Thieme

Association Between Papillary Thyroid Carcinoma and Vertebral Fracture

Authors
Hazuki Otani[1] , Masakazu Notsu[1] , Mika Yamauchi[2], Kiyoko Nawata[3], Keizo Kanasaki[1]

Affiliations
1 Internal Medicine 1, Shimane University Faculty of Medicine, Izumo, Japan
2 Research Institute for Metabolic Bone Diseases, Eikokai Ono Hospital, Ono, Japan
3 Health and Nutrition, The University of Shimane, Izumo, Japan

Correspondence
Dr. Masakazu Notsu
Shimane University Faculty of Medicine
Internal Medicine 1
Enya-cho 89-1
6938501 Izumo
Japan
Tel.: +91853202183
mnotsu25@med.shimane-u.ac.jp

ABSTRACT

Suppression of TSH levels associated with levothyroxine treatment is a known risk factor for fracture. However, it is unclear whether patients with papillary thyroid carcinoma (PTC) have a higher risk of vertebral fracture (VF) before TSH suppression. The aim of the study was to examine whether the risk of VF is higher in PTC than in healthy subjects. A hospital-based, matched case-control study was conducted comparing PTC and healthy individuals. We enrolled 43 postoperative patients with PTC scheduled for radioiodine therapy and 43 age- and sex-matched healthy controls. Serum and urinary biological parameters, bone mineral density (BMD), and presence of VFs were evaluated in both groups. We compared these indices using χ2 and Mann–Whitney U-test and analyzed the association between PTC and VF by logistic regression analysis. The PTC group had higher BMI, HbA1c and phosphorus, and lower intact PTH than the control group. Lumbar and femoral neck BMD did not differ between the two groups. Prevalence of VFs was significantly higher in the PTC group (44.1 %) than in the control group (16.3 %). Multivariate logistic regression analyses adjusted for age, sex, and BMI identified PTC as being associated with the presence of VFs (odds ratio, 5.63; 95 % confidence interval: 1.82 to 17.5). This relationship remained significant after additional adjustment for HbA1c and BMD. There is an association between PTC and a risk of VF independent of sex, BMI, glucose metabolism, and BMD, suggesting the importance of fracture risk assessment before TSH suppression.

Introduction

Vertebral fracture (VF) is one of a major osteoporotic fracture, which is associated with a shorter life expectancy and risk of cardiovascular events [1]. Fractures are consistently ranked as one of the leading causes of ADL (activities of daily living) decline and needs care. Their prevention is important for a healthy life expectancy and health economics [2].

Thyroid cancer is the most frequent endocrine malignancy, with papillary thyroid carcinoma (PTC) accounting for more than 90 % of cases. Although the frequency of PTC is increasing [3, 4], the 10-year survival rate is more than 95 % and the long-term prognosis is promising for most of the patients with PTC [5].

Cases with a history of thyroid cancer exhibits the lower mean age of first fracture than those with a history of other thyroid diseases [6]. Thyrotropin (TSH) suppression therapy by levothyroxine is commonly applied for the patients with thyroid cancer; the levothyroxine treatment suppressed TSH levels has shown to be the fracture risk [7]. Additionally, we have shown that PTC itself, before the TSH suppression therapy, has a high frequency of severe osteoporosis [8]. However, whether the risk of VFs is higher in PTC prior to TSH suppression therapy was not elucidated yet.

Subjects and Methods

Participants

We enrolled 66 patients after thyroidectomy due to thyroid cancer at Shimane University Hospital between September 2012 and November 2019 (▶ **Fig. 1**). The patients were evaluated according to the UICC-TNM classification (8th edition). Some were excluded due to using drugs affecting bone metabolism such as glucocorticoids or diagnosing with bone metastasis and osteoporosis secondary to renal failure or endocrinological abnormalities or having a history of traumatic fractures. Forty-three patients whose bone metabolism, including the presence or absence of VF, could be assessed were included in the PTC group. The control group comprised a stratified random sampling of 43 age- and sex-matched healthy individuals who underwent health screening for osteoporosis at a community health center. In addition to age, sex, and BMI, we asked them whether they smoked or drank alcohol, their age at menopause, and whether they had a family history of proximal femur fractures. This study was approved by the ethics review board of Shimane University Faculty of Medicine (No. 201809–1) and complied with the Helsinki Declaration. Since this study was retrospective design and collected data from our daily clinical practice, the formal written informed consent was not required. Therefore, we opened this research project to our hospital homepage for allowing participants to refuse research participation.

