Original Article, PET/CT.

Are Metabolic Parameters of 18 F- FDG PET/CT Affected by TSH level in Cases of Differentiated Thyroid Carcinoma with Biochemical Recurrence?

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ABSTRACT:

Aim: to evaluate the impact of TSH level on the outcomes of 18F-FDG PET/CT in patients with recurrent differentiated thyroid carcinoma (RDTC) with negative iodine-131 whole body scan (I-131 -WBS) along with raised tumor markers. Patients were divided into stimulated (TSH level > 30mIU/L) and non-stimulated groups and the 18F-FDG PET/CT findings of each group were compared. **Methods:** In this study, we recruited patients with biochemical recurrence of DTC (elevated serum thyroglobulin or thyroglobulin antibodies level) between March 2020 and May 2023 in nuclear medicine unit, Assiut University Hospital. The patients have been divided into two groups: Group A with stimulated TSH level (equal to or greater than 30mIU/L) and group B with unstimulated TSH level (less than 30mIU/L). For each group, the following PET/CT parameters, including standardized uptake value (SUV max), total lesion glycolysis (TLG), metabolic tumor volume (MTV), and lesion-to-liver ratio were extracted by drawing a volume of interest (VOI) over the main detected lesion and compared. **Results:** The study included 54 patients (33 females and 21 males). Group A contained 22 patients (17 with positive findings and 5 with negative findings) while group B contained 32 patients (23 with positive findings and 9 with negative findings). There was no significant difference between number of patients with negative and positive findings (P-value = 0.657) as well as

the different metabolic parameters (SUV max, TLG, MTV, and lesion-to-liver ratio) in patients with positive findings, with P-values of 0.95, 0.423, 0.548, and 0.976, respectively.

Conclusion: In RDTC patients with negative I-131-WBS and raised tumor markers, there was no significant difference regarding the metabolic parameters between the TSH-stimulated and non-stimulated groups. Hence, there is no need for levothyroxine withdrawal before ^{18}F-FDG PET/CT scan.

Keywords ^{18}F-FDG PET/CT, Recurrent Differentiated thyroid cancer, TSH level, Radioiodine whole body scan, stimulated tumor marker.

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INTRODUCTION:

Thyroid cancer is the most prevalent endocrine cancer, with a rising prevalence each year. It is the sixth most frequent cancer in women, accounting for around 1% of all cancers. It has an excellent prognosis in general. (1)

Surgery followed by radioactive iodine therapy (depending on risk stratification) is the usual treatment for differentiated thyroid carcinoma (DTC), and it is successful in the majority of cases. (2, 3)

DTC has positive outcomes and a long survival rate. Following therapy, patients are followed up using laboratory tests (thyroglobulin and anti-thyroglobulin), ultrasonography, and diagnostic I-131 whole-body scans (I-131 WBS). Thyroglobulin is a sensitive tumor marker for determining therapy success. (4)

Serum thyroglobulin (sTG) indicates the presence of persistent or recurrent disease when it is elevated. The majority of positive results from radioactive iodine whole-body scans are associated with elevated (sTG). Even at therapeutic doses, lesions can demonstrate poor or no radioactive iodine concentration. (5)

Rising TG levels (>5 mg/dl) with a negative radioactive iodine whole-body scan indicate biochemical recurrence in patients with differentiated thyroid cancer.

^{18}F-FDG-PET/CT can help identify the recurrent or metastatic in DTC patients with biochemical recurrence when radioiodine scan is negative. FDG accumulates within lesions missed by an iodine scan and usually

corresponds to aggressive clinical behavior.[6, 7]

Many studies have found that ^{18}F-FDG PET/CT can change management of biochemical RDTC by up to 50%. Higher levels of FDG uptake in lesions demonstrating no radioactive iodine uptake are associated with a more aggressive illness.[8]

This raises an important yet challenging question: Does TSH stimulation enhance the diagnostic performance of ^{18}F-FDG PET/CT scan? Should PET scanning for RDTC be done with or without TSH stimulation? The solution to this question is still controversial. [9]

This raises an important yet challenging question: Does TSH stimulation prior to an ^{18}F-FDG PET/CT scan improve the detection of tumor lesions?

