Pituitary 18F-FDG uptake correlates with serum TSH levels in subjects with diffuse thyroid 18F-FDG uptake

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Directed by Professor Mijin Yun

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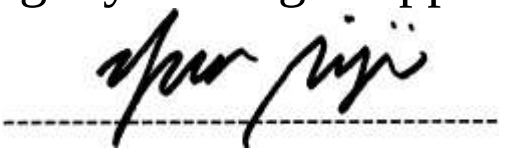
This certifies that the Master's Thesis of
Yong Hyu Jeong is approved.



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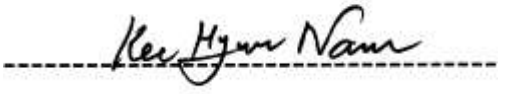

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ABSTRACT

Pituitary 18F-FDG uptake correlates with serum TSH levels in subjects with diffuse thyroid 18F-FDG uptake

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Purpose: The aim of this study was to evaluate the relationship among FDG uptake in the pituitary gland (FDGp), FDG uptake in the thyroid gland (FDGt), and serum thyroid-stimulating hormone (TSH) levels in patients with diffuse FDGt incidentally noted on positron emission tomography/computed tomography (PET/CT) scan.
Materials and Methods: This retrospective study was approved by our institutional review board. We retrospectively reviewed FDG PET/CT scans of 2,945 subjects who underwent health screening. Of these, 44 subjects had diffuse FDGt and available thyroid function tests. FDGt and FDGp were correlated with serum TSH. FDGp in 44 paired control subjects without FDGt and 15 thyroid cancer patients undergoing thyroid hormone withdrawal were additionally measured, and compared with FDGp in the 44 subjects with FDGt divided into three groups according to serum TSH levels.
Results: In the 44 subjects, there was a statistically significant ($p=0.034$) but weak correlation($r=0.320$) between FDGt and TSH. On the other hand, a strong correlation was found between FDGp and TSH ($p<0.001$, $r=0.618$). As well, there were statistically significant differences in FDGp between the low, normal, and high TSH groups ($p<0.001$). FDGp in the paired control subjects was not different from that in the normal TSH group ($p=0.384$), and FDGp in the TSH-stimulated thyroid cancer

patients was not different from that in the high TSH group (p=0.463).

Conclusion: In this study, we found a strong positive correlation between the degree of pituitary FDG uptake and serum TSH. It appears that FDG uptake in the pituitary gland holds an important clue to the functional status of the thyroid in subjects with diffuse thyroid FDG uptake.

Key words : diffuse uptake, ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (^{18}F-FDG PET), pituitary gland, thyroid gland

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I. INTRODUCTION

With the widespread use of 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) for evaluation of oncologic patients, various physiological and benign pathologic conditions associated with increased FDG uptake have been recognized[1-4]. Among them, one of the common findings is focal or diffuse FDG uptake in the thyroid gland (FDGt). Focal FDGt, if incidentally detected, raises the possibility of malignancy[5,6] while it increases the risk of aggressiveness if associated with proven differentiated thyroid cancer[7]. On the other hand, diffuse FDGt has often been found to be related to benign pathologies, such as chronic Hashimoto's thyroiditis, Graves' disease, or infrequently multinodular goiter[8-10]. However, one third of diffuse FDGt was considered as a normal variant since the patients had a normal thyroid on ultrasound examination with euthyroidism and negative autoantibodies[10]. It is currently unknown whether these patients without clinical or laboratory abnormalities will eventually develop hypothyroidism.

Although the exact mechanism for diffuse FDGt is not clear yet, it has mostly been attributed to inflammatory cells, especially lymphocytic infiltration, glandular cell proliferation, or active fibrotic changes in the thyroid[10-12]. Therefore, investigators

have attempted to predict the functional status of the thyroid gland by correlating standardized uptake values (SUVs) of diffuse FDGt with the level of serum thyroid-stimulating hormone (TSH). When compared to controls without diffuse thyroid uptake, patients with diffuse FDGt have increased serum TSH[12]. However, maximum SUV (SUV_{max}) of FDGt was not predictive of serum TSH levels among patients with diffusely increased FDGt[11].

