Utility of Short-Acting Intravenous Insulin Therapy in Preparation of F-18 Fluorodeoxyglucose Positron Emission Tomography Computed Tomography Scan in Cancer Patients Incidentally Detected with High Blood Glucose Levels on the Day of Test

Abstract

Background: In diabetic (DM) patients, hyperglycemia degrades image quality in F-18 FDG PET CT by altering bio-distribution of FDG in the body and augmenting soft tissue and muscular uptake. We intend to evaluate the use of short acting I.V insulin in minimising the rescheduling of patients detected with FBG>160 mg/dL on the day of scan. **Aim and Objectives:** To show the utility of short acting IV insulin therapy in preparation of cancer patients incidentally detected with high blood glucose levels for F-18 FDG PET CT scan, (>160mg/dL) and to compare the obtained image quality with patients detected with fasting blood glucose level (FBG) <100mg/dL and <160 mg/dL, using visual and semi quantitative methods. **Material and Methods:** 613 cancer patients referred for PET CT were divided into 3 groups, Group I (n=30): known diabetics (DM) or incidentally diagnosed with FBG >160 mg/dL, Group II (n=349): DM patients with FBG <160 mg/dL (100-160mg/dL), Group III (n=234): Non DM patients FBG <100mg/dL. In Group I short acting insulin was given intravenously using a sliding scale, post insulin after 90 minutes F-18 FDG (radiotracer) injection was given and PETCT scan was obtained 60 mins post radiotracer injection. Qualitative image analysis was done using biodistribution score and quantitative analysis was done by chi square test, ANOVA (analysis of variance) and paired t-test. **Results:** In group I patients post insulin there was significant decrease in FBG levels (216±22.2 to 136±13.4mg/dL) and acceptable image quality. Comparison of quantitative parameters (mean and maximum SUV calculated by drawing ROI around brain, heart, liver, muscle, subcutaneous fat) among the 3 groups showed significant intergroup difference with p value <0.05. **Conclusion:** This short acting I.V insulin protocol is safe and can be used to obtain optimal quality F-18 FDG PET CT scan images by alleviating the need for rescheduling patients though they present with high glucose levels.

Keywords: *Cancer, diabetes mellitus, F-18 fluorodeoxyglucose positron emission tomography computed tomography, hyperglycemia, intravenous insulin*

**Ramya Priya Rallapeta,
Ranadheer Gupta Manthri,
Tekchand Kalawat,
Alok Sachan[1],
A Y Lakshmi[2],
Narendra Hulikal[3]**

Departments of Nuclear Medicine, [1]Endocrinology, [2]Radiology, and [3]Surgical Oncology, SVIMS, Tirupati, Andhra Pradesh, India

Introduction

F-18 fluoro-deoxyglucose (FDG) is a time-tested molecular imaging radiopharmaceutical used in positron emission tomography computed tomography (PET CT) imaging with many applications in the field of oncology such as cancer staging, evaluation of unknown primary cancer, treatment response, and recurrence evaluation.[1] PET CT scan with F-18 FDG is technically demanding protocol-based test, as the image quality may be influenced by various factors such as physical exercise, brown fat activation, hyperglycemia, hyperinsulinemia, inflammation, and thyrotoxicosis.[2,3]

In diabetes mellitus (DM) patients, plasma glucose levels and serum insulin levels will affect the biodistribution of F-18 FDG. Increased glucose levels decrease the F-18 FDG uptake in the tumors because F-18 FDG and glucose compete for glucose transport and phosphorylation by hexokinase. Hyperinsulinemia in response to elevated blood glucose causes rapid shunting of F-18 FDG to organs with high density of insulin receptors (e.g., skeletal and cardiac muscles) by increased translocation of glucose transporter-4 (GLUT4), thereby resulting in altered radiotracer biodistribution and

Address for correspondence:
*Dr. Tekchand Kalawat,
Department of Nuclear Medicine, SVIMS, Tirupati, Andhra Pradesh, India.
E-mail: kalawat.svims@gmail.com*

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suboptimal image quality.[4] Therefore, preparation of DM patients with cancer requires more meticulous care, as some patients may report with high blood glucose levels on the day of test.

