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The utility of ^{18}F-fluorocholine PET/CT in the imaging of parathyroid adenomas

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Abstract

Introduction: The aim of the study was to estimate the sensitivity of ^{18}F-FCH PET/CT in preoperative localisation of hyperfunctioning parathyroid glands in patients with primary hyperparathyroidism (PHPT).
Material and methods: Sixty-five consecutive patients with PHPT, who underwent neck ultrasound (US) and ^{99m}Tc/^{99m}Tc-MIBI dual-phase parathyroid scintigraphy, were prospectively enrolled. Twenty-two patients had unsuccessful parathyroid surgery prior to the study. PET/CT scans were performed 65.0 ± 13.3 min after injection of 218.5 ± 31.9 MBq of ^{18}F-fluorocholine (FCH). Three experienced nuclear medicine physicians assessed the detection rate of hyperfunctioning parathyroid tissue. Response to parathyroidectomy and clinical follow-up served as a reference test. Per-patient sensitivity and positive predictive value (PPV) were calculated for patients who underwent surgery.
Results: ^{18}F-FCH PET/CT was positive in 61 patients, and negative in 4. US and parathyroid scintigraphy showed positive and negative results in 20, 45 and 17, 48, respectively. US showed nodular goitre in 31 patients and chronic thyroiditis in 9 patients. Parathyroid surgery was performed in 43 (66%) patients. ^{18}F-FCH PET/CT yielded a sensitivity of 100% (95% CI: 87.99–100) and PPV of 85.7% (95% CI: 70.77–94.06). Similar values were observed in patients with chronic thyroiditis, nodular goitre, and patients after an unsuccessful parathyroid surgery. PET/CT identified hyperparathyroidism complications (kidney stones, osteoporotic bone fractures, and brown tumours) in 11 patients.
Conclusions: ^{18}F-FCH PET/CT effectively detected hyperfunctioning parathyroid tissue and its complications. The method showed excellent sensitivity and positive predictive value, including patients with nodular goitre, chronic thyroiditis, and prior unsuccessful parathyroidectomy. PET/CT performance was superior to neck ultrasound and parathyroid scintigraphy. **(Endokrynol Pol 2022; 73 (1): 43–48)**

Key words: *^{18}F-FCH PET/CT; fluorocholine; hyperparathyroidism; parathyroid imaging*

Introduction

Primary hyperparathyroidism (PHPT) is an endocrine disease in which excessive amounts of parathormone (PTH) are produced and secreted autonomously by parathyroid glands. It is most commonly caused by a solitary parathyroid adenoma (80–85%), followed by glandular hyperplasia (10–15%) and double adenoma (4%) [1–4]. Surgical treatment is the only curative therapy. Image-guided, minimally invasive parathyroidectomy (MIP) should be the surgical technique of choice because it offers several advantages over the traditional bilateral neck exploration approach. MIP is associated with shorter operation time (local anaesthesia might be used), fewer complications, faster recovery, better cosmetic outcome, and lower incidence and severity of symptomatic and biochemical hypocalcaemia. At the same time, it shows similar efficacy to the classic surgery [2, 5]. However, for a minimally invasive approach a precise localisation is required.

Several imaging modalities have been proposed for preoperative detection and localisation of hyperfunctioning parathyroid glands. Neck ultrasound (US) and ^{99m}Tc-methoxy-isobutyl-isonitrile (^{99m}Tc-MIBI) scintigraphy are currently the most frequently used methods [6]. US, the most readily available and least expensive one, shows rather limited sensitivity, varying from 57% to 76%. It also fails to detect ectopic parathyroid adenomas [7]. On the other hand, ectopic parathyroid tissue can be detected in scintigraphy, which is reported to have a sensitivity of about 60%. It might be increased to 92% when single photon emission computed tomography/computed tomography (SPECT/CT) is performed [8–10]. Currently, it is considered the method of choice for the detection of parathyroid adenomas [2, 4].

