Factors influencing the pattern and intensity of myocardial ^{18}F-FDG uptake in oncologic PET-CT imaging

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ABSTRACT

Introduction: Myocardial ^{18}F-FDG uptake is highly variable in oncologic whole body ^{18}F-FDG PET/CT studies, ranging from quite intense to minimal distribution. Intense or heterogeneous myocardial ^{18}F-FDG uptake is undesirable as it may interfere with the visual or quantitative evaluation of tumoral invasion and metastases in pericardium, myocardium or adjacent mediastinal structures. The diet, as well as many other factors, is assumed to influence the myocardial ^{18}F-FDG uptake. Using a multivariate model, we tried to identify and predict the main factors influencing cardiac ^{18}F-FDG uptake in patients referred for oncologic PET/CT evaluation.

Methods: A total of 214 patients referred for oncologic ^{18}F-FDG PET/CT scan were enrolled in our study. Patients were randomly allocated into two groups according to the diet they were instructed to follow during 24-hour period before imaging. One hundred and seven cases with a routine diet (RD) and the same number of patients with a low carbohydrate, high fat (LCHF) diet were included. All patients were fast 6 hours before imaging. Weight, height, blood glucose, heart rate, systolic and diastolic blood pressure were measured before radiotracer injection. Visual and quantitative analysis were done after imaging and the pattern of ^{18}F-FDG uptake, as well as standardized quantitative value of cardiac uptake was determined for each case.

Results: The frequency of undesirable cardiac ^{18}F-FDG uptake in the LCHF group was significantly less than RD group (17% vs. 72%, p<0.001). The univariate analyses showed male gender, BMI>=30 as well as consumption of cardiotoxic chemotherapeutic agents, benzodiazepines and β blockers were significantly associated with higher intensity of myocardial ^{18}F-FDG uptake, while this undesirable finding was less evident in cases with diabetes mellitus. A multivariate logistic regression model including all of the mentioned variables revealed the diet was the only significant independent factor that predicted undesirable myocardial ^{18}F-FDG uptake (p<0.001).

Conclusion: LCHF diet 24 hours before PET/CT imaging is the only controllable independent factor influencing the intensity and pattern of myocardial ^{18}F-FDG uptake and is recommended as an optimal preparation to suppress cardiac ^{18}F-FDG uptake.

Key words: ^{18}F-FDG; Myocardial uptake; SUVmax; PET/CT; Oncology; Imaging

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INTRODUCTION

Positron emission tomography combined with computed tomography (PET/CT) is a useful imaging technique for determining cellular metabolism and viability that reveals cellular functional changes earlier than other conventional imaging modalities [1]. While most of PET-CT procedures are currently applied for oncologic indications, there is a growing trend toward its applications in neurology and cardiology due to the ongoing research in aforementioned fields. ^{18}F-Fluorodeoxy glucose (^{18}F-FDG) is the most popular tracer used worldwide for PET/CT scan that represents the glucose metabolism [1]. ^{18}F-FDG distributes over the whole body and its normal physiological uptake is seen in the brain, myocardium, liver, bladder and kidneys. In oncologic PET imaging, myocardial ^{18}F-FDG uptake is highly variable ranging from lack of visual uptake to quite intense and diffuse distribution [1-4].

For oncologic PET imaging, intense myocardial ^{18}F-FDG uptake is undesirable as it may mask visualization of abnormal uptake in adjacent mediastinal or upper abdominal structures. Increased cardiac uptake could be related to some primary cardiac diseases (primary tumors, metastatic disease, coronary artery disease, sarcoidosis, etc.) as well as treatment related conditions in noncardiac malignancies (drug-induced cardiotoxicity, post-radiation changes, etc.); however, physiologic myocardial ^{18}F-FDG uptake can obscure these abnormalities or mimic the corresponding findings [4, 5]. On the other hand, variable myocardial ^{18}F-FDG uptake in consecutive images may influence the real uptake of tumoral lesions leading to some misinterpretations during quantitative evaluation of metabolic activity in interim or follow-up assessment of the lesions during or after the treatment [6]. Thus, suppression of myocardial ^{18}F-FDG uptake is useful for the visualization and true quantification of lesions avoiding false positive or false negative results. Correspondingly, it is important to identify the factors that could influence the pattern and amount of myocardial ^{18}F-FDG uptake.

An independent controllable factor that may affect cardiac ^{18}F-FDG uptake is diet. Earlier studies have shown the rate of ^{18}F-FDG uptake by myocardium is proportional to free fatty acid (FFA) and serum glucose levels. In fasting state, blood glucose and insulin levels are low while FFA level is high due to their release from adipose tissue which makes FFA an important substrate for myocardial metabolism. In fed state, increased insulin levels accompanied by increased expression of glucose transporter 4 (GLUT4) in cardiac myocytes can lead to increased serum glucose availability which is a prominent feature of myocardial metabolism as compared with other substrates like FFA. Consequently, myocardial metabolism shifts away from FFA toward glucose [1-4].

Optimal patient preparation methods could suppress physiologic cardiac ^{18}F-FDG uptake and facilitate the evaluation of mediastinal regions for the cancer staging, detection of paracardiac abnormalities and determination of myocardial disease (atherosclerotic plaque, sarcoidosis, tumors, etc.) Fasting for 6 hours, has been found to inconsistently and variably minimize cardiac ^{18}F-FDG uptake; however, it is not effective enough to shift the metabolic substrate toward FFA. Thus, complementary preparations such as long fasting and dietary carbohydrate restriction are suggested before ^{18}F-FDG PET scan. However, the impact and proper duration of a low-carbohydrate high-fat (LCHF) diet before PET scan is still under study [7, 8].