Recently, we noticed various degrees of FDG uptake in the pituitary gland (FDGp) on PET/CT in patients with diffuse FDGt. Since the secretion of TSH from the pituitary gland is tightly regulated by the circulating thyroid hormone level, we hypothesized that FDGp is related to the functional status of thyroid gland and/or TSH. We assessed the relationship among FDGp, FDGt, and TSH.

II. MATERIALS AND METHODS

1. Patient Population

This retrospective study was approved by our institutional review board. Two imaging specialists reviewed the FDG PET/CT scans performed on 2,945 subjects for health screening from May 2006 to December 2012 in our medical center. Diffuse FDGt defined as diffuse uptake in the bilateral thyroid lobes that was greater than adjacent background uptake was identified in 180 subjects. Of these, 44 (9 men, 35 women; age range, 41–86 years; mean age, 57.2 years) satisfied all of the following inclusion criteria:

1. Thyroid function test was performed within 1 month of PET imaging
2. No prior history of thyroid disease
3. No known history of other endocrine problems
4. No prior history of brain surgery
5. Fully-covered field of view to afford complete evaluation of pituitary gland

In these 44 subjects, FDGt and FDGp were correlated with serum TSH levels. Additionally, we enrolled 44 paired age-and-sex-matched subjects without FDGt as a negative control group and 15 patients with metastatic thyroid cancer (4 men, 11

women; age range, 37–81 years; mean age, 56.5 years) who underwent PET/CT following 4 weeks of thyroid hormone withdrawal resulting in TSH stimulation as a positive control group.

2. Imaging Procedures

All subjects fasted for at least 6 h, and blood glucose concentration was confirmed to be less than 140 mg/dL before the injection of FDG. Approximately 5.5 MBq of FDG per kg of body weight were administered intravenously. Imaging was performed using a PET/CT scanner (DSTe; GE Healthcare, Milwaukee, WI, USA) with an axial field of view of 15.7 cm and a spatial resolution of 4.0 mm in full width at half maximum at 1 cm from the center. Sixty minutes after the FDG injection, a low-dose CT scan was obtained for attenuation correction with an 8-slice helical CT unit (Light Speed; GE Healthcare) using the following parameters: 140 kVp, 30 mA, 0.8-s rotation time, 3.3-mm scan reconstruction, 50-cm field of view, and 512 × 512 matrix. A PET imaging was followed covering the skull base to the mid-thigh in a three-dimensional mode at 3 minutes per bed position. PET data were reconstructed iteratively using an ordered subset expectation maximization algorithm with the low-dose CT datasets for attenuation correction.

3. Image and Data Analysis

For semi-quantitative analysis of FDGt in the 44 subjects and 44 paired-control subjects, a total of 6 regions of interest (ROIs) were drawn over the thyroid. Three ROIs were placed in the upper, mid, and lower poles in each lobe, respectively. SUV_{max} of each region was recorded and the average of the SUV_{max} from the 6 ROIs was calculated for each patient. For the measurement of SUV_{max} of FDGp in the 88 subjects and 15 patients with thyroid cancer, a ROI was drawn over the pituitary fossa, which was determined on co-registered transaxial CT images.

Thyroid function tests were performed within 1 month of PET/CT (mean interval, 0.6 days; range, 0–25 days) in the all subjects and control groups. Serum TSH and free thyroxine (T4) were measured using a chemiluminescent microparticle

immunoassay (CHIMA; ARCHITECT® System, Abbott Laboratories Diagnostic Division, Abbott Park, IL, USA). Normal reference ranges are 0.35–5.50 μIU/mL for TSH and 0.70–1.48 ng/dL for free T4. The 44 subjects were divided into three groups: high TSH group (>5.5 μIU/mL), normal TSH group (0.35–5.5 μIU/mL), and low TSH group (<0.35 μIU/mL).

The thyroid SUV_{max} and the pituitary SUV_{max} in the 44 subjects with diffuse FDGt were directly correlated with serum TSH levels. Additionally, the SUV_{max} of the pituitary gland in the negative or positive control group was compared with that of the pituitary gland in the low, normal, and high TSH groups.

4. Statistical Analysis

A correlation between pituitary or thyroid SUV_{max} and serum TSH levels in the 44 subjects was assessed using Spearman's rank correlation analysis.

