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18F-FDGPET/CT: diabetes and hyperglycaemia

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ABSTRACT

BACKGROUND: Some patients who undergo 18F-FDG PET/CT for neoplastic or benign disease are also affected by diabetes or hyperglycaemia. We propose different preparation procedures in patients (pts) with hyperglycaemia (acute, temporary or chronic) or diabetes (type 1 or 2) at the time of the 18F-FDG injection, in order to improve the diagnostic scheduling of 18F-FDG PET/CT.
MATERIAL AND METHODS: We evaluated a sample of 13,063 pts, examined in two different PET/CT centres, one with a stationary scanner (94.4%) and the other with a mobile device (5.6%). High blood sugar was present in 1,698 patients (13%) at the time of the 18F-FDG injection (hyperglycaemia was defined as fasting blood glucose > 11.1 mmol/l).
We considered all 18F-FDG PET/CT tests performed over a period of 4 years (2006–2009). In the first 2 years (6,236 tests), scheduling was done directly by the administrative secretary. In the next two years, 6,827 pts underwent a preliminary visit to assess the test indications, medical history, and therapy as well as pre-test preparation.
We evaluated different preparation protocols for hyperglycaemic or diabetic pts, especially those recommended in the guidelines of the European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine (SNM).
RESULTS: In the four-year period, 713/13,063 patients (5.45%) were rescheduled; of these, 78.8% were rescheduled in the two years before the implementation of our preparation protocols and 21.2% in the next two years.
Before the implementation of our preparation protocols, 562 patients (9%) presented occasional, acute or chronic hyperglycaemia (56.7%), or diabetes (43.3%), requiring postponement of the test to a later date. The test was not performed in 17 of 6,236 pts (0.27%) because of blood glucose levels above 11.1 mmol/l for several days, while in 16/6236 pts (0.26%) the 18F-FDG injection was performed despite high blood glucose levels, in view of the clinical urgency.
After the implementation of the preparation protocols, 2.2% of pts were rescheduled because of occasional, acute or chronic hyperglycaemia (79%), or diabetes (21%); 0.1% of pts did not undergo the test because of chronic high blood glucose levels. Although the administration of insulin is recommended in the EANM and SNM guidelines, in our new preparation procedures experience it was not necessary, because we reduced the numbers of hyperglycaemic pts thanks to screening at the preliminary visit and a subsequent good preparation of the patient before scheduling.
CONCLUSIONS: The application of our preparation protocols improves the on-time performance and diagnostic accuracy, and increases patients' compliance.
KEY words: hyperglycaemia, diabetes, 18F-FDG PET/CT, preparation protocols, EANM guidelines, SNM guidelines, insulin

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Background

Several per cent of patients who undergo 18F-FDG PET/CT for neoplastic or benign disease are also affected by diabetes or hyperglycaemia. 18F-FDG, like glucose, is taken up by tumour cells via a sodium-independent facilitated diffusion [1]. The glucose transporter proteins are encoded by at least 7 different genes (GLUT1-GLUT7). Except for GLUT1, the glucose transporters genes are differently expressed according to the tissue. An intense uptake of 18F-FDG can suggest the presence of neoplastic cells, which produce energy primarily through anaerobic glycolysis [2]. The mechanisms regulating glucose uptake in cancer cells have not been completely clarified. Some authors have suggested that 18F-FDG uptake may be impaired in diabetes and hyperglycaemia, due to direct competition between 18F-FDG and glucose for uptake by cancer cells [3].

Hyperglycaemia is defined as fasting glycaemia levels higher than 7 mmol/l or a random plasma glucose finding of >11.1 mmol/l.

High blood glucose levels are present in diabetic disease and in other conditions without specific signs or symptoms. Certain medications increase the risk of hyperglycaemia, such as corticosteroids, cyclosporine, isoniazid, protease inhibitors, etc. [4, 5]. Chemotherapy drugs also induce high blood sugar, alter immune functions and cause severe side effects that can complicate the diagnosis [6].

Acute hyperglycaemia (blood glucose levels above 8 mmol/l — range 8 to 15 mmol/l), often present in uncontrolled diabetes or as a consequence of drug toxicity, is treated with insulin injections to avoid the failure of various organs.

