

Clinical Significance of Diffusely Increased ^{18}F -FDG Uptake in the Thyroid Gland

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Our purpose was to determine the clinical significance of diffusely increased ^{18}F -FDG uptake in the thyroid gland as an incidental finding on PET/CT. **Methods:** All patients who were found to have diffuse thyroid uptake on ^{18}F -FDG PET/CT in our institution between November 2004 and June 2006 were investigated and compared with an age- and sex-matched control group. The ^{18}F -FDG uptake in the thyroid was semiquantified using maximum standardized uptake value and correlated to the available serum thyroid-stimulating hormone (TSH) and thyroid peroxidase (TPO) antibody levels using regression analysis. **Results:** Of the 4,732 patients, 138 (2.9%) had diffuse thyroid uptake. Clinical information was available for 133 of the 138 patients. Sixty-three (47.4%) had a prior diagnosis of hypothyroidism or autoimmune thyroiditis, of whom 56 were receiving thyroxine therapy. In the control group, consisting of 133 patients with no thyroid uptake, there were 13 (9.8%) with a prior diagnosis of hypothyroidism, 11 of whom were receiving thyroxine therapy. In the study group, 38 (28.6%) of 133 patients did not undergo any further investigation for thyroid disease, whereas 32 (24.1%) of 133 patients were examined for thyroid disease after PET. Nineteen were found with autoimmune thyroiditis or hypothyroidism, and replacement therapy was initiated in 12. No significant correlation was found between maximum standardized uptake value and TSH ($P = 0.09$) or TPO antibody ($P = 0.68$) levels. **Conclusion:** The incidental finding of increased ^{18}F -FDG uptake in the thyroid gland is associated with chronic lymphocytic (Hashimoto's) thyroiditis and does not seem to be affected by thyroid hormone therapy. SUV correlated neither with the degree of hypothyroidism nor with the titer of TPO antibodies.

Key Words: endocrinology; oncology; PET/CT; ^{18}F -FDG; diffuse thyroid uptake; thyroid incidentaloma

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PET is commonly used in the field of oncology as a staging and diagnostic tool and plays an essential role in

response assessment and prognostic evaluation of patients. With the recent widespread use of ^{18}F -FDG PET in clinical practice, the accurate interpretation of unexpected findings remains a challenge, because the impact of an incidental finding on the clinical management and overall health of the patient can be significant.

^{18}F -FDG accumulation in normal thyroid tissue is usually low to absent (1,2). Normally, the thyroid is not visualized on 3-dimensional maximum-intensity-projection images (Fig. 1). This observation is in keeping with the suggestion that free fatty acids are the preferred substrates for the thyroid gland (3)—a suggestion that is supported by studies on animal models (4) and cell cultures (5).

In ^{18}F -FDG PET, unexpected findings in the thyroid gland fall into 2 distinct categories: focal or diffusely increased ^{18}F -FDG uptake. Focal ^{18}F -FDG uptake in the thyroid occurs in 1%–2% of non-thyroid cancer patients referred for PET and is reported to be associated with malignancy—most commonly, papillary thyroid cancer—in 27%–50% of those cases (6,9,10). Although no uniform agreement exists, most authors have found no definite value in quantifying ^{18}F -FDG uptake to discriminate between a malignant and benign cause.

Diffusely increased ^{18}F -FDG uptake in the thyroid (Fig. 2) has been reported in 0.6%–3.3% of the cases. Although some authors (11,12) stated that diffusely increased ^{18}F -FDG uptake in the thyroid may be a normal variant, several other studies (7,8,13) suggested that such uptake is primarily associated with autoimmune thyroiditis or hypothyroidism.

We undertook this study to investigate this finding in a wider patient population that includes patients already receiving thyroid hormone therapies for benign thyroid disease. The goal of this study was to interpret the significance of diffuse ^{18}F -FDG uptake in the thyroid relative to its implications for recommendations regarding the further evaluation of patients having this finding.