Kruskal–Wallis test and Dunn's post-hoc analysis were performed to determine the differences in SUV_{max} among the high, normal, and low TSH groups. The pituitary SUV_{max} in the normal paired-subjects and TSH-stimulated patients groups were compared with that in each of the high TSH, normal TSH, and low TSH groups using Mann–Whitney *U*-test. All statistical computations were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) and a p-value < 0.05 was considered statistically significant.

III. RESULTS

In the 44 subjects with diffuse FDGt who underwent PET/CT for health screening, the thyroid SUV_{max} ranged from 1.80 to 9.00 (median, 3.15), the pituitary SUV_{max} ranged from 1.70 to 4.50 (median, 2.80), and the serum TSH ranged from 0.03 to 159.63 μIU/mL (median, 2.86 μIU/mL). There was a statistically significant but only marginal correlation (Fig. 1a; $p = 0.03$, $r = 0.320$) between the thyroid SUV_{max} and TSH level. On the other hand, a strong correlation was found between FDGp and TSH (Fig. 1b; $p < 0.001$, $r = 0.618$).

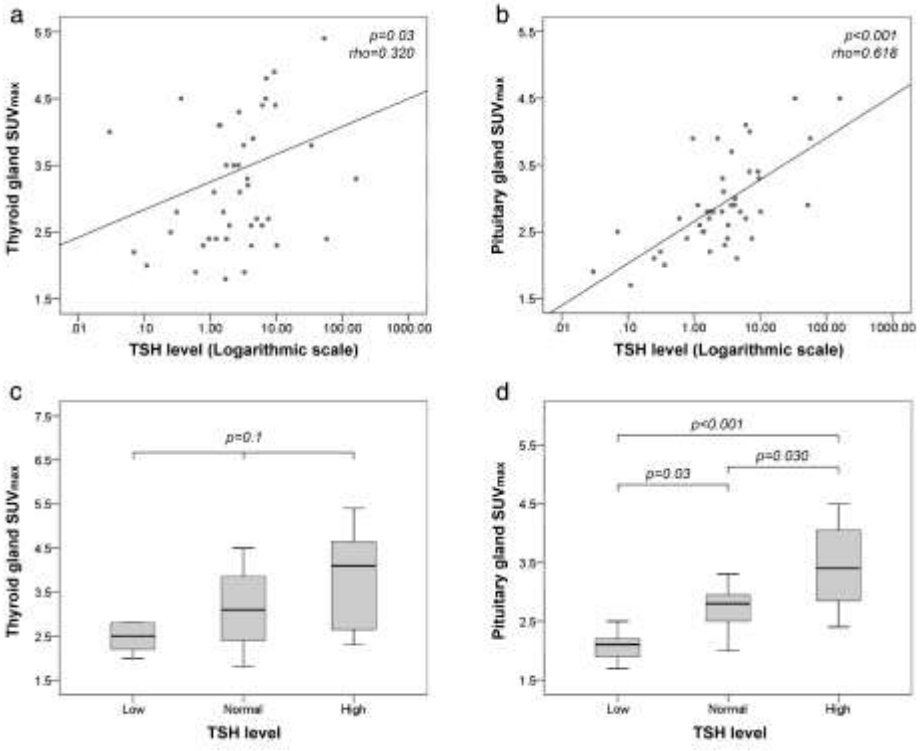

Fig. 1 SUV_{max} of thyroid gland (**a**, **c**) and pituitary gland (**b**, **d**) on PET/CT. Side by side box plots of SUV_{max} by each groups and Spearman's rank analysis. Statistically significant differences were found in SUV_{max} of pituitary gland between groups, but not in SUV_{max} of thyroid gland.

When the 44 subjects were divided into three groups according to the reference TSH ranges, there were 12 subjects (27%) in the high TSH group, 27 subjects (61%) in the normal TSH group, and 5 subjects (12%) in the low TSH group. The free T4 level in the high TSH group was 1.01 ± 0.39 μIU/mL (median ± interquartile range), 1.10 ± 0.15 μIU/mL in the normal TSH group, and 1.23 ± 0.88 μIU/mL in the low TSH group. Free T4 levels between the three groups were significantly different ($p = 0.01$). The clinical characteristics and results of thyroid function test in those three groups are summarized in Table 1.