Chronic hyperglycaemia is characterized by high blood glucose levels over a long period (> 7 mmol/l), causing damage to the blood vessels and to the organs they supply, leading to the complications of diabetes. Chronic hyperglycaemia can be measured via the HbA_{1c} test. The most common causes of chronic hyperglycaemia are: diabetes mellitus, endocrinopathies, drugs that induce impaired insulin secretion, infections, and autoimmune disorders.

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Diabetic patients present an increased incidence of atherosclerotic, cardiovascular, peripheral arterial, and cerebrovascular diseases that may be silent until major damage has been done [7], so many different new therapies are continually being proposed [8]. Hyperglycaemia, diabetes or anti-diabetic therapy may reduce the sensitivity of 18F-FDG PET/CT in the assessment of malignancy [9]. Normally, the main patient preparation instructions for 18F-FDG PET/CT include fasting for at least 6 h prior to the start of the PET study, measuring the blood glucose level by a glucometer prior to administering FDG, then waiting for 40 minutes before the test. Blood glucose should be less than 11.1 mmol/l [10–12]. In case of higher blood glucose levels, many guidelines propose the administration of insulin [10], under the control of the endocrinologist.

Aim of the study

The aim of this work was to propose simple, different preparation procedures in patients with hyperglycaemia (acute, temporary or chronic) or diabetes (type 1 or 2) at the time of 18F-FDG injection, thus improving the diagnostic scheduling of stationary or mobile 18F-FDG PET/CT facilities.

The second endpoint was to evaluate how the application of rational preparation procedures improves the on-time performance and quality of the PET/CT exam.

Finally, the compliance of hyperglycaemic or diabetic patients who followed the preparation protocols was evaluated.

Material and methods

We evaluated a sample of 13,063 patients, examined at two different PET/CT centres, one with a stationary scanner (94.4%) and the other with a mobile device (5.6%). Hyperglycaemia (fasting blood glucose > 11.1 mmol/l) was present in 1,698 patients (13%) at the time of the 18F-FDG injection. Of these, 653 patients were insulin-dependent diabetics, 914 patients were non-insulin-dependent diabetics treated with oral anti-diabetic drugs, 131 patients presented hyperglycaemia in the absence of diabetes (1% chronic hyperglycaemia and 0.4% temporary hyperglycaemia).

The 18F-FDG PET/CT tests performed over a period of 4 years were analysed. In the first 2 years (6,236 tests), the scheduling was performed directly by the administrative secretary. In the next two years, 6,827 patients underwent a preliminary visit before the PET/CT to assess medical history, on-going treatments, to check the test indications and identify causes that could interfere with the 18F-FDG PET/CT good quality.

We prescribed a different preparation protocol in patients with hyperglycaemia or diabetes.

Protocol for patients with hyperglycaemia

Non diabetic patients who presented with hyperglycaemia (> 11 mmol/l) on the day of the test were invited to sit in a warm waiting room, stay relaxed and drink plenty of fluids; blood glucose levels were measured every 20 minutes in the next three hours. If the glycaemia decreased below 11.1 mmol/l, we proceeded with the administration of 18F-FDG, otherwise the PET/CT test was postponed, and patients were advised to check daily fasting glycaemia in the morning for 5 days and to communicate these values to the nuclear medicine physician responsible for PET/CT. We rescheduled the test when the glycaemia decreased. If the blood glucose levels remained persistently high, the nuclear medicine physician sent the rescheduled patients to a diabetologist for management of the glycaemic status by basal and nutritional insulin therapy.

Protocol for patients with diabetes

The diabetic patients on oral antidiabetic drugs were asked to check their fasting blood glucose level in the morning for at least 7 days before the 18F-FDG PET/CT, without any interruption of medication. For these patients, the 18F-FDG PET/CT was scheduled leaving an interval of at least 180 minutes between the administrations of antidiabetic drugs and the administration of 18F-FDG.

Patients with insulin-dependent diabetes mellitus were asked to check their fasting blood glucose level in the morning for at least 5 days before the 18F-FDG PET/CT. We advised these patients to observe the following preparation protocol on the day of the test: breakfast at 6.30 AM with 1-2 bread rusks and a cup of tea without sugar, followed by a half-dose of the prescribed insulin. The 18F-FDG PET/CT was scheduled in the late morning with an interval of 180-300 minutes between the insulin and 18F-FDG administrations.

Results

In the four-year period, 713/13063 (5.45%) patients were rescheduled. Of these, 562 patients (78.8%) were rescheduled in the two years before the implementation of our preparation protocols and 151 patients (21.2%) in the next two years.