Biochemical measurements

Blood and urine samples were collected just before TSH suppression therapy. Serum concentrations of albumin, creatinine, calcium, phosphorus, intact parathyroid hormone (PTH), urine type I collagen cross-linked N-telopeptide (NTX, as a marker of bone resorption), were evaluated in both groups by automated techniques at the central laboratory of our hospital. Intact PTH and urine NTX were evaluated using ECLIA and CLEIA, respectively. Reference ranges of them were: urine NTX 13.0–66.2 (male), 9.3–54.3 (premenopausal female), 14.3–89.0 (postmenopausal female) nmol·BCE/mmol·Cre, intact PTH 10–65 pg/ml. Estimated glomerular filtration rate (eGFR) was calculated using the equation proposed by the Modification of Diet in Renal Disease Study with modified coefficients for the Japanese population. Hemoglobin A1c (HbA1c) (International Federation of Clinical Chemistry) was determined by high-performance liquid chromatography.

In the PTC group, preoperative free T3, free T4, TSH thyroglobulin (Tg), were measured. Anti-thyroid peroxidase antibodies (TPO-Ab) and anti-thyroglobulin antibodies (Tg-Ab) were evaluated using the two-step chemiluminescence enzyme immunoassay kits "CL AIA-PAC TRAb", "CL AIA-PAC TPOAb" and "CL AIA-PACK TgAb", respectively. Reference ranges of the variables used to assess thyroid function were: Free T3 2.1–3.8 pg/ml, Free T4 0.8–1.5 ng/dl, TSH 0.45–4.5 μIU/ml, TPO-Ab ≤ 3.2 IU/ml and Tg-Ab ≤ 13.6 IU/ml.

Bone mineral density (BMD) measurements

BMD at the lumbar spine and femoral neck were measured by dual-energy X-ray absorptiometry using the QDR-4500 system (Hologic, Waltham, MA). Automatically calculated BMD based on the bone mineral content (in grams) and bone area (in square centimeters) were shown as an absolute value in grams per square centimeter.

T-score, the number of standard deviations (SDs), indicates difference from the mean for a normal young adult reference population.

Radiography

In the same week as serum collection, the lateral X-rays of the thoracic and lumbar spine were performed. VF was diagnosed by semiquantitative assessment of 13 vertebral bodies from Th4-L4 [9].

Diagnosis of osteoporosis

Osteoporosis was diagnosed according to WHO criteria. The WHO defines normal BMD as a T score of –1 and above, low bone mass as a T score between –2.5 and –1, osteoporosis as a T score of –2.5 and below, and severe osteoporosis as a T score of –2.5 and below with a fragility fracture.

Definition of vertebral fracture

We defined VFs as grades 1 to 3 according to the classification by Genant et al. [9]. Grade 1 corresponds to a 20 % to 25 % reduction in at least one height (anterior, middle, or posterior) along the length of the same vertebra compared with the height of the nearest uncompressed vertebral body. Grade 2 VF corresponds to a 25 % to 40 % reduction in vertebral height, and grade 3 corresponds to a more than 40 % reduction in any height. We defined severe fracture as grade 2 or 3 VF. VFs were diagnosed by two investigators who were blinded to each other's readings and also blinded to PTC group and control group status. Fractures were assessed at the same time, and if there was disagreement between the two investigators, the findings were assessed by a third investigator. No participants had any history of serious trauma.

Statistical analysis

Significant differences between groups were determined using the chi-square and Mann–Whitney U-test, and the association with VF was analyzed by logistic regression analysis. Statistical analysis was performed using SPSS software (ver. 19; IBM Corporation, Tokyo, Japan) and statistical significance was determined at $p < 0.05$.

