Editorial

Original articles

Agata Danilczuk, Anna Nocuń, Beata Chrapko
Normal ranges of renal function parameters for $^{99m}$Tc-EC renal scintigraphy ................................................................. 53

Andreas Fotopoulos, Petros Petrikis, Ioannis Iakovou, Athanasios Papadopoulos, Sakelariou Konstantinos, Evangelia Gkika, Lampros Lakkas, Christos Touzios, Konstantinos Pappas, Antonios Klaroudas, Argyrios Doumas, Chrissa Sioka
The impact of depression and anxiety in prognosis of patients undergoing myocardial perfusion imaging with $^{99m}$Tc tetrofosmin SPECT for evaluation of possible myocardial ischemia ................................................................. 58

Beata Ewa Chrapko, Marek Chrapko, Anna Nocuń, Tomasz Zubilewicz, Boguslaw Stefanik, Jakub Mitura, Andrzej Wolski, Piotr Terelecki
Patterns of vascular graft infection in 18F-FDG PET/CT ............................................................................................................. 63

Maria Henryka Listewnik, Hanna Piwowarska-Bilska, Krzysztof Safranow, Marek Ostrowski, Jacek Iwanowski, Maria Chosia, Bozena Birkenfeld
The diagnostic value of dual-phase SPECT/CT scintigraphy based on transport kinetics of $^{99m}$Tc-sestamibi confirmed with histopathological findings in patients with secondary hyperparathyroidism — practical consideration .......... 71

Pawel Cichocki, Krzysztof Filipczak, Anna Plachcinska, Jacek Kusmierek
Kidney efficiency index quantitative parameter of a dynamic renal scintigraphy. II. usefulness in the diagnosis of obstructive nephropathy ........................................................................................................ 78

Ebru Salmanoglu, Ergul Belge Kurutas
The levels of oxidative and nitrosative stress in patients who had $^{99m}$Tc-MIBI myocardial perfusion scintigraphy and $^{99m}$Tc-DMSA, $^{99m}$Tc-MAG-3 renal scintigraphy ........................................................................................................... 83

Review

Vincenzo Cuccurullo, Giuseppe Danilo Di Stasio, Giuseppe Lucio Cascini
PET/CT in thyroid cancer: the importance of BRAF mutations ......................................................................................... 91

Clinical vignette

Shirin Shahlaei, Farnaz Nesri Javan, Atena aghaeae, Ramin Sadeghi
Catheter malposition during a direct radionuclide cystography: case report .................................................................................. 97

Maria Gazzilli, Domenico Albano, Laura Ardighieri, Francesco Bertagna, Raffaele Giubbini
Primary nasal-ethmoid choriocarcinoma detected by 18F-DG PET/CT: a rare tumor with complete remission ........................................ 99

Fatemeh Farahmandfar, Sara Shakeri, Sadegh Moradian, Shirin Shahlaei, Ramin Sadeghi
Primary skeletal muscle lymphoma with unusual soft tissue metastases in the stomach and pancreas detected by 18F-DG PET/CT ............................................................................................. 102

Salah Nabih Oueriagli, Yassir Bennameur, Omar At Sahel, Abdelhamid Biyi, Abderrahim Doudouh
Unusual 18F-DG PET-CT finding of paraneoplastic polymyositis in a patient with lung epidermoid carcinoma ........................................ 104

Ali Sellem, Wassim Elajmi, Hatem Hammami
Technetium pertechnetate uptake in parathyroid adenoma ....................................................................................................... 106
Dear Sirs and Madams,

It’s summer time, holidays but still we have one of the worst crises in the world. Fighting against COVID-19 pandemia became the most important target for everyone. Good luck! Nevertheless, I am happy introducing the second in 2020 issue of “Nuclear Medicine Review”. The Polish authors open the chapter “Original articles” with paper Normal ranges of renal function parameters for \( ^{99m}\text{Tc-EC} \) renal scintigraphy. The second article by Greek investigators concluding that patients who exhibit depression, anxiety, or both, have high rates of myocardial ischemia, and thus are at risk for subsequent cardiological events. The two next papers are from Poland. The first one raised that \( ^{18F}\text{FDG PET/CT} \) is a very useful tool for assessment of vascular graft infections. CT findings like gas bubbles, or peri-graft fluid retention were associated with significantly higher glucose metabolism, however, in some cases without anatomic alterations, increased metabolic activity was the only sign of infection. The second one gives us the practical consideration about The Diagnostic Value of Dual-Phase SPECT/CT Scintigraphy Based on Transport Kinetics of \( ^{99m}\text{Tc-Sestamibi} \) Confirmed with Histopathological Findings in Patients with Secondary Hyperparathyroidism. Turkish colleagues — in article titled The levels of oxidative and nitrosative stress in patients who had \( ^{99m}\text{Tc-MIBI} \) myocardial perfusion scintigraphy and \( ^{99m}\text{Tc-DMSA}, ^{99m}\text{Tc-MAG-3} \) renal scintigraphy — concludes that oxidative and nitrosative balance is impaired due to ionization radiation. These reactive species might stimulate adaptive and protective cellular defense mechanism in irradiated cells soon after exposing to radiation and protect organism from effects of low dose ionizing radiation. And again Polish authors and kidneys: chapter ends an original paper Kidney Efficiency Index — Quantitative Parameter of a Dynamic Renal Scintigraphy. II. Usefulness in the Diagnosis of Obstructive Nephropathy.

The Review part consists of the general state of knowledge concerning PET/CT in thyroid cancer and the importance of BRAF mutations by Italian authors.

In chapter Clinical vignette there are discussed five interesting clinical cases from Iran, Italy, Morocco and Tunisia.

In the end of my letter I would like to wish all of you joyful and healthy vacation!

Yours,
Grzegorz Kamiński
Editor-in-Chief
Nuclear Medicine Review

G. Kamiński
Normal ranges of renal function parameters for $^{99m}$Tc-EC renal scintigraphy

Agata Danilczuk $^{a}$, Anna Nocun $^{b}$, Beata Chrapko $^{c}$
Medical University of Lublin, Poland

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Abstract

BACKGROUND: Dynamic renal scintigraphy remains the recognized method for evaluation of kidney function and perfusion. Although there is an extensive body of knowledge about the use of technetium-99m-mercaptoacetyltriglycine ($^{99m}$Tc-MAG3), much less has been written about renal technetium-99m-ethylenedicysteine ($^{99m}$Tc-EC) scintigraphy.

The aim of this study was to determine the normal value of renal function parameters in $^{99m}$Tc-EC dynamic renal scintigraphy: Tmax and T1/2. The effects of age, left or right side in the retroperitoneal space, and sex on those parameters were examined.

MATERIAL AND METHODS: The research was conducted on 123 patients (F/M: 70/53; aged 2–71; averaging 14.8 years of age) with at least one normal kidney. A total of 194 healthy kidneys were examined, including pediatric kidneys.

RESULTS: According to this study, the normal value of Tmax is 2.85 min ($\pm$ 1.16) and T1/2 is 8.7 min ($\pm$ 3.61). Values calculated for pediatric studies are Tmax is 2.81 ($\pm$ 1.16) and T1/2 is 8.63 ($\pm$ 3.71).

CONCLUSIONS: The normal value of secretory and excretory renal function parameters was calculated. Although the value is slightly lower for children, this is not statistically significant, as globally there are no differences between the kidney-location sides and sexes for any parameter.

KEY words: radionuclide imaging; dynamic renal scintigraphy; technetium-99m-ethylenedicysteine; pediatric renal scintigraphy; renal function; renal function parameters

Introduction

Dynamic renal scintigraphy is based on physiological processes, is minimally invasive, and repeatable. It allows recognition of various renal abnormalities in an early stage [1, 2]. That is why it remains the gold standard for assessing renal function, despite some shortcomings of this method [3].

The studies examining the dynamic renal scintigraphy performed with the use of the $^{99m}$Tc-ethylenedicysteine ($^{99m}$Tc-EC) in normal human volunteers revealed that the renal clearance of $^{99m}$Tc-EC is higher than that of $^{99m}$Tc-mercaptoacetyltriglycine ($^{99m}$Tc-MAG3) and more similar to that of 131I-orthoiodohippurate (OIH). $^{99m}$Tc-EC is characterized by faster and more complete renal washout and similar good imaging properties [1, 4, 5].

Dynamic renal scintigraphy includes quantitative estimates of renal perfusion and function. Through the renographic curve shows the change of the radioisotope concentration in renal parenchyma as a function of time [6]. According to the EANM, following the intravenous administration of $^{99m}$Tc-EC, some part (17%) of it is filtered in the glomeruli while a major portion (50%) is secreted in the proximal part of the tubules by organic anion transporters [7]. 70% of the marker is extracted from the body after about 40 minutes and 95% after 1,5 hours following the injection [6]. Three phases can be distinguished in the dynamic renal scintigraphy a vascular phase, a parenchymatous phase (secretory), and an excretory phase with a decline in radioactivity. Three parameters can be obtained from the curve: Tmax, T1/2 and split function (uptake). Tmax is the time to reach the maximum amplitude of the observed activity, and it depends on the transport efficiency of the parenchyma. T1/2 denotes the time when radioactivity in the region of interest is reduced by half. The determination of ROI for both kidneys makes it possible to plot a create renographic curve describing the radioisotope concentration as a function of time (time-activity curves) [8]. The time-activity curve is determined.

Correspondence to: Agata Danilczuk
Medical University of Lublin, Poland, Aleje Rakowickie 1
20–069 Lublin, Poland
e-mail: agata@swietlicki.net
after the correction of extra-renal background as recommended by the EANM [9]. The normal state of the split function is considered to range from 45% to 55% of the total uptake for both healthy kidneys [9], although some sources give the range of 42–58% [10].

Up to date, the parameters of dynamic renal scintigraphy with \(^{99m}\text{Tc-EC}\) have only been studied either on small groups of adult volunteers [10, 11] or a small pediatric group [12].

In light of the above, the aim of this study was to evaluate the normal value of renal function parameters in \(^{99m}\text{Tc-EC}\) dynamic renal scintigraphy: \(T_{\text{max}}\) and \(T_{1/2}\), basing on a larger group of patients with at least one kidney considered as normal. The effects of age left or right side in the retroperitoneal space and sex on those parameters were examined.

**Material and methods**

**Patients**

All data were collected in the Department of Nuclear Medicine over a period from 6.09.2012 to 13.11.2014 and then analyzed retrospectively. The study was performed on a population of patients referred for diagnostic tests for suspected kidney diseases or dysfunctions. Patients whose scintigraphy did not confirm the disease and patients diagnosed with one dysfunctional and one healthy kidney were included in the study. Due to a large number of tests, we examine not only patients with renal disease, but also a certain number of patients with at least one kidney considered normal in our dynamic renal scintigraphy study. 123 patients (F/M: 70/53; aged 2–71; averaging 14.8 years old) were selected from 259 patients with at least one kidney correct by visual assessment, based on the criteria listed in Table 1. The evaluation was based on 104 patients who were 2–18 years old (F/M: 61/43; aged 2–18; averaging 9.5 years old) and 19 patients above the age of 18 (F/M: 9/10; aged 21–71; averaging 43.8 years old), which does not confirm the suspicion of doctors issuing the referrals.

The total number of kidneys considered normal in the study was 194 (F/M: 113/81; one /two normal kidneys: 52/142; left/right: 104/90; aged 2–71; averaging 14.8 years old). There were 28 kidneys considered normal in the adult population (F/M: kidneys: 12/16; left/right: 16/12; aged 21–71; averaging 45.2 years old). There were 166 kidneys considered normal in the pediatric population (F/M: 101/65; left/right: 88/78; aged 2–18; averaging 9.7 years old) that were available for renogram parameters analysis (Fig. 1). The kidneys were divided into 5 groups: 4 pediatric (2–5, 6–9, 10–13 and 14–18 years old) and adults (19–71 years old). The number of kidneys versus patient age is shown in Figure 1.

**Radiopharmaceuticals and imaging**

The scintigraphic examination was performed using a dual-head gamma-camera, immediately after the intravenous injection of \(^{99m}\text{Tc-EC}\) prepared using a sterile cold kit (Institute of Isotopes, Budapest, Hungary). The dose range from 18.5MBq to 111MBq, containing 0.3–0.7 mg of the \(^{99m}\text{Tc-EC}\) complex [13]. The amount of radioactivity for infants and children was based on their body weight [14]. Study was performed without furosemide injection, and the patients were asked to void before image acquisition. The \(^{99m}\text{Tc-EC}\) complex was administered intravenously as the acquisition on gamma camera was launched.

The study was performed using the Symbia T16 SPECT/CT hybrid gamma camera (Siemens, Erlangen, Germany). The low-energy high-resolution collimator was used. The analyzer window was set at 140 keV. The data were collected on a 128 × 128 matrix. The examination was carried in the posterior-anterior projection, having a kidney in the field of view. In the first minute of the study, the scintigraphy was recorded with a time resolution of 2 seconds (30 projections) and during the remaining 20 minutes with a time resolution of 30 seconds (40 projections). The test time was 21 minutes in total. The percentage uptake of both kidneys (split function) was determined automatically using the method of comparing fields under the time-activity curves after extrarenal background correction [9].

The manual postprocessing and the designation of the regions of interest (ROI) were performed with the use of the dedicated built-in software provided by Syngo (version: SymbianetVA10D) on a generic protocol. The renographic curves were drawn for each

![Figure 1. Number of tested healthy kidneys versus the age of patients](image-url)
ROI, for both kidneys separately. The drawing of ROI was performed for the entire kidney and the area between the kidneys (blood background) [7].

Statistics

Peak time (Tmax) was defined as the minutes from the 99mTc-EC injection to the point of highest radioactivity over the kidney. Half-clearance time (T1/2) was calculated from the peak time to the point when half of the radioactivity in the kidney disappeared. The split function represented the ratio of one kidney function to the global renal function as a percentage of all measured activity [15].

Statistical analysis was performed using the Statistica 13.1 software (Stat Soft, Poland). All values derived in this study are shown as the mean value ± coefficient interval (95%). The distribution was examined using the Shapiro–Wilk test of normality. Dependencies between the parameters were estimated using the nonparametric Mann–Whitney U test for two independent samples and the Kruskal–Wallis test for more than two independent samples. The statistical significance was defined as p ≤ 0.05. Pearson linear correlation coefficients were applied.

Results

Mean values, standard deviation (SD) and coefficient interval (CI) of the renographic curve parameters for all kidneys obtained in this study are listed in Table 2. Normal values [here assumed to be the mean value (mean SD)] of Tmax is 2.85 min [0.58 min] and T1/2 is 8.7 min [1.83 min]. The values obtained in the pediatric study are different and age-dependent. They are also given in Table 2. The normal value of Tmax is 2.81 min (0.59 min) and that of T1/2 is 8.63 min (1.86 min).

A comparison of Tmax, T1/2 in different age groups (5 groups: 2–5, 6–9, 10–13, 14–18, 19–71 years) shows that age has no significant effect on both parameters: Tmax (p = 0.061) and T1/2 (p = 0.386). In the pediatric groups (4 groups: 2–5, 6–9, 10–13 and 14–18 years), too, the differences are insignificant: Tmax (p = 0.07) and T1/2 (p = 0.192).

The normal values of renographic curve parameters for both sexes and sides are given in Table 3. A comparison of Tmax, T1/2 for female and male patients shows that the sex of the patient does not affect Tmax (p = 0.339) and T1/2 (p = 0.256). In the case

Ethics

Every patient signed an informed consent from. The study protocol and informed consent forms were approved by the ethics committee of the Bioethical Council, Medical University of Lublin, Poland.

The tests were tolerated well by all patients.

| Table 2. Normal values of the renographic curve parameters  Tmax, T1/2 depending on the total number of tested kidneys, pediatric study, and age group |
|---|---|---|---|---|---|---|---|
| Age group | n | Min [min] | Max [min] | Median [min] | Mean [min] ± SD | conf. interval (95%) lower | conf. interval (95%) upper |
| Tmax | all | 194 | 1.50 | 4.50 | 3.00 | 2.85 | 0.58 | 1.16 | 1.69 | 4.00 |
| | pediatric | 166 | 1.50 | 4.50 | 3.00 | 2.81 | 0.59 | 1.16 | 1.65 | 3.97 |
| | 2–5 years | 31 | 1.50 | 4.00 | 2.50 | 2.68 | 0.53 | 1.09 | 1.59 | 3.77 |
| | 6–9 years | 54 | 2.00 | 4.00 | 2.50 | 2.68 | 0.56 | 1.14 | 1.54 | 3.81 |
| | 10–13 years | 44 | 2.00 | 4.00 | 2.50 | 2.87 | 0.60 | 1.23 | 1.66 | 4.10 |
| | 14–18 years | 37 | 2.00 | 4.50 | 3.00 | 3.05 | 0.59 | 1.21 | 1.85 | 4.26 |
| | 19–71 years | 28 | 2.00 | 4.50 | 3.00 | 3.06 | 0.53 | 1.12 | 1.94 | 4.17 |
| T1/2 | all | 194 | 5.15 | 14.90 | 8.50 | 8.70 | 1.83 | 3.61 | 5.10 | 12.32 |
| | pediatric | 166 | 5.15 | 14.90 | 8.50 | 8.63 | 1.86 | 3.71 | 4.90 | 12.32 |
| | 2–5 years | 31 | 5.50 | 14.90 | 8.70 | 8.93 | 1.98 | 4.11 | 4.82 | 13.04 |
| | 6–9 years | 54 | 5.15 | 12.10 | 7.70 | 7.99 | 1.65 | 3.34 | 4.65 | 11.33 |
| | 10–13 years | 44 | 6.10 | 13.50 | 8.58 | 8.98 | 1.82 | 3.72 | 5.27 | 12.70 |
| | 14–18 years | 37 | 5.40 | 14.10 | 8.70 | 8.91 | 1.93 | 3.96 | 4.95 | 12.87 |
| | 19–71 years | 28 | 6.00 | 12.80 | 9.24 | 8.96 | 1.63 | 3.40 | 5.68 | 12.48 |

| Table 3. Comparison of normal values of the renographic curve parameters  Tmax, T1/2 for both sexes and sides |
|---|---|---|---|---|
| Age group | Female | Male | Left kidney | Right kidney |
| Mean Tmax [min] | all | 2.88 | 2.90 | 2.86 | 2.64 |
| | children (2–18) | 2.85 | 2.75 | 2.82 | 2.90 |
| | adults | 3.17 | 2.97 | 3.03 | 3.08 |
| Mean T1/2 [min] | all | 8.57 | 8.88 | 8.74 | 8.64 |
| | children (2–18) | 8.42 | 8.97 | 8.66 | 8.61 |
| | adults | 9.82 | 8.52 | 9.22 | 8.89 |
of children, the differences between Tmax and T1/2 for female and male patients are Tmax (p = 0.408) and T1/2 (p = 0.075). T1/2 correlates with Tmax (p = 0.004). The correlation between these values depending on the age group is (r = 0.604) for all kidneys and (r = 0.59) for children.

**Discussion**

We have developed the standards of dynamic renal scintigraphy parameters for the nuclear medicine department in which the study was conducted. This will facilitate the preliminary assessment of kidney health, which is particularly useful in the study of children. At the same time, to obtain comprehensive results, a more accurate visual assessment of the images is necessary to exclude focal defects in the parenchyma as they may be invisible on the renographic curve. The Tmax and T1/2 parameters were evaluated. The split function ranging from 45% to 55% for each kidney was considered only in the case of patients having both kidneys normal.

Comparing the differences between the obtained calculated parameters one can observe that:

1. The normal value of the secretory function parameter does not significantly depend on age. The changes developing in the kidneys with age are related to all kidney structures. First of all, a reduction in the size and weight of the organ can be observed. The study shows that the size of the glomeruli does not change with age, however, the number of cells in the glomeruli decreases to a significant degree. This may eventually lead to renal function impairment [1]. The scatter plot in Figure 2 shows both parameters tend to slightly increase with age (which demonstrates a slight increase in the parameters for older patients), but the correlation is under the assumed significance level of p = 0.05. This indicates that there is no need to establish separate norms for adults and children. Only healthy kidneys were taken into consideration, so we do not obtain any information about differences in kidney diseases between adults and children.