F-18 FDG PET CT scan is usually performed following the procedure guidelines prescribed by the European Association of Nuclear Medicine and Molecular Imaging and Society of Nuclear Medicine.[1,5] It is ideal to reschedule the patients for PET CT scan during conditions of hyperglycemia and hyperinsulinemia; however, rescheduling delays the diagnosis and also adds on to the financial burden of the center. In literature, to overcome these, some alternative methods using various insulin protocols have been proposed to prepare the patient.[6]

The use of insulin lowers fasting blood glucose (FBG) levels in DM patients presenting with hyperglycemia; however, if F-18 FDG injection was given before the complete physiological neutralization of insulin, it may cause suboptimal image quality with uptake in muscles and soft tissue.[7] Therefore, the present study was designed to use short-acting intravenous (IV) insulin to lower hyperglycemia, and timing of F-18 FDG injection was delayed to 90 min, postinsulin therapy to obtain the optimal image quality.

Materials and Methods

Ethics approval was obtained from the Institutional Ethics Committee.

Study design

The design was a prospective interventional study.

Study population

A total of 613 patients referred for F-18 FDG whole-body PET CT scan who met the inclusion criteria [Table 1] were prospectively studied. Written informed consent was obta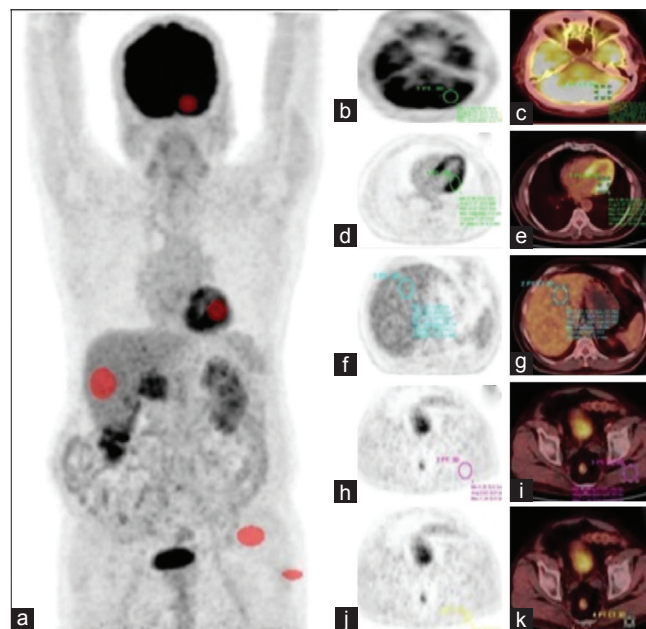ined from all patients. FBG levels were estimated, and patients were divided into three groups, namely Group I: DM patients with FBG >160 mg/dL (known diabetics or incidentally diagnosed), Group II: DM patients with FBG <160 mg/dL (100–160 mg/dL), and Group III: nondiabetic patients with normal FBG (<100 mg/dL).

Patient preparation and insulin administration

All patients in Group I were given short-acting IV insulin (injection human insulin 40 IU/mL) diluted in 10 mL normal saline, using a sliding scale [Table 2]. Patients with FBG >280 mg/dL were excluded from the study. Postinsulin therapy blood glucose monitoring was done at every 30 min till 90 min, and all precautions were taken to treat patients with hypoglycemia. All patients in three groups were given 370 MBq (10 mCi) of F-18 FDG through IV cannula. Group I patients received F-18 FDG injection after 90 min of insulin therapy. In all other patients (Groups II and III), scan was acquired 60 min post F-18 FDG injection.

Acquisition protocol and image analysis

Images were obtained in caudocranial orientation of supine position, covering body from thigh to vertex on a dedicated Siemens PET CT scanner (Biograph-06). PET CT images were analyzed visually, and FDG biodistribution was graded on a five-point scale [Table 3] as described earlier in similar type of the study.[6,8] Quantitative F-18 FDG uptake, that is, maximum standard uptake values (max SUVs) of cerebellum, cardiac muscle, liver, skeletal muscle, and fat tissue were obtained by manually drawing