Results

Baseline characteristics of subjects

Forty-three healthy individuals and 43 patients with PTC (15 males and 28 females) were included in this study. Their ages ranged from 27 years at the youngest to 82 at the oldest, with an average of 61 years old (mean ± standard deviation, 61 ± 11.8 years). Characteristics at baseline are shown in ▶ **Table 1**. The PTC patients had a mean duration after operation of 4.0 months at the time of study enrollment. The number of patients with the different PTC stages as diagnosed by UICC 8th criteria were: Stage I: 4, Stage II: 3, Stage III: 14, and Stage IV: 22. Patients with PTC had a higher body mass index (BMI), phosphorus, and HbA1c, as well as lower intact PTH ($p < 0.05$ for all). There was no significant difference in serum calcium, urinary NTX, femoral neck and lumbar spine BMD. On the other hand, the prevalence of osteoporosis, severe osteoporosis, VFs, or severe VFs was higher in the PTC group compared to the control group (27.8 vs. 14.0 %, 25.0 vs. 7.0 %, 44.1 vs. 16.3 %, 14.0 vs. 4.7 %, $p < 0.05$ for all).
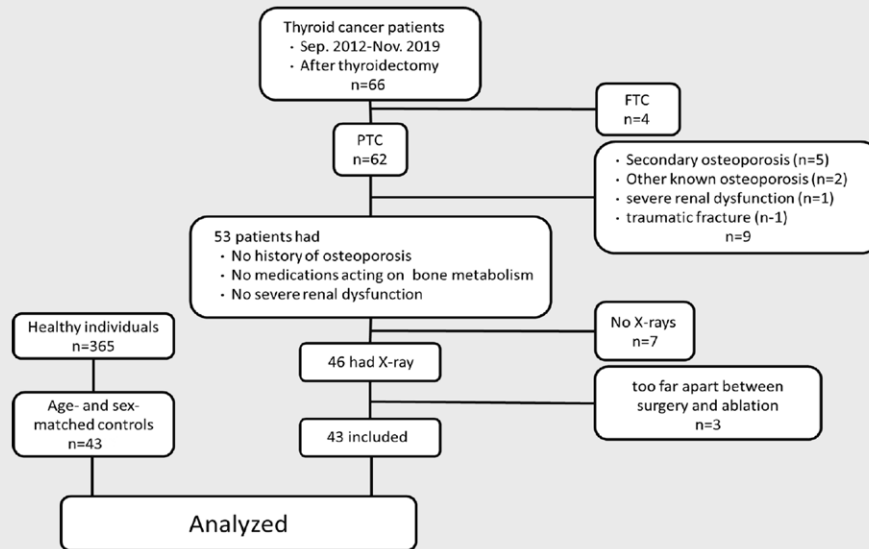
▶ **Fig. 1** Flowchart of the study population. We enrolled 62 patients who were diagnosed with PTC from September 2012 to November 2019 and 19 were excluded due to using drugs affecting bone metabolism or diagnosed with secondary osteoporosis or having a history of traumatic fractures. The control group comprised a stratified random sample of 43 age- and gender-matched healthy individuals. PTC: Papillary thyroid carcinoma; FTC: Follicular thyroid carcinoma.

Vertebral Fracture and severity

Patients were excluded if they had traumatic fractures or known fractures diagnosed prior to the study. All of VFs were morphometric fracture. In PTC group, the site of VF was Th5 in two, Th6 in one, Th11 in three, Th12 in seven, L1 in six, L2 in six, L3 in three (▶ **Fig. 2a**). Of the 19 patients who had more than two VFs, 9 had severe VFs. Forty percent of the PTC group in their 40 s, 40 % in their 50 s, 47 % in their 60 s, 33 % in their 70 s, and 50 % in their 80 s had VFs. Notably, fractures were more prominent in the younger generation compared to the control group (▶ **Fig. 2b**). In the control group, the VFs were located mainly at the thoracolumbar transition: Three patients had Th11 fractures, five had Th12 fractures, one had L1 fractures, and one had L3 fractures (▶ **Fig. 2a**). Of the seven patients with more than two fractures, three were severe fractures. Ten percent of the patients in their 50 s, 11.8 % in their 60 s, 25 % in their 70 s, and 50 % in their 80 s had fractures. The fracture rate increased with older age (▶ **Fig. 2b**). Previous non-VF s were found in one patient in the PTC group (left forearm) and four patients in the control group (toe, foot, ribs, and wrist). There was no statistically significant difference between the two groups.

Comparison of parameters between patients with or without VFs in PTC patients

We compared the demographic and biochemical parameters of PTC patients with or without VFs (▶ **Table 2**). The patients with VFs showed significantly lower T-score of lumbar spine and femoral neck compared to patients without VFs. Serum creatinine levels were also significantly lower in patients without VFs (0.68 vs. 0.76, $p < 0.05$). Other variables such as BMI, eGFR, HbA1c, serum Ca, intact PTH, urinary NTX, preoperative free T3, free T4, preoperative

TSH and tumor size were not significantly different between the PTC group with and without VF.

Association between PTC and presence of VF

Multivariate logistic regression analysis adjusted for age, sex, BMI revealed that PTC was associated with the presence of VF (odds ratio 5.68: 95 % confidence interval 1.77–18.2; $p < 0.05$). This relationship remained significant after additional adjustment for HbA1c, lumbar and femoral neck BMD (▶ **Table 3**).

Discussion

Not only as the risk for severe osteoporosis [8], here, we report for first time that there is an association between PTC and the risk of VF. In our cohort, most PTC patients displayed VFs before receiving TSH suppression therapy and only five out of 43 patients with PTC had low TSH level at diagnosis. Therefore, this study suggested that PTC itself was associated with VFs. Our analysis demonstrated that evaluation of VFs is important in PTC patients with indications for TSH suppressive therapy.