2. In terms of the sex, globally, there are no significant differences for any parameters, as can be concluded from Table 3, even though that there are differences in the structure and function of the kidneys depending on the gender [16].

3. Globally, there are no significant differences between the sides.

4. There is a strong positive correlation between the excretory function parameter and the secretory function parameter for normal kidneys.

Compared to Van Nerom first evaluation on healthy volunteers from 1993 [11], calculated times for adults are slightly different (our results are given in Tab. 3). The Tmax mean value [min] for the left and the right kidney is 3.3 and 5.0 (Van Nerom) vs. 3.03 and 3.08. The T1/2 mean value [min] for the left and the right kidney is 6.5; 10.0 (Van Nerom) vs. 9.22; 8.89. The differences might result from the size of the test group; the above-mentioned study was conducted on a group of only six adult male volunteers (averaging 27.5 years old), while the present study was conducted on 27 adults (F/M: 9/10; aged 21–71; averaging 43.8 years old).

In a 1997 study examining 4 children with normal kidneys and 15 children with various renal disorders [12], the calculated renal function parameters for normal kidneys were found to be similar for 99m Tc-EC and 99m Tc-MAG3. The mean Tmax values (min) were 3.2 and 3.1, respectively, and the mean T1/2 values were 6.3 and 6.4, respectively. Again, the difference might stem from the size of the test group. The differences might also depend on the group selection because in the aforementioned study both normal kidneys and kidneys with various renal disorders were examined.

Compared to the Sohaib data from 2013 [15], the calculated function parameters are much lower. More specifically, the Tmax mean value (min) is 4.6 (Sohaib) vs. 3.06, while the T1/2 mean value [min] is 14.5 (Sohaib) vs. 8.96. Again, the research group is smaller and contains only adult male volunteers (averaging 30 years old). This difference may also result from the fact that all curves were considered correct in the data collecting process. There are also significant differences in the parameters of kidney perfusion that were obtained in the studies conducted with other dynamic renal scintigraphy radiopharmaceuticals such as 99mTc-MAG3 [15, 17].

International Scientific Committee of Radionuclides in Nephrology (ISCORN) noted that the final urine flow depends on the hydration state. Dehydration can cause false-positive results and hydration degrees significantly affected renogram pattern and renal parameters [18]. When the ROI was placed over the whole kidney, the parameters that increased statistically significantly in the dehydrated state where Tmax, T1/2 [5, 17, 19]. The quality of dynamic renal imaging can be degraded by a full bladder, the patient should void before image acquisition, to promote drainage, or it can influence renal function parameters [5]. Our study was performed without furosemide injection, and the patients were asked to void before image acquisition.

In this study mean values, standard deviation (SD) and coefficient interval (CI) were used. The use of the standard error of the mean (SEM) should be limited to inferential statistics where the author explicitly wants to inform the reader about the precision of the study and how well the sample truly represents the entire population. In terms of diagrams and figures, too, the use of SD is preferable to the SEM. To determine the standard range for the biological parameter, it is proposed that the coefficient interval

![Figure 2. Scatter plot of secretion and extraction times (Tmax and T1/2) versus the age of patients in 99mTc-EC dynamic renal scintigraphy.](image-url)
(the level of confidence of 95%) should be used to ensure that the deterministic parameter is captured by the interval [20].

A great advantage of this study is that it concerns the problem that has not been widely discussed in the literature and that it was conducted on a larger research group. Although the $^{99m}$Tc-MAG3 dynamic renal scintigraphy has been investigated by many studies, the standards of $^{99m}$Tc-EC dynamic renal scintigraphy have not yet been sufficiently defined. At the same time, it should be noted that the calculated norms for the analyzed parameters may disagree with the standards obtained in other research centers, due to the subjectivity of ROI selection and renographic curve correctness assessment. The results of this study can be a starting point for further research on the establishment of renographic curve parameter norms for patients with particular kidney diseases.

The best cutoff value to separate normal from abnormal values would be obtained by comparing results for normal and diseased populations. In practice, it is often difficult to generalize such a comparison because the degree of abnormality can depend on the selection criteria used to define the disease population. Any value lying outside of the fifth or 95th percentile is considered abnormal. Values outside the lower range of normal are likely to represent a processing problem rather than an abnormality of renal function.

Conclusions

In this study, we proposed the range of normal renal function parameters for $^{99m}$Tc-EC dynamic renal scintigraphy. The study has demonstrated that the normal value of the secretory and excretory function parameter does not depend on age, and that, globally, there are no differences between the sexes and the sides for any parameter.

Conflicts of interest

There are no conflicts of interest.

References


The impact of depression and anxiety in prognosis of patients undergoing myocardial perfusion imaging with $^{99m}$Tc tetrofosmin SPECT for evaluation of possible myocardial ischemia

Andreas Fotopoulos1, Petros Petrikis2, Ioannis Iakovou3, Athanasios Papadopoulos4, Sakelariou Konstantinos1, Evangelia Gkika1, Lampros Lakkas5, Christos Touzios1, Konstantinos Pappas5, Antonios Klaroudas1, Argyrios Doumas2, Chrissa Sioka1

1Department of Nuclear Medicine, Medical School, University Hospital of Ioannina, Greece, Ioannina, Greece
2Department of Psychiatry, Medical School, University Hospital of Ioannina, Ioannina, Greece
32nd Nuclear Medicine Laboratory, AHEPA University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece
4Department of Medical Physics, University Hospital of Ioannina, Greece
5Department of Cardiology, University Hospital of Ioannina, Greece

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Abstract

BACKGROUND: The goal of this study was to evaluate the prevalence of depression and anxiety in patients subjected to myocardial perfusion imaging (MPI) with $^{99m}$Tc tetrofosmin stress-rest single-photon emission computer tomography (SPECT), and their impact on their cardiological events or disease.

MATERIAL AND METHODS: Patients referred to the Nuclear Medicine Department for $^{99m}$Tc tetrofosmin myocardial MPI-SPECT were asked to fulfill the Zung Self-Rating Depression Scale (ZDS) and Hamilton anxiety questionnaire (HAQ). Among 213 patients who completed the ZDS and HAQ, 80 patients (59 males and 21 females) were selected for this study because they had no known psychological disease, other disease that could influence psychological status, or use of narcotic drugs. Collected data from MPI and psychological status were subsequently analyzed.

RESULTS: Among all 80 patients, 52 patients (65%) had abnormal MPI of whom 28/52 (53.8%) exhibited either depression, anxiety or both, and 28 (35%) patients had normal MPI of whom 10/28 (35.7%) had abnormal psychological status. The higher number of patients with abnormal psychological status in association with abnormal MPI was noted predominantly in patients with previously established coronary artery disease. A correlation was also noted between obesity, cardiac heredity and depression or anxiety in patients with abnormal MPI.

CONCLUSIONS: Patients that exhibit depression, anxiety, or both, have high rates of myocardial ischemia, and thus are at risk for subsequent cardiological events.

KEY words: myocardial perfusion imaging; myocardial ischemia; depression; anxiety; psychological status; MPI; SPECT

Introduction

Anxiety and depression are frequently manifested in patients with cardiovascular diseases. Prevalence may vary between 15 and 50%, according to diagnostic criteria used and demographic characteristics of the patients [1]. Depression may be associated with coronary artery disease (CAD) and its consequences such as cardiac arrhythmias, myocardial infarction (MI) and heart failure. Although the exact physiological mechanisms for this association remain unclear, it may be due to hypothalamic–pituitary dysregulation, altered immune function or existence of common unknown risk factors for both medical conditions [2, 3]. Scientific evidence over the last few years reported significant association between anxiety or depression and various organic conditions including cardiac
diseases [1, 4]. Furthermore, patients with cardiac diseases and depression tend to exhibit poor risk factor control resulting into further deterioration of their cardiac disease and prognosis [1]. Anxiety has been also linked to increased mortality in patients with CAD but this association was reported less strong than that of depression [5]. It is interesting that anxiety seems to improve in patients that have detailed imaging studies concerning their disease and good communication with their physician about the status of their medical condition [6].

Myocardial perfusion imaging (MPI) SPECT may be used to assess the myocardial condition either in patients with known MI, or post either percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) [7], or with silent myocardial ischemia due to non-specific cardiac complaints [8–10]. The MPI grading may be able to provide an excellent tool to monitor response to treatment, follow-up status and long term prognosis [11, 12].

Women overall appear to display more nonspecific cardiac complaints than men. However, these symptoms by themselves have unknown clinical significance not necessarily linked to myocardial ischemia in the absence of other relative clinical manifestations [10]. However, MPI may be able to identify myocardial ischemia in elderly women with angina or in asymptomatic women with concomitant diabetes mellitus or hypertension [13]. Female patients with CAD demonstrate positive MPI [14] with sensitivity of 87.16% and specificity of 97% [15]. In such cases, a summed stress score (SSS) ≥ 14 denoted an increased risk for cardiac events and an SSS ≥ 22 for subsequent significant cardiac events such as acute MI and cardiac death [16].

In the present retrospective study, we evaluated the rate of myocardial ischemia in patients who were subjected to MPI with 99mTc-TF-SPECT, due to non-specific cardiac complaints of various types, or in patients that had known myocardial disease for follow up after CABG or PTCA. Furthermore, in all patients we evaluated the association of anxiety and/or depression with the known cardiovascular risk factors such as age, smoking, obesity, diabetes mellitus (DM), arterial hypertension, dyslipidemia and cardiac heredity.

Material and methods

Patients

In the present study there were 80 patients, 59 men and 21 women, that had MPI either for non-specific cardiac symptoms (workup to rule out CAD), or patients with known CAD and previous PTCA or/and CABG for follow up of their myocardial status. Cardiac risk factors were noted in each patient’s medical history (obesity, smoking, arterial hypertension, diabetes mellitus, dyslipidemia, and cardiac heredity). Patients were considered as smokers when smoking habits were active or stopped during the last 3 months. Females under anti-hypertensive drugs or with systolic blood pressure (BP) ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg were noted as having hypertension as risk factor. Diabetes mellitus as risk factor was noted in females under anti-diabetic medication and fasting glucose > 126 mg/dL. Finally, dyslipidemia was considered in patients receiving therapy with statins or exhibiting fasting cholesterol level > 220 mg/dL.

SPECT MPI

All study participants had been subjected to 99mTc-TF-SPECT before and after stress using a 1-day imaging protocol according to published guidelines [17]. Stress protocol was consisted either of a dynamic exercise (Bruce protocol treadmill exercise test) or a pharmacological test with either dipyridamole or dobutamine. The electrocardiography was continuously monitored during stress. All patients were first injected with 8 mCi Tc-99m tetrofosmin after stress or 20 mCi at rest followed by acquisition of images 40 minutes later via a 90°-angled dual-head camera, employing a collimator with 64 stops and 25 s per projection over a 180° arc. Reconstruction of images was consisted of filter back projection without attenuation correction [18].

MPI was visually evaluated by two nuclear medicine specialists, using a 17 scoring each segment on a scale of 0 to 4 according to the severity of the myocardial perfusion deficit [18]. Thus, score 0 was designated when there was no decreased myocardial activity, score 1 with mildly decreased activity, score 2 for moderate decreased activity, score 3 for severely decreased activity and score 4 for absent tracer activity. All individuals scores at rest and stress were combined and produced the summed rest score (SRS) and summed stress score (SSS). The difference of the two scores (S-RSS) was also calculated and evaluated. A summed difference score (SDS) was obtained by subtracting the rest score from the stress score; in the presence of a reversible defect (or ischemia) the score was positive. Myocardial ischemia (MIS) was graded as mild when SSS was 4 to 8, moderate from 9 to 13, and severe when SSS over 13 [19].

Evaluation of psychological status

Patients who were subjected to 99mTc-TF-SPECT-MPI in the Department of Nuclear Medicine were asked to fulfill the Zung Self-Rating Depression Scale (ZDS) and Hamilton anxiety questionnaire (HAQ). The ZDS consists of 20 items that quantify the depressive symptoms of a patient. Each item is scored on a range from 1 to 4. Total score lower than 50 is considered as normal, between 50 and 59 as mild depression, between 60 to 69 as moderate depression, while score over 70 as severe depression [20]. The HAQ consists of 14 items and is widely used to assess both psychic and somatic anxiety. Each item is scored on a range of 0 (not present) to 4 (severe anxiety), with a total score ranging from 0 to 56 [21].

Among the patients who agreed to participate to the study, those with known disease such as cancer, multiple sclerosis, chronic kidney disease or any other condition that could influence psychological status were excluded from the study. Furthermore, those with known psychological disease, use of narcotic drugs were also excluded. ZDS and HAQ results were evaluated by a psychiatrist.

Statistical analysis

The evaluation of the myocardial perfusion studies were analyzed utilizing the statistical software SPSS version 20 for windows (SPSS, Chicago, IL). Several groups of patients were developed based on the gender, the degree of abnormality and their correlation with the specific characteristics of depression, anxiety, obesity, cardiac heredity, smoking and hypertension.

Baseline characteristics were described using, median and frequencies for categorical variables. For the verification of correlation
“N-1” Chi-squared test has been utilized to determine the significant difference between the means of two groups, which may be related in certain features. The alpha of 0.05 was used as the cutoff for significance and thus if the p-value was less than 0.05, the difference of the two groups was significant. Additionally, a Spearman’s rho methodology applied for the identification of the correlation among the different characteristics and features. A Spearman’s rank-order correlation between the groups of features provides a degree of correlation regarding the level of the r_s score. Thus, r_s of 0.2 to 0.39 describe as weak correlation and 0.4 to 0.59 as moderate correlation, respectively.

**Results**

The patients’ age, medical history of myocardial infarction and cardiac risk factors are shown in Table 1. Abnormal MPI was found in 52 of 80 patients (65%), and normal MPI in 28/80 (35%) patients. Among all study participants with abnormal MPI 53.8% exhibited depression, anxiety or combination of both (Tab. 2). However, patients with normal MPI demonstrated lower rate of psychological abnormalities at 35.7%. Statistical analysis did not reveal any statistical significance possibly due to the small number of patients studied; however, a statistical trend was noted (p = 0.1244). Patients that had previously established CAG and had abnormal MPI performed for follow-up after PTCA or CABG had significantly higher rates of depression or anxiety (57.1%) compared to those that had normal MPI (28.6%). However, such a difference was less pronounced in patients that were undergoing MPI as an initial evaluation of myocardial status either as a follow-up after cardiologic intervention; p* — trend of statistical significance; p** — statistical significance.

Furthermore, evaluation of the results according to sex demonstrated that men had much higher percentage of abnormal MPI (47/59, 80%) compared to women (5/21, 24%) p < 0.0001 (Tab. 3). In addition, our results suggested that women had a higher rate of anxiety than men; however, due to the small numbers of female patients it was not able to document it statistically, even though a trend of statistical significance was noted, p = 0.1363.

In addition, a Spearman’s rank-order correlation was run to determine the relationship between the depression and anxiety with several cardiological risk factors. In patients with abnormal MPI, depression and anxiety found to have a moderate correlation (r = 0.411, p = 0.001) and weak correlation (r = 0.369, p = 0.001), respectively, with obesity. On the other hand, in normal MPI group, the obesity was only correlated weakly with the anxiety (r = 0.351, p = 0.001). Another feature that appears correlation with the MPI patient’s condition is the cardiac heredity. Thus, weak correlation (r = 0.231, p = 0.001) appeared for abnormal MPI patients between the cardiac heredity and the depression.

**Discussion**

Depression and anxiety are frequently observed in patients with cardiovascular disease and linked with increased morbidity and poor prognosis. Apart from a possible direct effect on several cardiovascular risk factors such as blood pressure, they lead the patient into neglecting the physician-directed therapeutic interventions and further deterioration of their cardiovascular status [22, 23].

In the present study, 80 patients were subjected to MPI in order to assess their myocardial status either as an initial evaluation of possible CAD or as a follow-up of known CAD. Among all patients examined, 52 patients (65%) had abnormal MPI and 28 (35%) normal examination. In the group with the abnormal

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**Table 1. Characteristics of the patients [mean value ± standard deviation (min-max)]**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All 80 patients</th>
<th>Male 59 patients</th>
<th>Female 21 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic MPI</td>
<td>45/80 (56%)</td>
<td>28/45 (62%)</td>
<td>17/35 (38%)</td>
</tr>
<tr>
<td>PTCA &amp; CABG MPI</td>
<td>31/80 (39%)</td>
<td>17/31 (55%)</td>
<td>14/49 (23%)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>66.69 ± 11.61</td>
<td>66.72 ± 11.59</td>
<td>66.57 ± 13.10</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>20/80 (25%)</td>
<td>10/20 (16%)</td>
<td>10/20 (16%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>25/80 (11%)</td>
<td>16/25 (27%)</td>
<td>9/25 (20%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>59/80 (74%)</td>
<td>43/59 (73%)</td>
<td>16/20 (40%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>35/80 (44%)</td>
<td>20/35 (58%)</td>
<td>15/45 (40%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>54/80 (67%)</td>
<td>42/54 (67%)</td>
<td>12/26 (23%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>26/80 (33%)</td>
<td>17/26 (36%)</td>
<td>9/24 (20%)</td>
</tr>
<tr>
<td>Heart heredity</td>
<td>27/80 (34%)</td>
<td>20/27 (74%)</td>
<td>7/23 (26%)</td>
</tr>
</tbody>
</table>

**Table 2. Rates of abnormal MPI, depression, anxiety, or both in patients subjected to myocardial scintigraphy either for diagnostic reasons or after cardiologic intervention (follow-up)**

<table>
<thead>
<tr>
<th>Psychological status</th>
<th>MPI (+) 52/80 (65%)</th>
<th>MPI (+) 28/80 (35%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients that had MPI (N = 80)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>10/52 (19.2%)</td>
<td>3/28 (10.7%)</td>
<td>0.3284</td>
</tr>
<tr>
<td>Anxiety</td>
<td>13/52 (23.1%)</td>
<td>4/28 (14.3%)</td>
<td>0.3512</td>
</tr>
<tr>
<td>Both</td>
<td>5/52 (9.6%)</td>
<td>3/28 (10.7%)</td>
<td>0.8764</td>
</tr>
<tr>
<td>Total</td>
<td>28/52 (53.8)</td>
<td>10/28 (35.7%)</td>
<td>0.1244 *</td>
</tr>
</tbody>
</table>

**Table 3. Patients with abnormal MPI and depression, anxiety, or both**

<table>
<thead>
<tr>
<th>Sex</th>
<th>No MPI (+)</th>
<th>Depression</th>
<th>Anxiety</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>32/59 (54%)</td>
<td>17/32 (27%)</td>
<td>10/32 (31%)</td>
<td>5/32 (16%)</td>
</tr>
<tr>
<td>Female</td>
<td>14/21 (67%)</td>
<td>7/14 (50%)</td>
<td>7/14 (50%)</td>
<td>0/14 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>46/80 (58%)</td>
<td>24/46 (52%)</td>
<td>17/46 (37%)</td>
<td>5/46 (6%)</td>
</tr>
</tbody>
</table>

**N-1** Chi-squared test has been utilized to determine the significant difference between the means of two groups, which may be related in certain features. The alpha of 0.05 was used as the cutoff for significance and thus if the p-value was less than 0.05, the difference of the two groups was significant. Additionally, a Spearman’s rho methodology applied for the identification of the correlation among the different characteristics and features. A Spearman’s rank-order correlation between the groups of features provides a degree of correlation regarding the level of the r_s score. Thus, r_s of 0.2 to 0.39 describe as weak correlation and 0.4 to 0.59 as moderate correlation, respectively.