Before the implementation of our preparation protocols, 562/6236 patients (9%) presented occasional, acute or chronic hyperglycaemia (56.7%), or diabetes (43.3%), requiring postponement of the test.

Seventeen of 6236 patients (0.27%) did not undergo the test because of blood glucose levels above 11.1 mmol/l for several days, whereas 16/6236 patients (0.26%) underwent the 18F-FDG injection despite high blood glucose, in view of the clinical urgency (Fig. 1A).

After the application of the preparation protocols, 151/6,827 patients were rescheduled (2.2%), for occasional, acute or chronic

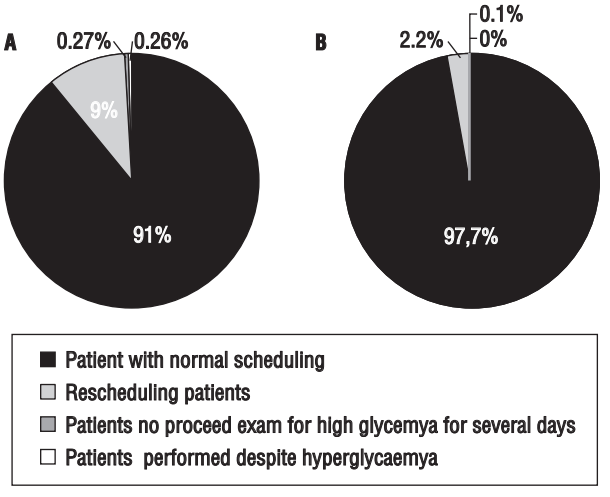

Figure 1. The results of scheduling of patients before and after our preparation protocols: the number of rescheduled patients decreased from 9% before the application of the preparation protocols (**A**) to 2.2% after (**B**). No patients underwent 18F-FDG injections despite high blood glucose after the application of our preparation protocols

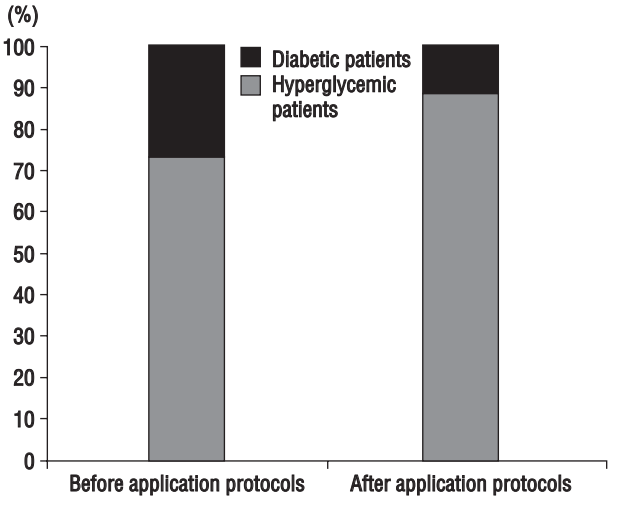

Figure 2. Rescheduled patients before and after our preparation protocols: the number of rescheduled diabetic patients reduced from 43.3% before the application of our protocols to 21% after, while the number of rescheduled hyperglycaemic patients increased from 56.7% before to 79% after, caused by not fasting or corticosteroid drugs

hyperglycaemia (79%), or diabetes (21%) (Fig. 2). Seven of 6,827 patients (0.1%) did not undergo the test because of chronic high blood glucose (Fig. 1B).

Discussion

There are few literature data about the influence of diabetes on the outcome of 18F-FDG PET/CT, and the results are sometimes contradictory. The issue is important because of the high prevalence of hyperglycaemia or diabetes in the population.

Until a few years ago, 18F-FDG PET/CT was not performed in patients with diabetes because of direct competition between high blood glucose levels and 18F-FDG. [3]. Blood glucose must also be considered in patients in whom 18F-FDG PET/CT is performed several times for the evaluation of chemotherapy or radiotherapy response [9].

Torizuka et al. compared the kinetics and the uptake of 18F-FDG in non-diabetic and diabetic patients and concluded that the uptake of 18F-FDG in patients with diabetes was less than in the non-diabetic control group [13]. Gorenberg et al. reported that the SUV was similar between diabetic and non-diabetic patients [14].

Acute hyperglycaemia is a factor known to decrease tumour uptake of 18F-FDG [15, 16] and increase uptake in the muscles [9], but these effects are demonstrated only by the oral loading glucose test [9, 17].