MATERIALS AND METHODS

The study was approved by the Mayo Clinic Institutional Review Board. All patients with diffuse high ^{18}F -FDG uptake in the thyroid gland from November 2004 through June 2006 were

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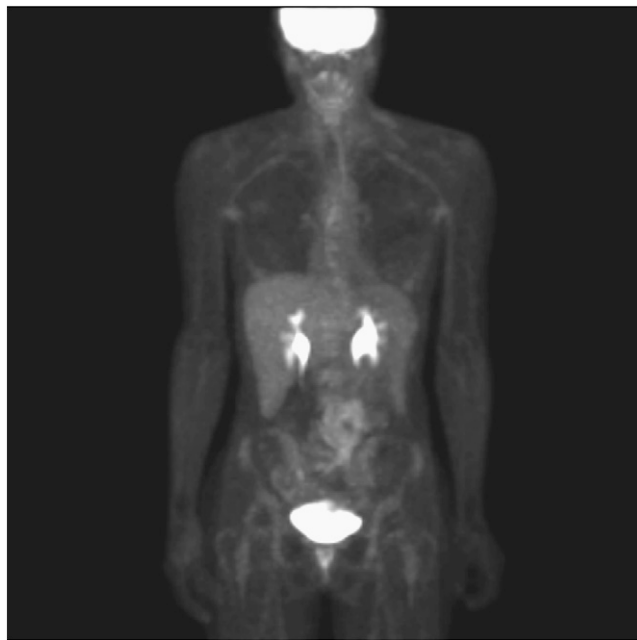


FIGURE 1. Normal, low ^{18}F -FDG uptake in thyroid of 37-y-old woman referred for restaging of previously treated tongue cancer. Thyroid is not normally visible on 3-dimensional maximum-intensity-projection images.

studied. Patients with focal thyroid uptake and those having a history of thyroid cancer were excluded.

Patients were prospectively enrolled at the time each PET examination was done during the enrollment period. Patients who had more than one examination during the study period were counted only once. Distinctly increased ^{18}F -FDG uptake in the thyroid, resulting in visualization of both thyroid lobes on the 3-dimensional maximum-intensity-projection images, was used as the sole criterion for inclusion. Only the first PET examination demonstrating this finding was studied for each patient. The intensity level was set manually, with liver being set at a light-gray level. Thyroid uptake was always then confirmed on axial PET/CT fused images. Inclusion was decided by a consensus of 2 experienced PET/CT readers.

Uptake in the thyroid was measured in a semiquantitative manner as maximum standardized uptake value (SUV_{max}) corrected for body weight. The SUV is the decay-corrected ratio between the measured uptake in a region of interest and the expected uptake if ^{18}F -FDG were distributed evenly throughout the body. A circular region of interest with a fixed diameter of 1.5 cm was placed over the region of highest intensity in each lobe of the thyroid, and uptake was automatically quantified as SUV_{max} . The higher of the 2 values between the thyroid lobes was used in the statistics.

Patients included in the study were followed for any subsequent clinical or laboratory evaluation of thyroid status. Clinical information was also reviewed retrospectively to determine whether there had been a previous diagnosis of thyroid disease; ultrasound studies of the thyroid or neck; measurements of serum thyroid-stimulating hormone (TSH), thyroid hormones, antithyroglobulin, anti-TPO, or anti-TSH-receptor antibody levels; or use of thyroid hormone medication. This review was done through a detailed study of the medical records.

A control group of patients with no thyroid uptake was also studied. This group was included to determine the proportion of patients already carrying the diagnosis of (nonmalignant) thyroid disease when there was no thyroid uptake. The control group consisted of the same number of patients as those found to have diffuse thyroid uptake. The 2 groups were matched for age and sex. Similarly, the charts of these patients were studied for evidence of any prior benign thyroid disease.

Finally, from those patients with diffuse thyroid uptake and no prior history of thyroid disease, we selected only those having serum TSH measured within 8 wk after the PET study. The relationship between the levels of serum TSH and the SUV_{max} of their thyroid was studied using bivariate analysis. Similarly, correlation analysis was performed between SUV_{max} of the thyroid and available TPO antibody levels measured within 6 wk of the PET study.