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In the present study, 80 patients were subjected to MPI in order to assess their myocardial status either as an initial evaluation of possible CAD or as a follow-up of known CAD. Among all patients examined, 52 patients (65%) had abnormal MPI and 28 (35%) normal examination. In the group with the abnormal
MPI, 53% exhibited depression (19.2%), anxiety (23.1%) or both (9.6%). In contrast only 35.7% (p = 0.1244/indicating a trend of statistical significance) of patients with negative MPI exhibited any psychological abnormality (depression 10.7%, anxiety 14.3%, both 10.7%) (Tab. 2). This trend towards statistical significance of increased frequency of psychological abnormalities in patients with positive MPI, but not definite statistical significance, may be due to the relative small number of patients. It suggests though that psychological abnormalities may predispose to the development of CAD, independently of the other well established risk factors. Interestingly, in our study, these differences were more pronounced in the group of patients with known CAD, undergoing the MPI for follow up rather than the group that test for diagnostic purposes, supporting the same conclusion. Definitely, larger studies are needed to verify these findings. A prospective cross-sectional study of 314 patients presented with chest pain showed a significant association between degree of depression and CAD in female patients [24]. Similar results of female predominance of depressive symptoms as well as higher incidence of anxiety and CAD were reported in a Chinese study [25]. Another large study in 514 German CAD patients, evaluated by the Mini International Neuropsychiatric Interview and the Global Assessment of Functioning (GAF) scale demonstrated comorbidity of depression with CAD and treatment of the depression resulted in improvement of this condition [26]. Interestingly, patients undergoing CABG operation, depression and anxiety were increased after the operation compared to the pre-operative period [27].

Evaluation of our results according to sex, demonstrated predominance of men rather than women as having abnormal MPI and thus CAD (Tab. 3). In addition, although our findings suggested that women had a higher rate of anxiety than men, the numbers of female patients were too small to establish any significance; however, with caution we noted a trend of statistical significance. A previous study in patients undergoing MPI for assessing myocardial status in patients with known or unknown CAD was consistent with our findings showing high level of anxiety mostly in women prior to the examination [28]. Other studies in women reported positive MPI findings in 32% [29], and a sensitivity of 91% and specificity of 70% when SSS was > 8 [30]. In general, patients with anxiety disorders or co-existence of anxiety/depression are associated with increased prevalence of coronary heart disease [31]. Although in some studies depression seems to be the most important factor associated with CAD [32, 33], other studies indicate anxiety as the predominant psychological factor contributing to CAD [31]. Nevertheless, co-existence of both psychological factors appears to have added validity towards this regard. A study on 118 men without history of psychological disturbances demonstrated that after CABG, 16–39.8% of them developed depression and 27.1% anxiety independent of CAD severity [33]. However, female patients demonstrate further reduced quality of life after a cardiac event compared to men. This quality of life refers to appearance anxiety, depression and low self-esteem among other things and may last for over one year [34]. In another study, the reported rates of CAD in female veterans’ patients were 4.16%, reaching up to 36% when patients were smokers. Furthermore, those with depression had 60% higher chance of CAD [35].

The mechanisms that the described psychological parameters contribute to the development of CAD are not very well defined and could be multi sequential. Some investigators suggest that somatic-vegetative features of depression may be linked at an early stage to the development of coronary artery disease [36]. In our study, obesity and cardiac heredity were also associated with depression and anxiety. Previous studies have described an association between hypertension and anxiety, and both depression and anxiety have been linked to diabetes mellitus [37] and hypercholesterolemia [38].

Conclusions

In conclusion, our results showed that patients with myocardial dysfunction, as evident by abnormal MPI, have increased frequency of coexisting depression, anxiety or both, suggesting that these factors may be contributing risk factors. In addition, both males and females were at higher risk for CAD if depression and anxiety were combined with obesity or cardiac heredity. Further larger studies are needed to verify these findings.

References


Patterns of vascular graft infection in 18F-FDG PET/CT

Beata E.Chrapko, Marek Chrapko, Anna Nocuń, Tomasz Zubilewicz, Boguslaw Stefaniak, Jakub Mitura, Andrzej Wolski, Piotr Terelecki
Chair and Department of Nuclear Medicine, Medical University of Lublin, Lublin, Poland

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Abstract

BACKGROUND: 18F-FDG PET/CT has become an important tool in diagnosis of prosthetic vascular graft infections (PVGI). The aim of the study was to identify the patterns of vascular graft infection in 18F-FDG PET/CT.

MATERIAL AND METHODS: The study was performed in 24 patients with vascular graft infection, in 17 patients implanted in an open surgery mode and in 7 patients by endovascular aortic repair (EVAR). Vascular prostheses were evaluated by two visual scales and semi-quantitative analysis with maximum standardized uptake values (SUV max).

RESULTS: In the 3-point scale: 23 patients were in grade 1 and one patient was in grade 2. In the 5-point scale: 19 patients were in grade 5 with the highest activity in the focal area, 4 patients were in grade 4 and one patient in grade 3. The visual evaluation of 18F-FDG PET/CT study revealed that peri-graft high metabolic activity was associated with occurrence of morphological abnormalities (n = 21) like gas bubbles and peri-graft fluid retention or without abnormal CT findings (n = 3). The presence of the gas bubbles was linked to higher uptake of 18F-FDG (p < 0.01, SUVmax 11.81 ± 4.35 vs 7.36 ± 2.80, 15 vs 9 pts). In EVAR procedure, the highest metabolic activity was greater than in classical prosthesis (SUVmax 21.5 vs 13).

CONCLUSIONS: 18F-FDG PET/CT is a very useful tool for assessment of vascular graft infections. CT findings like gas bubbles, or peri-graft fluid retention were associated with significantly higher glucose metabolism; however, in some cases without anatomic alterations, increased metabolic activity was the only sign of infection.

KEY words: fluorodeoxyglucose; PET/CT scan; vascular graft infections

Introduction

The incidence of prosthetic vascular graft infections (PVGI) is ranging between 1 and 6%, depending on the location of the vascular graft — in intra-abdominal prostheses, the overall risk of infections is around 1%, but considerably increases to 6% when the graft is anastomosed to a femoral artery [1–3]. In 20–75% of cases PVGI may lead to the death, while in 50% it may result in morbidity such as loss of a limb [1, 4]. Regarding the onset of PVGI, there are early and late infections. The early PVGI starts at the time of surgery, when causative organisms infect the graft and may appear up to 4 months after surgery, whereas the more common type — the late one, occurs at least 4 months after the implantation of prosthesis. In the early infections the clinical manifestations of PVGI can be acute, whereas in the late one, may be more subtle. The clinical presentation of the PVGI also depends on the location of the graft. In deeply fashioned grafts, pathology can be faint and difficult to diagnose. In cases of shallow grafts, for example in an extremity, the manifestations are often overt [4].

There are three groups of predisposing risk factor: patient-related, procedure-related and pathogen-related. The patient-related aspects, among others, include: obesity, diabetes, immunodeficiency, infection at the time of graft placement, and prolonged preoperative hospital stay [5, 6]. The procedure-related factors connected with surgery are: prolonged, emergency or “redo” vascular surgery, bowel injury, groin incision, wound infections, postoperative hematoma, seroma, pseudoaneurysm or wound-bed bleeding [5–7]. The causative pathogens are Staphylococcus aureus and Pseudomonas aeruginosa in 80% of cases, which produce a very strong biofilm, and when they adhere to the graft, infections can easily develop along the prosthesis and adjacent tissue. The pathogens also release destructive endotoxins, which can cause anastomotic dehiscence [6]. Synthetic vascular graft prostheses are made of either polyester (Dacron®) or polytetrafluoroethylene (PTFE), both of which are also used in endovascular and open mode surgery. The incidence of PVGI is comparable in both materials [7].

The right diagnosis of PVGI is crucial, but there is no clear consensus of diagnostics criteria. The imaging of PVGI is still
challenging, because false-positive tests may lead to unnecessary surgery, whereas false-negative are associated with under-treatment and in consequence with high morbidity [4]. Routine tests in PVGI include: clinical, biochemical, microbiological and imaging studies. Laboratory analysis in prosthesis infection commonly reveal elevated white blood cell (WBC) count, increased C-reactive protein (CRP) serum level and increased sedimentation rate. Microbiological assessment is based on skin, wound, blood or graft surrounding tissue culture. An ultrasound scan can easily detect peri-graft fluid. In contrast enhanced computed tomographic angiography (CECT), which is considered as the test of choice, the manifestation of infection is peri-graft ectopic gas, fluid and soft tissue enhancement and formation of the pseudoaneurysm. In advanced PVGI the detection rate in CECT is close 100%. Morphologic abnormalities are often nonspecific in vascular graft infection, therefore the use of metabolic study increases. The positron emission tomography/computed tomography (PET/CT) with use of 18F-fluoro-2-deoxy-D-glucose (18F-FDG) has become an important method of diagnosing inflammation and infection. In early and low-grade PVGI, the utility of 18F-FDG PET/CT is increased. There are different grades of focal pattern of 18F-FDG uptake.

In the recommendation of Management of Aortic Graft Infection Collaboration (MAGIC) there are three main categories of diagnosis of graft infection: clinical/surgical, radiological and laboratory [8]. Diagnostic criteria were ranked as either “major” or “minor” within each category. As it is recommended in MAGIC, Aortic Graft Infection (AGI) is suspected if one isolated major criterion or two of minor criteria from different categories are present. AGI is confirmed if there is one major plus any other criterion (major or minor) from another category. The major clinical/surgical criteria include presence of pus, open wound, fistula development, graft insertion in infected site. The laboratory major criteria are pathogens recovered from explanted graft or intra-operative or from percutaneous aspirate of peri-graft fluid. The serum levels of inflammatory markers like erythrocyte sedimentation rate (ESR), CRP or WBC belong to the minor criteria in laboratory categories in MAGIC. Major radiological criteria on CT scan are peri-graft fluid more than 3 months or peri-graft gas more than 7 week after prosthesis insertion or increased peri-graft gas in serial imaging. Increased metabolic activity on 18F-FDG PET/CT belongs to minor radiological criteria of infections. In our opinion however, there is much more potential value in non-invasive examination like 18F-FDG PET/CT. There are a number of questions and concerns regarding the diagnosis of vascular prosthesis infections by 18F-FDG PET/CT, but the most important issue is finding the pattern of infection.

The aim of the study was to identify the pattern of aortic vascular graft infection in patients with high probability of infective process by use of 18F-FDG PET/CT.

**Material and methods**

**Patients**

The study was performed in 24 consecutive patients who attended Department of Nuclear Medicine University Hospital in Lublin, between March 2013 and October 2018, with vascular graft infection. Clinical material consisted of 21 male and 3 female patients, mean age 65 (35–84) years. Strong clinical suspicion of vascular graft infection was the start point of diagnosis. The definition of vascular prosthesis infection is graft colonization by pathological bacterial strains. According to mentioned above MAGIC criteria [8], the surgical manifestations were: fistula development, infected pseudoaneurysm, erythema, warmth, swelling purulent discharge and pain. Than the laboratory tests, bacteriological culture and radiological signs of infection like: peri-graft air, persistent fluid or abscess was noticed in these patients. The main reason of vascular prosthesis implantation was aneurysm of the aorta (19 patients) and Leriche’s syndrome (5 patients). In general, there were 4 patients with a thoracic aorta graft (TAG) and 20 patients with an abdominal aorta graft (AAG). In 7 patients endovascular aortic repair (EVAR) was performed: in one patient in the thoracic aorta and in 6 patients in the abdominal aorta. In 17 patients an open surgery mode was applied. In 4 patients the femoro-popliteal graft coexisted (in patients with classical abdominal prostheses). 18F-FDG PET/CT were performed from 12 months to 15 years after vascular graft implantation with the exception of one patient, when 18F-FDG PET/CT was performed 1 month after Bentall de Bono procedure, because of rapid progress of infection symptoms. There were 3 patients with diabetes mellitus in the group of stent-grafts patients. The blood serum inflammatory markers were: CRP mean 80.5 mg/L (range 9–300) and WBC mean 13.4 (range 7–38) K/mL. Baseline study population is presented in Table 1.

**18F-FDG PET/CT imaging**

Patients were prepared for the study with 24 hours of low carbohydrate diet, and fast for at least 6 hours prior to the examination. The interval between insulin and 18F-FDG administration was more than 6 hours. Blood glucose level was measured just before injection and the mean value was 104.7 mg/dL, range was 78–140 mg/dL. One hour before imaging, the subjects were injected with 3.5 MBq of 18F-FDG per kilogram of body weight, mean activity 241.5 MBq, range 198–334 MBq. During the uptake phase, patients were waiting in a quiet, dimly lit room. Patients were scanned in supine position, with arms overhead. 18F-FDG PET/CT scans were obtained from the vertex of skull to the mid-thigh level using 18F-FDG PET/CT system Biograph mCT S(64)-4R (Siemens, Erlangen, Germany).

### Table 1. Description of the study material

<table>
<thead>
<tr>
<th>Patient’s details</th>
<th>Localization of prosthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thoracic aortic graft</td>
</tr>
<tr>
<td>All</td>
<td>24</td>
</tr>
<tr>
<td>Age</td>
<td>24</td>
</tr>
<tr>
<td>Male</td>
<td>21</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
</tr>
<tr>
<td>EVAR</td>
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</tr>
<tr>
<td>Open mode</td>
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</tr>
<tr>
<td>Coexistence of femoral-popliteal</td>
<td>4</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3</td>
</tr>
<tr>
<td>Smoking</td>
<td>17</td>
</tr>
</tbody>
</table>

EVAR — endovascular aortic repair
PET data were collected in a three-dimensional mode, in the caudocranial direction with 2.5 minutes per bed position, and reconstructed with applied absorption and scatter correction. The reconstruction method was the following: True X+ time-of-flight (TOF) and ultra-high-resolution PET technology, 2 iterations, 21 subsets, Gaussian filter full width at half maximum 2.0 mm, image size 200 × 200 (matrix), zoom 1.0 and slice 3 mm. CT was performed prior to PET, without contrast enhancement, using the following parameters: voltage 120 kV, tube current 50, 150 or 200 mAs, pitch 0.8, and slice thickness 3 mm.

**Image analysis**

All 18F-FDG PET/CT studies were independently assessed by a consensus of two experienced nuclear medicine physicians. Images were evaluated visually and semiquantitatively on a dedicated workstation equipped with fusion software (Syngo Via VA30A, Siemens, Erlangen, Germany), which displays PET, CT, and PET/CT fused images.

Vascular prostheses were evaluated visually, with two visual scales applied [9, 10]. The first one, a three-point scale, with 18F-FDG uptake patterns scored as follows: 1. focal dominant area of 18F-FDG uptake; 2. inhomogeneous or patchy and 3. diffused or homogenous [9]. According to published recommendation, the first two were recognized as PVGI [9]. Second visual scale was also utilized. It was a 5-point scale described by Sah et al. [10] where 18F-FDG uptake patterns and CT information were taken into account. In this scale grade 1, 18F-FDG uptake in vascular graft was normal as in background activity; grade 2, mild increased but diffused along the graft; grade 3, focal, but mild uptake or strongly diffused; grade 4, focal and intense (and diffused 18F-FDG uptake along the graft); grade 5, focal and intense 18F-FDG uptake plus fluid collections or abscess formation [10]. According to this scale, "mild" increase of 18F-FDG uptake means less than twice the blood pool activity in the ascending aorta, whereas "strong" means more than twice the blood pool activity in the ascending aorta. Similarly as described by Sah et al., in this work, in score 1 and 2 images were considered as negative, whereas in score 3, 4 and 5 as positive for graft infection.

Metabolic activity assessed by 18F-FDG uptake in of the vascular graft was also evaluated by semi-quantitative analysis by use of maximum standardized uptake values (SUV max). The SUV max was calculated as the ratio of decay-corrected activity per cubic centimeter of tissue to the injected dosage divided by body weight. For the semi-quantitative evaluation of the SUV max value, the region of interest (ROI) was placed in the focal area of the most intense 18F-FDG uptake. The background region, for background SUV max evaluation, was placed in the ascending aorta in case of abdominal prosthesis, and in abdominal aorta in case of thoracic one.

There was also visual assessment of non-contrast enhanced CT performed during the 18F-FDG PET/CT examination. The CT findings in the vascular graft location were: gas bubbles, peri-graft fluid retention, thickening of the graft wall, adjacent blurred fat, soft tissue swelling, fistula and pseudoaneurysms.

In the final diagnosis of PVGI the MAGIC criteria of clinical, radiological and laboratory tests were taken into account.

**Statistical analysis**

All calculations were expressed as mean ± standard deviation (SD), as well as minimal and maximal values. Differences between study groups were assessed with the U-Mann-Whitney test; p value < 0.05 was considered to indicate statistical significance. Data were evaluated using the statistical package Statistica, version 7.

**Ethics**

The study was approved by the Bioethical Council, Medical University of Lublin, Poland. Informed consent was obtained from all participants. No side effects were observed after the radionuclide procedure.

**Results**

The analysis of vascular prostheses according to the both applied visual scales [9, 10] provided very similar results. In the 3-point scale: 23 patients were in grade 1 and one patient was in grade 2. In the 5-point scale: 19 patients were in grade 5 with the highest activity in the focal area, 4 patients were in grade 4 and one patient in grade 3. The first two points in 3-point scale and 3 last points in 5-point scale were recognized as PVGI.

The visual assessment revealed that peri-graft high metabolic, focal activity was associated with occurrence of gas bubbles, peri-graft fluid retention, thickening of the graft wall, adjacent blurred fat, soft tissue swelling, fistula and pseudoaneurysms (Fig. 1). In 3 cases (12.5%) increased focal 18F-FDG uptake in the infected grafts was found without morphological abnormalities (Fig. 2). The peri-graft fluid retention was observed in 16 patients, peri-graft gas in 15 patients, thickening around the graft wall, adjacent blurred fat and soft tissue swelling in 16 patients, fistula in 13 patients, pseudoaneurysm in 15 patients and metabolically active lymph nodes in the area of PVGI in 10 patients. The triad of CT sign as pseudoaneurysms, soft tissue swelling and peri-graft fluid deposition were seen in 15 patients.

The synthetic vascular graft prostheses were made of either polyester or PTFE, which are both used in endovascular and in open mode surgery. The highest metabolic activity, which was seen in the area of infection, was expressed by SUV max. In infected stent-grafts the metabolic activity came to SUV max 21.5, whereas in infected classical prosthesis was lower and came to SUV max 13. Only in one patient stent-graft was inserted in the thoracic aorta, and in 6 patients in the abdominal aorta. So because of the overall highest metabolic activity in the stent-graft generally, higher SUV max were observed in the abdominal prosthesis than in the thoracic one (21.5 vs.12.5). The metabolic activities expressed by SUVs in the infection area are presented in Table 2.

There were statistically significant differences (p < 0.01) between mean SUV max in the infected area of stent-grafts compared to classical prostheses (SUV max 14.4 ± 5.1 vs 8.39 ± 2.56; 7 vs 17 pts). This difference was less distinctive after background correction (p<0.02; SUV max 7.38 ± 4.07 vs 3.94 ± 1.31) (Tab. 3).

The adjacent blurred fat and soft tissue swelling were combined with higher glucose metabolism compared to prostheses without these signs on CT scans (p < 0.005, SUV max 11.79 ± 4.08 vs 6.84 ± 2.90, 16 vs 8 pts), with similar p value after background...
Figure 1. Increased 18F-FDG uptake associated with irregular peri-graft soft tissue swelling and fluid retention around infected aortic stentgraft, demonstrated on coronal and sagittal projections of 18F-FDG PET/CT. Infection in the paraaortic lymph node with high radiopharmaceutical activity (arrow).

Figure 2. Focal 18F-FDG uptake (arrow) in infected classical prosthesis displayed on coronal and sagittal projections of 18F-FDG PET/CT.
from blood (Escherichia coli, Enterobacter cloacae, Streptococcus zooepidemicus), in one patient Candida albicans were detected in urine. Some cultures were not conclusive (physiological skin culture or no bacterial growth). But in all patients, further clinical observation confirmed infections of PVG.