Should PET scanning for RDTC be done with or without TSH stimulation? The solution to this question is still controversial.[10]

TSH promotes thyroid cell metabolism, glucose transfer, and glycolysis in DTC. TSH also acts as a growth factor for these cells by stimulating their proliferation, invasion, and angiogenesis. TSH stimulation, according to some authors, increases FDG uptake even in de-differentiated lesions. They rely on the TSH effect to increase metabolic activity, GlUT-1 receptor overexpression, and glucose consumption. The other authors that oppose this view believe that de-differentiation (De-DTC) is autonomic. Because observed lesions may be de-differentiated, I-131-WBS cannot detect them. De-DTC cells exhibit more aggressive behavior and are incapable of concentrating radioactive iodine. Poor or no RAI concentration causes false-negative WBS and the disease becomes resistant to RAI therapy. Anatomical imaging alone does not provide information about the functional status of the detected lesions, making it less reliable in the decision making process. On the other hand, ^{18}F-FDG PET/CT scan can additionally provide information about the metabolic state of the lesions. [11]

Various studies assessed how TSH stimulation affects the reliability of the ^{18}F-FDG PET/CT scan in lesion detection. Yet, and to our knowledge, no research has examined the effect of TSH stimulation over ^{18}F-FDG PET/CT metabolic parameters.

PATEINTS AND METHODS:

This study was done in nuclear medicine unit, Assiut university hospital after obtaining the medical ethics committee approval (IRB number 042023300219) from March 2020 to May 2023.^{18}F-FDG PET/CT scan was performed for patients with pathologically proved DTC, who received one or multiple radioactive iodine therapeutic doses with elevated tumor markers (sTG greater than 10 ng/mL) and negative radioiodine whole body scan after obtaining written inform consent. We excluded patients with blood glucose >200 mg/dl immediately before PET/CT scan, pregnant women and patients unable to remain quiet without movement during imaging time. The patients were divided into two groups based on their TSH levels prior to the scan: group (A) with stimulated TSH level (equal to or greater than 30 mIU/L) after levothyroxine withdrawal, and group (B) non-stimulated, with a TSH level below 30 mIU/L.

^{18}F- FDG PET/CT scan protocol

Patients with at least 4 hours fasting and blood glucose level below 200 mg/dL underwent an IV injection of ^{18}F-FDG dose between 150 to 435 MBq (roughly 5.18 MBq/kg body weight). Patients were instructed to be relaxed and recumbent in a comfortable, quiet, warm room for 45–60 minutes after injection (the uptake period) and have good oral hydration by drinking around one liter of plain water and empty their bladder before the scan. Patients were allowed to breathe normally during acquisition but were instructed to minimize movement.

^{18}F- FDG PET/CT image acquisition and reconstruction

Using a high-spatial-resolution, full-ring PET scanner (Biograph mCT Flow, Siemens Healthcare), lutetium oxy orthosilicate (LSO)-based PET crystals, and 16-slice CT components, imaging was performed between 45 and 80 minutes following ^{18}F-FDG injection. An integrated CT machine obtained a low-dose non-contrast CT image for attenuation correction and fusion with the PET images to allow anatomical localization of its findings. The field of view extended from the vertex of the skull to the middle of the thighs, preferably with the arms raised above the head. Emission PET images were collected in a 3D mode over the same anatomical regions immediately after the non-contrast CT images. Reoriented tomograms that were shown in the axial, coronal, and sagittal planes were used to undertake iterative reconstruction. The manufacturer's software was used to analyze non-fused and fused photos.

^{18}F- FDG PET/CT image analysis:

Two experienced nuclear medicine physicians visually interpreted the ^{18}F- FDG PET/CT images for any abnormal findings. A positive lesion was considered in ^{18}F-FDG PET/CT scans if the FDG uptake was more than or equal to the background tissue in the area with a CT correlation. A negative scan was considered if there was no abnormal ^{18}F-FDG uptake other than the physiological uptake or no CT correlation. The resulting scans are divided into positive and negative scans, and they are subsequently evaluated via TSH group analysis. Patients whose ^{18}F- FDG PET/CT scans came out negative were then not included in the analysis. Additionally, the scans showing positive lesions are examined. Drawing a 3-dimensional region of interest over the lesions to get the metabolic parameters allowed for a quantitative assessment of the lesions.

Another region of interest is drawn over the liver to obtain liver SUV max. We record the results for the main lesion of positive cases and calculate (LL) ratio for them. These parameters were compared to both groups to know if there is a significant difference between the stimulated and non-stimulated groups in order to decide if it is valuable to stop Eltroxin replacement therapy for the patients before the ^{18}F- FDG PET/CT scan.

Clinical, radiological and laboratory follow up and/or biopsy was done for histopathologic examination, was considered the gold standard in our study.