PET/CT

All PET scans were performed on a combined PET/CT system (Discovery LS, DST, or DRX; GE Healthcare). The ^{18}F -fluoride was produced by an on-site cyclotron (Trace; GE Healthcare). ^{18}F -FDG was synthesized by an automated Hamacher method and tested for sterility, pyrogenicity, and radiochemical purity on each production run. All patients had been fasting for at least 6 h before injection of 555–740 MBq (15–20 mCi) of ^{18}F -FDG. Imaging was started 1–1.5 h after injection. Patients were scanned from at least the base of the skull through the pelvis, applying a 2-dimensional mode with a 5-min acquisition per bed position. The studies were reconstructed using a default vendor-implemented iterative reconstruction algorithm.

Laboratory Evaluation

All thyroid function testing was performed at Mayo Medical Laboratories. Serum TSH was measured using a 2-site immunoenzymatic sandwich assay (Unicel DXI 800 instrumentation; Beckman Coulter). Serum free thyroxine was measured with an automated, competitive chemiluminescent immunoassay on an Advia Centaur instrument (Bayer). Total thyroxine was measured with a competitive-binding immunoenzymatic method (Access Total T4 assay; Beckman Coulter Ireland Inc.). TSH receptor autoantibody quantitation was performed using a third-generation 2-step immunoenzymatic sandwich assay and DXI 800 instrumentation (Beckman Coulter). Serum thyroglobulin antibody screening used a sequential 2-step immunoenzymatic sandwich assay (Access Thyroglobulin Assay; Beckman Coulter Inc.). Serum thyroperoxidase (TPO) antibody screen was performed using an automated, competitive, chemiluminescent immunoassay (Bayer Advia Centaur Assay).

Ultrasound

Ultrasound examinations were performed at the Mayo Clinic Department of Radiology using a commercially available ultrasound machine (Acuson Sequoia; Siemens) with multifrequency transducers (15L8 and 15L8W) operating at 10 MHz. The indication for ultrasound was a palpable abnormality in the thyroid, and ultrasound was ordered at the discretion of the clinician. Interpretation was performed by radiologists experienced in thyroid ultrasound. Ultrasound-guided fine-needle aspiration biopsy was performed by a radiologist or endocrinologist experienced in thyroid fine-needle aspiration biopsy techniques. Interpretation was performed by a cytopathologist experienced in thyroid cytology interpretation.