It is well known that suppressed TSH or hyperthyroidism is associated with a risk of osteoporotic fracture [7, 10]. From population-based cohort, elderly women with low TSH had a four times higher risk for VFs [11]. Even in subclinical hyperthyroidism, the risk of fracture increased to 1.28 (95 % CI: 1.06–1.53) [12]. From a study in patients with thyroid cancer, randomized trial from Japan showed that BMD was predominantly decreased in women over 50 years of age who received TSH suppression [13]. In patients at low to medium risk as defined by the American Thyroid Association, TSH suppression therapy with levothyroxine has shown to increase the risk of osteoporosis without altering to life expectancy [14], and the manage-

▶ **Table 1** Baseline characteristics of patients with papillary thyroid carcinoma and controls.

Parameter	Papillary thyroid carcinoma (n = 43)	Control subjects (n = 43)	p
Male/Female (%)	15 (35)/28 (65)	15 (35)/28 (65)	–
Ages (years)	61.2 ± 12.0	61.5 ± 12.1	0.921
BMI (kg/m2)	24.7 ± 3.60	22.8 ± 2.30	0.019
Creatinine (mg/dl)	0.71 ± 0.17	0.64 ± 0.14	0.062
eGFR (ml/min/1.73 m2)	74.3 ± 13.0	83.1 ± 18.3	0.058
HbA1c (mmol/mol)	42.6 ± 9.92	35.6 ± 8.79	< 0.001
Alb-corrected Ca (mg/dl)	9.10 ± 0.53	9.20 ± 0.36	0.575
Phosphorus (mg/dl)	3.80 ± 0.51	3.25 ± 0.49	< 0.001
Intact PTH (pg/ml)	22.6 ± 17.5	44.5 ± 13.2	< 0.001
U-NTX (nMBCE/mM·Cr)	46.7 ± 41.2	51.5 ± 107	0.451
Preoperative Free T3 (pg/ml)	2.66 ± 0.390	–	
Preoperative Free T4 (ng/dl)	1.14 ± 0.19	–	
Preoperative TSH (µU/ml)	2.05 ± 1.64	–	
Preoperative Tg (ng/ml)	180.5 ± 581.8	–	
Tumor size (cm)	1.93 ± 1.09	–	
Postoperative period (months)	4.0 ± 3.0	–	
L2–4 BMD (g/cm²)	0.975 ± 0.198	0.942 ± 0.184	0.570
T-score	−0.566 ± 1.60	−0.740 ± 1.51	0.68
Neck BMD (g/cm²)	0.693 ± 0.139	0.717 ± 0.14	0.668
T-score	−1.03 ± 1.14	−0.858 ± 1.01	0.760
Diabetes mellitus (%)	9 (20.9)	–	–
Osteoporosis (%)	10 (27.8)*	6 (14.0)	0.128
Severe osteoporosis (%)	9 (25.0)*	3 (7.0)	0.026
Vertebral fracture (%)	19 (44.1)	7 (16.3)	0.004
Severe vertebral fracture (%)	9 (14.0)	3 (4.7)	0.0015

Values are expressed as mean ± SD.; BMI: Body mass index; eGFR: Estimated glomerular filtration rate; HbA1c: Hemoglobin A1c; PTH: Parathyroid hormone; U-NTX: Urine type I collagen cross-linked N-telopeptide; TSH: Thyroid hormone stimulation hormone; L BMD: Bone mineral density at the lumber spine 2–4; Neck BMD: Bone mineral density at the femoral neck.;
* BMD assessment was performed on 36 patients with PTC group.

ment of bone fragility is essential for cases with a promising long-term prognosis. However, these studies evaluated fractures during TSH-suppressive therapy, and none has examined whether PTC itself is associated with fractures. In the current study, the duration of TSH suppression supposed to be too short to affect bone metabolism leading to the fracture. Also, we found no significant differences in thyroid hormones or TSH level when comparing patients with or without VFs. Taken together, PTC could be a risk factor for VFs.

In our study, the prevalence of VF and osteoporosis were higher in PTC patients compared to that of control subjects [8]. There are a few reports on thyroid cancer and osteoporosis. The population-based cohort study in Taiwan showed that osteoporosis was significantly higher risk factor for the development of thyroid cancer [15]. The authors discussed why osteoporosis is associated with the development of thyroid cancer and described the involvement of potential selection bias. We previously showed that patients with PTC had a higher prevalence of osteoporosis compared to patients

without PTC, and that patients with severe osteoporosis had significantly higher rates of anti-TPO antibodies [8]. According to a study using a questionnaire, subjects with a history of thyroid cancer have shown to display a lower mean age of first fracture when compared to those with a history of other thyroid diseases [6]. The reason why patients with PTC exhibited an increased risk of VF was not elucidated yet. Our study revealed that PTC was a risk factor for VF in age- and sex-matched subjects, independent of BMI, glucose profile and BMD. It suggests that there is an increased risk of fracture independent of BMD in the PTC group. Because bone strength is defined by BMD and bone quality, evaluation of bone quality is important. Unfortunately, we were not able to examine parameters to assess bone quality such as TBS or bone metabolism markers in the present study. In order to elucidate the bone fragility mechanism in PTC, accumulation of bone quality parameters is a future issue.