In the follow-up of the studied group, 3 patients died in the course of infection: one patient with stent-graft of the ascending aorta in course of an esophageal fistula and two patients with aorto-bi-iliac stent-grafts. There was one patient who lost a lower limb. In 4 patients surgical treatment of infected vascular graft was not performed because of general bad condition and instability of the patients. In those patients antibiotic therapy was continued. In the rest of our patients surgical replacement of prosthesis was performed.

**Discussion**

Removal of the infected prosthesis, and replacement with another device to revascularization by anatomical or uninfected extra-anatomical route is an essential vascular graft infection treatment, beyond antibiotic therapy [11]. There is 18–30% mortality rate after surgical explantation of infected aortic prosthesis whereas leaving the prosthesis at the site of infection, despite prolonged antimicrobial treatment, results in 100% mortality over the course of 2 years [10, 12, 13]. The distinction

**Table 2. SUV max in the area of suspected infection**

<table>
<thead>
<tr>
<th>Prosthesis</th>
<th>n</th>
<th>SUV max in area suspected of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>24</td>
<td>median 9.0 MIN 4.2 MAX 21.5</td>
</tr>
<tr>
<td>EVAR</td>
<td>7</td>
<td>median 8.3 MIN 4.2 MAX 13.0</td>
</tr>
<tr>
<td>Open mode</td>
<td>17</td>
<td>median 14.4 MIN 4.8 MAX 21.5</td>
</tr>
<tr>
<td>Abdominal</td>
<td>20</td>
<td>median 9.3 MIN 4.8 MAX 12.5</td>
</tr>
<tr>
<td>Thoracic</td>
<td>4</td>
<td>median 10.2 MIN 4.2 MAX 21.5</td>
</tr>
</tbody>
</table>

EVAR — endovascular aortic repair

correction (5.83 ± 3.12 vs 3.22 ± 1.39). The presence of the gas bubbles in adjacent tissue of prosthesis was linked to high uptake of 18F-FDG (p < 0.01, SUV max 11.81 ± 4.35 vs 7.36 ± 2.80, 15 vs 9 pts) as well as the peri-graft fluid retention, thickening of the peri-graft wall (p < 0.05, SUV max 5.61 ± 3.21 vs 3.62 ± 1.68, 16 vs. 8 pts). Findings are presented in Table 4. Table 5 contains correlation between visual grading scales and CT findings.

Microbiological findings were based on vascular graft, blood, wound, skin and fistula bacterial cultures. The culture were positive from prosthesis (Proteus mirabilis, Staphylococcus aureus, Entercoccus faecalis, Clostridium difficile), from fistula (Proteus mirabilis, Staphylococcus aureus, Klebsiella pneumonia, Escherichia coli), in one patient Candida albicans were detected in urine. Some cultures were not conclusive (physiological skin culture or no bacterial growth). But in all patients, further clinical observation confirmed infections of PVG.

**Table 3. Statistically significant differences between SUVs in the stent-grafts compared to classical prostheses**

<table>
<thead>
<tr>
<th>SUVmax</th>
<th>Type of prosthesis</th>
<th>Mean (SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without background correction</td>
<td>Stent-grafts</td>
<td>14.40 (SD = 5.01) n = 7 pts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>classical prostheses</td>
<td>8.39 (SD = 2.64) n = 17 pts</td>
<td></td>
</tr>
<tr>
<td>With background correction</td>
<td>Stent-grafts</td>
<td>7.38 (SD = 4.07) n = 7 pts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>classical prostheses</td>
<td>3.94 (SD = 1.30) n = 17 pts</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4. Statistically significant differences between SUVs in the prosthesis with and without anatomic alterations on CT scans**

<table>
<thead>
<tr>
<th>SUVmax</th>
<th>CT finding</th>
<th>Mean (SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without background correction</td>
<td>Gas bubbles</td>
<td>yes 11.81 (SD = 4.35) n = 15 pts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>no 7.36 (SD = 2.80) n = 9 pts</td>
<td></td>
</tr>
<tr>
<td>With background correction</td>
<td>Gas bubbles</td>
<td>yes 5.76 (SD = 3.23) n = 15 pts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>no 3.58 (SD = 1.24) n = 9 pts</td>
<td></td>
</tr>
<tr>
<td>With background correction</td>
<td>Peri-graft fluid retention</td>
<td>yes 5.61(SD = 3.21) n = 16 pts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>no 3.62(SD = 1.68) n = 8 pts</td>
<td></td>
</tr>
<tr>
<td>Without background correction</td>
<td>Soft tissue swelling</td>
<td>yes 11.79(SD = 4.08) n = 16 pts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>no 6.84(SD = 2.90) n = 8 pts</td>
<td></td>
</tr>
<tr>
<td>With background correction</td>
<td>Soft tissue swelling</td>
<td>yes 5.80(SD = 3.02) n = 16 pts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>no 3.23(SD = 1.39) n = 8 pts</td>
<td></td>
</tr>
</tbody>
</table>

**Table 5. Correlation between CT findings and visual grading scales**

<table>
<thead>
<tr>
<th>3-point scale</th>
<th>5-point scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Gas bubbles</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

*Three-point scale 1) focal (one dominant area of uptake), 2) inhomogeneous or patched uptake, and 3) diffuse or homogenous uptake. **Five-point scale 1), normal background activity, 2), mildly increased, but diffuse FDG uptake along the graft (mildly uptake: less than twice the blood pool activity in the ascending aorta; strong uptake: more than twice the blood pool activity in the ascending aorta); 3), focal, but only mild FDG uptake or strong diffuse FDG uptake along the graft; 4), focal and intense FDG uptake (= diffuse FDG uptake along the graft); 5), focal and intense FDG uptake plus fluid collections/abscess formation
between infection and inflammation in reference to vascular prosthesis is very challenging, but absolutely crucial for the proper treatment. There are many various diagnostic schemes which include clinical, biochemical, microbiological and imaging procedures [12]. As in the MAGIC recommendation, the clinical criteria of PVGI were the start point of diagnosis [8]. There were major criteria like fistula development and infected pseudoaneurysm as well as minor criteria like erythema, warmth, swelling purulent discharge and pain. They occurred in all patients in various degrees. The serum levels of CRP and WBC belonging to the minor criteria in laboratory categories in MAGIC were increased in the studied patients. The golden standard in the diagnosis of PVGI is confirmation of bacterial colonization of prosthesis. In MAGIC criteria organisms recovered from explanted graft or recovered from intra-operative or radiologically guided aspiration of peri-graft belong to the major criteria of infections. Positive blood culture with no apparent source of infection except of AGI, are the minor criteria of infections [8]. Staphylococcus species are the most common causative organisms, Staphylococcus aureus are more likely in early infection and Staphylococcus epidermidis in late infections [13]. However, many suspected PVGI are treated without knowing the causative organisms, because as described by FitzGerald et al. suitable specimens could not be obtained or antibiotic treatment was applied before collection of samples [13]. Some authors stress that even if the specimens are taken from blood or from the suspicious location, there could be negative bacterial culture in active vascular prosthesis infections [14]. On the other hand, same pathogens isolated from superficial specimens may be misleading, but influence the choice of antimicrobial agents [13]. For this reason, antimicrobial treatment is empirical and based on clinical manifestations and findings, as well as on radiological/nuclear medical imaging.

Contrast-enhanced computed tomography has close to 100% sensitivity and specificity in diagnosis of acute PVGI, whereas in chronic PVGI up to 55% [15]. Presentation of periprosthetic air bubbles, abscesses or infiltration suggests vascular graft infections in CT. Nevertheless, it should be kept in mind that one week after vascular prosthesis implantation, air bubbles are present around the vascular prosthesis in 65% of patients [16]. Moreover, in 100% of patients periprosthetic hematoma is present in CT one week after surgery and in 10% of patients at 100 days post-surgery [17]. However, in all patients presenting air bubbles, periprosthetic infiltration or fluid collections 3 months post-surgery, the possibility of a vascular graft infection should be taken into account [13].

In nuclear medicine procedures there are two main techniques, SPECT and PET, and several radiopharmaceuticals like Gallium 67-citrate, radiolabeled white blood cells, antigranulocyte antibody. In the PET technique there is the main radiotracer 18F-FDG. According to the EANM/SNMMI guidelines [18], the advantage of use of 18F-FDG PET/CT over radiolabeled WBC scintigraphy in detection of infection in vascular prosthesis is unclear. However, the usage of 18F-FDG PET/CT is less time-consuming and much easier to perform compared to radiolabeled WBC scintigraphy. The reported sensitivity, specificity and accuracy of scintigraphy with radiolabeled WBC in PVGI is 100%, 92%, 97% respectively [19], whereas the latest study of 18F-FDG PET/CT presents sensitivity, specificity, positive and negative predictive value 88%, 79%, 67%, and 93% respectively [9].

18F-FDG PET/CT provides information regarding not only of the anatomy but also the metabolism of lesions. Three cases (12.5%) in the studied population presented increased 18F-FDG uptake in the infected grafts without morphological abnormalities on CT scans. In some patients 18F-FDG PET/CT also revealed extra-prosthetic infection in the lymph nodes. Therefore, an additional value of PET/CT over CT alone was documented in this study. Recently the combination of PET/CT with contrast enhanced CT is postulated in diagnosing PVGI as it was proved to be more accurate than stand-alone imaging and may be supportive in future management of difficult cases [20].

In the studied patients there were two types of vascular graft prosthesis: stent-grafts (EVAR procedure) and classic prostheses. All prostheses were made of either polyester or [7], which are both use in endovascular and open surgery. Synthetic vascular grafts provoke a chronic low-grade inflammation, therefore could be a cause of a false positive diagnosis [21]. Our material revealed higher metabolic activity in stent-grafts than classical prosthesis, but further studies are needed because of potentially higher artifacts from metallic elements contained in the stent-grafts. On the other hand, the number of patients in both groups was not very high.

Testing a short time after implantation could be a source of a false positive finding [22]. The mean time between the surgery and 18F-FDG PET/CT in the studied group of patients was 51 months, but in one patient imaging was performed 1 month after Bentall de Bono procedure, because of rapid progress of infection symptoms. This patient died over the course of the infection. However, generally in cases of very early assessment of vascular prosthesis, the diagnosis should be made very carefully. In the early period after implantation there are post-surgical inflammatory changes in the area of implantation, with physiological activation of leukocytes. Peri-graft fluid and peri-graft gas observed in CT integrated with PET meet the major criteria of aortic graft infection enclosed in MAGIC criteria [8]. They depend on the time after surgery, so persistent peri-graft fluid after more than 3 months and peri-graft gas after more than 7 weeks after insertion, suggest PVGI. In our analysis, except one patient, the time criteria have been met. In this study peri-graft fluid was observed in 16 and peri-graft gas in 15 patients. Presence of pseudoaneurysm and fistula are the minor criteria of MAGIC and in our study were observed in 15 and in 13 patients respectively.

Pattern of 18F-FDG uptake in patients with suspicion of vascular graft infection is very important. Focal or heterogeneous accumulation is highly suggestive of infection whereas moderate, homogeneous, linear uptake in the graft and/or surrounding tissue is often recognized as non-infectious [22, 23]. However, some authors underline that patterns of FDG uptake for uninfected grafts largely overlap with those of infected vascular graft [24]. In these cases it is very important to recognize all the additional signs of potential infection. Concerning the 18F-FDG uptake and distribution patterns, reported sensitivity, specificity, positive predictive value and negative predictive value in PVGI are 93%, 91%, 88%, 96% respectively [25]. In this study of analysis of 18F-FDG uptake in prosthesis and in the surrounding tissues two visual scales were applied [9, 10]. Both of them presented very similar results. FDG uptake was focal (mild to intense) in all patients. 18F-FDG PET/CT as hybrid study additionally revealed in our patients signs of infections in CT, like: gas bubbles, peri-graft fluid retention, thickening of...
the graft wall, adjacent blurred fat, soft tissue swelling, fistula and pseudoaneurysm. All the patients in the study were positive in reference to infection. Moreover, in MAGIC criteria increased peri-graft 18F-FDG activity fulfills the minor criteria of aortic graft infection [8].

On the other hand, based only on assessment of 18F-FDG uptake it is very difficult to differentiate a quite rare condition like retroperitoneal fibrosis (RPF), which could be also secondary to vascular graft implantation from a simple inflammatory reaction to a foreign body or the early phase of an infection. In all these conditions there is increased 18F-FDG uptake and serum level of inflammatory markers, as well as clinical symptoms like fever and pain. In RPF treatment is based on glucocorticosteroids application, in inflammation as foreign body reaction – watchful waiting in inflammatory markers, as well as clinical symptoms like fever and pain. In RPF treatment is based on glucocorticosteroids application, in inflammation as foreign body reaction – watchful waiting is much advisable, whereas in the last case redo surgery is usually performed. Therefore, it should be kept in mind, that diagnosis of PVGI should be based on multidisciplinary consensus [26].

Conclusions

18F-FDG PET/CT is a very useful, non-invasive tool for assessment of vascular graft infections. It should be interpreted with caution in multidisciplinary team, CT findings like gas bubbles, peri-graft fluid retention, thickening of the graft wall and adjacent blurred fat soft tissue swelling are associated with significantly higher glucose metabolism: however, in some cases without anatomic alterations, increased metabolic activity is the only sign of infection. A useful marker of infected graft is focal not homogeneous pattern of 18F-FDG uptake found in all examined cases.

Conflict of interest

The authors declare that they do not have any conflict of interest.

References


The diagnostic value of dual-phase SPECT/CT scintigraphy based on transport kinetics of 99mTc-sestamibi confirmed with histopathological findings in patients with secondary hyperparathyroidism — practical consideration

Maria H. Listewnik1, Hanna Piwowarska-Bilska1, Krzysztof Safranow2, Marek Ostrowski2, Jacek Iwanowski1, Maria Chosia4, Bozena Birkenfeld1
1Department of Nuclear Medicine, Pomeranian Medical University in Szczecin, Poland
2Department of Biochemistry and Medical Chemistry, Pomeranian Medical University in Szczecin, Poland
3Department of General Surgery and Transplantology, Pomeranian Medical University in Szczecin, Poland
4Department of Pathology, Pomeranian Medical University in Szczecin, Poland

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Abstract

BACKGROUND: Dual phase 99mTc-sestamibi SPECT/CT preoperative parathyroid scintigraphy (PPS) is seldom discussed in terms of the transport kinetics of the tracer.

Objectives: To assess the relationship between the characteristic type of tracer transport in particular PPS and histopathological findings in patients with secondary hyperparathyroidism (sHPT).

MATERIAL AND METHODS: The study comprised 27 patients (13 females and 14 males) with sHPT. Based on tracer accumulation in early phase (EP) and delayed phase (DP), the following types of accumulation for PPS(+) lesions were identified: EP(−)/DP(+) (type I), EP(+)/DP(+) (type II), EP(+)/DP(−) (type III). EP(−)/DP(−) (type IV) lesions constituted PPS(−) group invisible in SPECT/CT. Overall, 69 lesions 59 PPS(+) and 10 PPS(−) were evaluated histopathologically.

RESULTS: Among SPECT/CT PPS(+), types I, II and III occurred in 9 (15%), 49 (83%), and 1 (2%) lesions, respectively. The frequency of histopathological diagnosis of normal and abnormal (APG — adenoma or hyperplasia) parathyroid gland, as well as non-parathyroid (thyroid, lymph nodes, or fat) lesions differed significantly between type I, II, and III lesions (p = 0.036). APG histopathological diagnosis was significantly more frequent in lesions with type II uptake than in lesions with type I uptake (76% vs. 33%, p = 0.0197). Type II lesions had significantly higher odds for histopathological diagnosis of APG or NPG than type IV, PPS(−) lesions [odds ratio = 13.1 (95% CI: 2.75 to 63.27)].

CONCLUSIONS: For SHP patients evaluated with SPECT/CT PPS accumulation type I is a weak premise for surgeon to find parathyroid pathology. Only persistent 99mTc-sestamibi accumulation in both phases - equivocal with accumulation type II — effectively differentiates parathyroid and non-parathyroid lesions as well as indicates with high probability the presence of adenoma or hyperplasia. Type III consistent with washout pattern is rare in sHPT.

KEY words: secondary hyperparathyroidism; single photon emission computed tomography; technetium-99m sestamibi; parathyroid hormone; parathyroid adenoma; hyperplasia
Introduction

Secondary hyperparathyroidism (sHPT) is usually caused by chronic kidney disease in response to hypocalcaemia, which leads to diffused or nodular hyperplasia of the parathyroid glands. Even after successful renal replacement therapy, this condition can be difficult to control using conservative treatments, and hence require parathyroid surgery [1–3]. If surgical intervention is not performed in the optimal time, some patients can develop autonomous adenoma with a constant elevation of PTH [4, 5]. Among various preoperative imaging techniques, single-photon emission computed tomography (SPECT) is an accurate method used for the localization of abnormal parathyroid gland method. Recently, new hybrid imaging using SPECT in combination with computed tomography (CT) has improved precision in the morphological and metabolic assessment of focal lesions [6].

\(^{99m}\text{Tc}\)-methoxyisobutylisonitrile (\(^{99m}\text{Tc}\)-sestamibi) SPECT/CT preoperative parathyroid scintigraphy (PPS) can be performed as dual-phase single-tracer scintigraphy (washout method). There are two patterns of washout from the parathyroid glands: delayed (parathyroid gland retention of radiopharmaceutical on delayed images, usually accompanied by normal washout from the thyroid) and early (minimal or no retention of the radiotracer in the parathyroid gland on delayed-phase images). It was shown that the metabolic activity of the thyroid tissue diminishes with time while in the parathyroid tissue is more protracted; hence, early phase (EP) in SPECT/CT refers to the thyroid washout and the delayed phase (DP) to the parathyroid washout [7, 8]. Accumulation of \(^{99m}\text{Tc}\)-sestamibi may be visible either in one phase only or both phases, thus leading to three different types of trace patterns [9].

The purpose of this study was to evaluate the relationship between the transport kinetics of \(^{99m}\text{Tc}\)-sestamibi in SPECT/CT PPS phases, thus leading to three different types of trace patterns [9].

Material and methods

We included 78 patients with sHPT (30 females, 48 males; mean age of 49.9 years, range: 22–86 years). Patients were examined with planar and SPECT/CT PPS (GE INFINIA Hawkeye 4 with a low-energy high-resolution collimator and 2.0 zoom) following intravenous administration of \(^{99m}\text{Tc}\)-sestamibi 762 ± 60.7 MBq (range: 600–850) with washout technique (dual-phase, single-tracer), in accordance with EANM guidelines [8]. The SPECT/CT study in EP was started following thorax planar acquisition (but not later than 20 min after administration of the tracer), and DP was performed 127 ± 28 min after tracer administration.

Pathological lesions on SPECT/CT were observed in 73 patients, and negative results in 5 patients. Among them, 27 patients (14 males and 13 females; mean age 46.3 years, range: 22–77 years) with abnormal lesions seen in the SPECT/CT study and inadequately controlled sHPT despite standard medical therapy were qualified for parathyroid surgery. PTH plasma concentration exceeding 600 pg/ml was an eligibility criterion for surgery. Among 26 patients with renal sHPT, 25 received kidney replacement therapy. Coeliac disease was diagnosed in one patient with sHPT. Two patients required second parathyroid surgery 4 and 19 months after the first operation.

Sonography of the neck was performed parallel to the scintigraphy at the same department in all cases, but results of the study had only a supportive function in terms of the results of the study [10]. Measurements to estimate accurately their volume were performed in 18.8% of all histopathologically assessed lesions.

We defined a positive result in early and delayed SPECT/CT as the presence of identifiable focus of increased \(^{99m}\text{Tc}\)-sestamibi accumulation in the vicinity of the thyroid gland, or localized outside of the thyroid gland in the neck or mediastinum.