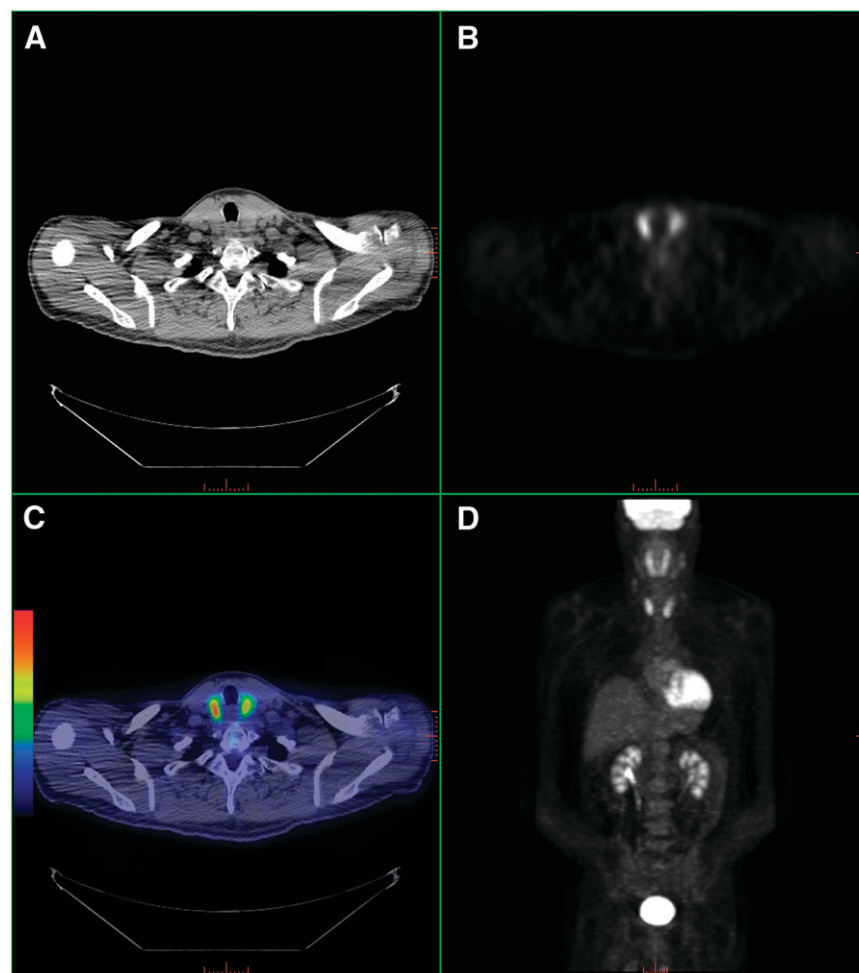


FIGURE 2. Diffusely increased ^{18}F -FDG uptake in thyroid of 47-y-old man referred for evaluation of neck lymphadenopathy. Patient was taking thyroxine replacement therapy for hypothyroidism. On ultrasound examination, thyroid gland was prominent and heterogeneous. Fine-needle aspiration biopsy of thyroid revealed chronic thyroiditis. Serum TSH was 0.2 mIU/L (reference range, 0.3–5.0 mIU/L), free thyroxine was 1.6 ng/dL (reference range, 0.8–1.8 ng/dL), and TPO antibodies were elevated at 6,160 IU/mL (reference range, <40 IU/mL), suggesting diagnosis of lymphocytic thyroiditis. Shown are transaxial CT image (A), transaxial PET image (B), transaxial fused PET/CT image (C), and 3-dimensional maximum-intensity-projection image (D).

RESULTS

Between November 2004 and June 2006, 4,732 patients without thyroid cancer underwent ^{18}F FDG PET of the body. One hundred thirty-eight (2.9%) were found to have diffusely increased ^{18}F -FDG uptake in the thyroid. Ninety-one were female and 47 male, and their mean age was 58.8 y.

Four of these patients were denied access to their data for research purposes, and 1 patient received no care other than the PET scan at our institution. Therefore, 133 patients with available data were included in the study. In most patients, the indication for the PET study was oncology imaging. The finding of diffusely increased thyroid uptake was reported on the PET scan interpretation as “suggestive of thyroiditis.”

Findings are demonstrated in Figure 3. Sixty-three patients (47.4%) carried the clinical diagnosis of hypothyroidism or autoimmune thyroiditis before undergoing the PET scan, and 56 of those patients were already receiving replacement therapy with thyroxine. Importantly, in 26 of 56 patients already receiving thyroxine replacement therapy at the time of the PET examination, the finding of diffuse increased ^{18}F -FDG uptake prompted repeated determination of TSH levels; in 7 of those, TSH was found to be above 5 mIU/L. Two of the patients having prior thyroid

disease had a history of Graves’ disease. One was hyperthyroid on propylthiouracil therapy, and the other euthyroid at the time the PET study was performed. The SUVs in those patients were low, at 3.1 and 3, respectively.

In 4 patients with a prior history of thyroid disease, ultrasound with fine-needle aspiration biopsy performed after the PET scan revealed cytologic features consistent with chronic thyroiditis. All 4 patients were already receiving thyroxine replacement therapy at the time of the PET study. The SUV_{smax} were 6.5, 8.4, 11.2, and 16.8. Ultrasound and fine-needle aspiration biopsy results from those patients are shown in Table 1.

Thirty-eight (28.6%) of the 133 study patients did not have any further work-up for thyroid disease, usually because of the terminal nature of their primary disease.

Thirty-two (24.1%) of the 133 study patients were examined for thyroid disease after PET. Nineteen patients (14.3%) were found to have either subclinical or overt hypothyroidism or autoimmune thyroiditis. In this group, 14 had elevated TSH values (TSH > 5 mIU/L), 6 of whom had overt hypothyroidism (serum free thyroxine < 0.8 ng/dL). Eleven patients had elevated serum TPO antibody levels (>40 IU/mL), and 9 had ultrasound findings suggestive of chronic