The effect of chronic hyperglycaemia on 18F-FDG PET/CT is controversial in the literature and there are even fewer data. Chronic hyperglycaemia has a similar effect to acute hyperglycaemia on muscle uptake, but a smaller effect on tumour uptake, which remains high and allows recognition of the lesions [18].

In patients with diabetes the diagnostic accuracy of 18F-FDG PET/CT is debated. Some authors do not recommend the performance of 18F-FDG PET/CT [18], while others consider it reliable [18, 19].

The use of insulin has been proposed to regulate blood glucose in diabetic patients prior to 18F-FDG PET/CT. The appropriate use of insulin for the control of blood glucose increases the uptake ratio between tumour and normal tissue of the liver and lung but, on the contrary, it reduces the uptake ratio between tumour and muscle tissue [20]. Based on these data, the administration of insulin 60 minutes before the 18F-FDG has been proposed as a means of reducing the blood glucose, without compromising the quality of the images or the SUV [21, 22].

The use of oral hypoglycaemic agents to prepare patients with hyperglycaemia or diabetes for 18F-FDG PET/CT is very limited. These drugs are used in insulin resistant patients. Oral hypoglycaemic agents also have different effects on glucose metabolism in different tissues. It has been reported that glitazone has a powerful effect on increasing glucose uptake in skeletal muscle [23], while metformin reduces glucose production by the liver [24].

Metformin, due to its prolonged plasma half-life (15 hours), determines an increased 18F-FDG uptake in skeletal muscle and adipose tissue. Other authors have reported an increased 18F-FDG uptake also in the bowel, which may reduce the test sensitivity for recognizing cancerous lesions in the abdomen. It has therefore been recommended that metformin should be suspended at least 12 hours prior to the 18F-FDG PET/CT [25]. Lin et al concluded that metformin and rosiglitazone do not affect the uptake of 18F-FDG. Medications that stimulate the secretion of insulin (tolbutamide) have a limited use as compared to other oral antidiabetics, influence blood glucose by stimulating insulin secretion, and it may be appropriate to recommend their suspension before 18F-FDG PET/CT [29].

Fasting for 6 hours cannot be prescribed in diabetic patients, while for the execution of 18F-FDG PET/CT, blood glucose levels below 11.1 mmol/l are required. Patients with higher glucose values cannot undergo the test because of the significant change in the biodistribution of 18F-FDG and the SUV reduction in tumour lesions [26].

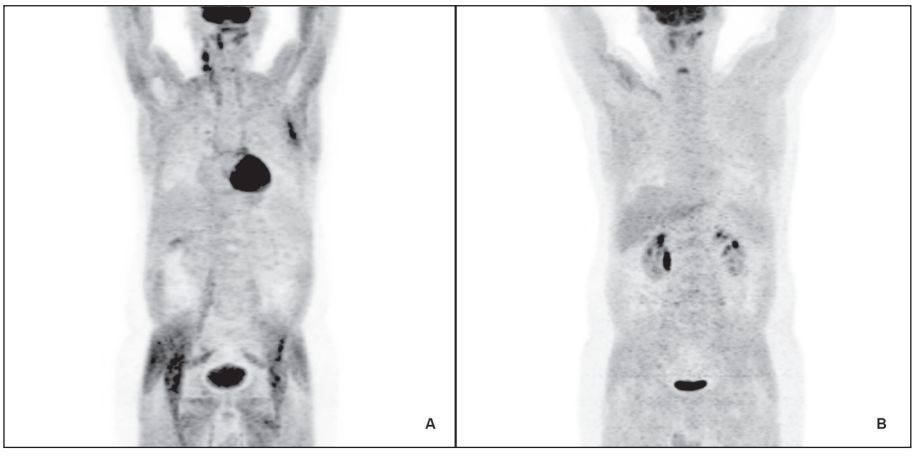

Figure 3. 18F-FDG PET/CT during follow-up in a patient with lung cancer. A. MIP showed no evidence of disease recurrence but increased uptake in the myocardium and muscles. At the time of 18F-FDG administration the patient had acute hyperglycemia (blood glucose > 11.1 mmol/l); **B**. 8 months later and after the application of our simple preparation protocols, MIP showed no evidence of disease recurrence and the best quality images. At the time of 18F-FDG administration the patient was euglycemic

The American Society of Nuclear Medicine suggests the use of insulin before the administration of 18F-FDG in patients with glucose values above 11.1 mmol/l. If the patient takes insulin therapy at home, the administration of 18F-FDG may need to be delayed according to the dose of insulin administered [10], in order to avoid an increased uptake in the myocardium, liver, muscles and adipose tissue. A negative effect of the use of insulin on tumour uptake has never been demonstrated. Insulin acts on GLUT4 transporters in the myocardium, striated muscle and adipose tissue, but has no effect on GLUT1 and GLUT 3 receptors in tumours [27].