The SPECT/CT method of PPS allowed positioning the anatomic localization of metabolically active lesions in three-dimensional projections. Separate sets of fusion images were delivered to the surgeon to facilitate surgical treatment planning. Removed tissue specimen were secured and, after recording their location, transferred to the pathology lab for histopathological examination.

The specific histopathological diagnoses were correlated with the type of \(^{99m}\text{Tc}\)-sestamibi uptake in the lesions, serum PTH, phosphate, total, and ionized calcium.

In surgical centres, PTH measurements were performed post-operatively. Direct, postoperative PTH assays were performed in 22 patients.

SPECT/CT results were considered true positive (TP) if a lesion was SPECT/CT PPS(+) and diagnosed as an abnormal parathyroid gland (APG — parathyroid adenoma and parathyroid hyperplasia) or normal parathyroid gland (NPG) on histopathological diagnosis; false positive (FP) if a lesion was SPECT/CT PPS(+) but not parathyroid lesions (lymph nodes, fat, thyroid tissue) (Non-PL) on histopathological diagnosis, true negative (TN) was characterized as SPECT/CT PPS(–) and confirmed as not of parathyroid origin on histopathological diagnosis and false negative (FN) as SPECT/CT PPS(–) and diagnosed as APG or NPG histopathologically.

The study was approved by the Pomeranian Medical University Ethics Committee and all patients gave their written consent.

Statistical analysis

Normality of distribution for serum PTH concentration was examined by the Kolmogorov-Smirnov test. Since the PTH distribution was significantly different from normal, the Kruskal-Wallis test was used to compare PTH between independent groups. Fisher’s exact test was used for assessing the significance of the association between types of accumulation and histopathological diagnosis. Statistical analysis was performed with IBM SPSS 23. The threshold for statistical significance was p < 0.05.

Results

In 27 patients 65 lesions SPECT/CT PPS(+) on SPECT/CT were detected, but 6 of them were not found during surgery. During operations on 7 patients from this group, the surgeon additionally removed 10 lesions not indicated on SPECT/CT, and then we called it SPECT/CT PPS(–). As a result, 69 lesions were validated on the histopathological diagnosis. In total, 5 patients had a single lesion, 9 patients had 2 lesions, 7 patients had 3 lesions, 5 patients had 4 lesions, and 1 patient had 5 lesions.

The group of 59 lesions SPECT/CT PPS(+) with an additional 10 lesions SPECT/CT PPS(–) had the following histopathological diagnoses: 28 + 0 (40.6%) — parathyroid adenoma, 12 + 2 (20.3%) — parathyroid hyperplasia, 10 + 2 (17.4%) — NPG, 3 + 1...
Table 1. Baseline biochemical analyses before surgery

<table>
<thead>
<tr>
<th>Serum concentration (reference range)</th>
<th>Mean (± SD)</th>
<th>Median (Q25–Q75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionized calcium (1.05–1.35 mmol/L)</td>
<td>1.49 ± 0.47</td>
<td>1.35 (1.15–1.9)</td>
</tr>
<tr>
<td>Total calcium (2.1–2.6 mmol/L)</td>
<td>2.29 ± 0.23</td>
<td>2.32 (2.08–2.51)</td>
</tr>
<tr>
<td>Phosphorus (0.87–1.45 mmol/L)</td>
<td>1.90 ± 0.63</td>
<td>1.76 (1.33–2.54)</td>
</tr>
<tr>
<td>PTH (16–65 pg/mL)</td>
<td>1701.92 ± 763.40</td>
<td>1600.00 (1272–2500)</td>
</tr>
<tr>
<td>Creatinine (0.7–1.5 mg/dL)</td>
<td>5.71 ± 2.18</td>
<td>5.92 (4.90–6.93)</td>
</tr>
<tr>
<td>Urea (15–40 mg/dL)</td>
<td>74.18 ± 37.69</td>
<td>71 (51–91.15)</td>
</tr>
</tbody>
</table>

Q25–Q75 — interquartile range; SD — standard deviation

(5.8%) — lymph node and 6 + 4 (14.5%) — normal thyroid gland tissue, 0 + 1 (1.4%) — fatty tissue.

Biochemistry data obtained before surgery are presented in Table 1.

To analyze the association between PTH and the histopathological diagnosis we compared PTH concentrations between three groups of patients: 1) 16 patients with parathyroid adenoma in histopathological diagnosis for at least one location, 2) 7 patients with parathyroid hyperplasia in histopathological diagnosis for at least one location, and 3) 4 patients with NPG or other histopathological diagnosis but without parathyroid adenoma or parathyroid hyperplasia at any location. There was no single patient with both parathyroid adenoma and parathyroid hyperplasia in different locations. There was no significant difference between those groups as regards PTH concentration (p = 0.18, Kruskal-Wallis test).

In a positive SPECT/CT PPS (PPS+), we identified three types of the uptake accumulation: Type I with the absence of accumulation in the early phase and retention in the delayed phase (EP-/DP+), Type 2 with accumulation in both phases (EP+/DP+), Type III with the uptake observed only in the EP (EP+/DP–).

Additionally, we identified Type IV, in which the lesions were not detected by SPECT/CT but were found and removed during surgery (Type IV EP-/DP–). The parathyroid lesion was defined if it was localized dorsally to the thyroid lobe and the uptake in SPECT/CT was classified either as type I or type II [11]. In the type III uptake, the localization criterion was decisive. None of the patients had ectopic localization of lesions.

In the lesion-based analysis, there were 9 (15.3%), 49 (83%) and 1 (1.7%) lesions SPECT/CT PPS(+) characterized as types I, II and III, respectively (Fig 1).

Figure 1. Three types of 99mTc-sestamibi SPECT/CT uptake in fusion coronal cross-sections; A. Type I — the tracer is visible in the delayed phase for right upper parathyroid gland. HP proved as adenoma (patient ZG, 56 y.o.); B. Type II — tracer is visible in both phases for right lower parathyroid gland. HP proved as adenoma (patient LM, 57 y.o.); C. Type III — the tracer is visible in the early phase for right upper parathyroid gland HP proved as NPT (patient LM, 57 y.o.). White arrows show lesions with or without uptake in corresponding phases of SPECT/CT PPS.
Among 69 removed lesions 50 were acknowledged as TP, 9 lesions as FP, 4 lesions as FN, 6 lesions as TN. In type I the rate of TP achieved 5(55%) lesions, in type II — 44 (90%), in type III — 1(100%) lesion, whereas in type IV SPECT/CT PPS(-) achieved 4 (40%) lesions (Tab. 2).

In 13 (18.8%) lesions removed by the surgeon in 3 hyperplasia and 7 adenomas the average volume was 0.38 mL and 0.41 mL, respectively. All those lesions presented as type II on PPS SPECT/CT study.

The statistical analysis for the whole PPS(+) group showed significant differences between accumulation types I, II or III and results of histopathological examination (p = 0.036). A comparison between types I and II of 99m Tc-sestamibi accumulation showed significant (p = 0.025) differences in histopathological diagnosis (Tab. 2).

The association of detailed histopathological diagnosis with SPECT/CT uptake type is shown in Table 3.

There were no significant differences between lesions with type I and type II uptake as regards proportions of parathyroid adenomas (33% vs. 51%, p = 0.473) and parathyroid hyperplasia (0% vs. 24%, p = 0.181) in relation to histopathological diagnosis. However, when parathyroid adenomas and parathyroid hyperplasia were combined as APG, this diagnosis was significantly more frequent in lesions with type II uptake than in lesions with type I uptake (76% vs. 33%, p = 0.0197). The frequency of APG was significantly different between types II and IV (76% vs. 20%, respectively, p = 0.0016), but not between types I and IV (33% vs. 20%, p = 0.628).

Combined lesions with positive uptake (types I, II and III) had significantly higher odds for combined histopathological diagnosis of APG and NPG than lesions with negative uptake (type IV) [OR = 8.33 (95% CI: 1.95–35.54), p = 0.004]. Type II lesions had the highest odds ratio for APG or NPG when compared to type IV lesions [OR = 13.1 (95% CI: 2.75 to 63.27), p = 0.001], while type I lesions did not have significantly higher odds for APG or NPG than type IV lesions [OR = 1.88 (95% CI: 0.30 to 11.63), p = 0.499].

The SPECT/CT 99m Tc-sestamibi PPS quality parameters for detecting APG or NPG on the basis of positive (type I-III) uptake were sensitivity 92.6%, specificity 40.0%, accuracy 81.2%, positive predictive value 84.7% and negative predictive value 60.0% was achieved.

**Discussion**

Even if some articles are focused on parathyroid scanning with 99mTc-sestamibi in sHPT, there is limited data about its correlation with histopathology [12, 13]. SPECT/CT PPS has lately been regarded as the method of choice [6, 14, 15].

In our study special attention was paid to the presence or absence of tracer accumulation in particular phases of the study. In this context, our approach is quite innovative. In the current paper, lesions were assessed according to their visibility in both phases of PPS and compared with histopathology.

To our knowledge, this is the first comparison performed between the transport kinetics of 99mTc-sestamibi and histopathological results in particular lesions for sHPT patients.

In our material type I turned out not to be diagnostic for discrimination of whether the lesion is or is not of parathyroid origin. This is depicted by significantly lower odds for histopathological diagnosis of APG or NPG for type I in comparison to type II.

<table>
<thead>
<tr>
<th>Table 2. Association of SPECT/CT 99mTc-sestamibi results and type of uptake with parathyroid or non-parathyroid lesions in histopathological evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of uptake</strong></td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>TYPE I (EP–/DP+)</td>
</tr>
<tr>
<td>TYPE II (EP+/DP+)</td>
</tr>
<tr>
<td>TYPE III (EP+/DP–)</td>
</tr>
<tr>
<td>TYPE IV (EP–/DP–)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

* Fisher exact test for types I–III; EP — early phase; DP — delayed phase; N/A — not applicable; **SPECT/CT PPS(+) for types I–III lesions visible in SPECT/CT preoperative parathyroid scintigraphy; *SPECT/CT PPS(−) for type IV lesions not visible in SPECT/CT preoperative parathyroid scintigraphy.

<table>
<thead>
<tr>
<th>Table 3. Association of SPECT/CT 99mTc-sestamibi results and uptake types with histopathological diagnosis in sHPT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histopathological findings</strong></td>
</tr>
<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td><strong>Type I</strong></td>
</tr>
<tr>
<td>EP–/DP+</td>
</tr>
<tr>
<td>EP+/DP+</td>
</tr>
<tr>
<td>EP+/DP–</td>
</tr>
<tr>
<td><strong>Negative</strong></td>
</tr>
<tr>
<td>Non–PL</td>
</tr>
<tr>
<td>Thyroid tissue</td>
</tr>
<tr>
<td>Lymph node</td>
</tr>
<tr>
<td>Fatty tissue</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

*TP — true positive; *FP — false positive; *FN — false negative; *TN — true negative; APG — abnormal parathyroid gland; NPG — normal parathyroid gland; SPECT/CT PPS(+) — lesions visible in SPECT/CT preoperative parathyroid scintigraphy; SPECT/CT PPS(−) — lesions not visible in SPECT/CT preoperative parathyroid scintigraphy; EP — early phase; DP — delayed phase.
Type II uptake was predominant in the examined group. As a practical remark, it might be valuable to point out in the report of the PPS study the type $^{99m}$Tc-sestamibi uptake. Such lesions would have higher odds of being APG or NPG. The explanation might be the greater number of mitochondrias, and the ability of parathyroid cells to persistently capture $^{99m}$Tc-sestamibi in comparison with Non-PL.

For parathyroid adenomas and parathyroid hyperplasias, type II accumulation was observed in 90% and 86%, respectively, while type I accumulation was noted in 10% of adenoma lesions. The examined group consisted of patients with relatively high ratios of parathyroid adenoma to hyperplasia (ratio 2:1) and was different compared with data obtained by Yuan [6]. The explanation for this fact might be the relatively long waiting time for kidney transplantation in our country [18]. This fact in patients with sHPT refractory to medical treatment promoted the evolution of parathyroid gland hyperplasia into adenoma [2, 19, 20]. This happens because of alteration in parathyroid tissue growth pattern from polyclonal to monoclonal or multiclonal proliferation [21].

The presence of increased uptake of $^{99m}$Tc-sestamibi only in DP or increased activity of a tracer in both phases (EP and DP) are the main principles of the washout protocol [22, 23]. The $^{99m}$Tc-sestamibi clearance from the lesion is a well-known phenomenon in the case of pHPT patients, and it is assessed from as from 17% to 40% of all cases of parathyroid scintigraphy [24–27]. In our material type III uptake was presented only in one case, perhaps because there is a different aetiology of primary hyperparathyroidism (pHPT) and sHPT [6, 28]. The lesion with this kind of uptake misleading nuclear medicine practitioners suggesting the thyroid origin of the lesion. Quick clearance typical of thyroid tissue is a cause of false-negative findings, and researchers overcome it by performing thyroid scans with $^{123}$I after the $^{99m}$Tc-sestamibi scan [14]. On the other hand, it leads to a disadvantage in image interpretation because of the “shine through” phenomenon [29]. In our opinion, it is not necessary when the SPECT-CT technique is applied. Localization of the lesion behind the thyroid gland indicates its parathyroid rather than thyroid origin regardless of the type of transport kinetics [14, 30]. Furthermore, the better technical possibilities related to the use of hybrid techniques and structural imaging have resulted in better sensitivity compared to previous planar or SPECT modality, even if in sHPT lesions are multiple and smaller [6, 14, 31, 32].

Surgeons removed 12 (17.4%) lesions of NPT because they were visible in parathyroid scintigraphy. These findings are similar to the 15.8% noted in the publication by Yuan [6]. High PTH plasma concentration (greater than in pHPT) might influence and stimulate to some extend NPG [7, 33]. However, Balosco found one case of shPT treated with cinacalcet where despite the lowering PTH plasma level $^{99m}$Tc-sestamibi uptake in APG was unchanged [34].

SPECT/CT PPS helped in choosing lesions to be removed. Nowadays, it is believed that if four glands exploration parathyroid surgery is necessary, surgeons should remove three glands and a half of the fourth with the most normal appearance, leaving the remaining half in situ [6]. For the 27 patients, the estimated number of removed parathyroid glands should have been minimum 81 glands, but 69 glands were removed. So, SPECT/CT PPS results helped to limit the number of resected glands, shortened the duration time of the surgery, and diminished the failure rate. However, it is possible that in the operating theatre lesions suspected of pathology by the surgeon would be removed during the exploration, even if there is no indication in preoperative diagnosis. It is important to admit this in terms of the limitation of our study. The study was conducted in just one university centre. The surgeons’ skills, preoperative assessment, and the experience of nuclear medicine specialists will affect the outcome of the study.

A sensitivity of 92.6% and accuracy of 81.2% is comparable with the literature data [2, 30]. A specificity of 40% is much lower than that achieved by other authors [2, 6, 9, 30, 35]. This could have been affected by including Type IV lesions in the calculation. Type IV consisted of lesions removed by the surgeon despite the lack of accumulation of the tracer in scintigraphy. It is worth mentioning in this context that our study provides additional quality parameters not available in other papers as the odds ratio for successful surgery in particular transport kinetics types in patients with sHPT.

In the current study as well as in the literature there was no statistical relation between histopathological diagnosis and PTH level. The explanation may be that pharmacological treatment in sHPT patients influences their PTH level [36]. In our study, the recommendation for surgery was PTH level of more than $600$ pg/mL. The same criteria were applied by Souberbielle and Rosato [33, 37].

Separation into three groups of tracer uptake was used in previous studies with $^{99m}$Tc-sestamibi performed for different indications. For example, the kinetics of the tracer was used as a predictor of tumour response to chemotherapy treatment. It combined imaging findings with prognostic value in patients with breast cancer, lymphoma, and small and non-small cell lung cancer [38]. Different kinetics of $^{99m}$Tc-sestamibi depicted a multidrug resistance phenotype prior to preoperative diagnosis or any treatment. The above idea inspired us to perform the comparison between $^{99m}$Tc-sestamibi uptake in SPECT/CT PPS and different histopathological diagnosis in sHPT.

The genetic factors influencing parathyroid uptake in patients with hyperparathyroidism were postulated in some publications [39–41]. But there is still a limited number of genetics studies investigating the background of the transport kinetics of $^{99m}$Tc-sestamibi in patients with sHPT. Also, different mathematical models of transport kinetics have been created but there is a lack of clinical studies [42]. The authors of the presented study performed genetic studies in patients with hyperparathyroidism and proved the significant negative correlation of mRNA expression for the ABCB1 gene with maximal $^{99m}$Tc-sestamibi uptake values in patients with hyperparathyroidism [43, 44]. There is a need for further investigation in this field.

**Conclusions**

For sHPT patients evaluated with SPECT/CT PPS accumulation type, I is a weak premise for a surgeon to find parathyroid pathology. Only persistent $^{99m}$Tc-sestamibi accumulation in both phases — equivocal with accumulation type II — effectively differentiates parathyroid and non-parathyroid lesions as well as indicates with high probability the presence of adenoma or hyperplasia. Type III, consistent with washout pattern, is rare in sHPT.

**Conflict of interest**

The authors declare no conflicts of interest.
Acknowledgments

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References


Kidney efficiency index quantitative parameter of a dynamic renal scintigraphy. II. usefulness in the diagnosis of obstructive nephropathy

Pawel Cichocki¹, Krzysztof Filipczak², Anna Plachcinska², Jacek Kusmierek¹
¹Medical University of Łódź, Department of Nuclear Medicine, Poland
²Medical University of Łódź, Department of Quality Control and Radiological Protection, Poland

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Abstract

BACKGROUND: One of the main indications for DSN is a diagnosis of obstructive uro-/nephropathy. In standard practice, this study includes the assessment of sequential scintigraphic images, renographic curves and such quantitative parameters as T_max, T_1/2 and split function of each kidney (SF). Due to the relative nature of SF and limitations of diagnostic capabilities of T_max and T_1/2, DSN was expanded to include new quantitative parameters describing kidney function in absolute values. This study aims to evaluate the usefulness of kidney efficiency index (KEi) — new, in-house developed parameter proportional to the average clearance function of the kidney.

MATERIAL AND METHODS: The study included 156 people aged 18–84 (average 51) years. The first group, from which normative values of new parameters were determined, consisted of 20 healthy volunteers. The second group consisted of 136 patients selected retrospectively, based on archived scintigraphic data. “Normalcy rate” (percentage of normal results among selected 62 patients with a low likelihood of obstructive uro-/nephropathy) was used to evaluate the reliability of KEi. A comparative differential analysis of obstructive uro-/nephropathy, based on standard and new DSN parameters, was performed on selected 74 patients (92 kidneys) with single functioning kidney or bilateral obstructive uropathy, where SF is unreliable.

RESULTS: Normative values: KEi ≥ 8; Normalcy rate for KEi: 95%. In comparison with standard DSN evaluation, application of KEi changed the diagnosis in 1/3 of assessed kidneys (from uropathy to nephropathy in 27/92 kidneys and vice versa in 4 kidneys).

CONCLUSIONS: KEi enables reproducible, quantitative assessment of absolute kidney function without any modifications of the standard DSN protocol. Its values can be compared between independent studies (e.g. follow-up examinations). KEi corrected the diagnosis of obstructive uro-/nephropathy in cases of single functioning kidney or bilateral obstructive uropathy.

KEY words: humans; kidney; radioisotope renography; radiopharmaceuticals; technetium Tc 99m-ethylenedicysteine

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Introduction

Dynamic renal scintigraphy (DRS) allows the evaluation of two functions of the kidney — uptake function and transport function. Interpretation of this study consists of visual assessment of sequential scintigraphic images, renographic curves and analysis of quantitative parameters, such as an individual contribution of each kidney to their total function (SF — split function) as well as times T_max and T_1/2[1–3].

