimmunity [30]. All these findings suggest that TSH plays a vital role in thyroid cancer initiation and aggressiveness. In this study, we found that serum TSH levels in PTC patients were significantly higher than those in patients with benign thyroid nodules, which was consistent with these findings. In contrary to these findings, Kim *et al.* did not find higher TSH levels in advanced stage of differentiated thyroid cancer, which may be attributed to the imbalance between patients with benign disease (249 cases) and patients with PTC (1,080 cases) [31]. Another study also did not demonstrate association between serum TSH

concentration and the prevalence of lymph node metastasis, extrathyroidal invasion, diffusion, and advanced stages in differentiated thyroid cancer patients [32]. Our multivariate model analysis did not found that serum TSH levels were associated with the prevalence of PTC. There may be some explanations for these results. The sample size in this study was small. In addition, the number of undiagnosed diabetes in the included subjects is not clear, which may be a factor lead to no statistical differences on the association between serum TSH and the prevalence of PTC.

This study has several limitations. First, this is a single-center study and the sample size was not large enough. Second, glucose clamp method is the gold standard in measuring insulin resistance. However, using it to estimate insulin resistance is unrealistic in our clinical practice. Third, this was a retrospective study; therefore, section or confounding bias may occur. Fourth, we only excluded the subjects with a history of diabetes and the number of undiagnosed diabetes in the included subjects is not clear. Therefore, analysis on the association between metabolic factors and the prevalence of PTC may be affected.

In conclusion, hyperinsulinemia and high TPOAb levels are the risk factors of PTC in China. However, as this study is a cross-sectional design and it was difficult to know their causal relationship with PTC. Therefore, additional longitudinal and observational studies with a large sample size are needed to further evaluate the effects of hyperinsulinemia and TPOAb level on the development and progression of PTC.

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Disclosure

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

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the local institutional ethics committee of the Second Affiliated Hospital in Dalian Medical University.

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