Contemporary research suggests that ^{18}F-fluorocholine (FCH) positron emission tomography/computed

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tomography (PET/CT) might be a feasible tool in this clinical setting [6]. Fluorocholine is a phospholipid analogue that is integrated into the newly synthesized membranes of proliferating cells. Choline uptake increases with the upregulation of choline kinase. Furthermore, its upregulation is linked to PTH secretion [11]. ^{18}F-FCH PET/CT, like scintigraphy, allows for the detection of ectopic parathyroid adenomas, but its superior spatial resolution is an additional advantage, especially in small lesions. It also exerts lower radiation than scintigraphy and has a shorter scanning time (20 min vs. 120 min) [6, 12].

The aim of the study was to assess the feasibility of ^{18}F-FCH PET/CT in preoperative localisation of hyperfunctioning parathyroid tissue in patients with PHPT.

Material and methods

Patients

Between January 2018 and November 2019, 65 consecutive patients with primary hyperparathyroidism referred to the Affidea Mazovian PET/CT Centre in Warsaw, Poland for ^{18}F-FCH PET/CT were prospectively enrolled in the study (Tab. 1). The patients were referred by a single centre — the Department of Endocrinology and Radioisotope Therapy in the Military Institute of Medicine in Warsaw. The eligibility criteria were as follows: (1) PHPT and (2) neck US and the dual-phase and subtraction ^{99m}Tc/^{99m}Tc-MIBI SPECT/CT scintigraphy performed prior to the PET/CT scan (both were done in accordance with the recommendations of the European Association of Nuclear Medicine) [9]. Primary hyperthyroidism was diagnosed when elevated levels of calcium and parathyroid hormone were observed with increased excretion of calcium in the urine and with normal vitamin D levels, normal renal function parameters, and without gastrointestinal diseases causing malabsorption. Forty-three patients had newly diagnosed hyperparathyroidism, and 22 patients had a history of parathyroid surgery prior to the referral. The average concentration of PTH in the group of enrolled patients was 165 pg/mL (range 81–575; normal level 15–65 pg/mL).

All patients signed a written informed consent form. The study was approved by the Military Institute of Medicine Ethical Committee (44/WIM/2016). The study was carried out in accordance with the Declaration of Helsinki and its later amendments and was registered at ClinicalTrials.gov website (NCT04570033; 30/09/2020)

Table 1. *Characteristics of patients and performed positron emission tomography/computed tomography (PET/CT) scans*

Characteristic	Value
Number of patients	65
Gender	59 (91%) women, 6 (9%) men
Age	
Mean ± SD	57.8 ± 16.7 years
Median (range)	63.0 (14.0–81.0) years
Neck US	20 (31%) positive 45 (69 %) negative
^{99m}Tc-MIBI SPECT/CT	17 (26%) positive 48 (74%) negative
Administered activity	
Mean ± SD	218.5 ± 31.9 MBq
Median (range)	210.0 (173.0–351.0) MBq
Uptake time	
Mean ± SD	65.0 ± 13.3 min
Median (range)	62.0 (30.0–114.0) min

SD — standard deviation, MBq — megabecquerels, US — ultrasound

Imaging protocol

PET/CT imaging was performed using a Discovery 710 PET/CT system (GE Healthcare, Chicago, Illinois, US). PET/CT scans were performed 65.0 ± 13.3 min after injection of 218.5 ± 31.9 MBq of ^{18}F-fluorocholine. A scout view and a non-contrast-enhanced low-dose spiral 64-slice CT scan was performed prior to PET scan for attenuation correction and anatomic localization. The CT scan was performed with a tube voltage of 140 kV in the helical mode with a Smart/Auto mA (range: 40–120 mA); pitch and table speed were as follows: 0.984:1 and 39.37 mm/rot; the helical thickness was 3.75 mm; X-ray tube rotation time was 0.6 s; and the slice thickness was 1.25 mm. The GE Adaptive Statistical Iterative Reconstruction with the level of 20% was used to reduce patient radiation dose from CT scans.

Immediately after CT scanning, mid-skull to mid-thigh 3-dimensional PET was acquired. The acquisition time was 1 min 45 sec for each bed position (the axial field of view was 15.7 cm with 23% bed overlap). The emission data were corrected for geometrical response and detector efficiency (normalisation) as well as for system dead time, random coincidences, scatter and attenuation. For attenuation-corrected images reconstruction was conducted with 3D iterative algorithm with time-of-flight PET reconstruction and resolution recovery algorithm with 3 iterations/18 subsets and a filter cut-off of 5.5 mm. The matrix size was 256 × 256.