The vitamin D deficiency is a known risk for osteoporosis [16, 17] and fractures [18]. Sahin et al. reported that vitamin D3 levels were
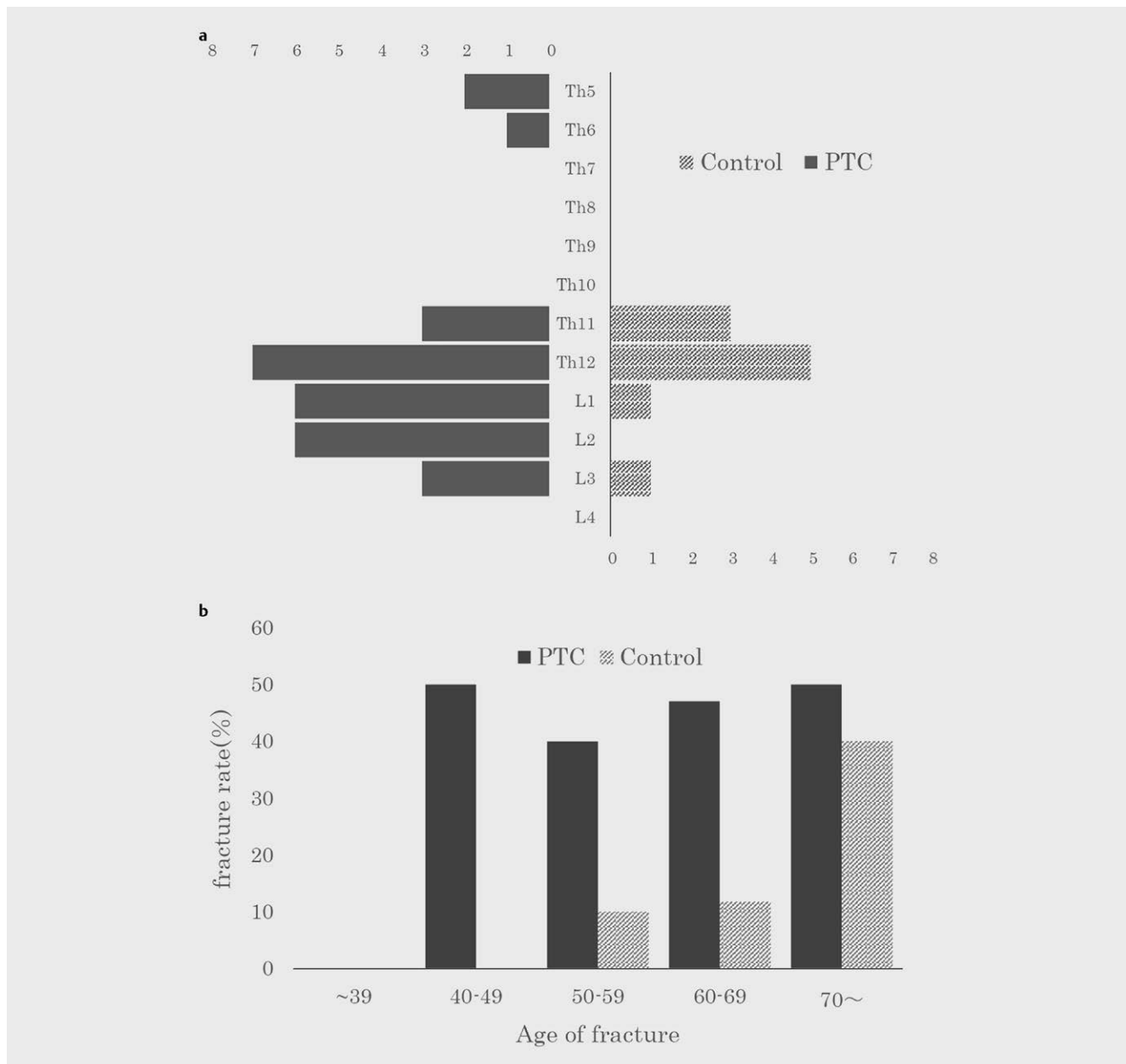
▶ **Fig. 2** **a**: Location and number of fractures. In the papillary carcinoma group, two patients had fractures outside the thoracolumbar transition. On the other hand, the location of the fracture was only at the thoracolumbar transition. PTC: Papillary thyroid carcinoma; Th: Thoracic vertebra; L: Lumber vertebra. **b**: Age of fracture victims and number of fractures. In the papillary carcinoma group, fractures were more prominent in the younger generation compared to the control group. In the control group, the fracture rate increased with age. PTC: Papillary thyroid carcinoma.