Table 1 Characteristics of subjects according to serum TSH concentration

	Serum TSH concentration (μIU/mL)			p
	<0.35	0.35–5.5	>5.5	
Patients (no.)	5	27	12	
Sex (no.)				0.5
Male	1	7	1	
Female	4	20	11	
Age (years)	55.4 ± 6.2	58.5 ± 10.7	54.9 ± 7.8	0.5
TSH (μIU/mL)				
Median	0.11	2.26	9.45	
Interquartile range	0.07–0.25	1.39–3.46	6.96–38.43	
Free thyroxine (ng/dL)				0.001
Median	1.23	1.10	1.01	
Interquartile range	1.19–1.80	0.99–1.13	0.76–1.07	

Data are expressed as mean ± SD, median and interquartile range, or the number of patients in each group.

The thyroid SUV_{max} was 2.50 ± 1.30 in the low TSH group, 3.10 ± 1.50 in the normal TSH group, and 4.10 ± 2.10 in the high TSH group. Despite the trend, there was no statistically significant difference in SUV_{max} of the thyroid gland between these groups (Table 2 and Fig. 1c; p = 0.1 by Kruskall–Wallis test). In contrast, the pituitary SUV_{max} was 2.10 ± 0.55 in the low TSH group, 2.80 ± 0.50 in the normal TSH group, and 3.40 ± 1.25 in the high TSH group. The median values of SUV_{max} of the pituitary gland were significantly different among the three groups (Table 2; p < 0.001). Dunn's post-hoc test also showed statistically significant differences in SUV_{max} between low and normal TSH groups, low and high TSH groups, and normal and high TSH groups (Fig. 1d; p = 0.03, <0.001, and 0.030, respectively). All 44 paired negative control subjects had normal TSH levels (median, 1.53;

interquartile range, 1.35) and a median FDGp of 2.70 ± 0.33. There was no difference in FDGp between the negative control group and the normal TSH group ($p = 0.3$), whereas it was significantly different from the low and high TSH groups ($p < 0.001$, both; Fig. 2 & 3). In the 15 positive control patients, TSH levels were >30 μIU/mL (median, 94.64 μIU/mL; interquartile range, 39.25 μIU/mL) for each patient, with a median FDGp of 3.20 ± 0.60. There was no difference in FDGp between the positive control group and the high TSH level group ($p = 0.5$), whereas it was significantly higher than that in the low and normal TSH groups ($p = 0.001$ and 0.007, respectively; Fig. 2).

Table 2 Comparison of SUV_{max} in thyroid gland and pituitary gland according to serum TSH concentration

	Serum TSH concentration (μIU/mL)			p
	<0.35	0.35–5.5	>5.5	
Pituitary SUV_{max}	2.10 ± 0.55	2.80 ± 0.50	3.40 ± 1.25	<0.001
Thyroid SUV_{max}	2.50 ± 1.30	3.10 ± 1.50	4.10 ± 2.10	0.1

Data are expressed as median ± interquartile range.

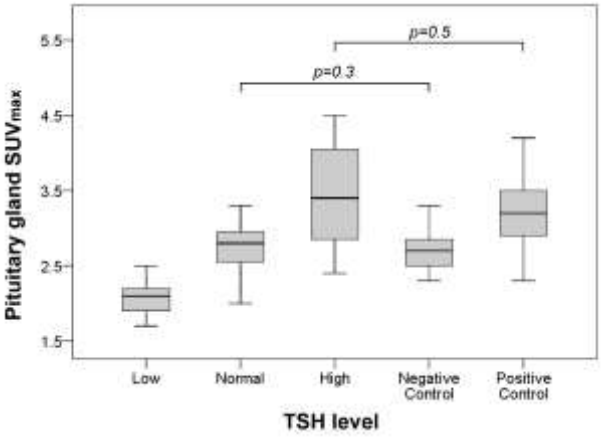

Fig. 2 SUV_{max} of pituitary glands in paired normal thyroid patients and TSH-stimulated patients. Side by side box plots of SUV_{max} by each groups. SUV_{max} of pituitary gland in the paired normal thyroid groups was not different from that in the normal TSH group, and FDGp in the TSH-stimulated thyroid cancer patients was not different from that in the high TSH group.