Image analysis

PET/CT images were analysed with GE Healthcare Advantage Workstation 8.0 (Chicago, Illinois, United States) by 3 experienced nuclear medicine physicians. The reviewers did not know the results of the neck US and scintigraphy the patients had performed prior to PET. We reported PET/CT results as positive and negative (US and SPECT/CT results were divided alike). ^{18}F-FCH PET/CT scans were considered positive for hyperfunctioning parathyroid tissue if at least one tracer-avid focus was identified with a corresponding lesion in CT. All disagreements were resolved by consensus. We also recorded the number of discordant results.

Surgery was performed on the basis of PET/CT results. PET/CT findings were correlated with parathormone levels during and after the operation. Surgery was regarded as successful if intraoperative parathormone decreased ≥ 50% and, within a 6-month follow-up, PTH and calcium levels were normal.

SPSS Statistics 25 software (Armonk, New York, United States) was used for statistical analysis. A p value < 0.05 was considered significant. Descriptive analysis was performed by calculating the mean, median, standard deviation, and range. The data were tested for normality using the Shapiro-Wilk test. The chi^2 test was used to determine if the difference between positive and negative results of PET/CT, US, and ^{99m}Tc-MIBI SPECT/CT was significant. Diagnostic efficacy of ^{18}F-FCH PET/CT was measured for the general studied population as well as for the subgroups of patients with nodular goitre, patients with chronic thyroiditis, and patients with a history of parathyroid surgery prior to the study.

To calculate the sensitivity and positive predictive values (PPV) we assumed that PET/CT was true positive (TP) if a scan was positive and surgery successful; false positive (FP) if a scan was positive and surgery unsuccessful; and false negative (FN) if a scan was negative and surgery successful.

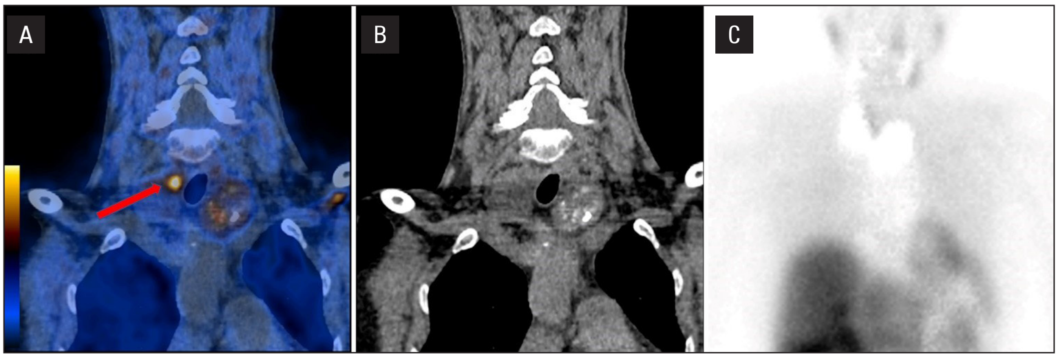

Figure 1. *18F-choline positron emission tomography/computed tomography (PET/CT) (**A**), CT (**B**) and subtraction scintigraphy (**C**) coronal scans of a 53-year-old woman with primary hyperparathyroidism and nodular goitre. The images show a choline-avid focus (parathyroid adenoma) by the upper right lobe of the thyroid (**A**). Subtraction scintigraphy (**C**) and neck ultrasound were negative. The adenoma was excised and, after the surgery, calcium and parathormone levels normalised*

Results

No adverse effects were observed after the injections of ^{18}F-FCH. Patients did not report any alarming symptoms.

Twenty-two (33.8%) patients had a history of parathyroid surgery prior to the referral, 31 (47.7%) had nodular goitre, and 9 (13.8%) had chronic thyroiditis (Hashimoto's disease) on neck US. ^{18}F-FCH PET/CT was positive in 61 (94%) patients. In 47 (72%) patients a single choline-avid focus was detected, and 8 (12%) patients had 2–4 foci indicative of parathyroid adenoma. PET/CT was negative in 4 (6%) patients. Hyperfunctioning parathyroid tissue seen in PET/CT scans was located in the neck (Fig. 1).