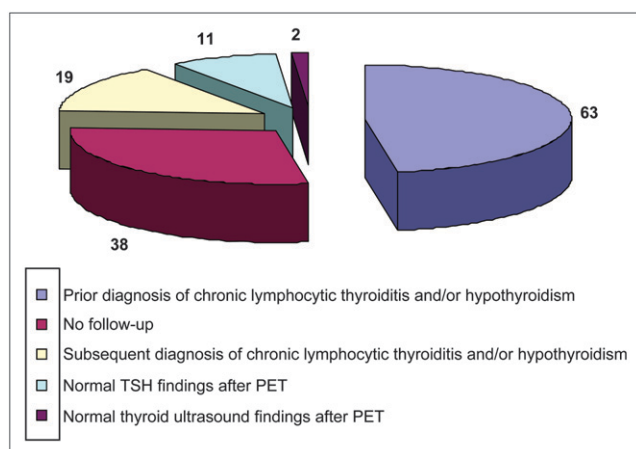


FIGURE 3. Thyroid-related findings in 133 patients with diffuse thyroid ^{18}F -FDG uptake.

autoimmune thyroiditis (Table 2). On the basis of these results, thyroxine replacement therapy was instituted in 12 of 19 patients. Finally, in 13 patients (9.8%), either TSH was normal (11 patients) or ultrasound of the thyroid was negative (2 patients); thyroid autoantibodies were not measured in these patients.

Overall, of the 70 patients with no prior history of thyroid disease, 29 had serum TSH measured and 12 had serum TPO antibodies determined. We found that 14 (48.3%) of the 29 had elevated serum TSH levels (above 5 mIU/L) and 11 (91.7%) of 12 were positive for elevated TPO antibodies.

In the control group of 133 patients without thyroid uptake, only 13 (9.8%) had a prior history of hypothyroidism; 11 of those were receiving thyroxine replacement therapy. This percentage is significantly lower than the corresponding percentage (47.4%) in the group having diffuse increased thyroid uptake ($P < 0.0001$). Interestingly, no patient in the control group carried a definite diagnosis of chronic autoimmune thyroiditis before undergoing PET, whereas 1 had a prior diagnosis of Graves' disease treated with radioactive iodine.

Twenty-one of the patients with diffuse thyroid uptake and no prior history of thyroid disease had serum TSH

levels determined within 8 wk after the PET study. For those 21 patients, serum TSH values correlated with the SUV_{max} of the thyroid. The mean SUV_{max} for this group was 8.01 (range, 3.8–14.3), and the mean serum TSH value was 24.83 mIU/L (range, 0.2–159 mIU/L). No significant correlation ($P = 0.089$) was found between TSH levels and ^{18}F -FDG uptake in the thyroid (Fig. 4).

Serum TPO antibody levels within 6 wk after PET/CT were available in 19 patients. Similarly, serum TPO antibody levels correlated with ^{18}F -FDG uptake in the thyroid. The mean SUV_{max} was 7.69 (range, 4.3–13.4), and the mean serum TPO antibody level was 1,855 IU/mL (range, 20–7,520 IU/mL). No significant correlation was found between the levels of TPO antibodies and SUV_{max} ($P = 0.675$).

DISCUSSION

The expanding use of PET in clinical practice underlines the need to clarify the clinical significance of and further evaluate incidental findings. To our knowledge, there have been no previous studies regarding diffusely increased ^{18}F -FDG uptake in patients already receiving replacement thyroxine therapy or other therapy for nonmalignant thyroid disease. In addition, the literature does not address whether the level of ^{18}F -FDG uptake in the thyroid might itself have clinical significance.

Other studies relative to ours include one by Yasuda et al. (13) in which diffuse ^{18}F -FDG uptake was found in the thyroid in 36 (3.3%) of 1,102 healthy subjects who underwent PET as part of a cancer screening program in Japan. Kim et al. (8) found, in a retrospective study, diffuse thyroid uptake in 45 (1.1%) of 4,136 patients undergoing PET for non-thyroid-related malignancies. Kang et al. (7) reported this finding in only 8 (0.6%) of 1,330 subjects (999 cancer patients and 331 healthy subjects). Are et al. (14), in a recent study, reviewed the PET examinations of 8,800 patients for thyroid incidentaloma (diffuse or focal ^{18}F -FDG uptake), looking for evidence of malignancies. They reported that 162 patients (1.8%) were found to have diffuse thyroid uptake, and only 2 of them (1.2%) were found to have malignancy.