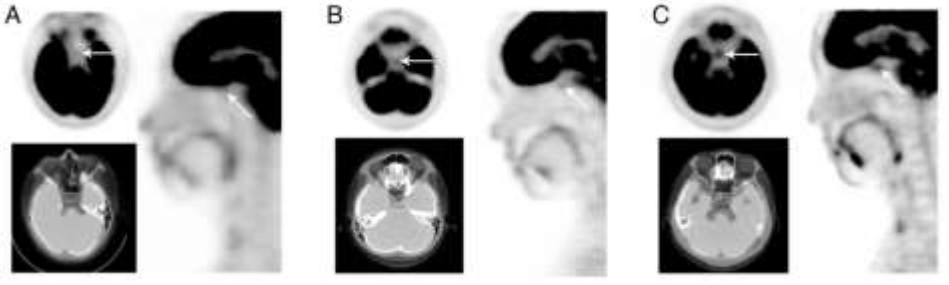

Fig. 3 FDG PET images showing various levels of FDG uptake in the pituitary fossa in subjects with different serum TSH levels. (**A**) Scanty pituitary FDG uptake in a subject with low TSH (0.11 μIU/mL); (**B**) moderate pituitary FDG uptake in a subject with normal TSH (3.27 μIU/mL); and (**C**) intense pituitary FDG uptake in a subject with high TSH (9.28 μIU/mL).

IV.DISCUSSION

Thyroid gland preferentially uses free fatty acids for energy metabolism and thus generally does not show significant FDG uptake on PET[8, 10]. However, diffuse FDGt has been seen in 2.9–3.5% of the study population, and even up to 20% in patients with breast cancer, suggesting a correlation between thyroid disease and the risk of breast cancer[10-13]. In the present study, we found diffuse FDGt in 6.1% of the subjects undergoing health screening examinations.

In patients whose FDGt was considered to be a normal variant, FDGt was less than (63.6%) or equal to (22.7%) that of the liver[10]. The mechanism of increased FDGt as a normal variant is not known yet. On the contrary, in most (76.9%) patients with chronic thyroiditis, FDGt was higher than or equal to the liver uptake. Although diffuse intense uptake seemed to have some correlation with hypothyroidism compared to normal control, no significant correlation was found between SUV_{max} of the thyroid and the degree of hypothyroidism measured by serum TSH[11]. In our study, a marginal correlation was found between the SUV_{max} of the thyroid and serum TSH. The correlation was mildly significant statistically but probably not significant enough to be clinically useful. Indeed, there was no significant difference in FDGt in the three groups divided by the reference TSH ranges.

There are known factors affecting FDGt. In chronic thyroiditis, the severity of inflammation including lymphocytic infiltration is considered the main reason for the increased FDGt[14]. There can be a time lag from the diagnosis of chronic thyroiditis with increased FDGt until the sufficient loss of thyroid cells to cause clinically overt hypothyroidism[13]. In addition, small, atrophic thyroid as a result of longstanding destruction by chronic inflammation may show low uptake but increased serum TSH levels. The mixture of different stages of disease pathology might be one of the reasons that FDGt is not consistently predictive of serum TSH levels. To make the matter more complicated, FDGt may also be seen in patients with the opposite disease entities associated with low serum TSH levels, e.g., Graves' disease or multinodular goiter. All of these probably explain why there is no significant correlation or very

weak correlation, if present, between diffuse FDGt and serum TSH.