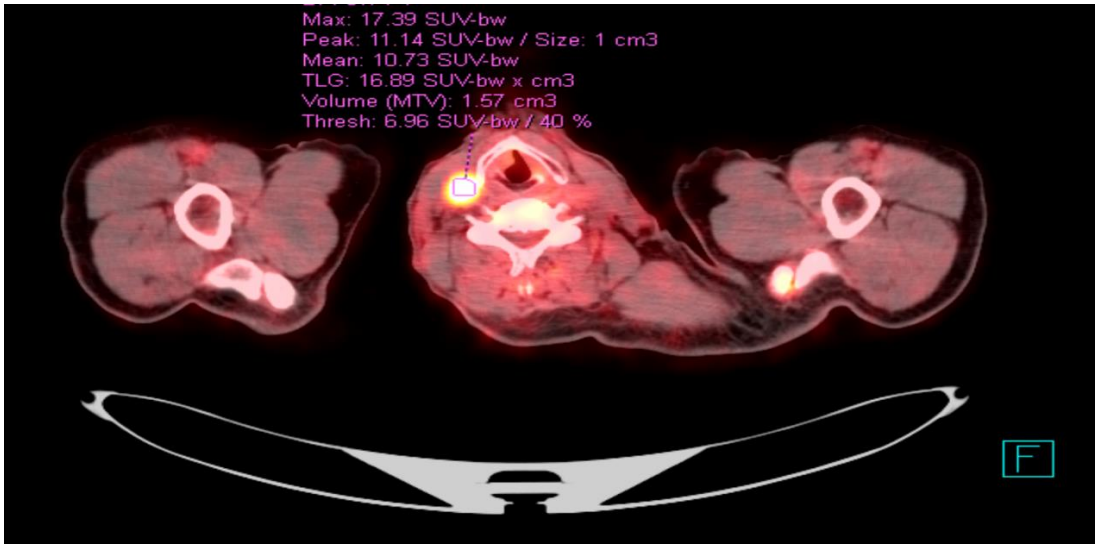

Figure1: 3-D region of interest is drawn over the lesion to obtain the metabolic parameters (SUV max, TLG, and MTV).

Statistical analysis

Data were analysed by the researcher using SPSS 24.0 (IBM-SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as means and standard deviations. We compare different metabolic parameters in the two groups using independent sample T-test. Significant test results were considered when the p-value was <0.05.

RESULTS:

Fifty-four patients had met the inclusion and exclusion criteria (33 females and 21 males), so they were submitted to ^{18}F-FDG PET- CT evaluation. The patients were classified into two group based on the level of TSH at the time of the scan:

group (A): TSH stimulated group; included 22 patients (17 show positive findings and 5 patients with negative findings),

group (B): TSH non-stimulated group; included 32 patients (23 show positive findings and 9 patients with negative findings).

The demographic data for both TSH stimulated & non-stimulated groups are given in Table 1.

Table 1: The demographic data of both stimulated & non-stimulated groups.

	Stimulated group	**Non-stimulated group**	**P-value**
Age	47 ± 15.7	41.4 ±15.7	0.85
Sex (M/F)	8/14	13/19	
Mean FDG dose per patient	7.4 ± 1.4	7.1 ± 1.7	0.48
Mean weight	77.2 ± 13.8	76.5 ± 21.3	0.09
Mean height	160.7 ± 7.4	161.4 ± 8.3	0.57
Mean blood sugar before PET/CT scan	94.8 ± 18.1	97.7 ± 19.4	0.96
Scans with positive results	17	23	0.657
Scans with negative results	5	9	

The number of patients with negative and positive findings were insignificantly different between both groups (P-value = 0.657). The fourteen patients who showed negative findings were excluded from the final analysis.

The mean values of different metabolic parameters (SUV max, TLG, MTV and LL ratio) were calculated for the remaining forty patients with positive findings. The mean values of all calculated metabolic parameters showed no significant difference between stimulated and non-stimulated groups with P-values (0.95, 0.423, 0.548, 0.976) respectively as shown in table 2.

Table 2: Mean values and P-values of the different metabolic parameters for stimulated and non-stimulated groups.

	Stimulated group	**Non-stimulated group**	**P-value**
Main lesion SUV max	6.5229 ± 8.45159	6.7096 ± 9.78546	0.950
Main lesion TLG	20.9665 ± 68.65894	8.8409 ± 18.70569	0.423
Main lesion MTV	2.8724 ± 4.85333	2.2126 ± 1.68616	0.548
LL ratio	2.3841 ± 2.98373	2.3526 ± 3.53090	0.976

The sensitivity, specificity, PPV, NPP and accuracy were calculated for both groups. They were 88%,50%, 83%, 60% and 78% respectively for the non-stimulated group. The

sensitivity, specificity, PPV, NPP and accuracy for the stimulated group were 100%,60%, 86%, 100% and 88% respectively.

Moreover, we determined the correlation between serum TG level and the MTV of the main detected lesion in the positive cases. There is a significant moderate positive correlation between the main lesion MTV and thyroglobulin level measured at the time of PET/CT scan (Pearson correlation 0.457).

