18F-FLUORODEOXYGLUCOSE PET/CT CAN BE AN ALTERNATIVE METHOD TO ASSESSMENT OF INSULIN RESISTANCE

S. Altun Tuzcu^{1,*}, F.A. Cetin², Z. Pekkolay³, A.K. Tuzcu³

¹Dicle University Department of Nuclear Medicine, ²Private Baglara Hospital - Radiology, ³Dicle University - Endocrinology, Diyarbakir, Turkey

Abstract

Background. Insulin resistance is routinely measured by homeostasis model assessment of insulin resistance (HOMA-IR). Positron emission tomography of 18F-fluorodeoxyglucose combined with computed tomography (18F-FDG PET/CT) is a valuable assessment tool for patients with cancer or staging tumors. 18F-FDG PET/CT imaging can also be utilised to detect the metabolic activity of glucose in the adipose tissue, liver and muscles. The aim of this study was to determine insulin sensitivity in the liver, muscle visceral adipose and subcutaneous adipose tissue separately via 18F-FDG PET/CT.

Materials and method. Sixty three adult patients who underwent whole body 18F-FDG PET/CT scanning for clinical purposes (diagnosis or staging of cancer) between July and August of 2016 were included in the study. Patients were divided into two groups according to their BMI (Group 1: BMI < 25 kg/m², Group 2: BMI > 25 kg/m²). HOMA-IR, fasting glucose, insulin, triglycerides, total cholesterol, HDL levels were measured. We calculated SUV as the tissue activity of the ROI (MBq/g)/(injected dose [MBq]/ body weight [g]) on PET images and measured the maximum SUVs (SUVmax) of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), liver and rectus muscle ROIs (2 cm). SUV corrected by blood glucose level (SUVgluc) was calculated as SUVmax × blood glucose level/100. Student-t test, Chi-square test and Pearson correlation test were used for statistical analysis.

Results. Mean glucose, insulin, HOMA-IR levels of the group-2 were statistically higher than of group-1. Muscle SUVmax and liver SUVmax of group-1 were statistically higher than of group-2. Muscle SUVgluc of group-1 was statistically higher than of group-2. HOMA-IR was negatively correlated with both SUVmax (r = -0.340, p = 0.01) and muscle SUVmax (r = -0.373, p = 0.005).

Conclusion. 18F-FDG PET/CT has shown that the muscle tissue maximum FDG uptake was lower in the insulin resistance group. Therefore, 18-FDG PET/CT could be a valuable tool for diagnosing insulin resistance.

Key words: HOMA, 18-FDG PET/CT, Insulin resistance.

INTRODUCTION

Insulin resistance is the insulin hormone's reduced ability to exert its biological effects on the target organs, namely adipose tissue, skeletal muscle and liver. Insulin resistance can be associated with multiple clinical conditions including these osteoporosis or chronic stress (1, 2). Insulin resistance has been measured by developing several clinical research techniques. Generally, they are divided into two: static tests performed in the state of fasting and dynamic tests evaluating the response to glucose or insulin administered. The dynamic method which is used widely is the euglycemic hyperinsulinemic clamp technique (3). The simple static test which is most widely used is the assessment of insulin resistance based on the homeostasis model (HOMA-IR) (4, 5).

Fluorodeoxyglucose (FDG) is a derivative of glucose which accumulates inside the cells in proportion to their metabolic activity. The emission tomography of 18F-fluorodeoxyglucose positron which is combined with computed tomography (18F-FDG PET/CT) in a single scanner is the "gold standard" in evaluating the cancerous patients, staging tumors, monitoring response to treatment, and diagnosing recurrence. 18F-FDG PET/CT imaging can also be utilised to study the glucose metabolic activity and can be used to investigate the metabolic activity of glucose in adipose tissue, liver and muscles. It has been found that there might be a differential regulation of the metabolic activity of the liver, visceral adipose tissue (VAT), tissue of muscle, and subcutaneous adipose tissue (SAT) and 18F-FDG PET/CT imaging can be used as a reliable tool to assess insulin resistance (6). This study aimed to determine insulin sensitivity differences in overweight or obese patients and normal weight patients in the liver, muscle, visceral adipose and subcutaneous adipose tissue in patients undergoing the 18F-FDG PET/CT imaging for different purposes.