significantly lower and vitamin D deficiency was more frequent in the patients with PTC [19]. In the PTC group, 97% of the patients were vitamin D deficient [20], suggesting the potential contribution of Vitamin D deficiency on fracture in PTC. In our cohort, 25-hydroxyvitamin D (25D) was measured in only 34.9% (15/43 patients) of the PTC group and 86.0% (37/43 patients) of the control group. Even though with such insufficient data set, 25D levels were significantly lower (p = 0.037) in the PTC group (15.5 ± 5.75) when compared to that of the control group (18.8 ± 4.93). Among the participants with 25D measured, VF was present in 10/15 in PTC group and 7/37 in control group.

The oxidative stress contributes to the development of osteoporosis [21, 22]. Ramli et al. showed that serum reactive oxygen species (ROS) levels in patients with PTC were significantly higher than those in controls, suggesting that thyroid cancer causes the generation of ROS and induces oxidative stress [23]. These reports suggest the pathomechanistical role of the oxidative stress in the development of VF in PTC patients.

Advancing age, as expected, is the most important risk factor for VF [24, 25]. Although prevalence of VF was increasing with age in control subjects, that of the PTC patients showed an age-independent distribution in this study. Furthermore, it is known that

▶ **Table 2** Comparison of demographic and biochemical parameters, as well as bone turnover markers, and bone mineral density between subjects with and without vertebral fracture in patients in papillary thyroid carcinoma.

	Without vertebral fracture (n = 24)	With vertebral fracture (n = 1 9)	p
Number of subject (Male/Female)	24 (6/18)	19 (9/10)	0.082
Age (years)	59.6 ± 12.9	63.2 ± 10.7	0.287
Duration after operation (months)	3.8 ± 2.2	4.7 ± 3.6	0.717
BMI (kg/m2)	25.3 ± 4.01	23.9 ± 2.87	0.24
Creatinine (mg/dl)	0.68 ± 0.17	0.76 ± 0.15	0.046
eGFR (ml/min/1.73 m2)	77.6 ± 14.3	70.0 ± 9.83	0.074
HbA1c (mmol/mol)	43.1 ± 11.4	42.2 ± 7.77	0.784
Ca (mg/dl)	9.1 ± 0.55	9.1 ± 0.52	0.825
Intact PTH (pg/ml)	23.6 ± 17.8	21.3 ± 17.4	0.696
U-NTX (nMBCE/mM·Cr)	46.0 ± 25.2	47.4 ± 53.7	0.215
Preoperative Free T3 (pg/ml)	2.64 ± 0.40	2.69 ± 0.38	0.663
Preoperative Free T4 (ng/dl)	1.10 ± 0.16	1.18 ± 0.22	0.279
Preoperative TSH (µU/ml)	2.02 ± 1.30	2.10 ± 2.05	0.404
Preoperative Tg (ng/ml)	262 ± 793	46.2 ± 48.6	0.229
L BMD (g/cm2)	1.03 ± 0.20	0.90 ± 0.18	0.039
T-score	0.035 ± 1.70	−1.37 ± 1.04	0.01
Neck BMD (g/cm2)	0.75 ± 0.12	0.63 ± 0.14	0.018
T-score	−0.54 ± 0.91	−1.64 ± 1.12	0.007
Tumor size (cm)	1.92 ± 1.30	1.94 ± 0.84	0.447
Tg-Ab positive (%)	5 (20.8)	4 (21.1)	0.292
TPO-Ab positive (%)	3 (17.6)	4 (22.2)	0.309
Smoking (%)	5 (20.8)	9 (47.4)	0.05
Drinking (%)	5 (20.8)	8 (42.1)	0.09

Values are expressed as mean ± SD.; BMI: Body mass index; eGFR: Estimated glomerular filtration rate; HbA1c: Hemoglobin A1c; PTH: Parathyroid hormone; U-NTX: Urine type I collagen cross-linked N-telopeptide; TSH: Thyroid hormone stimulation hormone; L BMD: Bone mineral density at the lumber spine 2–4; Neck BMD: Bone mineral density at the femoral neck.

▶ **Table 3** Associations between papillary thyroid carcinoma and vertebral fracture.