During the follow-up period 43 (66%) patients had parathyroid surgery (all operations were minimally invasive). All but 1 of the operated patients were PET-positive. The patient who was operated despite negative PET/CT also had a negative ^{99m}Tc-MIBI SPECT/CT, equivocal neck US, and nodular goitre — surgery was not effective in this patient (the patient was classified into the true negative group — TN). We observed 6 more cases of unsuccessful surgery in PET-positive patients (FP). PET/CT was TP in 36 of patients who underwent surgery. We did not observe FN results. In histopathological examination various types of tissues (lymph node, adipose and muscle tissue, thyroid fragment) were found in ineffectively operated patients. The sensitivity and positive predictive value (PPV) were 100% and 85.7%, respectively. We also calculated sensitivity and PPV in subgroups with chronic thyroiditis, nodular goitre, and a history of unsuccessful parathyroid surgery (Tab. 2).

^{18}F-FCH PET/CT detected 70 choline-avid lesions; 7 (10%) of them were equivocal, and the decision whether they could be reported as parathyroid adenomas was reached via consensus between the readers. Neck ultrasound showed 22 lesions, including 11 (50%) equivocal findings (resolved via consensus). In ^{99m}Tc-MIBI SPECT/CT 17 lesions were identified, and 6 (35%) of them were equivocal (resolved via consensus).

Table 2. *Sensitivity, specificity, and positive predictive value of 18F-FCH in different subgroups of patients. 95% confidence intervals are given in square brackets*

	Sensitivity	PPV
All patients	100% (88.0–100)	85.7% (70.8–94.1)
Nodular goitre (NG)		
NG (+)	100% (78.1–100)	90.0% (66.9–98.3)
NG (–)	100% (78.1–100)	81.8% 59.0–94.0)
Chronic thyroiditis (ChT)		
ChT (+)	100% (46.3–100)	83.3% (36.5–99.1)
ChT (–)	100% (86.3–100)	86.1% (69.7–94.8)
Previous surgery (PS)		
PS (+)	100% (67.9–100)	91.7% (60.0–99.6)
PS (–)	100% (83.4–100)	83.3% (64.5–93.7)

PPV — positive predictive value

We also verified whether the lesions visualised in PET/CT, US, and SPECT/CT were concordant. From 17 lesions reported in SPECT/CT 14 were visible in PET/CT, which yielded 82% accordance. From 22 lesions reported in US PET/CT showed 16, which yielded 75% accordance.

On a per-patient basis, the 3 methods were concordant (triple positive or triple negative) in 9% and 3% of

Table 3. *Positive and negative results of 18F-FCH PET/CT, neck ultrasound, and ^{99m}Tc-MIBI SPECT/CT on per-patient basis*

	US (+) SPECT/CT (+)	US (+) SPECT/CT (–)	US (–) SPECT/CT (+)	US (–) SPECT/CT (–)
PET/CT (+)	6 (9%)	11 (17%)	12 (18%)	32 (49%)
PET/CT (–)	0	0	2 (3%)	2 (3%)

PET/CT — positron emission tomography/computed tomography; SPECT/CT — single-photon emission tomography/computed tomography; US — ultrasound

patients. Conventional imaging was either discordant or negative in 91% of patients (n = 59). ^{18}F-FCH PET/CT was positive in 93% of them (Tab. 3).

There were significantly more positive than negative PET/CT results ($\chi^2 = 49.99$, $p < 0.001$). In neck US and ^{99m}Tc-MIBI SPECT/CT negative results were significantly more common than positive — $\chi^2 = 9.62$ ($p = 0.002$) and $\chi^2 = 14.79$ ($p < 0.001$).

PET/CT also identified hyperparathyroidism complications (kidney stones, osteoporotic bone fractures, and brown tumours) in 17% of patients (Fig. 2).