*Correspondence to: Sadiye Altun Tuzcu MD, Dicle University Department of Nuclear Medicine, Sur, Diyarbakir, 21200, Turkey, E-mail: sadiyetuzcu@yahoo.com.tr

MATERIALS AND METHOD

Subjects

The inclusion criteria included sixty-three adult patients under whole body 18F-FDG PET/CT scanning under clinical settings (staging of cancer or diagnosis) from July to August of 2016. Their clinical status of diabetes which includes medication or diabetes medical history, dyslipidaemia and hypertension were also collected. Patients with diabetes and who received treatments that could alter insulin sensitivity (metformin, corticosteroids) were excluded. Patients with pancreatic cancer, liver cancer or liver metastasis were not included to the study because these cancer types may affect glucose metabolism. All enrolled patients have given informed consent and Dicle University ethics committee has approved the study.

Anthropometric evaluations

The patients' height and weight were determined. The patient's BMI was calculated ($\text{bodyweight(kg)/height}^2(\text{m}^2)$). Patients were divided into two groups in terms of their BMI (Group-1 with $\text{BMI} < 25 \text{ kg/m}^2$, Group-2 with $\text{BMI} > 25 \text{ kg/m}^2$).

Blood samples and laboratory evaluation

During the period of fasting between the hours 08:30 and 09:30 in the morning, all the blood samples were taken within 10 to 12 hours. Immediate configuration and separation of the blood samples were done in tubes with citric acid and the samples were stored at -80°C until processing. Fasting glucose, total cholesterol, insulin, triglycerides, and HDL levels were determined. Insulin levels were measured with chemiluminescence immunoassay. The formula ($\text{HOMA-IR} = (\text{plasma insulin of fasting } (\mu\text{U/mL}) \times \text{plasma glucose of fasting } (\text{mmol/L}) / 22.5)$) was used to calculate HOMA-IR(2).

After eight hours of fasting, 18F-FDG was injected in vein of the patients (if blood glucose was $\leq 200 \text{ mg/dL}$) and images of the whole body were taken on a PET/CT scanner (Siemens Biograph 6, Siemens Medical Systems, CTI, Knoxville, TN, USA) within 55

to 75 minutes of administration of tracer (7).

Attenuation correction and anatomical localization required contrast CT scan with low dose (Biograph 6: 40 mA, 120 kVp). There was 3D acquisition of the PET scan from skull base to middle thigh. The standardized uptake values (SUVs) of the SAT, VAT, right rectus muscle, liver in each subject were measured by reviewing the images with round regions of interest (ROIs). SUV was calculated as the ROI tissue activity of ($\text{MBq/g} / (\text{body weight [g]} / \text{injected dose [MBq]})$) on images of PET and the maximum SUVs (SUVmax) of SAT(L3 level), VAT(omentum), rectus muscle ROIs (2 cm), and liver(right hepatic lobe) were measured. SUV with the blood glucose level (SUVgluc) corrected was measured as $\text{SUVmax} \times \text{blood glucose level} / 100$ (8). Normalized standard uptake value to the lean body mass (SUL) was measured. $\text{SUL} = \text{activity [kBq/mL]} / \text{injected dose [MBq]} \times \text{lean body mass [kg]}$. Among the women, LBM i.e. lean body mass was defined as $1.07 \times \text{BW} - 148 \times (\text{BW} / \text{height})^2$ and among the men, LBM was defined as $1.1 \times \text{BW} - 128 \times (\text{BW} / \text{height})^2$.

