Pituitary ^{18}F -FDG uptake correlates with serum TSH levels in thyroid cancer patients on ^{18}F -FDG PET/CT

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Objective The objective of this study was to evaluate the relationship between fluorine-18-fluorodeoxyglucose (^{18}F -FDG) uptake in the pituitary gland and serum thyroid-stimulating hormone (TSH) levels in differentiated thyroid cancer (DTC) patients on ^{18}F -FDG PET/computed tomography (CT).

Patients and methods A total of 215 DTC patients and 215 age-paired and sex-paired healthy screening participants were included. DTC patients were divided into hypothyroid, euthyroid and subclinical hyperthyroid patients according to their serum TSH levels. The relationship between ^{18}F -FDG uptake in the pituitary gland and serum TSH levels was evaluated in DTC patients, and the pituitary ^{18}F -FDG metabolism was compared in different thyroid status.

Results The standardized uptake value of pituitary (SUV_p) in all 430 patients was directly correlated with serum TSH levels ($r = 0.479$ and 0.432 , all $P < 0.05$). The SUV_p in DTC patients was higher than that in 215 healthy participants ($z = -10.4$, $P < 0.05$). No significant difference of SUV_p was observed between euthyroid patients and healthy participants ($P = 0.145$).

Conclusion Our study established the positive correlation between pituitary ^{18}F -FDG uptake and serum TSH. TSH values should be measured in patients with incidental pituitary uptake during ^{18}F -FDG PET/CT. L-T4 replacement for DTC patients may well have the same feedback on the thyroid-pituitary axis as the physiologic thyroid status. The diffuse ^{18}F -FDG uptake with normal CT or MRI appearance of the pituitary in patients with DTC indicates physiologic uptake. *Nucl Med Commun* 40:57–62 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

The thyroid is an important endocrine organ regulated by the pituitary through the hypothalamus-pituitary-thyroid axis. Multiple neurotransmitter systems, including catecholaminergic and serotonergic systems, are affected by the excess or deficit of thyroid hormones [1]. In the case of thyroid cancer patients who have undergone total thyroidectomy, the effects on the pituitary are complex. Although we can treat such patients with thyroid hormone replacement, it is still unclear whether there are other effects on the axis or even on normal brain function. A 0.8% incidence of incidentally detected focal pituitary uptake on whole-body fluorine-18-fluorodeoxyglucose (^{18}F -FDG) PET/computed tomography (CT) in 13 145 consecutive patients was reported [2]. However, we have frequently observed diffuse pituitary uptake on ^{18}F -FDG PET/CT scans in patients with differentiated thyroid cancer (DTC) after withdrawal of levothyroxine (L-T4). Is this a pathologic uptake, or is it just a physiologic sighting because of the total thyroidectomy and thyroid hormones' replacement? According to our knowledge, only a few in-vivo neuroimaging studies have examined hypothyroid patients following total thyroidectomy, and

no study mentioned the clinical significance of the ^{18}F -FDG uptake in the pituitary. The high uptake of ^{18}F -FDG in the pituitary was related to serum thyroid-stimulating hormone (TSH) level in a total of 44 participants [3]. We hypothesized that ^{18}F -FDG uptake in the pituitary correlated with serum TSH. Therefore, this retrospective study further investigated the relationship between ^{18}F -FDG uptake in the pituitary and serum TSH in a large population including DTC patients. We also studied the ^{18}F -FDG uptake of the pituitary in patients with different thyroid function status (euthyroid, subclinical hyperthyroidism) after thyroidectomy using levothyroxine sodium (Merck Sdn Bhd, Darmstadt, Germany) as replacement therapy.

Patients and methods

Patient population

From April 2015 to June 2017, two nuclear medicine specialists reviewed the ^{18}F -FDG PET/CT scans performed on 1035 consecutive DTC patients in the Department of Nuclear Medicine, Xinhua Hospital. The selection criteria were as follows: (a) all the selected patients received total thyroidectomy, and the histological result was differentiated

thyroid cancer (DTC); (b) thyroid function test was performed within 3 days of the PET/CT scan; (c) no known history of other endocrine problems and other malignant tumor diseases; and (d) no previous history of brain surgery. According to the selection criteria, 215 patients were eligible to participate in the study. We also enrolled another 215, following 1:1 pairing rules, age-matched and sex-matched healthy screening patients from the same period as a control group who had the ^{18}F -FDG PET/CT scans for physical examination. All of them had thyroid function tests within 3 days. Written Ethics Approval and Patient Consent from the Hospital Research Ethics Committee of Shanghai Jiaotong University, School of Medicine affiliated Xinhua Hospital was obtained.