Table 1: Inclusion and exclusion criteria of the study population

Inclusion criteria	Exclusion criteria
All cancer patients of either gender, age (years) >18-80	Patients not willing to participate in the study
Patients willing to participate in the study	Inflammation, infection, or trauma in the gluteal region
	FBG >280 mg/dL
	Pregnancy
	Nursing mothers
	Recent antiretroviral therapy (HAART)
	Neuromuscular disorders

HAART: Highly active antiretroviral therapy, FBG: Fasting blood glucose

Figure 1: F-18 fluorodeoxyglucose positron emission tomography maximum intensity projection image (a), positron emission tomography and positron emission tomography computed tomography axial images showing representative region of interests drawn over the brain (b and c), heart (d and e), liver (f and g), muscle (h and i), and fat tissue (j and k), respectively

three-dimensional (3D) region of interest (ROI) in transaxial images [Figure 1].

Statistical analysis

Demographic data were represented as mean ± standard deviation (SD). To compare pre-insulin FBG and postinsulin FBG levels, paired "*t*" test was used. Chi-square test was used to compare the biodistribution score among three Groups. $P < 0.05$ was considered statistically significant. Mean ± SD of different variables (max SUV in various ROIs) was obtained. For comparison of variables among groups, one-way ANOVA test was used.

Results

Total study population was 613 patients. Characteristics of the study population are described in Table 4. In Group I, a total of 30 patients were included who had FBG levels >160 mg/dL, with mean ± SD values of 214 ± 25.1 mg/dL. Among them, 18/30 (60%) were known diabetics, and 12/30 (40%) patients were detected incidentally with high FBG levels on the day of PET CT scan.

In Group I patients, IV short-acting insulin was given according to the glycemic correction sliding scale [Table 2]. The mean glucose levels at 60 min after IV insulin decreased from 216 ± 22.2 to 136 ± 13.4 mg/dL [Table 5]; it indicates that insulin doses were adequate, and there was statistically significant decrease ($P < 0.05$ using paired *t*-test) in postinsulin glucose levels. All patients in Group I tolerated IV insulin well; none of them developed hypoglycemia.

Visual image analysis [Table 3] showed acceptable quality of PET CT images in all patients with a score of "0" or "1" based on biodistribution scores (acceptable score 0, 1, and 2 and unacceptable score "3" and "4"). In Group I patients, 15/30 showed score 0, and other 15/30 showed score 1 (acceptable image quality with mild soft-tissue uptake).

Quantitative parameters and max SUV were obtained for all patients by drawing identical 3D ROI in transaxial PET CT images as shown in Figure 1. at brain (cerebellum), heart, liver, skeletal muscle, and fat. Mean ± SD values of max SUV of different regional variables, respectively, are shown in Table 6. One-way ANOVA analysis for variables showed statistically significant intergroup difference with $P < 0.05$ [Table 6].

Discussion

PET CT requires meticulous patient preparation as image quality may be influenced by machinery error, patient disease status, comorbid illness such as diabetes (high FBG levels), medications, radioactivity administered, extravasation, and variation in imaging protocols.[9,10]

Various types of insulin include long acting, intermediate acting, short acting, and rapid acting; among them,

Table 2: Sliding scale for intravenous insulin in Group I patients

Glucose level (mg/dL)	Insulin dose (U)
160-180	4
180-200	6
200-220	8
220-240	10
240-260	12
>260	14

Table 3: Biodistribution score for visual image analysis

Pattern of FDG biodistribution	Score
Normal biodistribution	0
Mild muscular uptake	1
Muscular uptake involving ≥1 muscle group	2
Diffuse muscular uptake of moderate intensity	3
Diffuse, intense muscular uptake causing nondiagnostic examination	4

FDG: Fluorodeoxyglucose

Table 4: Characteristics of study population (*n*=613)

Patient characteristics	Mean + SD, No of patients (*n*)
Age (years), mean±SD (range)	55±12 (30-80)
Sex[a]	
Female	334 (55)
Male	279 (45)
Groups[a]	
Group I	30 (5)
Known DM	18
De novo DM	12
Group II	349 (55)
Known DM	349
Group III	234 (40)

[a]Values are represented as *n*. DM: Diabetes mellitus, SD: Standard deviation

Table 5: Comparison of blood glucose levels preinsulin and postinsulin

Preinsulin and Postinsulin FBG levels	Mean + SD, Range	Paired *t*-test (*P*)
Preinsulin (mg/dL)		<0.05
FBG, mean±SD	216±22	
Range	182-260	
Postinsulin (mg/dL)		
FBG, mean±SD	136±13	
Range	110-168	