SF is the most important quantitative parameter in the standard DRS study and is often critical when making crucial clinical decisions (e.g. qualification of patients for nephrectomy). However, it has a significant limitation. Due to the fact that it shows the function of one kidney relative to the other, there are situations in which its value loses credibility, e.g. when assessing the function of a single kidney, or in case of disorders affecting both kidneys. Due to significant, often fundamental importance of DRS in making decisions about further management of patients, there are attempts to expand this study with additional parameters allowing
Table 1. Demographic data of all examined groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Total (number of kidneys in parentheses)</th>
<th>Age</th>
<th>Number of people (number of kidneys in parentheses) and their sex</th>
<th>Age</th>
<th>Total Women</th>
<th>Total Men</th>
<th>Min.</th>
<th>Max.</th>
<th>Avg. ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>20 (40)</td>
<td></td>
<td></td>
<td></td>
<td>15</td>
<td>5</td>
<td>26</td>
<td>66</td>
<td>50 ± 11</td>
</tr>
<tr>
<td>Group II</td>
<td>136 (216)</td>
<td></td>
<td></td>
<td></td>
<td>94</td>
<td>42</td>
<td>18</td>
<td>84</td>
<td>52 ± 18</td>
</tr>
<tr>
<td>Subgroup IIA</td>
<td>62 (124)</td>
<td></td>
<td></td>
<td></td>
<td>48</td>
<td>14</td>
<td>18</td>
<td>79</td>
<td>48 ± 17</td>
</tr>
<tr>
<td>Subgroup IIB</td>
<td>74 (92)</td>
<td></td>
<td></td>
<td></td>
<td>46</td>
<td>28</td>
<td>18</td>
<td>84</td>
<td>57 ± 19</td>
</tr>
</tbody>
</table>

the assessment and monitoring of absolute renal function also in the above-mentioned situations.

One such option is to determine the value of glomerular filtration rate (GFR) and compare it with SF to calculate single-kidney GFR (SKGFR) [4]. However, this requires additional radioisotope studies of blood samples taken from the patient after intravenous administration of the radiopharmaceutical (99mTc-DTPA), which are not widely available. Assessment of renal function in absolute values within the DRS itself, without the need for additional tests, is made possible by calculating clearance of radiopharmaceuticals using gamma-cameras (camera-based clearance), but its determination requires extending the DRS protocol by accurate measurement of injected activity and the depth of kidneys [5, 6].

This study evaluates the diagnostic potential of a new, original parameter — Kidney Efficiency index (KEI), generated using software developed in our Department [7, 8], that allows the assessment of renal function in absolute values, but without the need for additional tests or modification of the standard DRS protocol. A model clinical problem for analyzing the usefulness of the above-mentioned parameters is the differential diagnosis of obstructive uro- and nephropathy, which is the most common indication for DRS.

**Material and methods**

The study covered 156 people aged 18–84 (average 51) years. The subjects were separated into two groups. Group I — control, consisting of 20 healthy, adult volunteers (40 kidneys), which was used to determine normative values of evaluated parameters. Inclusion criteria for this group were as follows:

- no history of past or ongoing urinary tract diseases or other conditions that may lead to impaired renal function (such as systemic lupus, diabetes or uncontrolled hypertension)
- no features of urolithiasis, hydronephrosis, scarring or other focal lesions (e.g. cysts) in the kidneys in ultrasound, performed on the same day as DRS
- serum urea and creatinine levels within normal limits in tests performed on the same day as DRS

Group II included 136 adult patients, retrospectively selected from among those who underwent DRS in our Department in the years 2016–2019, based on archived medical documentation, including full data from the DRS study. In total, 216 kidneys were assessed (some patients from group IIB had only one functioning kidney). This group consisted of:

- Subgroup IIA — 62 patients without scintigraphic features of obstructive uropathy or nephropathy (124 kidneys)
- Subgroup IIB — 74 patients with no or trace function of one kidney (defined as SF < 10%); or with features of obstructive uropathy of both kidneys in standard study (92 kidneys in total)

Demographic data of all examined groups is summarized in Table 1.

All subjects underwent DRS performed according to the standard protocol used in our Department. All subjects drank 0.5 l of water about 30 minutes before the study and urinated just before commencing image acquisition. DRS was performed in the supine position using one of the GE scintillation cameras: Infinia Hawkeye 1, Infinia Hawkeye 4 or Optima NM/CT 640, equipped with low-energy general-purpose collimators (LEGP), after administration of standard activity of 111 MBq 99mTc-EC [9, 10]. Field of view of the detectors covered both the kidneys and the heart of the subject and the images were recorded in a 128 x 128 pixel matrix. In case of a significantly slowed down urine outflow, i.e. renographic curve remaining above 30% of the peak level for the entirety of the base study (20 min.), DRS was extended by a diuretic test, carried out in accordance with the ”F + 20” protocol for additional 10 minutes [11].

Routine visual assessment of 2-minute sequential scintigraphic images and renographic curves were performed in all subjects, as well as the assessment of basic quantitative parameters obtained after conventional scintigraphic data processing. In group II, kidneys with features of obstructive uropathy or nephropathy were distinguished on this basis. Kidneys meeting at least 2 of the following 3 criteria were considered nephropathic: SF < 42%, T_{max} > 7 min. or presence of uptake defect(s) in the peripheral part of the kidney cortex determined as a consensus by two specialists based on visual assessment of sequential images obtained in the uptake phase. On the other hand, absence of renographic curve decrease, or its decrease by less than 50% from the end of the case study after the diuretic test, were considered as features of obstructive uropathy (total or incomplete obstructive uropathy, respectively).

Afterwards, additional post-processing of scintigraphic data was performed, using the ImageJ program with the original plugin developed in our Department. The method of determining ROIs of heart, kidneys and extrarenal background was shown in the work by Filipczak et al. [7, 8]. ROIs plotted in this way were then used to generate time-activity curves showing changes of the radiopharmaceutical concentration in the heart and kidneys (the latter being corrected by subtracting non-renal background activity). These curves served as the basis for the calculation of all assessed parameters.

Based on Rutland’s theory [12], uptake constant K was determined for each kidney [7, 8]. Its value is proportional to the
clearance function of a kidney. Then the average value of this parameter per pixel of whole kidney ROI was calculated, to make it independent from the size of the organ, which leads to obtaining KEi.

Reliability of assessed parameters was evaluated in multiple ways. KEi values, as shown in work by Filipczak et al. [7, 8], were strongly correlated with single-kidney eGFR (SKeGFR), where eGFR was calculated using the CKD-EPI formula [13–15] and multiplying it by SF value of each kidney.

“Normalcy rate” — the percentage of results within the normal range (according to normative values determined in the group of healthy volunteers) in group IIA, that is, in patients with no scintigraphic features of uropathy or obstructive nephropathy in standard DRS, was also used as a verification of the reliability of the method.

Next, a comparative analysis of the differentiation of obstructive uro-/nephropathy was performed based on standard and new DRS parameters in IIB subgroup, i.e. in situations where SF is unreliable.

Statistica version 13.1 was used for statistical analysis. Normality of data distributions was tested using Shapiro-Wilk’s test. In group I, the distribution of KEi values was normal, while values of TMAX deviated from normal distribution. In group II and each of its subgroups, values of both parameters deviated from normal distribution. The statistical significance level (p) used in the study was 0.05.

Results

Due to normal distribution of KEi values in the control group (I), its normative value was assumed as mean — 2 standard deviations, while for TMAX, mean + 3 standard deviations were taken as normal limit. The results are summarized in Table 2.

KEi was within normal range in 118/124 kidneys from subgroup IIA (with very low probability of obstructive uro-/nephropathy) — “normalcy rate” 95%. The distribution of KEi values in group I and subgroup IIA was very similar (Fig. 1A and 1B, respectively).

In subgroup IIB (patients with bilateral uropathy or single active kidney), according to the standard DRS criteria assumed in this study, obstructive uropathy was found in 18/92 kidneys, and obstructive nephropathy was diagnosed in 25/92 kidneys. Distribution of KEi values in this subgroup was significantly different than in groups of healthy kidneys (Fig. 1C). Use of KEi changed the qualification in 31/92 kidneys (1/3) — in 4 cases (4%) corrected the qualification from nephropathy to uropathy, while in 27 cases (29%) KEi was below normal limit despite of lack of features of nephropathy in the evaluation of standard scintigraphic parameters (Fig. 2).

Table 2. Values of assessed parameters in examined groups with assumed normative limits

<table>
<thead>
<tr>
<th></th>
<th>TMAX [min]</th>
<th>KEi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>3.6 ± 1.1</td>
<td>12.78 ± 2.46</td>
</tr>
<tr>
<td>Normal limits</td>
<td>&lt; 7</td>
<td>≥ 8</td>
</tr>
<tr>
<td>Group II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgroup IIA</td>
<td>4.4 ± 2.2</td>
<td>12.20 ± 2.87</td>
</tr>
<tr>
<td>Subgroup IIB</td>
<td>13.8 ± 11.3</td>
<td>9.32 ± 5.45</td>
</tr>
</tbody>
</table>

Figure 1A. Distribution of KEi values in kidneys from group I

Figure 1B. Distribution of KEi values in kidneys from subgroup IIA

Figure 1C. Distribution of KEi values in kidneys from subgroup IIB
Values of KEi

Figure 2. Change of kidney qualification in group IIB based on the values of KEi

There were 3 patients qualified as bilateral uropathy, whose kidneys had SF well within normal ranges and displayed no significant uptake defects, while KEi showed features of bilateral nephropathy. In the group of patients with single functioning kidney, in 7 cases KEi changed the classification to nephropathy while all 3 standard criteria suggested normal function of the kidney, that is SF was between 90 and 100%, T_{Max} between 3 and 6 min. and visual assessment revealed no uptake defects at all.

Discussion

SF, which is the main quantitative parameter of DRS, due to its relative nature has significant limitations reducing its usefulness in certain clinical situations. In case of bilateral renal dys-function or only a single functioning kidney, reliable assessment of renal function is only possible by supplementing SF with the value of GFR of a given patient. However, this requires performing additional studies, e.g. using accurate, but time-consuming and labor-intensive methods for determining glomerular filtration with radioisotopes (99mTc-DTPA clearance) or as a simpler, but less accurate method for calculating estimated GFR using biochemical studies (e.g. serum creatinine level).

Therefore, methods that allow an assessment of renal cortex function in absolute values are being developed, based only on scintigraphic data obtained with gamma-cameras in DRS, without the need for taking blood samples or urine collection. Several such protocols have been created and camera-based clearance methods are even an integral part of modern scintillation camera software. However, for these techniques acquisition of additional - non-standard data is necessary, as described in the work by Filipczak et al. [7, 8], which in turn requires modification and expansion of the standard DRS protocol.

Original parameter KEi does not have these disadvantages. It is relatively easy to determine and relies only on post-processing of standard scintigraphic data. Hence it can be used both routinely, or only in cases in which assessment of classic DSN parameters does not provide a conclusive diagnosis. It can also be applied retrospectively with ease, for example for scientific purposes.

One of the important arguments supporting the usefulness of this parameter, apart from its strong correlation with SKeGFR shown in work by Filipczak et al. [7, 8], is its high normalcy rate. In a group of patients with a very low probability of uropathy or nephropathy according to the standard DSN evaluation — subgroup IIA, KEi also showed values within the normal range in 95% of cases and the distribution of its values was very similar to group I. This confirms the accuracy of the normative limit established on a selected group of healthy volunteers. Distribution of KEi values in subgroup IIB, which consisted of both normally functioning and nephropathic kidneys, was significantly different.

Value of KEi, that represents the average clearance function of a kidney, is completely independent of its size. This allows determination of normative values, based on a group of healthy volunteers with no impairments of kidney function, that can later be used for evaluation of other kidneys, regardless of their size. This parameter can be useful not only in the diagnosis of obstructive nephropathy, but also for the differentiation of a small, but normally functioning (hypoplastic) kidney from an insufficient one (e.g. cirrhotic), and in assessing a small kidney in the diagnosis of renovascular hypertension. This will be the subject of our further research.

In summary, it should be noted that KEi extends the capabilities of DRS with a repeatable, quantitative assessment of absolute, individual kidney function. This parameter does not require any modifications of a routine protocol of the study (and thus can be determined in post-processing, e.g. only if the standard DRS result is ambiguous). It was shown that use of this parameter improves the diagnostic effectiveness of DSN in the differential diagnosis of obstructive uropathy and nephropathy.

References

The levels of oxidative and nitrosative stress in patients who had $^{99m}$Tc-MIBI myocardial perfusion scintigraphy and $^{99m}$Tc-DMSA, $^{99m}$Tc-MAG-3 renal scintigraphy

Ebru Salmanoglu$^1$, Ergul Belge Kurutas$^2$

$^1$Department of Nuclear Medicine, Kahramanmaras Sutcu Imam University, Faculty of Medicine, Kahramanmaras, Turkey
$^2$Department of Medical Biochemistry, Kahramanmaras Sutcu Imam University, Faculty of Medicine, Kahramanmaras, Turkey

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Abstract

BACKGROUND: Ionizing radiation is a strong stimulator of reactive oxygen species (ROS) and reactive nitrogen species (RNS). These reactive species may cause oxidative and nitrosative stress. In this study, we aimed to evaluate possible effects of $^{99m}$Technetium ($^{99m}$Tc)-methoxyisobuthylisonitrile (MIBI), $^{99m}$Tc-dimercaptosuccinic acid (DMSA), $^{99m}$Tc-mercaptoacetyltriglycine (MAG-3) on oxidative and nitrosative stress biomarkers in patients who were performed myocardial perfusion scintigraphy (MPS) and renal scintigraphy.

MATERIAL AND METHODS: Patients ($n = 29$) who were referred to nuclear medicine department were chosen as the patient group. They were divided into three subgroups according to the type of disease and $^{99m}$Tc labelled agent. The first patient group had MPS ($n = 9$). The second patient group had $^{99m}$Tc-DMSA renal scintigraphy ($n = 12$). The third patient group had $^{99m}$Tc-MAG-3 renal scintigraphy ($n = 8$). The blood samples were taken from first, second and third patient groups 1 h, 3 h, 45 min after injection of the agent, respectively. The samples were taken from healthy volunteers ($n = 25$) as a control group. Alterations in catalase (CAT), superoxide dismutase (SOD), malondialdehyde (MDA) levels as oxidative stress biomarkers and nitric oxide (NO) and 3-Nitrotyrosine (3-NTx) levels as nitrosative stress biomarkers in all blood samples were evaluated.

RESULTS: Results of MPS and renal scintigraphy performed patients were compared with control group separately. CAT, SOD, MDA and 3-NTx levels were higher in the first group than the control group ($p < 0.05$). Although NO levels were higher in the first group than the control group, it was not statistically significant ($p > 0.05$). CAT and SOD levels were lower in second and third groups than the control group ($p < 0.05$). However, MDA, NO, 3-NTx levels were higher in second and third groups than the control group ($p < 0.05$).

CONCLUSIONS: These results show that oxidative and nitrosative balance is impaired due to ionization radiation. These reactive species might stimulate an adaptive and protective cellular defense mechanism in irradiated cells soon after exposure to radiation. Thereby, this mechanism protect organism from the effects of low dose ionizing radiation.

KEY words: ionizing radiation; oxidative stress; nitrosative stress


Introduction

$^{99m}$Technetium ($^{99m}$Tc) and $^{99m}$Tc-labeled radiopharmaceuticals widely are used more than 50 years in clinical nuclear medicine applications. $^{99m}$Tc has both 140 keV gamma emission...
and approximately 5 low energy Auger and internal conversion electrons per decay. $^{99m}Tc$’s half-life (t1/2) is six hours. $^{99m}Tc$-methoxyisobutylisonitrile (MIBI) is used for myocardial perfusion scintigraphy (MPS) [1, 2]. $^{99m}Tc$-dimercaptosuccinic acid (DMSA) is used for renal cortical scintigraphy and $^{99m}Tc$-mercaptaoacetetyltriagnlycine (MAG-3) is used for dynamic renal scintigraphy [3]. Although the importance of $^{99m}Tc$ has been accepted in the worldwide, it results high ionization radiation intensity near the radionuclide’s decay position due to emitted beams [2]. After intravenous (i.v.) injection of the radiopharmaceutical, it distributes into living cells and ionizing radiation is absorbed by these living cells. Cellular exposure to ionizing radiation initiates oxidizing process. This process damages cells and their structures at the atomic level via direct interactions with macromolecules such as DNA, RNA, proteins and lipids or radiolysis of water. Furthermore, this damage might spread to neighbour cells via bystander effect and persist in the progeny for many generations [4–7].

During the radiosynthesis of water-reactive oxygen species (ROS) including superoxide anion, hydrated electron, hydroxyl radical, hydrogen peroxide, organic hydroperoxides, alkoxy and peroxy radicals, hypochlorite, peroxynitrite are produced. Ionizing radiation also causes the production of reactive nitrogen species (RNS). As a result of that, large amounts of nitric oxide and peroxynitrite anion are produced [7, 8].

ROS/RNS initiate harmful process in cells. Different signalling cascades adaptive responses including DNA repair, antioxidation reactions and different signalling cascades are stimulated to overcome these harmful process. Ionizing radiation regulates antioxidant enzyme activity depending on dose and linear energy transfer. While a low dose of LET radiation (gamma rays) at low dose-rate stimulates antioxidant defense system, high LET radiation spreads oxidative stress both in the irradiated cells and nearby cells by means of bystander effect [7]. Antioxidants defense systems play a crucial role for preventing damage caused by ROS/RNS and eliminating ROS/RNS. The imbalance in the production and the elimination of ROS/RNS and various reducing or antioxidant systems of the body causes oxidative/nitrosative stress [7, 9, 10].

To our knowledge, this is the first study in the current literature that investigates the effects of $^{99m}Tc$-MIBI, $^{99m}Tc$-DMSA and $^{99m}Tc$-MAG-3 oxidative/nitrosative damage in human. The present study was aimed to evaluate levels of both oxidative stress biomarkers including catalase (CAT), superoxide dismutase (SOD), malondialdehyde (MDA) and nitrosative stress biomarkers including nitric oxide (NO) and 3-Nitrotyrosine (3-NTx) in patients who were clinically indicated and underwent $^{99m}Tc$-MIBI MPS, $^{99m}Tc$-DMSA renal cortical scintigraphy and $^{99m}Tc$-MAG-3 dynamic renal scintigraphy.

Material and methods

Ethics

This study was conducted after obtaining approval from the local ethical committee of Sutcu Imam University, Medical Faculty, Kahramanmaras, Turkey. Also, the study was conducted in accordance with the Declaration of Helsinki on medical protocols and ethics. As we used routinely generated data with no identifying information, the study carries no harm whatsoever to patients. Data were used only for scientific purposes. All participants were informed extensively about this study and signed an informed-consent form before they were enrolled in this study.

Study population

A total of 29 patients who were referred to the nuclear medicine department and who were routine scintigraphic imaging methods were indicated were chosen as the patient group. The patients were divided into three subgroups based on the type of disease and $^{99m}Tc$ labelled agent. The $^{99m}Tc$ labelled imaging agents were administered at clinical doses.

In 9 patients (2 female, 7 male) with a mean age of 52 ± 9.7 years (range 38-67 years), MPS with $^{99m}$Tc-MIBI was obtained (group 1).

In 12 patients (8 female, 4 male) with a mean age of 20 ± 21.6 years (range 1-66 years), renal cortical scintigraphy with $^{99m}Tc$-DMSA was carried out (group 2).

In 8 patients (6 female, 2 male) with a mean age of 28 ± 21.4 years (range 6 and 66 years) dynamic renal scintigraphy with $^{99m}Tc$-MAG-3 was performed (group 3).

The blood samples were taken from first group 1h after intravenous (i.v.) injection of $^{99m}$Tc-MIBI, from second group 3h after i.v. injection of $^{99m}Tc$-DMSA, from third group 45min, after i.v. injection of $^{99m}Tc$-MAG-3. The samples were also taken from a total of 25 healthy volunteers with a mean age of 39 ± 13.1 years (range 18–63 years) as a control group.