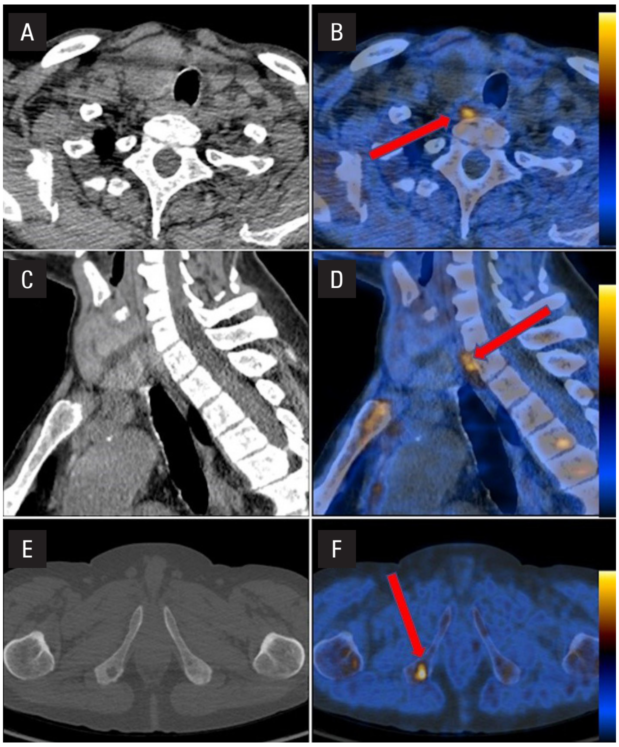

Figure 2. *Images (**B**, **F** — transaxial and **D** — sagittal fused 18-choline positron emission tomography/computed tomography (PET/CT); **A**, **E** — transaxial and c-sagittal axial CT) of a 61-year-old patient with primary hyperparathyroidism. Fused scans (**B**, **D**) show a choline-avid focus (parathyroid adenoma) between the right thyroid lobe and C6–C7 vertebral bodies. Neck ultrasound and scintigraphy were negative. The adenoma was successfully excised after ^{18}F-FCH PET/CT. PET/CT also showed a brown tumour of the right ischium (**F** — transaxial fused PET/CT scan; **E** — transaxial CT scan)*

Almost a third of subjects had unsuccessful parathyroidectomy prior to the study. After ^{18}F-FCH PET/CT they were reoperated, and surgery resulted in a positive outcome in 85% of them (Fig. 3).

Discussion

In our study we performed ^{18}F-FCH PET/CT in patients with primary hyperparathyroidism who had already had US and scintigraphy. The following surgical treatment was based on PET/CT results — choline-avid lesions were excised.

In our paper we showed that ^{18}F-FCH PET/CT is a feasible method for localisation of parathyroid adenomas. It presents excellent sensitivity and positive predictive value, even in patients with chronic thyroiditis, nodular goitre, or with a history of unsuccessful parathyroid surgery. PET/CT also showed superiority over conventional imaging (neck ultrasound and ^{99m}Tc-MIBI SPECT/CT).

These results are in line with contemporary publications. A systematic review and meta-analysis published by Treglia et al. confirms ^{18}F-FCH PET/CT as an outstanding diagnostic tool for the detection of hyperfunctioning parathyroid tissue. In the analysis of 14 articles (517 patients) the authors reported PET/CT to have per-patient sensitivity of 95% (ranging from 85% to 100%), PPV of 97% (86% to 100%), and a detection rate of 91% (76% to 100%). A subgroup analysis including only research with PHPT yielded pooled sensitivity, PPV, and detection rate of 96%, 96%, and 92%, respectively [13]. It has been proven (both in our study and in the published research) that ^{18}F-FCH PET/CT is similarly effective in localising hyperfunctioning parathyroid tissue in patients with nodular goitre or with prior unsuccessful surgery [9, 13, 14]. In our paper we report that PET/CT also maintains its excellent performance in patients with chronic thyroiditis.

^{18}F-FCH PET/CT is useful in the detection and localisation of hyperfunctioning parathyroid tissue in patients with negative, equivocal, or discordant US and scintigraphy findings. The APACH1 study (including 25 patients with PHPT and negative or inconclusive conventional imaging) yielded a sensitivity of 90.5% and PPV of 86.4% [6]. Fischli et al. and Grimaldi et