While looking for a potential predictor of thyroid function in subjects with diffuse FDGt, we found increased FDGp in many of them. It was conceivable that pituitary hyperplasia secondary to hypothyroidism could occur due to the loss of T4 feedback inhibition resulting in the over-production of thyrotropin-releasing hormone (TRH)[15-17]. Indeed, there was a case report showing secondary pituitary hyperplasia with increased FDG uptake by adrenal cortical insufficiency[18]. Accordingly, we assessed whether FDGp could be a predictor of the functional status of the thyroid gland. The pituitary SUV_{max} was indeed different between each of the three groups with low, normal, and high TSH levels. More significantly, there was a strong positive correlation between the continuous SUV_{max} values of the pituitary gland and serum TSH levels. The finding supports our hypothesis that FDGp is related to the functional status of thyroid gland and/or TSH. FDGp may be an imaging representative of physiologic regulation status of hypothalamus–pituitary–thyroid axis in subjects with diffuse FDGt and no other known endocrine disorders. This was further supported by FDGp in the two control groups. In the negative control group, FDGp was no different from that of the normal TSH group, whereas it was significantly different from that in the low and high TSH groups. FDGp in the positive control group was as high as FDGp in the high TSH group, but significantly higher than FDGp in the low and normal TSH groups.

Our study has some limitations. Although we tried to exclude those with known history of any endocrine disease, we had limited data regarding other hormonal profiles in the subjects. Therefore, we did not evaluate the effect of hormones other than thyroid hormones in FDG uptake in the pituitary gland.

V. CONCLUSION

While diffuse thyroid uptake of FDG was marginally correlated with serum TSH levels, we found a strong positive correlation between the degrees of FDG uptake in the pituitary gland and serum TSH levels. FDG uptake in the pituitary gland appears

to hold an important clue to the functional status of the thyroid in subjects with diffuse thyroid FDG uptake. Those subjects with abnormal pituitary FDG uptake could be offered a further evaluation of thyroid function test.

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Clin Nucl Med 2011;36:731-2.

ABSTRACT (IN KOREAN)

양전자방출단층촬영술 시행 시 갑상샘의 미만성 FDG 섭취를 보이는 환자에서 우연적 뇌하수체의 FDG 섭취 정도와 혈중 갑상선 자극 호르몬 농도의 관계 파악 및 그에 따른 임상적 유용성

<지도교수 윤미진>

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정용휴

연구목적: 양전자방출단층촬영 시행 시에 우연히 발견된 미만성 갑상선 섭취 환자에서 뇌하수체의 과증식으로 인한 FDG 섭취 증가 정도와 혈중 갑상선 자극 호르몬 농도와의 연관성을 알아보고 이에 대한 임상적 의미를 알아 보고자 하였다.

대상 및 방법: 2006년 5월부터 2012년 12월까지 신촌세브란스 병원에서 건강검진을 목적으로 양전자방출단층촬영술을 시행한 사람 중 미만 성 갑상선 섭취 증가를 보이는 44명을 대상으로 갑상선 및 뇌하수체의 FDG 섭취와 갑상선 자극 호르몬 농도를 비교하였으며, 검증을 위해 갑상선 섭취증가를 보이지 않는 44명의 음성 대조군과 방사성 옥소 치료를 위해 인위적으로 갑상선 자극 호르몬 수치를 높인 15명의 양성 대조군을 설정하였다.

결과: 44명의 대상자에서 갑상선의 FDG 섭취와 갑상선 자극 호르몬 농도는 약한 상관관계($p=0.034$, $r=0.320$)를 보인 것에 반해 뇌하수체의

FDG 섭취와 갑상선 자극 호르몬 농도는 더 강한 상관관계를 보였다 ($p<0.001$, $r=0.618$). 또한, 갑상선 자극 호르몬의 농도에 따라 갑상선 기능 저하, 정상, 갑상선 기능 항진 세 군으로 나눴을 때 각 군의 뇌하수체의 FDG 섭취는 유의한 차이를 보였다($p<0.001$). 음성 대조군 44명의 뇌하수체의 FDG 섭취는 정상 갑상선 기능 군과($p=0.384$), 양성 대조군 15명의 뇌하수체의 FDG 섭취는 갑상선 기능 항진 군과($p=0.463$) 차이가 없어 본 결과를 뒷받침 해주었다.

결론: 미만 성 갑상선 섭취를 보이는 환자에서 뇌하수체의 FDG 섭취는 갑상선 자극 호르몬 농도와 밀접한 관계가 있으며, 이는 뇌하수체의 FDG 섭취를 통해 환자의 갑상선 기능을 평가할 수 있음을 나타낸다.

핵심되는 말 : 미만성 섭취, 양전자방출단층촬영술, 갑상선, 뇌하수체