SD: Standard deviation, FBG: Fasting blood glucose

short-acting insulin will have onset of action at 30–60 min.[11] Insulin decreases FBG levels by acting through GLUT receptors. Insulin-independent GLUT receptors are GLUT 1 (red blood cell, brain, and cornea), 2 (beta cells of pancreas, liver, and small intestine), 3 (brain and placenta), and insulin dependent are GLUT

4 (skeletal muscle and fat). Insulin can be administered subcutaneous (SC) or IV routes. Administration of SC insulin causes increased muscular uptake as documented in Garcia *et al*.'s study;[12] it also requires more time delay for action, multiple doses to lower FBG levels which may delay injection of F-18 FDG and scan acquisition. To perform the scan in patients with high FBG levels on the same day in a remote center away from cyclotron facility, we used short-acting IV insulin protocol.

The short-acting IV insulin therapy used in Group I patients worked well and lowered the mean ± SD blood glucose levels from 216 ± 22.2 to 136 ± 13.4 mg/dL, which was statistically significant with $P < 0.05$. In a similar study done by Roy *et al*., using short-acting IV insulin therapy, the mean ± SD blood glucose levels decreased from 234 ± 36 to 126 ± 36 mg/dL.

Visual image analysis of positron emission tomography scan

In Group I, 15/30 (50%) patients showed score "0," and 15/30 (50%) patients showed score "1" with decreased blood glucose levels but values remained between 130 and 160 mg/dL, mean value (148 ± 7 mg/dL); however, there was 100% acceptable image quality in all patients. Roy *et al*. documented 75% of study population with acceptable image quality and 25% with altered biodistribution manifested as increased muscular uptake (unacceptable image quality).[6] Residual physiological effect of insulin might be the reason for score "1" in visual image analysis (mild muscular uptake). In our study, F-18 FDG injection was given after a gap of 90 min of insulin therapy, and all studies were of visually acceptable quality. Figures 2, 3 and 4 shows the representative images of Group I, II and III patients with optimal image quality respectively.

SUV and related parameters in PET technology are simple and popular tools for metabolic activity quantification in cancer sites and normal tissue. To know the effect of hyperglycemia on quantitative measurements, max SUV values of the brain, heart, liver, skeletal muscle, and fat tissue were measured in all patients, and they were compared statistically between groups.

In our study, brain max SUV (6.1 ± 1.85) in Group I patients was lower than Group II and III max SUV values (8.2 ± 2.15 and 8.7 ± 2.33), and it was statistically significant with $P < 0.05$ [Table 6]. In Group I patients with high FBG level (>160 mg/dL) physiologically, there will be increased competition between elevated plasma glucose and F-18 FDG for carrier enzymes to enter in the brain cell. Ishizu *et al*. studied the impact of glucose loading on visualization of brain tumors and glioma. In their study, they observed fractional decreased F-18 FDG uptake in normal brain cortex and brain tumor causing an increment in tumor to brain cortex ratio.[13,14] In our study also, we were able to identify and better delineate brain metastases in Group I patients [Figure 2].

**Table 6: Maximum standardized uptake value over different region of interests**

ROI	Groups	Mean of max SUV + SD	Frequency	*P*
Brain	I	6.1±1.8	30	**0.000**
	II	8.2±2.1	349	
	III	8.7±2.3	234	
Heart	I	2.9±1.8	30	**0.007**
	II	3.7±2.9	349	
	III	4.4±3.6	234	
Liver	I	2.9±0.6	30	**0.000**
	II	2.8±0.7	349	
	III	2.4±0.6	234	
Muscle	I	1.0±0.3	30	**0.001**
	II	0.8±0.5	349	
	III	0.6±0.2	234	
Fat	I	0.4±0.2	30	**0.001**
	II	0.4±0.1	349	
	III	0.3±0.1	234	

ANOVA was used to analyze the differences between group means. Bold values were statistically significant. ANOVA: Analysis of variance, ROI: Region of interest, max SUV: maximum standardized uptake value, SD: standard deviation