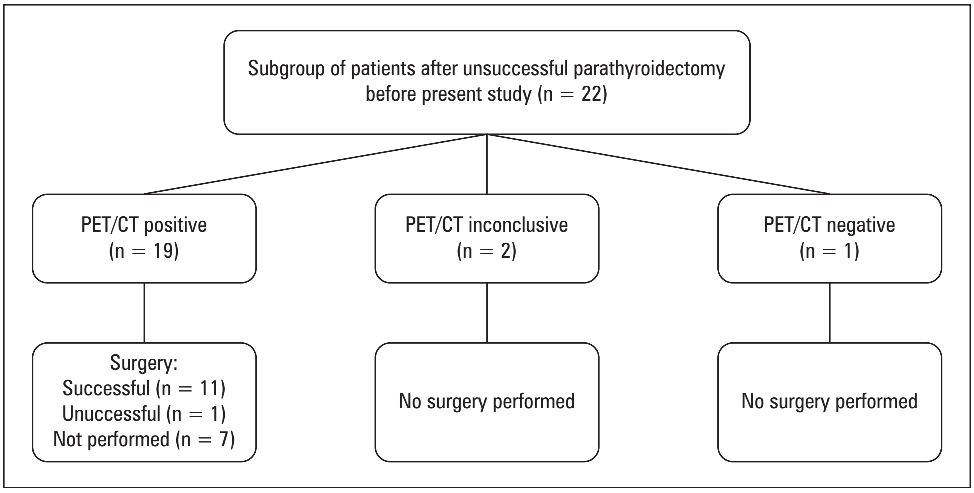

Figure 3. *Positron emission tomography/computed tomography (PET/CT) and surgery results of a subgroup of patients who had unsuccessful parathyroidectomy prior to our study*

al. reported that the PET/CT detection rate in this clinical setting reaches 91% and 89%, respectively [15, 16]. Treglia et al. concluded that ^{18}F-FCH PET/CT was able to detect hyperfunctioning parathyroid tissue in a high percentage (72–91%) of patients with negative or inconclusive ^{99m}Tc-MIBI SPECT/CT [13]. In our study 91% of patients were either negative both on US and ^{99m}Tc-MIBI SPECT/CT or had discordant results of conventional imaging. The PET/CT detection rate in this group was 93%.

It is important to detect complications of hyperparathyroidism because it often quickens the decision of surgery. Current PET/CT protocols may miss them as they cover only the neck and upper chest, while the most common complications — kidney stones, lumbar spine fractures, and pancreatic calcifications — localise in the abdominal area [13]. Hence, in our study we decided to perform mid-skull to mid-thigh scans. We believe this extended protocol should be the standard procedure in the parathyroid PET/CT imaging.

During the preparation of the current article for publication, the guidelines of the European Association of Nuclear Medicine (EANM) on the imaging of hyperparathyroidism were published. The authors of the guidelines, based on data from the literature, concluded that the ^{18}F-FCH PET/CT "is therefore considered an alternative first-line imaging method" [17].

Taking into account the results of our study, we agree with the conclusions of the authors of the EANM guidelines. It should be noted that our clinical trial is the first study assessing the usefulness of ^{18}F-FCH PET/CT in the population of Polish patients with hyperparathyroidism. We hope that the results of our clinical trial will contribute to the routine use of ^{18}F-FCH PET/CT in the diagnosis of hyperparathyroidism in Poland and this new diagnostic method will be reimbursed by the National Health Fund.

The lack of histopathological validation of the PET/CT results may be a limitation in this study. However, we believe that biochemical criteria — normalisation of calcium and parathormone levels — are a more reliable reference test. Some factors such as surgeon's experience and distorted neck anatomy (in patients after parathyroidectomy) may still affect it — choline-avid lesions may be overlooked during surgery because of scar tissue (and the PET/CT result would be regarded as false positive). Another potential limitation is that only 2/3 of PET-positive patients had surgery prior to the statistical analysis, meaning that only 2/3 of the PET/CT results were verified. The remaining 1/3 of patients were awaiting surgical treatment at the time of study closure (the waiting time for parathyroid surgery in Poland is currently up to 2 years).

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Conclusions

^{18}F-FCH PET/CT proved utile in detecting hyperfunctioning parathyroid tissue in patients with PHPT. The method showed excellent sensitivity and positive predictive value, including patients with nodular goitre, chronic thyroiditis, or previous parathyroid surgery. PET/CT also showed superior diagnostic performance to neck ultrasound and ^{99m}Tc-MIBI SPECT/CT.

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