Imaging procedures

Cases with intermediate or high risk for recurrence had a PET/CT scan (Biograph mCT64; Siemens Medical Systems, Knoxville, Tennessee, USA). Each patient fasted for at least 6 h to ensure a serum glucose concentration of less than 150 mg/dl before imaging. ^{18}F -FDG (5.55 MBq/kg) was intravenously administered, and whole-body PET images were obtained ~1 h (ranging from 45 to 60 min) later. As regards transmission CT images for attenuation correction and lesion localization, the CT acquisition parameters were slice thickness of 0.3 cm, 0.8 s tube rotation, table speed 1.5 cm/rotation, pitch 1.5:1, 120 kV, 90 mA, with dose modulation. The range of scanning extended from the parietal region to the midfemur. After acquiring CT images, 3D PET images were acquired in the same area with 4–9 beds. Each bed was scanned for 2 min. After data acquisition, the PET images were subject to attenuation correction before image reconstruction and fusion using computer software. The standardized uptake value (SUV) was corrected for the injected dose of ^{18}F -FDG and the patient's body weight.

Six patients had brain MRI with a 1.5-T MR unit (Twinspeed; GE Medical Systems, Milwaukee, Wisconsin, USA) for concurrent headache or dizziness. The imaging protocol involved axial noncontrast T1-weighted (TR/TE, 2000–2202/9–10 ms) and axial T2-weighted (TR/TE, 8000–8600/110–125 ms) imaging. Sagittal T1-weighted and T2-weighted (TR/TE, 2200–2500/90–95 ms) fast spin-echo imaging was also performed. Diffusion-weighted MRI was acquired in the axial plane using a single-shot echo-planar imaging sequence (TR/TE effective range: 5000–5500/70–80).

Image and data analysis

For the measurement of standardized uptake value of pituitary (SUV_p) in both DTC patients and healthy participants, a 10-mm-diameter circular region of interest (ROI) was drawn over the pituitary fossa, which was determined on the transaxial CT images. We also measured the uptake of the brain and liver ($\text{SUV}_{\text{brain}}$ and

$\text{SUV}_{\text{liver}}$) as reference background tissues. Two 10-mm-diameter circular ROIs were placed bilaterally in the frontal lobe cortex of and in the right and left lobes of the liver. SUV_{max} of each region was recorded, and the average of the SUV_{max} from the two ROIs was calculated for each patient. We also calculated a target-to-background ratio (TBR) to rule out other factors affecting the pituitary uptake. The maximum TBR (TBR_{maxb} or TBR_{maxl}) was determined by the ratio of SUV_p to average standardized uptake value of the brain or liver. The average TBR (TBR_{avgb} or TBR_{avgl}) was determined by the ratio of SUV_p to the average standardized uptake value of the brain or liver.

Thyroid-secreting and pituitary-secreting hormone test

Thyroid function tests were performed within 3 days of PET/CT scans in all participants. Serum TSH was measured using a time-resolved immunofluorometric assay (Anytest; Sym-Bio Lifescience Co. Ltd, Shanghai, China). The normal reference range of TSH is 0.3–4.6 $\mu\text{IU/ml}$ for TSH in our laboratory. The 215 DTC patients were divided into hypothyroid (TSH > 4.6 $\mu\text{IU/ml}$), euthyroid (TSH in 0.3–4.6 $\mu\text{IU/ml}$), and subclinical hyperthyroid (TSH < 0.3 $\mu\text{IU/ml}$) patients.

The prolactin (PRL), luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels were also measured in the 215 DTC patients using chemiluminescent microparticle immunoassay (Maglumi 2000; Shenzhen New Industries Biomedical Engineering Co. Ltd, Shenzhen, China).

Statistical analysis

A correlation between SUV and TBR with serum TSH levels in the participants was assessed using Spearman's rank correlation analysis. We used Kruskal–Wallis analysis of variance or a Mann–Whitney *U*-test to compare the differences in SUV and TBR among the four groups, and a Dunn–Bonferroni test for post-hoc comparisons. The age and sex in thyroid cancer patients and healthy group was compared using *t*-test or χ^2 -test. The levels of TSH and FT4 in the DTC patients and healthy participants were compared using a Mann–Whitney *U*-test. All statistical computations were performed using SPSS 22.0 software (SPSS Inc., Chicago, Illinois, USA), and a *P* value less than 0.05 was considered statistically significant.