Figure 2: F-18 fluorodeoxyglucose positron emission tomography maximum intensity projection image of Group I patient with optimal image quality with visual image analysis score of 0 (no abnormal muscle and soft-tissue uptake). Postinsulin therapy, there was physiological decreased fluorodeoxyglucose concentration in brain that enhanced visualization of the left cerebellar metastases

In whole-body F-18 FDG, PET CT used for cancer staging nonspecific uptake in the myocardium is a common finding
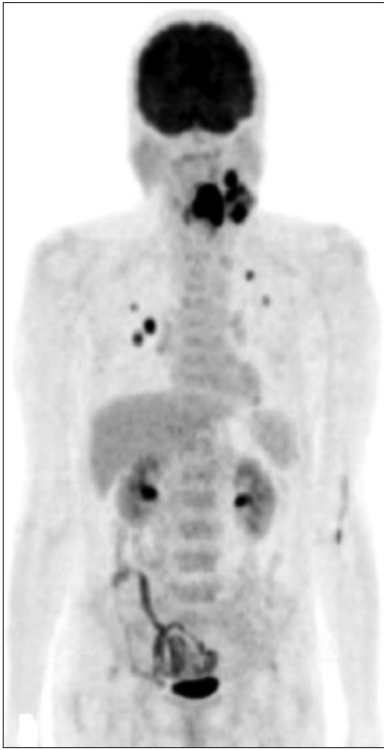
Figure 3: F-18 fluorodeoxyglucose positron emission tomography maximum intensity projection image of Group II patient with optimal image quality with visual image analysis score of 0 (no abnormal muscle and soft-tissue uptake)

Figure 4: F-18 fluorodeoxyglucose positron emission tomography maximum intensity projection image of Group III patient with optimal image quality with visual image analysis score of 0 (no abnormal muscle and soft-tissue uptake)

which depends on the dominance of energy substrate metabolism, glucose, or free fatty acids.[15-17] In Group I compared to noninsulin group [Table 6], there was significant decreased heart uptake (max SUV: 2.9 ± 1.8) which was consistent with the findings of Israel *et al*., who showed that myocardial F-18 FDG uptake was significantly lower in diabetics.[18] In addition, insulin therapy and other dietary factors may also cause rapid clearance of F-18 FDG, causing decrease in circulating radiotracer available for myocardial uptake.[19,20]

Variations in blood glucose levels are known to affect the F-18 FDG uptake in the liver cell;[21] physiologically, this is mediated by insulin-independent GLUT-2 transporters. In our study, there was no significant difference between max SUV values of liver among Group I and Group II patients. In Group III patients, liver max SUV values were 2.4 ± 0.6, which showed statistically significant difference from Group I and II values [Table 6]; however, values in all groups were within acceptable limits.

Glucose enters through insulin-dependent GLUT-4 receptors present in the cell wall of myocardial and striated muscle.[22,23] In our study, we observed statistically significant mild increased muscle activity in both Group I and II max SUV (1.03 ± 0.33, 0.86 ± 0.57) [Table 6]. Our results in Group II were in accordance with Hara *et al*. who reported increased muscle F-18 FDG uptake due to chronic hyperglycemia.[24] Studies done by Kelley *et al*. found that

glucose phosphorylation in muscles was altered in diabetic patients and that it increased in a dose-responsive manner with insulin infusion resulting in muscular uptake.[25,26]

During hyperglycemia, insulin lowers plasma glucose by stimulating insulin-dependent GLUT-4 receptors causing glucose uptake into skeletal muscle and adipose tissue. Hence, under insulin effect, adipose tissue also takes up F-18 FDG.[6,24] Fat uptake in Group I (0.48 ± 0.20) and Group II (0.40 ± 0.14) was slightly higher than the value in Group III (0.37 ± 0.17) and showed significant difference [Table 6] but well within acceptable limits. Thus, our study findings are consistent with previous studies done by Roy *et al*. and Garcia *et al*.[6,12]

Conclusion

Using short-acting intravenous insulin therapy protocol, optimal quality F-18 FDG PET CT scan images can be obtained in patients detected with hyperglycemia on the day of test. This short-acting IV insulin therapy protocol is not only safe and easy to perform but avoids potential delay in diagnostic work up and save resources.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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