Adjusted variables	OR (95 % CI)	p
None	4.07 (1.49–11.2)	0.006
Age	4.51 (1.58–12.8)	0.005
Age + gender	4.81 (1.64–14.1)	0.004
Age + gender + BMI	5.63 (1.82–17.5)	0.003
Age + gender + BMI + HbA1c	5.68 (1.77–18.2)	0.004
Age + gender + BMI + L2–4 BMD	6.37 (1.83–22.2)	0.004
Age + gender + BMI + neck BMD	4.31 (1.32–14.0)	0.015

BMI: Body mass index; HbA1c: Hemoglobin A1c; L2–4 BMD: Bone mineral density at the lumber spine 2–4; neck BMD: Bone mineral density at the femoral neck.

VFs are generally more likely to occur at the thoracolumbar junction [26]. In the control group, the thoracolumbar junction was the most common site of VF, but VFs of PTC patients are found in the upper thoracic and lower lumbar vertebrae in this study. These differences suggest that PTC-related bone deterioration has a different mechanism than age-related osteoporosis.

In our study, there was no difference in BMD between PTC patients and control; however, the prevalence of VFs was significantly higher in PTC patients. Evaluating the BMD in post-thyroidectomized PTC patients by both DXA and central quantitative computed tomography (cQCT), the total prevalence of osteoporosis and osteopenia was higher by cQCT (92.6 %) compared to that by DXA (37.0 %) [27]. The volumetric BMD calculated by cQCT is much strongly associated with bone microarchitecture, the potential determinant of bone strength independent of bone density [28]. Therefore, PTC patients would display the deterioration of bone microarchitecture without altering the BMD levels. The interaction between PTC and bone microarchitecture is important research topic and further investigation would be required.

Inflammatory cytokines affect osteoporosis because high cytokine content promotes bone resorption. Within the tumor microenvironment of PTC, the presence of cancer proteins induces an inflammatory state that upregulates several chemokines [29, 30]. The genes encoding chemokines are induced in PTC compared to normal thyroid, suggesting that chemokines are associated with tumor-associated inflammation [30]. In this study, there was no association between tumor size, lymph node metastasis, distant metastasis, or thyroglobulin levels and prevalence of VFs in PTC patients. PTC stage and disease activity would be not involved in the development of VFs. The present study included only either intermediate- or higher-risk patients who were treated with intravenous radioiodine therapy; therefore, further studies with lower-risk patients are needed.

Study limitation

Several limitations of this study must be clarified. First of all, the number of subjects is small, and all subjects are Japanese. Second, this is a retrospective study, which means that many people at high risk of fracture might be included in the study (involving subjects who are interested in fractures tend to undergo bone health screening). Third, we could not exclude all influence of hospitalization/immobilization/inflammation caused by the surgical treatment in the VFs occurrence. We need a prospective study to measure each confounding factors before surgery including patients with early-stage PTC who are not candidates for radiotherapy. Fourth, in this report, we have not collected enough clinical indicators to adequately assess the fracture mechanism of PTC. Fifth, 70 % of the

fractures were grade 1, which may include some fractures that are usually overlooked or considered to be just deformities. Careful consideration is still required regarding the pathological significance of mild fractures. Finally, we did not fully evaluate factors that may be involved in the pathophysiology, such as concentrations of serum 25-hydroxyvitamin D and oxidative stress marker. Lastly, this study did not include lower-risk PTC patients.

Conclusion

We found that PTC itself was a risk factor for VF independent of age, sex, BMI, glucose metabolism, and BMD. Bone densitometry and fracture evaluation by chest and lumbar X-ray could be recommended for those considering TSH suppression therapy.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Tankó LB, Christiansen C, Cox DA et al. Relationship between osteoporosis and cardiovascular disease in postmenopausal women. J Bone Miner Res 2005; 20: 1912–1920

[2] Moriwaki K, Komaba H, Noto S et al. Cost-effectiveness of alendronate for the treatment of osteopenic postmenopausal women in Japan. J Bone Miner Res 2013; 28: 395–403

[3] La Vecchia C, Malvezzi M, Bosetti C et al. Thyroid cancer mortality and incidence: a global overview. Int J Cancer 2015; 136: 2187–2195

[4] Haymart MR, Banerjee M, Reyes-Gastelum D et al. Thyroid ultrasound and the increase in diagnosis of low-risk thyroid cancer. J Clin Endocrinol Metab 2019; 104: 785–792

[5] Kitahara CM, Sosa JA. The changing incidence of thyroid cancer. Nat Rev Endocrinol 2016; 12: 646–653

[6] Solomon BL, Wartofsky L, Burman KD. Prevalence of fractures in postmenoposal woman in thyroid disease. Thyroid 1993; 3: 17–23