Results

Patients' clinical characteristics

The patients' clinical characteristics and the SUV_p in the total of 430 participants are listed in Table 1. Among 215 DTC patients, 164 had preablation hypothyroidism after thyroid hormone withdrawal, while 33 patients were euthyroid after thyroid hormone replacement and 18 had subclinical hyperthyroidism on thyroid hormone replacement and suppression therapy, respectively. There

were no differences concerning sex and age between all DTC patients and healthy participants.

The PRL, FSH and LH were 226.0 (166.0–273.5) and 220.8 (164.0–284.0), 6.6 (4.8–11.5) and 6.2 (4.5–33.9), 4.2 (3.0–10.4) and 4.4 (3.1–15.3), respectively, in DTC patients and healthy participants ($P=0.889$, 0.430, and 0.173).

Correlation of fluorine-18-fluorodeoxyglucose uptake of the pituitary with serum thyroid-stimulating hormone levels

The SUV_p in the entire 430 participants was directly correlated with serum TSH levels ($r=0.479$ and 0.432 , all $P<0.05$; Fig. 1a and b). No significant relationship between ^{18}F -FDG uptake in the pituitary with serum TSH levels was found in healthy screening participants ($r=0.029$, $P=0.335$), but a very weak correlation of ^{18}F -FDG uptake in the pituitary with FT4 was found in

healthy screening participants ($r=0.14$, $P=0.02$). TBR_{maxb} , TBR_{avgb} , TBR_{maxl} and TBR_{avgl} were tested and were found to be less correlated than SUV_p ($r=0.387$, 0.378 , 0.333 and 0.305 , respectively, all $P<0.05$; Table 2).

Comparisons of fluorine-18-fluorodeoxyglucose uptake of the pituitary in patients with different thyroid status

There was a significant difference in SUV_p between all DTC patients and healthy screening patients ($\bar{x}=-10.4$, $P<0.05$; Table 3). The hypothyroid status of thyroid cancer patients was correlated with much more ^{18}F -FDG uptake than hyperthyroid or normal thyroid function status in DTC patients who used L-T4 as a replacement. No statistical differences were observed among euthyroid patients, subclinical hyperthyroid patients and healthy participants (Table 3 and Fig. 2a–c).

Table 1 Characteristics of thyroid cancer patients and healthy screening participants

	All participants ($n=430$)	DTC patients ($n=215$)	Healthy screening participants ($n=215$)	Effect value	P value
Age (mean $\pm$ SD) (years)	47.67 $\pm$ 11.26	46.61 $\pm$ 12.52	48.73 $\pm$ 9.74	$t=1.96$	0.51
Sex (n)				$\chi^2=2.69$	0.101
Male	213	98	115		
Female	217	117	100		
TSH level ($\mu\text{IU/ml}$)				$Z=-12.03$	0.0
Median	2.63	68.22	1.55		
Interquartile range	1.27–68.57	8.66–121.13	1.03–2.47		
FT4 (pmol/l)				$Z=-13.59$	0.0
Median	14.54	1.04	16.54		
Interquartile range	1.03–17.0	0.01–7.6	14.79–18.3		
SUV_p				$Z=-10.41$	0.0
Median	3.04	3.94	2.60		
Interquartile range	2.26–4.17	2.90–4.89	1.69–3.19		

DTC, differentiated thyroid cancer; SUV_p , standardized uptake value of the pituitary; TSH, thyroid-stimulating hormone.

Fig. 1

(a, b) The maximum standardized uptake value (SUV_p) of the pituitary gland on fluorine-18-fluorodeoxyglucose PET/computed tomography. Side-by-side box plots in the total 430 participants and thyroid cancer patients and Spearman's rank analysis indicated that SUV_p directly correlated with serum thyroid-stimulating hormone (TSH) levels ($r=0.479$ and 0.432 , all $P<0.05$).

Table 2 Standardized uptake value in the pituitary gland and the target-to-background ratio of the pituitary to the brain and liver