Alterations in both CAT, SOD, MDA levels as oxidative stress biomarkers and NO and 3-NTx levels as nitrosative stress biomarkers in all blood samples were evaluated.

Biochemical analysis in erythrocytes

The blood samples were centrifuged at 3000 g for 10 minutes at 4°C. Plasma was separated and the buffy coat was discarded by aspiration. Erythrocytes were washed 4 times with cold physiological saline and stored at −70°C until analysis. The CAT activity in erythrocyte was measured in samples by the method applied by Beutler [11]. The decomposition of the substrate H2O2 was monitored spectrophotometrically at 240 nm. The activity of CAT was expressed as U/g Hb. The SOD activities in erythrocytes were estimated by the use of the method described by Fridovich [12]. SOD activity was expressed as U/g Hb. Lipid peroxidation level in the plasma samples was expressed in MDA. Measurement was based on the method of Ohkawa [13]. MDA levels were expressed as nmol/mL. NO and 3-NT levels in plasma samples were determined with a “sandwich” enzyme-linked immunosorbent assay kits (mybiosource human elisa kits, USA) according to the manufacturers’ protocol. Then, 3-NT levels were given as nmol/L.

Statistical analysis

Data were analyzed using the statistical package SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL.). Results were expressed as mean±SD. The conformability of the quantitative data to the normal distribution was examined by the Kolmogorov–Smirnov test. The Mann–Whitney U-test was used to compare mean values for all parameters between patients and control groups. p value < 0.05 was accepted as statistically significant.
Results

Results of MPS and renal scintigraphy performed patients were compared with control group separately.

Initially, MPS performed patients group were evaluated. The antioxidant enzyme activities of CAT and SOD were statistically significantly higher in the first patient group than the control group (p < 0.05) as shown in Figure 1A and 1B. CAT and SOD levels were approximately 1.9 and 1.7 fold higher in the first patient group than healthy subjects, respectively. In addition, MDA levels were also statistically significantly higher in the first patient group than the control group (p < 0.05) and its levels were nearly 1.6 fold higher in the first patient group as shown in Figure 1C. 3-NTx levels were statistically significantly nearly 1.8 fold higher in the first patient group than control group (p < 0.05) as shown in Figure 2A. NO levels were nearly 1.2 fold higher in the first patient group than control group (p > 0.05) as shown in Figure 2B.

Then, renal scintigraphy performed patients group were evaluated. CAT and SOD levels were statistically significantly lower in second, third and total renal scintigraphy performed patient groups than control group (p < 0.05). CAT and SOD levels were nearly 2 and 3 fold lower in the second patient group than control group, respectively (Fig. 3A and 3B). CAT and SOD levels were nearly 1.7 and 3 fold lower in the third patient group than control group, respectively (Fig. 4A and 4B). CAT and SOD levels were nearly 2 and 3 fold lower in total renal scintigraphy performed patients group than control group, respectively (Fig. 5A and 5B). MDA levels were statistically significantly higher in second, third and total renal scintigraphy performed patient groups than the control group (p < 0.05). MDA levels were nearly 2, 2 and 1.6 fold higher in second, third and total renal scintigraphy performed patient groups than the control group, respectively (Fig. 3C, 5C and 7C). NO levels were nearly 1.5, 2 and 1.6 fold higher in second, third and total renal scintigraphy performed patient groups than the control group, respectively (Fig. 4A, 6A and 8A). 3-NTx levels were nearly 2.3, 2.85 and 2.6 fold higher in second, third and total renal scintigraphy performed patient groups than the control group, respectively (p < 0.05) (Fig. 4B, 6B and 8B).

Discussion

In this study, we investigated the effect of ionizing radiation on both oxidative and nitrosative stress parameters in patients who were clinically indicated \(^{99}\text{Tc-MIBI}\) MPS, \(^{99}\text{Tc-DMSA}\) renal cortical scintigraphy, \(^{99}\text{Tc-MAG-3}\) dynamic renal scintigraphy. This is the first study that evaluates levels of nitrosative stress parameters in patients with these scintigraphic imaging agents.

\(^{99}\text{Tc-MIBI}\) is a lipophilic cationic complex, enters cells by passive diffusion. It is localized mostly in the mitochondria of myocytes due to negative mitochondrial membrane potential [1, 2, 15]. \(^{99}\text{Tc-DMSA}\) is a renal cortical agent that primarily bound in the proximal tubule in the renal cortex for a prolonged time after injection. \(^{99}\text{Tc-MAG-3}\) is commonly used renal tubular agent in nuclear medicine practice [3]. It is known that the DNA-binding traits of \(^{99}\text{Tc}\) labelled agents augments radiotoxicity of these agents [1, 2, 14–16].

AT, SOD, MDA, 3-NTx levels were found statistically significantly higher in patients than control group (p < 0.05) and 1.9, 1.7, 1.6, 1.8 fold higher in patients, respectively. NO levels were 1.2 fold higher in patients than control group (p > 0.05) AT, SOD, MDA, 3-NTx levels were found statistically significantly higher in patients than control group (p < 0.05) and 1.9, 1.7, 1.6, 1.8 fold higher in patients, respectively. NO levels were 1.2 fold higher in patients than control group (p > 0.05). The results of this study showed that antioxidant enzyme activities of CAT and SOD levels were significantly higher
Figure 2. The activities of nitric oxide (NO); A. and nitrotyrosine (3-NTx); B. Levels as nitrosative stress biomarkers in first patient group and control group.

Figure 3. The activities of catalase (CAT); A. Superoxide dismutase (SOD); B. and malondialdehyde (MDA); C. Levels as oxidative stress biomarkers in second patient group and control group.

In $^{99m}$Tc-MIBI administered group than the control group ($p < 0.05$). Because shortly after exposure to $^{99m}$Tc-MIBI, cellular protective pathways are triggered to overcome radiation-induced ROS. In addition, we previously reported same results in patients have thyroid and bone scintigraphy [17, 18]. However, $^{99m}$Tc-MIBI caused decreased SOD levels in mice [19].

In contrast to MIBI administered group, CAT and SOD levels were significantly lower in $^{99m}$Tc-DMSA, $^{99m}$Tc-MAG-3 administered patients and total renal scintigraphy performed patients than control group in this study ($p < 0.05$). $^{99m}$Tc-DMSA stays in the proximal tubule in the renal cortex for a prolonged time after injection. $^{99m}$Tc-MAG-3 is a renal tubular agent. Renal imaging agents might induce free radical production more than MPS imaging agent. In addition, renal diseases cause oxidative stress. Therefore, antioxidant enzyme levels decreased in this group of patients. It has also been reported in the literature that exposure to radiation due to different radiopharmaceuticals including $^{99m}$Tc-diethylene trimine pentaaceticacid (DTPA) [20], $^{67}$Tc-MIBI, $^{201}$Thallium, $^{99m}$Tc-MIBI, $^{99m}$Tc-methylene-diphosphonate (MDP) [19, 21–23] and 2.45 GHz microwave radiation [24] in animal and human studies.

MDA levels were significantly higher in $^{99m}$Tc-DMSA, $^{99m}$Tc-MAG-3 administered patients and total renal scintigraphy performed patient groups than the control group ($p < 0.05$). In addition, researchers stated that gamma radiation at clinically used doses stimulates lipid peroxidation in human red cells [25]. ROS can initiate...
lipid peroxidation that is a chain reaction. Once lipid peroxidation
is initiated, it results in the oxidative deterioration of polyunsaturated
fatty acids and caused increased MDA levels [25]. Furthermore,
these results are in agreement with previous animal and human
studies that demonstrated 99mTc-DTPA [20], 99mTc-MIBI [21] and
microwave radiation [24] caused increased MDA levels. However,
99mTc pertechnetate caused decreased MDA levels in patients [26].

The results acquired in this research study confirms that ionizing
radiation causes different changes at antioxidant enzyme levels.
However, to the best of our knowledge there is no similar clinical
study reports on the effect of ionizing radiation due to 99mTc-MIBI
and 99mTc-MDP on nitrosative stress parameters (NO, 3-NTx) in
human. Therefore, we could not compare our results with those of
others. We only could compare our findings on nitrosative stress pa-
rameters only with our previous reports that were performed in
different patients groups and with different radiopharmaceutical
agents including 99mTc pertechnetate and 99mTc-MDP.

NO levels were higher in the first patient group than the con-
control group but it was not statistically significant (p > 0.05). 3-NTx

levels were statistically significantly higher in the first patient group
than the control group (p < 0.05).

NO, 3-NTx levels were higher in 99mTc-DMSA, 99mTc-MAG-3 ad-
ministered patients and total renal scintigraphy performed patient
groups than the control group (p < 0.05).
We reported that NO and 3-NTx levels were increased in patients who have performed thyroid scintigraphy with $^{99m}$Tc pertechnetate and bone scintigraphy with $^{99m}$Tc-MDP [17–18].

Nitric oxide (NO) has one unpaired electron, hence it is accepted as a radical. NO is produced in biological systems via specific nitric oxide synthases (NOSs). NO plays an important role in various physiological conditions, such as neurotransmission, blood pressure regulation, defence mechanisms, smooth muscle relaxation and immune regulation. NO chemically reacts with oxygen and water, as a result of that nitrate and nitrite anions are produced. NO also reacts with superoxide anion and peroxynitrite (ONOO–) is produced. Reactivity of ONOO– is higher than NO. ONOO– reacts with proteins, thus nitrotyrosine (3-NTx) is produced. 3-NTx is a characteristic marker of nitrosative stress. It is known that NO and 3-NT levels are increased in various diseases such as skin cancers, systemic lupus erythematosus, and atopic dermatitis [27].

NO, is produced by endothelial and endocardial tissue, has a significant effect on myocard and its vascular function. Coronary heart disease (CHD) is a chronic inflammatory process that becomes against vascular damage. Endothelial disfunction causes CHD when endothelial cells cannot perform their functions including NO production. Furthermore, free oxygen radicals negatively effect NO production in MPS performed patients. Because of that, NO levels might not statistically increased in $^{99m}$Tc-MIBI administered group in this study [28–30].
different effects on antioxidant enzyme levels. All of these methods increased MDA levels and nitrosative stress parameters. Our study will contribute current literature understanding radiobiological effects of scintigraphic imaging agents on especially nitrosative stress parameters. However, further studies in a larger number of the population are needed to fully understand this topic.

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**References**


PET/CT in thyroid cancer — the importance of BRAF mutations

Vincenzo Cuccurullo1, Giuseppe Danilo Di Stasio1, Giuseppe Lucio Cascini2

1Nuclear Medicine Unit, Department of Precision Medicine, Università della Campania “Luigi Vanvitelli”, Napoli, Italy
2Department of Diagnostic Imaging, Nuclear Medicine Unit, Magna Graecia University of Catanzaro, Catanzaro, Italy

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Abstract

Thyroid cancer (TC) represents less than 1% of all newly diagnosed malignancies. In some selected cases, with a high clinical suspicion for disease but negative I-131 scan, positron emission tomography/computed tomography (PET) with F-18-Fluorodeoxyglucose (FDG) could be helpful in the detection of disease and the definition of its extent. FDG PET/CT, better if performed after TSH stimulation analogously to patient preparation done for radioiodine scintigraphy, could be useful mainly in the detection of metastatic and recurrent disease since the uptake and diagnostic sensitivity of FDG are increased by TSH stimulation. Recently, the role of oncogenic mutations in the tumorigenesis of TCs has become clearer. Among such mutations, BRAFV600E represents the most common genetic alteration. Mutated BRAF may define a more aggressive papillary carcinoma with poorer prognosis and therefore its analysis has been extensively studied as a rule-in test for thyroid carcinoma.

In this paper, we try to outline the possible role of FDG PET/CT in the management of patients with TC and positive BRAF mutations and the impact that it could have on their therapeutic algorithm, in terms of thyroidectomy and radioactive iodine (RAI) therapy.

KEY words: BRAF mutation; fluorodeoxyglucose F18; positron emission tomography; thyroid neoplasms

Introduction

Thyroid nodules (TN) are extremely common in general population and also thanks to their subclinical detection via ultrasound imaging (US), the incidence of thyroid cancer is increasing [1]; in Europe for example, it has increased in the last decade by 69% in men and 65% in women. In fact, it has been estimated that one person out of five, despite gender, age and other epidemiological characteristics has a palpable thyroid nodule, which can be detected by US in most of cases [2]. The prevalence of TN is greater in women than in men, with multiple nodules that are more common than solitary ones [3]. In the diagnostic algorithm of TN, the differential diagnosis includes numerous clinical entities, both benign and malignant; therefore, the pathological examination has an important role in their evaluation. Thanks to fine needle aspiration cytology (FNAC) biopsy the identification of high-risk situations has significantly improved so that their management has now become more effective [4]. However, there are still cases in which patients require surgery for further confirmation of the disease, thus relying upon the pathologist to correctly characterize their nodule [4].
Molecular pathophysiology

Thyroid epithelial cells have a transport mechanism, the sodium/iodide symporter (NIS), which enables thyroid concentration of iodide to subsequently undergo organization and incorporation into thyroid hormones [12]. This mechanism is influenced primarily by a pituitary hormone, the thyroid-stimulating hormone (TSH), which increases the transport of iodide [13]. B-type RAF kinase (BRAF) is a serine-threonine kinase that belongs to the rapidly accelerated fibrosarcoma (RAF) family, and represents the most potent mitogen activated protein kinase (MAPK) pathway activator [14]. The MAPK pathway is a signal transduction cascade driven by phosphorylation that leads to intracellular responses such as cell proliferation [15]. Thus, BRAF acts as a protooncogene and has an important function in cell growth, differentiation and apoptosis, with its point mutations that have been noted in various human cancers [16]. In PTC, a common mutation in the BRAF gene comprises a missense mutation that consists of a thymine-to-adenine transversion at nucleotide 1799 (T1799A) within exon 15, which increases the transport of iodide [17]. B-type RAF kinase (BRAF) mutation is associated with tumorigenesis [17].

FDG PET/CT is routinely used to evaluate disease burden in a variety of neoplasms, with FDG uptake that is based on enhanced aerobic glycolysis in cancer cells, known as Warburg effect. In TC there is an inverse relationship between FDG avidity and radiiodine uptake mainly in case of metastatic lesions, a phenomenon which was originally described as ‘flip-flop’ [18–20].

Thyroid nuclear medicine imaging

Thyroid gland imaging is routinely done with different radiopharmaceuticals that are used in specific clinical contexts. Among them, Tc-99m-pertechnetate is widely used and owes its popularity to easy availability, low absorbed radiation dose compared to I-123 or I-131 and lower costs. The tracer is trapped by the thyroid, but it does not undergo organification, remaining in the gland for a relatively short period which allows imaging for diagnostic purposes mainly related to thyroid morphology and function, i.e. hypo- or hyper-thyroidism [21].

Iodide radioisotopes (I-123, I-131) are trapped and organified inside the thyroid, providing higher thyroid-to-background uptake ratios; however, in order to achieve sufficient iodine uptake into tumor cells, high levels of TSH are required (serum TSH levels > 30 mU/L), thus implying either thyroid hormone withdrawal or intramuscular injection of rh-TSH (Thyrogen©). I-123 and I-131 could be used to interrogate the NIS sympporter to assess thyroid nodule functioning in order to distinguish “hot” (autonomous) from “cold” (hypofunctioning) nodules but their main application is the detection of thyroid cancer metastases, which as the primary tumor are usually iodine avid [23].

FDG PET/CT in the management of patients with DTCs

As stated above, due to either BRAFV600E mutation or tumor dedifferentiation, when the ability to synthesize hormones from iodine is lost, tumors show increased glucose metabolism [24]. In such cases, patients will present with elevated human thyroglobulin levels (i.e. serum specific marker of TC) and with negative post-therapeutic I-131 whole body scans. Here, FDG PET/CT, better if performed after TSH stimulation analogously to patient preparation done for radiiodine scintigraphy, could be useful mainly in the detection of metastatic and recurrent disease since the uptake and diagnostic sensitivity of FDG are increased by TSH stimulation [25]. In fact, although the current ATA guidelines do not routinely recommend FDG-PET/CT for the diagnostic workup of indeterminate thyroid nodules due to limited clinical validation, several studies and meta-analysis already demonstrated the opposite [7].

More in particular in a recent paper by Piccardo et al., the Authors compared the accuracy of FDG PET/CT with Tc-99m-MIBI scintigraphy and multiparametric neck ultrasonography (US) demonstrating that the former has significantly higher performances in terms of sensitivity and NPV than the latters [26]. They also evaluated the possible role of FDG PET/CT in different diagnostic contexts in terms of impact on clinical management. It emerged that FDG PET/CT could be of use already at a preoperative stage to define the nature of indeterminate TNs thanks to its high sensitivity and NPV, especially in patients with lesions > 15mm with sensitivity ranging from 77 to 100% and NPV from 81 to 100% [26]. More specifically, we know that focal uptake of FDG within the thyroid gland, as incidental finding during evaluation of non-thyroid cancers, may be related to both benign and malignant pathology [27]. In this sense, De Koster et al. suggested that the number of futile hemithyroidectomies for benign nodules could be reduced thanks to the implementation of FDG-PET/CT by 66%, implying the cost-effectiveness of this technique in the pre-operative setting [28]. However, overall reported sensitivity and specificity of FDG-PET/CT in this specific scenario ranged from 77% to 100% and from 33% to 64%, respectively, with small nodule size being the main reason for false-negativity, since FDG-avidity in very small nodules may
be missed due to both low volume of malignant cells and partial volume effect, which underestimate the real FDG-concentration [28]. Moreover, the radiation exposure of FDG-PET/CT that patients should undergo before surgery represents another limitation to this possible application since it is largely accounted for by the FDG dosage (approximately 3 to 4 mSv for a typical activity of 185 MBq administered to an average adult) whereas the CT radiation dose greatly varies, being less than 0.5 mSv for a low-dose CT of the neck region only [29].

Pre-operative FDG PET/CT could also be used in the assessment of biological behavior of DTCs in order to predict the aggressiveness of the tumor pre-surgically [30]. In this sense, BRAF molecular test already represents the most reliable tool to identify the most aggressive subgroup of papillary thyroid carcinomas, but due to the relatively high costs and low availability, its use in clinical practice remains not applicable [31, 32]. Therefore, as some studies report, FDG PET/CT could be used to reduce costs and provide analogous information, with a more intense FDG uptake at pre-operative PET/CT that might be associated with a poorer prognosis and more aggressive histological subtype [33]. In this sense, Trimboli and colleagues used a SUV ratio of 3.0 as a cut-off to distinguish patients with higher rather than lower risk of disease progression. However, after a multivariate analysis, they concluded that only tumor size remained associated with disease persistence/progression; therefore, the evidence of this possible application of FDG PET/CT remains to be further evaluated [34].

Recent 2015 ATA Guidelines recommend neck US as first-line imaging technique to stage DTCs before thyroidectomy, whereas the use of CT or multiparametric magnetic resonance imaging (MRI) is reserved for high risk patients in which the probability to have distant metastases or mediastinal/neck nodal involvement at time of diagnosis is elevated [7]. In this context PET/CT does not have a role yet, even if some studies have been already published in this sense [35]. Specifically, Agate et al. compared the performance of FDG-PET/CT, CT alone and US in the diagnosis of cervical lymph node metastasis in patients with PTC and concluded that US had the best diagnostic accuracy among the three (64.9%, 61.9% and 82% respectively) thus confirming ATA guidelines preference of neck US as best methodology for preoperative assessment of nodal status. However, FDG PET/CT might still be useful in aggressive DTC subtypes such as tall-cell, solid/trabecular, insular and diffuse sclerosing or in patients with suspected distant metastases for staging purposes and to predict the preoperatively the risk of recurrence [37]. A Japanese group retrospectively analyzed in a recent paper the benefit of FDG PET/CT at initial diagnosis in 114 patients with DTC for predicting the high-risk for recurrence by assessing seven parameters including among the others SUVmax, SUVmean and MTV (metabolic tumor volume expressed in cm³). They identified 88 patients with FDG-avid tumor and 26 patients with FDG-non-avid tumor and demonstrated that the former group resulted to have significantly larger lesions (21 vs 13 mm), more advanced ATA-risk classification, but at the same time, only 10 out of 88 patients were classified as high-risk and the parameters themselves revealed a wide range of sensitivity, specificity and accuracy. So, they divided patients according MTV, if greater than 10.0 cm³ or not, and introduced a scoring system that takes in consideration each of the seven diagnostic parameters assigning a score of 0 if negative for high-risk or 1 if positive using each threshold criterion. Summing these scores to differentiate between high-risk and non-high-risk patients they demonstrated that a summed score ≥ 5 in 44 patients with an MTV > 10.0 cm³ was associated with 100% sensitivity, 91.7% specificity and 93.2% accuracy (AUC: 0.98) in predicting the high-risk for recurrence. Therefore, they concluded that FDG-non-avid primary DTCs are less inclined to post-operative recurrence whereas in FDG-avid primary DTCs with MTV > 10.0 cm³, the combination of SUV-related, volumetric and texture parameters could significantly increase the ability to identify high-risk patients, thus confirming the prognostic value of FDG PET in advanced thyroid cancer [38].