DISCUSION:

The main purpose for ^{18}F-DG-PET/CT in DTC patients is biochemical recurrence to determine the cause of rising tumor markers and the site of recurrence. Several studies have been performed to investigate the effect of TSH levels on the diagnostic characteristics of ^{18}F-FDG PET/CT (accuracy, sensitivity, specificity, etc.). To the best of our knowledge, no studies have been done on the effect of TSH levels on the different metabolic parameters of ^{18}F-FDG PET/CT in these cases.

The results of scans (either positive or negative) as well as diagnostic parameters are compared in both stimulated and non-stimulated groups in our study. We noticed that the number of patients with negative or positive findings differed insignificantly between the two groups. In our research the sensitivity, specificity, and accuracy were 88%, and 78% respectively for the non-stimulated group. They were 100%, 60%, and 88% respectively.

Younis, et al studied the role of ^{18}F-FDG PET/CT scan in the post-thyroidectomy stage in RDTC patients in general, without stratification based on TSH level. They found that it plays a crucial role in the therapy of these patients by providing anatomical localization of tumor foci, therefore raising diagnostic accuracy. Its accuracy and sensitivity were (84.2% and 80%, respectively), which matched with the accuracy of our result.[4]

In 2019, Larg M et al evaluated the effectiveness of PET/CT in RDTC patients. The ^{18}F-FDG PET/CT scan's sensitivity, specificity, positive predictive values, and accuracy were 88.09%, 98.6%, 93.1%, and 96.53%, respectively. 89.2% of patients with positive PET/CT findings had their treatment plan changed.[12]

In our study, we further discussed about whether the stimulated and non-stimulated groups' metabolic parameters differed. The mean values of these metabolic parameters (SUV max, TLG, MTV, and lesion to liver ratio) estimated for the cases with positive results did not significantly differ between the two groups.

Whether or not TSH influences the detection of lesions in PET/CT is an important question. So, does it deserve to stop thyroid replacement therapy for patients to perform the PET scan (with the known undesirable side effects of hypothyroidism). After TSH stimulation, the thyroglobulin level is assessed; however, PET/CT may not be performed simultaneously. In our country, patients may have to wait a long time to have a PET/CT appointment. It is challenging in this situation to wait for such a long time being hypothyroid.

According to the study's findings, thyroid replacement therapy is not required to be stopped in order to raise a patient's TSH level before an ^{18}F-FDG PET/CT scan.

We have concerns about the impact of elevated TSH levels (due to the withdrawal of thyroid replacement medicine) on the efficacy of FDG PET/CT. Kotb et al. investigated the influence of TSH levels on the outcomes of ^{18}F-FDG PET/CT in differentiated thyroid cancer patients with elevated serum thyroglobulin levels and negative I-131 WBS with regard to of lesion location. They observed that elevated TSH improves 18F-FDG PET/CT efficiency in nodal metastases rather than pulmonary metastases. TSH enhances the metabolism, glucose transport, and glycolysis of malignant differentiated thyroid cells, acting as a growth factor for these cells by stimulating tumor growth, invasion, and angiogenesis. As a result, it may play a role in increasing I-131 uptake and retention in patients with differentiated thyroid cancer.

Those who support this viewpoint point to its role in raising metabolic activity, GlUT-1 receptor expression, and glucose consumption. Others (who believe that TSH has no effect on FDG uptake) dispute TSH dependence and instead underline autonomic nature.

Bang et al. reported that patients who had TSH stimulation status at the time of the PET/CT had no appreciable variations in the diagnostic efficacy of FDG PET/CT. while, we focus on the differences in diagnostic accuracy between groups who have been stimulated and un stimulated group [(13)].

Dai In reviewed the metabolic parameters of ^{18}F-FDG PET/CT scan (SUV max, TLG, and MTV), as a predictive factors with TLG was the sole independent predictive value for progression-free survival, Additionally, he reported there is no metabolic parameter that can predict overall survival, however did not mention the TSH level of the patients while performing PET/CT.[(14,15)].

This study found a significant correlation between ^{18}F-FDG PET/CT total MTV and TLG and overall survival in RDTC patients, but not reflected on patient free survival. Additionally, it showed that MTV can identify patients with aggressive disease.

We noticed a moderately significant positive correlation between the thyroglobulin level recorded during the PET/CT scan and the lesion MTV. This implies a relationship between the amount of tumor tissue and the sTG level.

CONCLUSIONS:

In patients with differentiated thyroid carcinoma and biochemical recurrence, ^{18}F-FDG PET/CT scan were insignificantly different between stimulated and non-stimulated groups. Also, different metabolic parameters were insignificantly different in between both groups. Finally, according to these results, we conclude that there is no need to stop thyroxin replacement therapy before ^{18}F-FDG PET/CT scan.

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