In order to improve the reliability of the test and the quality of the images, some authors prescribe a high protein and low carbohydrate diet in diabetic patients on the day before 18F-FDG PET/CT and abstention from nicotine and caffeine on the day of the test to reduce cardiac stimulation and consequently myocardial glucose uptake [28]. Currently, the preparation protocols for 18F-FDG PET/CT are determined by individual experience and a review of the literature. We evaluated different preparation protocols for hyperglycaemic or diabetic patients, especially those recommended in the guidelines of European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine (SNM). The American guidelines considered mainly diabetic patients on insulin therapy [10].

The administration of insulin does not take into account the problem of hypoglycaemia on the day of the 18F-FDG PET/CT test. For this reason, we propose a protocol for the preparation of patients in the days before the 18F-FDG PET/CT test (blood glucose controls and half the insulin dose on the day of the test), direct contact with the nuclear physician and, if necessary, an interview with the diabetologist.

The 2003 EANM guidelines advised that blood glucose should be less than 7.22 mmol/l to perform the test and the not execusion of 18F-FDG PET/CT in patients with blood glucose values greater than 11.1 mmol/l [11]. Subsequently, in 2010, the EANM recommended management of diabetic patients depending on the type of therapy. Particularly, for diabetic patients on oral therapy, 18F-FDG PET/CT is recommended preferably in the late morning with no therapy suspension. For patients on insulin therapy, preparation of the patient and a glycaemic control prior to the test is recommended. These patients should eat a normal breakfast at 7 am, and then proceed with a normal amount of insulin injection, and 18F-FDG PET/CT should be scheduled for the late morning [12].

In diabetic patients receiving oral antidiabetics our protocol, by leaving an interval of 180 minutes between the hypoglycaemic oral therapy and the 18F-FDG administration, reduced the diagnostic interference of these drugs on 18F-FDG uptake.

The systematic application of the preparation protocols for 18F-FDG PET/CT allowed us to reduce the number of test postponements (from 9% of patients before the application of the preparation protocols to 2.2% after), and the number of rescheduled diabetic patients (from 43.3% before to 21% after) (Fig. 3).

The increased number of hyperglycaemic patients observed (from 56.7% before to 79% after) was caused by not fasting or the use of corticosteroid drugs for fear of adverse reactions (Fig. 2).

Although recommended by EANM and SNM guidelines, in our experience the administration of insulin was not necessary, because the preliminary visit and a good preparation of the patient before scheduling was successful in reducing the numbers of patients presenting with hyperglycaemia at the time of the test.

The protocols suggested by the guidelines are not always adaptable to diagnostic units with a stationary PET/CT scanner and much less so in those with a mobile device. In these, the PET/CT scanner may not be present on consecutive days, thus increasing the number of rescheduled patients or those who undergo 18F-FDG PET/CT despite high glucose values. Reducing the number of postponed tests also improved the assessment of the effectiveness of therapies (chemotherapy and radiotherapy). The waiting time between radiopharmaceutical administration and the PET/CT test has become more readily programmable and well accepted by patients. Finally, the reduction of rescheduled 18F-FDG PET/CT has also improved the operating costs of our PET/CT centre by increasing the number of 18F-FDG PET/CT tests performed daily and ensuring full use of the available radiopharmaceutical.

Conclusions

Two different protocols for hyperglycaemic and diabetic patients without the necessity of insulin administration were prepared. The protocols resulted well accepted by all patients. The application of these preparation protocols improved the management of hyperglycaemic or diabetic patients and is adaptable to routine diagnostic centres with stationary or mobile devices.

A preliminary examination of patients with hyperglycaemia (acute or chronic) or diabetes (type 1 or 2) and the correct application of the preparation protocols has reduced the number of the rescheduled patients. In short, the application of our preparation protocols improves the on-time performance, the diagnostic accuracy and increases patient's compliance.

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