TABLE 1
Patients Undergoing Fine-Needle Aspiration Biopsy After PET

Patient no.	Reason for PET/CT	SUV_{max}		Sonography findings	Cytology report	Thyroid status
		Right lobe	Left lobe			
1	Restaging of lung cancer	6.5	5.6	Diffusely heterogeneous parenchyma	Hashimoto's thyroiditis	Was already taking thyroxine
2	Evaluation of pigmented choroidal mass	9	11.2	Heterogeneous parenchyma; increased vascularity	Hashimoto's thyroiditis	Was already taking thyroxine
3	Evaluation of neck lymphadenopathy	8.4	7.4	Mildly prominent, heterogeneous thyroid gland	Chronic thyroiditis	Was already taking thyroxine
4	Restaging of non-Hodgkin's lymphoma	16.8	15.1	Enlargement with diffusely heterogeneous parenchyma	Hashimoto's thyroiditis	Was already taking thyroxine

TABLE 2
Results of the 19 Patients Subsequently Found to Have Thyroid Disease/Abnormality

Patient no.	SUV _{max}		TSH (mIU/L)	Free thyroxine (ng/dL)	TPO antibody (IU/mL)	Ultrasound report
	Right lobe	Left lobe				
1	11.3	11.1	70.0	0.5	—	—
2	5.7	4.0	—	—	—	Hashimoto's thyroiditis
3	6.5	6.3	23.1	0.6	—	Nodular goiter (coarsened echotexture, nodularity)
4	4.8	6.3	27.5	0.7	1,073	—
5	11.4	12.0	12.8	0.8	298	—
6	9.9	12.9	159	0.7	2,680	Hashimoto's thyroiditis
7	5.1	4.6	32.3	0.7	5,820	—
8	4.7	4.2	8.0	—	510	—
9	9.2	7.8	5.4	1.5	655	Likely Hashimoto's thyroiditis
10	9.0	11.2	2.5	1.9	33	Hashimoto's thyroiditis
11	5.6	6.8	7.1	1.5	7,520	Hashimoto's thyroiditis
12	6.5	6.3	1.8	0.9	272	—
13	5.2	5.8	4.9	—	—	—
14	8.1	3.3	56.6	0.6	—	Markedly heterogeneous parenchyma
15	4.7	4.9	64.1	0.8	3,680	—
16	12.9	14.2	2.5	1.0	120	Hashimoto's thyroiditis
17	5.7	5.6	6.0	—	—	Autoimmune thyroid disease
18	4.5	5.3	6.1	1.0	546	—
19	3.6	3.9	7.3	—	—	—

Reference values: TSH, <5 mIU/L; free thyroxine, 0.8–1.8 ng/dL; TPO antibody, <40 IU/mL.

In the present study, we found 2.9% of the patients to have diffusely increased ^{18}F -FDG uptake. This percentage is similar to the 3.3% found by Yasuda et al. (in a healthy population, though) and more than the percentages (0.6%–1.8%) found in the rest of the studies (7,8,14). The assumed exclusion in those studies of patients with any prior history of benign thyroid disease may account for that difference.

Yasuda et al. (13) reported that 7 (19.4%) of 36 had hypothyroidism and 27 (75.0%) of 36 had positive TPO antibodies. Kim et al. (8) found 10 (22.2%) of 45 to have

hypothyroidism and 6 (100.0%) of 6 with positive TPO or thyroglobulin antibodies. Similarly, we found 14 (48.3%) of 29 patients to have elevated serum TSH levels and 11 (91.7%) of 12 to have positive TPO antibodies.

Thyroid ultrasonography, fine-needle aspiration biopsies, and thyroid autoantibody studies done on patients with diffuse uptake were all suggestive of chronic lymphocytic (Hashimoto's) thyroiditis. The fact that we did not find any significant correlation between the levels of ^{18}F -FDG uptake in the thyroid and TSH levels in the serum suggests that even mild or low ^{18}F -FDG uptake in the thyroid gland should not be ignored. Although not reflecting thyroid status, such uptake may be associated with overt or subclinical hypothyroidism requiring thyroid hormone therapy, dose adjustment, or further evaluation.