Statistical analysis

Mean $\pm$ standard deviation (SD) were shown for all results. Laboratory or clinical parameters results were compared using student-t test and two groups sex distribution was compared using Chi-square (χ^2) tests. Pearson correlation test analysis was done to identify the correlation between HOMA-IR and the maximum FDG uptake of the liver, muscle, SAT and VAT. Statistical significance at $p < 0.05$ was defined. SPSS™ software version 18 was used to perform all statistical analyses.

RESULTS

Age and sex distribution of the two groups at baseline were identical. Total-cholesterol and HDL cholesterol of the groups were not statistically different. Triglycerides of the Group-1 were lower than of Group-2 (Table 1).

Mean glucose, insulin, were statistically higher HOMA-IR levels of the Group-2 than of Group-1.

Table 1. Sex distribution, age, anthropometric parameters, glucose and lipid parameters of the groups

	Group-1(BMI<25kg/m ²) n=33	Group-2(BMI>25kg/m ²) n=30	p values
Sex female/male	13/20	13/17	NS
Age (years)	54.5 $\pm$ 17.9	52.6 $\pm$ 14.1	NS
BMI (kg/m ²)	20.9 $\pm$ 2.24	30 $\pm$ 4.1	p<0.001
Total-cholesterol (mg/dL)	187.8 $\pm$ 55.5	181.6 $\pm$ 34.4	NS
Triglycerides (mg/dL)	114.4 $\pm$ 36.5	185.3 $\pm$ 80.9	p<0.001
HDL-cholesterol (mg/dL)	35.3 $\pm$ 12.8	43.1 $\pm$ 16.4	NS

(NS: non-significant).

Table 2. Parameters related to insulin sensitivity and FDG uptake (NS: non-significant)

Variables	Group-1(BMI <25 kg/m ²)	Group-2(BMI >25 kg/m ²)	p values
Glucose (mg/dL)	90.3± 15.3	102.2 ±14.8	p=0.003
Insulin (μU/mL)	8.6 ±7.1	14.1 ±7.9	p=0.007
HOMA-IR	2.03 ±2.0	3.62±2.26	p=0.006
Muscle SUVmax	0.84 ±0.2	0.50 ±0.2	p<0.001
Liver SUVmax	2.3± 0.9	1.84 ±0.3	p=0.02
VAT SUVmax	0.87± 0.3	0.84± 0.3	NS
SAT SUVmax	1.14± 0.3	0.99± 0.3	NS
Muscle SUVgluc	0.75 ±0.2	0.51 ±0.2	p<0.001
Liver SUVgluc	2.09±1.0	1.91 ±0.6	NS
VAT SUVgluc	0.77± 0.3	0.88± 0.3	NS
SAT SUVgluc	1.03± 0.3	1.03± 0.4	NS
Muscle SULmax	0.61±0.1	0.34±0.1	p<0.001
Liver SULmax	1.66±0.65	1.19± 0.3	p<0.001
VAT SULmax	0.63± 0.25	0.52± 0.21	NS
SAT SULmax	0.83 ±0.22	0.61± 0.25	p<0.001

Figure 1. HOMA-IR was negatively correlated with both liver SUVmax ($r=-0.340$, $p=0.01$).

Figure 2. HOMA-IR was negatively correlated with muscle SUVmax ($r=-0.373$, $p=0.005$).

Figure 3. BMI of the groups negatively correlated with muscle SUV max ($r=-0.532$, $p=0.001$).

There were statistically higher Muscle SUVmax and liver SUVmax of Group-1 than of Group-2. VAT SUVmax and SAT SUVmax of the groups were not different (Table 2). There was a statistical higher Muscle SUVgluc of Group-1 than of Group-2. Liver SUVgluc, VAT SUVgluc and SAT SUVgluc of the groups were not different (Table 2).

There was a negative correlation between HOMA-IR and both liver SUVmax ($r=-0.340$, $p=0.01$) and muscle SUVmax ($r=-0.373$, $p=0.005$) (Figs 1 and 2). HOMA-IR was not correlated with VAT SUVmax and SAT SUVmax.