[7] Flynn RW, Bonellie SR, Jung RT et al. Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy. J Clin Endocrinol Metab 2010; 95: 186–193

[8] Notsu M, Yamauchi M, Morita M et al. Papillary thyroid carcinoma is a risk factor for severe osteoporosis. J Bone Miner Metab 2020; 38: 264–270

[9] Genant HK, Wu CY, van Kuijk C et al. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993; 8: 1137–1148

[10] Vestergaard P, Mosekilde L. Hyperthyroidism, bone mineral, and fracture risk – a meta-analysis. Thyroid 2013; 13: 585–593

[11] Study of osteoporotic fractures research groupBauer DC, Ettinger B, Nevitt MC et al. Risk for fracture in women with low serum levels of thyroid-stimulating hormone. Ann Intern Med 2001; 134: 561–568

[12] Blum MR, Bauer DC, Collet TH. Thyroid studies collaboration. Subclinical thyroid dysfunction and fracture risk: a meta-analysis. JAMA 2015; 313: 2055–2065

[13] Sugitani I, Fujimoto Y. Effect of postoperative thyrotropin suppressive therapy on bone mineral density in patients with papillary thyroid carcinoma: a prospective controlled study. Surgery 2011; 150: 1250–1257

[14] Wang LY, Smith AW, Palmer FL et al. Thyrotropin suppression increases the risk of osteoporosis without decreasing recurrence in ATA low- and intermediate-risk patients with differentiated thyroid carcinoma. Thyroid 2015; 25: 300–307

[15] Sun LM, Liang JA, Lin CL et al. Cancer risk in patients with osteoporosis: a population-based cohort study. Curr Med Res Opin 2017; 33: 733–739

[16] Steingrimsdottir L, Halldorsson TI, Siggeirsdottir K et al. Hip fractures and bone mineral density in the elderly--importance of serum 25-hydroxyvitamin D. PLoS One 2014; 9: e91122

[17] Cauley JA, Greendale GA, Ruppert K et al. Serum 25 hydroxyvitamin D, bone mineral density and fracture risk across the menopause. J Clin Endocrinol Metab 2015; 100: 2046–2054

[18] Wang N, Chen Y, Ji J et al. The relationship between serum vitamin D and fracture risk in the elderly: a meta-analysis. J Orthop Surg Res 2020; 15: 81–90

[19] Sahin M, Uçan B, Giniş Z et al. Vitamin D3 levels and insulin resistance in papillary thyroid cancer patients. Med Oncol 2013; 30: 589–594

[20] Ahn HY, Chung YJ, Park KY et al. Serum 25-hydroxyvitamin D level does not affect the aggressiveness and prognosis of papillary thyroid cancer. Thyroid 2016; 26: 429–433

[21] Almeida M, Han L, Martin-Milan M et al. Skeletal involution by age-associated oxidative stress and its acceleration by loss of sex steroids. J Biol Chem 2007; 282: 27285–27297

[22] Zhou Q, Zhu L, Zhang D et al. Oxidative stress-related biomarkers in postmenopausal osteoporosis: a systematic review and meta-analyses. Dis Markers 2016; 7067984:

[23] Ramli NSF, Junit SM, Leong NK et al. Analyses of antioxidant status and nucleotide alterations in genes encoding antioxidant enzymes in patients with benign and malignant thyroid disorders. Peer J 2017; 5: e3365

[24] Pizzato S, Trevisan C, Lucato P et al. Identification of asymptomatic frailty vertebral fractures in post-menopausal woman. Bone 2018; 113: 89–94

[25] Schousboe JT. Epidemiology of vertebral fractures. J Clin Densitom 2016; 19: 8–22

[26] Van der Klift M, De Laet CEDH, McCloskey EV et al. The incidence of vertebral fractures in men and women: the Rotterdam study. J Bone Miner Res 2002; 17: 1051–1056

[27] Kim K, Kim IJ, Pak K et al. Evaluation of bone mineral density using DXA and cQCT in postmenopausal patients under thyrotropin suppressive therapy. J Clin Endocrinol Metab 2018; 103: 4232–4240

[28] Liu XS, Cohen A, Shane E et al. Bone density, geometry, microstructure, and stiffness: Relationships between peripheral and central skeletal sites assessed by DXA, HR-pQCT, and cQCT in premenopausal women. JBMR 2010; 25: 2229–2238

[29] Guarino V, Castellone MD, Avilla E et al. Thyroid cancer and inflammation. Mol Cell Endocrinol 2010; 321: 94–102

[30] Muzza M, Deg'Innnocenti D, Colombo C et al. The tight relationship between papillary thyroid cancer, autoimmunity and inflammation: clinical and molecular studies. Clin Endocrinol 2010; 72: 702–708