In the present study, we also found that even patients receiving replacement therapy for primary hypothyroidism can demonstrate diffusely increased ^{18}F -FDG uptake in their thyroid gland. This finding appears to be quite common, representing 47.4% of our 133 study patients with the incidental finding of diffusely increased ^{18}F -FDG uptake.

Yasuda et al. (13) suggested that lymphocytic infiltration of the thyroid may account for increased ^{18}F -FDG uptake. Autoimmune thyroiditis is characterized by lymphocytic infiltration of the thyroid (15,16). Lymphocytes within the thyroid gland are reportedly the source of TPO antibodies (17,18). It has been suggested that the titer of TPO antibodies reflects the degree of lymphocytic infiltration in the thyroid (19,20). In the present study, no correlation was found between the TPO antibody titers and SUV_{max}.

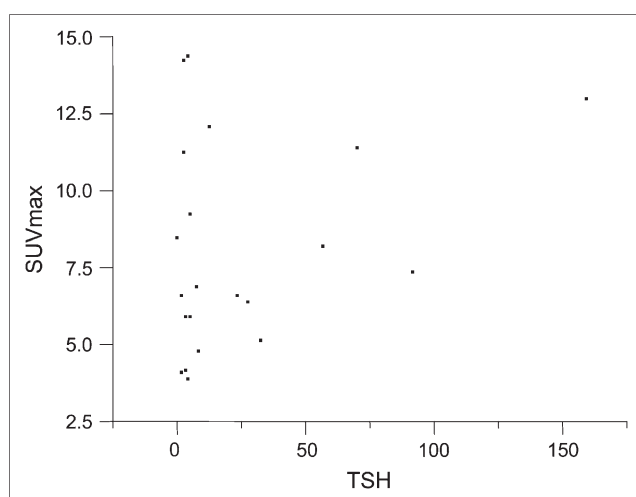


FIGURE 4. Plot of serum TSH vs. SUV_{max} in 21 patients with no prior history of thyroid disease. *P* value was found to be 0.089.

Therefore, we believe that lymphocytic infiltration, per se, is not solely responsible for the increased accumulation of ^{18}F -FDG seen in the thyroid of these patients with lymphocytic thyroiditis. Rather, these changes may reflect some other related intrathyroidal process, such as the active formation of fibrosis.

A potential limitation of the current study was its use of the SUV_{max} of a visually selected region of the thyroid. Placing the region on the transaxial slice of visually greatest activity conforms to common clinical practice. We assumed that because the activity in the thyroid glands was diffusely increased visually, a single measurement should have reflected a reasonable sample and therefore the activity of the underlying disease.

Questions may also arise regarding the reliability of uptake measurements using SUV_{max} instead of the mean SUV. SUV_{max} was used with the intention of avoiding error introduced by region-of-interest size and of enhancing reproducibility. Nevertheless, we correlated the 2 values (SUV_{max} and the mean SUV) in a sample of 21 patients from our study. Using a circular region of interest with a fixed diameter of 1 cm placed over the most intense region of ^{18}F -FDG uptake, we calculated both SUV_{max} and the mean SUV and correlated them using bivariate analysis. We found a strong statistical correlation ($P < 0.0001$) between the 2 values. Therefore, we assumed that uptake measurements done with either SUV_{max} or the mean SUV would have yielded similar results.

CONCLUSION

The results of the present study suggest that the incidental finding of diffusely increased ^{18}F -FDG uptake in the thyroid gland is associated with chronic lymphocytic (Hashimoto's) thyroiditis, with or without the presence of hypothyroidism. These findings seem to be unaffected by thyroid status or treatment with thyroid hormone. The level of ^{18}F -FDG uptake was neither suggestive of the degree of the hypothyroidism nor correlative with the levels of TPO antibodies in the serum. This finding is significant and should always be reported as likely abnormal. Some of these patients may require follow-up, the instigation of thyroid hormone therapy, or adjustment of their thyroid hormone dose. Longer follow-up studies would be needed to determine whether increased ^{18}F -FDG uptake in euthyroid patients might predict future development of hypothyroidism.

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