There was a negative correlation between BMI of the groups and muscle SUVmax ($r=-0.532$, $p=0.001$) (Fig. 3).

DISCUSSION

Insulin hormone inhibits the production and release of glucose from the liver. In case of insulin resistance the fasting glucose concentration increases due to the suppression of gluconeogenesis. On the other hand, the hepatic glucose production increases as a result of insulin resistance and this reduces the glucose uptake of liver. This could explain the 18F-FDG uptake of obese insulin resistant patients was statistically lower than of the lean insulin sensitive group under this study. There was a negative correlation between hepatic glucose uptake and HOMA-IR. In contrast to this current research, Nam HY *et al.* (9) showed that patients with increased liver uptake had higher HOMA-IR levels. We were not able to find many studies which evaluate the relationship between HOMA-IR and liver FDG uptake. Authors mostly examined plasma blood glucose levels and liver FDG uptake relationship.

As reported by Viglianti *et al.* (10), there was a significant relation between liver SUV and the level of plasma blood glucose. A systematic review showed that the glycaemic levels affected the liver uptake of 18F-FDG while this effect is small in magnitude (11). A study found a positive relationship between the level of fasting blood glucose and uptake of the liver. The author in the present study declared that the impact of blood glucose to increase liver FDG uptake was negligible (12). SUV corrected by blood glucose level (SUVgluc) of both groups was calculated (8). Liver SUVgluc uptake of the groups were not different, this result showed that plasma glucose level was an important determinant of liver glucose uptake.

Decreased glucose uptake in the adipose tissue could have been expected in the obese group as insulin resistance might reflect functional impairment of adipose tissue (13). A study found a positive relationship between resistance of insulin and VAT (14). In contrast, our study showed FDG uptake in SAT and VAT of obese patients were slightly lower than lean patients but these differences do not reach statistical significance. Christen *et al.* (15) confirmed our result and found similar FDG uptake in SAT and VAT in obese subjects versus fasting lean subjects. However, according to Oliveira *et al.* (16), obese patients had lower FDG uptake in VAT than the lean subjects who were metabolically healthy. Virtanen *et al.* (17) reported a significant reduction in SAT and VAT in the obese group. As a result, we can conclude that uptake of both SAT and VAT in FDG among the obese insulin resistant individuals were slightly lower

than in the lean insulin sensitive group. Our study found no relation between HOMA-IR and SAT and/or VAT. There are also several different articles claiming a weak negative correlation between HOMA-IR and SAT and/or VAT(15).

Muscle is the major insulin sensitive tissue and the principal site of insulin mediated glucose disposal. We have found that the FDG uptake in the rectus muscle was lower in the insulin resistant group as mentioned in many textbooks that the insulin uptake decreases in case of insulin resistance. The negative correlation between HOMA-IR and muscle tissue FDG uptake has been clearly detected with 18F-FDG PET/CT.

It is well known that obesity causes insulin resistance and, therefore, supports our result of negative correlation between HOMA-IR and muscle tissue FDG uptake. In the high BMI group, the uptake of glucose was significantly lower in the tissue of the muscle but it was not statistically prominent in the adipose tissue. One might think that muscle tissue constitutes the majority of glucose uptake of the human body and this uptake is initiated more rapidly in the muscles than in the adipose tissue. Triglyceride levels of insulin resistant obese group were significantly higher than of the lean group. In literature it was shown that patients with high HOMA-IR had also higher triglyceride levels that were compatible with our findings (18).

This study has some limitations one of which is that the enrolled population were cancer patients. This situation might affect the glucose uptake of tissue.

In conclusion, the 18F-FDG PET/CT has shown that the muscle tissue maximum FDG uptake was lower in the insulin resistance group. Therefore, we can use 18-FDG PET/CT as a valuable instrument for diagnosing insulin resistance.

Conflict of interest

The authors declare that they have no conflict of interest.

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