	Hypothyroid patients (n = 164)	Euthyroid patients (n = 33)	Subclinical hyperthyroid patients (n = 18)	P
SUV _{max brain} [median (interquartile range)]	11.14 (9.80–12.79)	10.90 (8.79–13.51)	10.73 (9.11–13.39)	0.79
SUV _{avg brain} [median (interquartile range)]	8.39 (7.36–9.69)	8.52 (7.44–9.66)	9.16 7.20–11.37	0.37
SUV _{max liver} [median (interquartile range)]	3.57 (3.09–4.08)	3.55 (2.81–4.02)	3.73 2.94–4.69	0.56
SUV _{avg liver} [median (interquartile range)]	2.27 (1.94–2.55)	2.05 (1.77–2.44)	2.05 (1.65–2.35)	0.05
TBR _{maxb} [median (interquartile range)]	0.5 (0.37–0.63)	0.34 (0.23–0.56)	0.33	0.00
TBR _{avgb} [median (interquartile range)]	0.33 (0.37–0.63)	0.25 (0.18–0.33)	0.26 (0.18–0.31)	0.00
TBR _{maxl} [median (interquartile range)]	1.90 (0.26–0.40)	1.39 (1.18–1.83)	1.49 (1.28–1.96)	0.00
TBR _{avgl} [median (interquartile range)]	1.28 (1.01–1.48)	1.02 (0.91–1.18)	1.15 (0.92–1.36)	0.001

NA, not available; SUV_p, standardized uptake value of pituitary; TBR, target-to-background ratio; TBR_{avgb}, the average standardized uptake value of pituitary to the average standardized uptake value of brain; TBR_{avgl}, the average standardized uptake value of pituitary to the average standardized uptake value of liver; TBR_{maxb}, the maximum standardized uptake value of pituitary to the maximum standardized uptake value of brain; TBR_{maxl}, the maximum standardized uptake value of pituitary to the maximum standardized uptake value of liver.

Table 3 Comparison of standardized uptake value in pituitary gland according to serum thyroid-stimulating hormone concentration

	Hypothyroid patients (n = 164)	Euthyroid patients (n = 33)	Subclinical hyperthyroid patients (n = 18)	Healthy participants (n = 215)	Effect value	P
TSH (μU/ml)						
Median	86.5	1.44	0.11	1.55		
Interquartile range	53.5–137.2	0.84–2.10	0.01–0.19	1.03–2.47		
SUV _p (n)					$\chi^2 = 102.33$	0.00
≥ 4.1	86	7	5	14		
< 4.1	78	26	13	201		
SUV _p					M = 129.61	0.00
Median	4.32	3.04	2.98	2.60		
Interquartile range	3.08–5.04	2.22–3.88	1.37–4.20	1.69–3.19		
SUV _{avgp}					M = 21.61	0.00
Median	2.75	2.10	2.30	NA		
Interquartile range	2.10–3.30	1.60–2.45	1.95–2.60			

NA, not available; SUV_p, standardized uptake value of pituitary; TSH, thyroid-stimulating hormone.

Fourteen (6.5%, 14/215) healthy screening participants and 98 (45.6%, 98/215) DTC patients had high pituitary uptake (SUV_p ≥ 4.1) on ¹⁸F-FDG PET/CT ($\chi^2 = 102.33$, $P < 0.05$; Table 2). Hypermetabolism of the pituitary was mostly found in hypothyroid patients (86/98) and in 7 (21.2%, 7/33) and 5 (27.8%, 5/18) in euthyroid and subclinical hyperthyroid patients, respectively.

Discussion

With rapid growth of thyroid cancer morbidity, ¹⁸F-FDG PET/CT scans are used more frequently for the assessment of recurrent DTC. ¹⁸F-FDG PET scanning is considered in high-risk DTC patients with negative WBS and positive Tg 131I body scan. A meta-analysis showed that TSH stimulation was carried out under thyroid hormone withdrawal or that recombinant human TSH slightly and significantly improves the diagnostic performance of PET for the detection of Tg-positive and radioiodine-negative metastases of DTC [4]; however, recombinant human TSH is not available in China. Therefore, ¹⁸F-FDG PET was performed under thyroid hormone withdrawal in most DTC patients in our study.

The volume of the pituitary is small and commonly the uptake is thought to manifest a background level on ¹⁸F-FDG imaging under physiological conditions [5]. The widespread use of ¹⁸F-FDG PET has resulted in an increase of incidentally detected pituitary lesions [6–9].

The hypermetabolism of ¹⁸F-FDG in the pituitary was frequently observed in DTC patients with hypothyroidism on ¹⁸F-FDG PET/CT images. The thyroid is an important endocrine organ regulated by the pituitary through the hypothalamus–pituitary–thyroid axis. We hypothesized that hypermetabolism of ¹⁸F-FDG in the pituitary may correlate with serum TSH.