Apart from the aforementioned scenarios in which FDG PET/CT might have or not a role in clinical practice, what remains clear as main indication for this technique is the post-operative stage, during follow-up, mainly in case of patients with aggressive histologies so to have a starting reference point or in chase of high or increasing Tg levels (Tg > 10 ng/mL or doubling time of less than 1 year) with negative post-therapeutic I-131 whole-body scan [39]. A meta-analysis performed by Wan et al. [40] evaluated 17 studies with 571 patients who had recurrent or metastatic DTC and I-131 negative whole-body scan and determined that FDG-PET/CT a pooled sensitivity and specificity of 93.5% and 83.9%, respectively, with an overall diagnostic accuracy of 90.9%. Moreover, studies have shown that the positivity rate of FDG-PET/CT increases as Tg level rises, though there is lack of consensus on what the precise threshold level of Tg should be since positive findings have also been reported in 10–20% of DTC patients with Tg levels ≤ 10 ng/mL [41]. In this sense, becomes crucial the comparison of post-therapeutic I-131 whole-body scan with FDG-PET/CT because the latter could be helpful in the reduction of unnecessary second administration of high I-131 activities, which means direct implication on patients’ clinical management [42]. In fact, the current guideline to define a radioactive iodine-refractory (RAIR) DTC is based on the clinical negative response to a cumulative I-131 dose of 600 mCi or more, which means at least 3 RAI therapies over a two-year period, taking in consideration a 6-month treatment interval [43]. This may lead to a therapeutic delay, i.e. to not receive an appropriate treatment at the earliest possibility [44]. FDG-PET/CT could be useful in this sense as an early response predictor, thus allowing the early implementation of alternate therapies such as Tyrosine Kinase Inhibitors (TKIs). Kang et al. recently studied this problem by evaluating 54 patients with metastatic DTC who underwent both RAI therapy scan and FDG PET/CT during the same period in order to predict the response rate of RAI itself. Of 54 patients, only 22 had a therapeutic response to RAI with a 43% rate of concordance between the two techniques and with significant negative correlation between FDG avidity of metastatic lesions and response rate. Therefore, they concluded that the patient group with FDG-avid metastasis showed poor response to RAI therapy regardless of the degree of RAI uptake at I-131 whole-body scan [45].

**BRAFV600E and FDG PET/CT**

Recent clinical studies demonstrated the relationship between BRAFV600E mutation and FDG uptake, showing that BRAFV600E mutation is associated with downregulation of the NIS symporter, loss of RAI avidity and increased glucose transporter (GLUT-1) expression in both primary and metastatic PTCs, thus determining poorer
prognosis, including events such as increased incidence of recurrence, extrathyroidal invasion and distant metastases [46]. More in particular, in BRAFV600E-positive PTCs, several studies demonstrated that at mitochondrial level there is a reduction of O2 consumption and increased glucose uptake, thus favoring an anaerobic glycolytic shift in cancer cells by targeting at transcriptional level both hypoxia inducible factor (HIF)-1 that acts on GLUT1, GLUT3 and hexokinase II, which play an important role in trapping FDG inside cancer cells and the M2 isoform of pyruvate kinase (the rate-limiting step of glycolysis) which showed significantly higher levels compared to BRAF wild-type PTCs [47]. Therefore, the association between BRAFV600E mutation and FDG uptake could be explained with the induction of MAPK transduction pathway and the subsequent activation of HIF-1 resulting in increased glycolysis and loss of RAI avidity [48]. In this sense, as a recent study reported, BRAFV600E mutations were present in 62% of RAIR recurrent/metastatic TCs: analogously, all patients with RAIR PTCs and FDG-PET/CT positive scan were BRAFV600E-positive, compared to 45% of positive PET/CT scans in PTCs in general [49]. In a recent meta-analysis, Santhanam and colleagues not only show the significant correlation in DTC patients between BRAFV600E-positiveness and the higher odds of having FDG-PET/CT avid lesions (OR = 2.12) but they also demonstrated that these patients tend to have relatively higher mean SUV values (although SUV values may vary greatly across institutions and the measurement itself depends on multiple factors), thus concluding that BRAFV600E mutation, when present, should prompt the treating clinician to consider FDG-PET/CT as a useful diagnostic test to localize residual disease [46]. Nagarajah et al. [50] specifically evaluated the differences in terms of glucose metabolism of the BRAFV600E versus BRAFWT in patients with DTC and poorly differentiated TCs. While in the first cohort median SUVmax was significantly higher in the mutated group versus wild-type (median SUVmax 6.3 versus 4.7), in the latter FDG uptake was not significantly different between the two groups.

A very interesting study design instead, was carried out by Choi et al. that retrospectively reviewed 106 patients with PTC who underwent FDG PET/CT scan before undergoing total thyroidectomy, scans that were subsequently compared with clinicopathological data collected from surgical specimens, such as primary tumor size, capsular invasion, metastases and BRAFV600E mutation among the others.

Reported SUVmax was significantly higher in primary tumors of size greater than 1 cm (SUVmax 6.6 vs 3.4), in PTCs with extra-thyroid extension of the tumor (SUVmax 5.8 vs 3.7) and in PTCs with BRAFV600E mutation (SUVmax 5.7 vs 3.0), whereas at a multivariate analysis only tumor size and BRAFV600E were significantly associated with the SUVmax of the primary tumor, as extra-thyroid extension and thyroid capsular invasion had no statistically significant association. Therefore, they concluded that FDG PET/CT may play an important role and yield additional information on tumor aggressiveness when associated to molecular biomarkers such as BRAFV600E mutation [51].

Conclusions

Differeniated thyroid cancers are the most common histological types of thyroid cancer which are characterized by a favorable prognosis thanks to surgical removal of the tumor and radioiodine ablation therapy, with an overall 5-year survival rate higher than 90%. However, in some patients we can have a more aggressive behavior that often becomes the cause of mortality due to tumor recurrence and RAI refractoriness. Neck US still represents the first-line imaging technique to stage DTCs before thyroidectomy and is the best methodology for preoperative assessment of nodal status; however, new possible scenarios of application seem to be possible when this PET/CT is associated with the presence of molecular biomarkers, such as BRAFV600E mutation. FDG PET/CT has already been used in clinical practice in cases of elevated serum thyroglobulin and negative I-131 whole-body scintigraphy, mainly to locate recurrent disease and for its prognostic role. Unfortunately, despite these promising reports, the relationship between F-18 FDG uptake and the BRAFV600E mutation for a possible pre-operative application is still poorly recognized as it will need further validation in consideration also of the genetic heterogeneity that has been reported (between different primary tumors and regional lymph node metastases), which requires that all lesions within the patient harbor the same genetic defect.

References


Catheter malposition during a direct radionuclide cystography — case report

Shirin Shahlaei, Farnaz Nesari Javan, Atena Aghaee, Ramin Sadeghi
Nuclear Medicine Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

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Abstract

We reported a 15-year-old girl with a history of mild left vesicoureteral reflux who underwent direct radionuclide cystography in our department. Bladder catheterization was mistakenly placed in the vagina. The filling phase showed vagina and uterine cavity which was similar to vesicoureteral reflux. The procedure was repeated with correct catheterization of the bladder and no vesicoureteral reflux was noted.

KEY words: vesicoureteral reflux; direct radionuclide cystography; vagina

A major health problem in childhood is vesicoureteral reflux (VUR) [1]. Since VUR may have negative effects on kidneys it is important to detect the VUR as soon as possible [2]. In this regard voiding cystourethrography (VCUG) and direct radionuclide cystography (DRC) are common methods to diagnose and follow VUR [1, 3]. Voiding cystourethrography (VCUG) have some disadvantages i.e. high gonadal radiation compared with DRC [4]. Instead, direct radionuclide cystography (DRC) has been proposed to detect VUR with better detection of intermittent reflux. However, this method is suffering from the lack of enough anatomical details [5–7]. Our case report showed the importance of careful attention to correct catheterization (Fig. 1 and 2). Catheter
insertion in the vagina has been reported before during VCUG and this pitfall should always be borne in mind in case of DRC procedure especially in those with an unusual pattern of tracer distribution.

References


Primary nasal-ethmoid choriocarcinoma detected by 18F-FDG PET/CT: a rare tumor with complete remission

Maria Gazzilli1, Domenico Albano1, Laura Ardighieri2, Francesco Bertagna1, Raffaele Giubbini1
1Nuclear Medicine, University of Brescia, Spedali Civili Brescia, Brescia, Italy
2Department of Pathology ASST Spedali Civili, Brescia, Italy

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Abstract

Choriocarcinoma is a highly malignant and rare tumor characterized by secretion of the beta-subunit of human-choriogonadotropin (β-HCG). We report a case of primary nasal choriocarcinoma with good response to chemotherapy.

A 36-year-old woman gravida 0 and with history of 4 spontaneous abortions, in December 2018 referred to Otorhinolaryngology Department for repeated episodes of epistaxis. Cervical Magnetic Resonance Imaging (MRI) revealed a tumor mass involving right nasal cavity, right ethmoid, sphenoidal and maxillary sinuses.

For a differential diagnosis between metastatic gestational choriocarcinoma and primary choriocarcinoma in January 2019 she underwent 18Fluorine-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (18F-FDG-PET/CT) scan that demonstrated intense uptake only in the nasal-ethmoid tumor mass showed by MRI. This was suggestive of primary nasal-ethmoid choriocarcinoma she received 3 courses of BEP – regimen and after β-HCG was reduced to 500 mIU/mL and 18F-FDG-PET/CT scan showed a decreased uptake in tumor mass but the appearance of a new uptake in cervical lymph node which was analysed and reported as metastatic localization of choriocarcinoma. Therefore she was treated with 2 cycles of TIP-regimen. Subsequents 18F-FDG-PET/CT and MRI showed a complete tumor remission.

This case proved the fundamental role of PET/CT to make diagnosis of primitive choriocarcinoma and to exclude the hypothesis of distant metastasis.

KEY words: choriocarcinoma; nasal-ethmoidal; PET/CT

(bleomycin, etoposide and cisplatin), but patients who relapse after initial treatment or patients who didn’t respond completely to chemotherapy have a poor prognosis [5, 6]. Motzer et al. [7, 8] showed in a study that it is possible to obtain promising results with a combination of paclitaxel, ifosfamide and cisplatin (TIP) as a salvage therapy.

According to literature, she received 3 courses of BEP regimen and after that β-HCG was reduced to 500 mIU/mL and

**Clinical vignette**

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**Figure 1.** A. Staging PET/CT showed intense uptake in nasal-ethmoidal mass; a. Fused image; b. MIP image; B. Staging Cervical MRI showed large tumor mass involving right nasal cavity, right ethmoid, sphenoidal and maxillary sinuses

**Figure 2.** End-of-treatment images: A. PET/CT; B. Cervical MRI; both showed complete remission of nasal-ethmoidal mass

**Figure 3.** A. Hematoxylin and eosin stain showing mononucleated and plurinucleate tumor cells with striking cytologic atypia and central hemorrhage (200× magnification); B. Tumor cells positive for cytokeratin AE1/AE3 (200× magnification)
18F-FDG-PET/CT scan showed a decreased uptake in tumor mass, but the appearance of a new uptake in cervical lymph node which was analyzed and reported as metastatic localization of choriocarcinoma. Therefore she was treated with 2 cycles of TIP regimen. Subsequent 18F-FDG-PET/CT and MRI showed a complete tumor remission.

Due to aggressive and malignant biology of the disease, a correct identification of this tumor is important to start an effective therapy to improve the poor prognosis of choriocarcinoma. This case proved the fundamental role of PET/CT in establishing diagnosis of primitive choriocarcinoma and excluding the hypothesis of distant metastasis.

References


Primary skeletal muscle lymphoma with unusual soft tissue metastases in the stomach and pancreas detected by $^{18}$F-FDG PET/CT

Fatemeh Farahmandfar¹, Sara Shakeri¹, Sadegh Moradian², Shirin Shahlaei¹, Ramin Sadeghi¹

¹Nuclear Medicine Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
²Department of Radiology, Amiralam Hospital, Tehran University of Medical Sciences, Tehran, Iran

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Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin’s lymphomas (NHL) [1], which usually arises from lymph nodes. It can also have an extra-nodal origin in approximately 30–40% of the cases [2]. The most common extra-nodal sites are testis, skin, lung, bone, central nervous system, respiratory and gastrointestinal tracts [3]. Primary skeletal muscle involvement is very rare [1–3]. It has also been reported that upper extremities and gluteal muscle involvements are more predominantly affected [1]. In muscular lymphoma which usually is FDG avid, diffuse enlargement or focal intramuscular mass are seen [4]. Bone involvement is not common [5] and secondary involvement of the pancreas is very rare [6]. In the present case report, we described an unusual pattern of primary skeletal muscle NHL detected by whole body $^{18}$F-FDG PET/CT.

Case report

A 69-year-old woman with a history of DLBCL within the right thigh muscle had been treated with chemoradiation. She experienced no pain in the involved region. The patient underwent MRI for response evaluation. MRI results were inconclusive and couldn’t differentiate between post-radiation changes and residual disease. She was referred for more assessment with $^{18}$F-FDG PET/CT. Whole body MIP image revealed multiple foci of increased FDG uptake in the right thigh, stomach, pancreas, pelvic lymph nodes and both tibiae (Fig. 1A). The axial images demonstrated increased FDG uptake throughout the right thigh muscles (Fig. 1B–D). Also, abnormal FDG uptake was noted in the thickened stomach wall (Fig. 1E–G) with SUVmax of 16.91 and pancreatic body and tail (Fig. 1H–J) with SUVmax of 17.79 which were in favor of secondary extranodal involvement. No further follow up scan was acquired.

Discussion

Although the secondary extranodal disease is common in lymphoma, it rarely occurs as a primary site of lymphoma [9]. Primary skeletal muscle involvement occurs in only 0.1% of all lymphomas [7]. In addition, the pancreas is rarely involved by lymphoma [6]. Although the stomach is the most common site of involvement as the primary extra-nodal site or secondary to disseminated nodal disease [7], majority of secondary gastric NHL couldn’t be detected by conventional diagnostic methods [8]. $^{18}$F-FDG PET/CT is a valuable diagnostic test for identifying extranodal sites involvement in lymphoma staging, treatment response or recurrence evaluation [8, 9] and it is more sensitive
and specific than conventional imaging for assessment of disease extension [10, 11]. Here, we showed an unusual pattern of NHL by emphasizing the role of $^{18}$F-FDG PET/CT in the differentiation of recurrence from post-radiation changes, as well as showing the extension of the disease.

References

Unusual 18F-FDG PET-CT finding of paraneoplastic polymyositis in a patient with lung epidermoid carcinoma

Salah Nabih Oueriagli, Yassir Benameur, Omar Ait Sahel, Abdelhamid Biyi, Abderrahim Doudouh
Department of Nuclear Medicine, Mohammed V Military Teaching Hospital, Mohamed V University Souissi, Rabat, Morocco

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We report the case of a 67 years old male patient, followed for epidermoid carcinoma of the right lung, and hyper-eosinophilia on peripheral blood exploration. 18F-FDG positron emission tomography-computed tomography (18F-FDG PET-CT) performed for initial extension assessment showed, in addition to the intense hypermetabolism in the right upper pulmonary lobe related to the primary tumor and the mediastinal lymph node involvement (Fig. 1A), an unusually intense muscular hypermetabolism in the long muscles of the neck, sterno-cleido-mastoid muscles, para-vertebral, iliac and ilio-psoas muscles. B. Whole body CT image and (C) 18F-FDG PET-CT fusion image in sagittal sections showing intense and symmetric hypermetabolism in ilio-psoas muscles.

Figure 1. A. Maximum intensity projection PET image revealing intense hypermetabolism in the right upper pulmonary lobe related to the primary tumor associated to mediastinal lymph node involvement with unusual intense hypermetabolism interesting long muscles of the neck, sterno-cleidomastoid muscles, para-vertebral, iliac and ilio-psoas muscles. B. Whole body CT image and (C) 18F-FDG PET-CT fusion image in sagittal sections showing intense and symmetric hypermetabolism in ilio-psoas muscles.

Correspondence to: Oueriagli Nabih Salah, Department of Nuclear Medicine, Mohammed V Military Teaching Hospital, BP 1018, Rabat, Morocco
phone: +212662101402
email: salah.nabihoueriagli@gmail.com
Clinical vignette

Figure 2: Biopsy of the right ilio-psoas muscle showing myofiber degeneration with predominant inflammatory cell (CD8+ T lymphocyte) compatible with polymyositis (Fig. 2). Serum CK (creatine kinase), aldolase and sedimentation rate levels were abnormally very high.

Our patient was put under corticotherapy with good clinical, biological and radiological evolution, even on 18F-FDG PET-CT.

In our knowledge, a link between paraneoplastic polymyositis and cancer has never been clearly defined [1–2], and its clinical expression does not differ from idiopathic polymyositis [3]. Clinicopathologic diagnosis is based on histology, electromyographic data, high-level serum of muscular enzymes (creatine kinase, aldolase), and also an elevated sedimentation rate [4]. This group of patients can be treated by corticotherapy or immunomodulators, and also by physiotherapy [5].

References

Technetium pertechnetate uptake in parathyroid adenoma

Ali Sellem, Wassim Elajmi, Hatem Hammami
Military Hospital of Tunis, Montfleury, Tunis

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We report the case of a 37-year-old woman newly diagnosed primary hyperparathyroidism with hypercalcemia 16.1 mg/dL (Ref range 8.5–10.1) and an increased parathyroid hormone level 110 pg/mL (reference range 10.0–70.0). She was referred to our department for scintigraphic localization of a parathyroid adenoma. The Tc-99m scintigraphy (Fig. 1) revealed a normal thyroid uptake associated with one focal uptake below the left lobe of the thyroid. A Tc-99m sestamibi parathyroid scan (Fig. 2) was performed showing an accumulation of the tracer in the same localization of Tc-99m focal uptake. It was a dilemma: is it an eccentric thyroid tissue that fixes the two radiotracers or a parathyroid adenoma fixing the $^{99m}$Tc. Since we do not have the iodine 123 we realized an image (Fig. 3) with a tracer dose of iodine 131 showing no uptake below the left lobe of thyroid which allowed us to conclude to a parathyroid adenoma. The patient subsequently underwent minimally invasive cervicotomy with the resection of this lesion which was histologically diagnosed as a parathyroid adenoma.

Figure 1. Tc-99m scintigraphy showing one focal uptake below the left lobe of thyroid

Figure 2. Sestamibi parathyroid scan showing an accumulation of the tracer in the same localization of Tc-99m focal uptake

Figure 3. Iodine 131 scintigraphy showing no uptake below the left lobe of thyroid

Correspondence to: Ali Sellem, Military Hospital of Tunis, Montfleury, 1009 Tunis
E-mail: sellem_ali@yahoo.fr