As expected, our study showed a positive correlation between pituitary ¹⁸F-FDG uptake and serum TSH. Similar to a small-sample (15 thyroid cancer) retrospective study [3], there were statistically significant differences in pituitary ¹⁸F-FDG uptake between the low, normal, and high TSH groups ($P < 0.001$). In the present study, pituitary ¹⁸F-FDG uptake in 215 DTC patients was compared with 1:1 paired 215 healthy screening participants. Our results found that the ¹⁸F-FDG metabolism of the pituitary was directly correlated with serum TSH levels. Up to 45.6% (98/215) of the pituitary showed hypermetabolism in DTC patients in the present study. Hypothyroid patients with DTC after thyroidectomy have a higher ¹⁸F-FDG uptake in the pituitary, which also correlated with serum TSH. The reason may be the loss of T4 feedback inhibition resulting in the overproduction of thyrotropin-releasing hormone in the hypothalamus [10,11]. Moreover, T4 affects the receptor (TSH receptor) in the pituitary, which releases more TSH to regulate thyroid function.

Fig. 2

(a, b) Kruskal–Wallis analysis of variance tests showed patients with hypothyroidism had significant high standardized uptake value of pituitary (SUV_p) as compared with patients with euthyroid, subclinical hyperthyroidism and healthy participants. No statistical differences were observed among patients with euthyroid, subclinical hyperthyroidism and healthy participants.

The pituitary gland releases multiple hormones, including certain tissue-targeting growth hormones and PRL as well as pituitary hormones such as TSH, adrenocorticotrophic hormone, FSH, and LH [12]. The available data in terms of FSH and LH were not significantly different among the included groups.

DTC patients after thyroidectomy used L-T₄, an artificial T₄ hormone to replace thyroid function. T₄ is deiodinated into T₃, which is biologically active. We also hypothesized that the L-T₄ replacement may have a different feedback on the thyroid–pituitary axis from the normal physiologic process, although it has not been reported yet to our knowledge. Therefore, the ^{18}F -FDG uptake of the pituitary in DTC patients with euthyroidism and subclinical hyperthyroidism ($N=51$) after L-T₄ replacement was compared with that of healthy participants ($N=215$). However, no significant difference of pituitary ^{18}F -FDG uptake was found in DTC patients who were euthyroid on L-T₄ replacement, which suggests that L-T₄ replacement has the same feedback on the thyroid–pituitary axis as the physiologic thyroid status. However, cases in the two groups were not well

matched in sex and number. The results need to be confirmed by a larger population.

In addition, we compared pituitary ^{18}F -FDG uptake in DTC patients with euthyroid, subclinical hyperthyroidism after L-T₄ replacement and healthy participants. Contrary to the study by Jeong *et al.* [3], no significant difference was found between these groups. The reason may be due to the small number ($N=5$) of patients with subclinical hyperthyroid.

The increased ^{18}F -FDG uptake in physiologic hyperplastic pituitary resulting from hypothyroidism was confirmed by our study. However, incidental uptake of ^{18}F -FDG in the pituitary should be differentiated from pathological conditions such as adenoma or metastases. Using SUV_p of at least 4.1 as the criterion for detecting pathologic ^{18}F -FDG uptake in the pituitary, the incidental focal uptake of the pituitary was reported at 0.8% (107/ 13,145) [2]. The incidental uptake of ^{18}F -FDG in the pituitary was higher in our study, which was seen in 14/215 healthy participants (6.5%) and in 12/51 (23.5%) in DTC euthyroid and subclinical hyperthyroid patients.

Contrary to the focal uptake, all the participants in the study have diffuse uptake of ^{18}F -FDG in the pituitary and without significant pituitary abnormalities on brain CT. Moreover, the available clinical and laboratory data and the medical history showed no definitive pituitary disease in those participants and in DTC patients. Therefore, TSH values should be measured in patients with incidental pituitary uptake during ^{18}F -FDG PET/CT (i.e. it occurs in about 1% of the general population) [13].

Our study has limitations. First, this was a retrospective study and the number of patients with hyperthyroidism and in euthyroid status was small ($n=51$), compared with the number of hypothyroid patients ($n=164$). A case-selective bias may exist. Second, we tried to exclude those with known history of any endocrine disease, but data with regard to other hormonal profiles in the patients and the other hormones, which may affect the uptake in the pituitary gland, were not available.

Conclusion

Our study established a positive correlation between pituitary ^{18}F -FDG uptake and serum TSH. TSH values should be measured in patients with incidental pituitary uptake during ^{18}F -FDG PET/CT. L-T4 replacement for DTC patients may well have the same feedback on the thyroid-pituitary axis as the physiologic thyroid status. The diffuse ^{18}F -FDG uptake with normal CT or MRI appearance of the pituitary in patients with DTC indicates physiologic uptake.

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Conflicts of interest

There are no conflicts of interest.

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