Cardiac metabolism is affected by availability of substrate, myocardial workload and adequacy of myocardial perfusion. There are also a few factors that could shift myocardial metabolism between FFA and glucose. This study was conducted to investigate various factors that could potentially affect the pattern and amount of myocardial ^{18}F-FDG uptake. For this purpose, the efficacy of a 24-hour period of carbohydrate restriction and relatively high fat intake compared to the ordinary diet was also considered as a controllable factor to adjust the real influence of the studied factors.

METHODS

Patient population

A total of 214 patients aged 18 years or older (107 male and 107 female, 47.5 ± 15.6yrs, ranging between 18 and 84yrs) with proven or suspected malignancy referred to our center for ^{18}F-FDG PET/CT scan were enrolled in the study.

Patients were requested to complete a clinical questionnaire to confirm the inclusion criteria. Exclusion criteria consisted of documented heart failure, lack of adequate preparation (i.e. non-fasting state or serum glucose level more than 180 mg/dL at the time of ^{18}F-FDG injection) and intense pathologic liver uptake making the comparison between cardiac and visceral uptake impossible. From all enrolled cases, 107 patients were randomly assigned to a predefined LCHF diet (LCHFD) while 107 cases were asked to have an ordinary diet (OD) 24 hours before the study. Both groups received detailed instructions on their assigned diets. All 214 patients were instructed to fast at least 6 hours prior to ^{18}F-FDG administration.

Foods in LCHFD includes boiled eggs for breakfast, grilled beef or fried chicken for lunch and dinner without any carbohydrate containing meal nor beverage on the day before the study.

Laboratory and imaging analysis

Blood glucose, heart rate, systolic and diastolic blood pressure were measured before tracer injection. Whole body PET/CT acquisition was done from skull base to mid-thigh (except for total acquisition in RCC, lung cancer, melanoma and cases with suspicious clinical history in brain or extremities) 60±5 minutes after tracer injection.

All PET/CT studies are performed using a SIEMENS Biograph 6 True Point (HD) PET/CT scanner (Siemens/CTI, Knoxville, USA). PET scan was acquired for 3 min/bed position in all patients. Low dose CT protocol (50 mA, 110-130 kV) was performed for anatomical localization and attenuation correction.

Visual and quantitative analysis were done after imaging. Visual assessment of ¹⁸F-FDG pattern in the heart was performed independently by two experienced nuclear medicine physicians. In case of disagreement, a third opinion was received from a third observer. The cases were classified into four subgroups on the basis of visual pattern of ¹⁸F-FDG distribution throughout myocardium, i.e. absent, diffuse, focoregional and heterogeneous (multifocal) uptake (Figure 1).
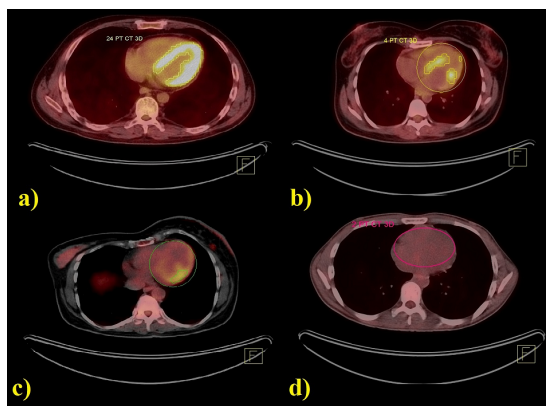

Fig 1. Different patterns of ¹⁸F-FDG uptake: a) Diffuse uptake, b) Heterogeneous uptake, c) Focoregional uptake and, d) Absent.

In addition, the amount of uptake was quantitatively estimated in comparison with liver. For the quantitative analysis, maximum standardized uptake value (SUVmax) and heart diameter were measured in all patients. Cardiac boundaries and regions of interest (ROIs) were drawn on coregistered PET-CT slices and SUVmax values, corrected for physical decay and attenuation, were measured. The ROIs was adjusted in size and position in such a way that whole myocardium was included in all 3 views defined by CT images.

Statistical analysis

The chi-square test is used for univariate analysis of the nominal variables. Numeric variables without normal distribution confirmed by Kolmogorov Smirnov test (such as SUVmax values) were examined using non-parametric Mann-Whitney U test in binominal groups and Kruskal-Wallis rank test in multiple groups. It should be noted that variables with frequencies less than 3% in the studied sample (e.g., some drugs or diseases) were not included in the final analysis. Relationships between myocardial ¹⁸F-FDG uptake and other normally distributed continuous variables were tested using Pearson's coefficient correlation while its nonparametric analogue (Spearman's rho test) was used for the data without normal distribution. Multivariate logistic regression analysis was used to simultaneously evaluate the association of multiple factors with myocardial uptake while adjusted for the effect of cofactor relationships. P values less than 0.05 were considered statistically significant.

RESULTS

In total, 214 patients were assessed (107 in LCHFD and 107 in OD groups). Table 1 shows the summarized baseline factors presumed to have a possible association with cardiac uptake in the two studied groups. As intended for random allocation of patients, all factors have the same distribution between groups implicating that the two groups are comparable for all possible factors interfering with cardiac uptake.

In patients allocated into routine diet group (107 cases), diffuse, locoregional and heterogeneous uptake patterns are detected in 43 (40%), 28 (26%) and 6 (6%) cases, respectively, while 30 individuals (28%) demonstrate no remarkable ¹⁸F-FDG uptake throughout the myocardium. On the contrary, 89 (83%) absent, 0 (0%) diffuse, 13 (12%) locoregional and 5 (5%) heterogeneous uptake are identified after using LCHF diet for the patients' preparation. Correspondingly, as a main result in our study, the pattern of myocardial ¹⁸F-FDG uptake is significantly affected by the diet on the day before the study (ordinary vs. LCHF diet, p<0.001) and generally less uptake is detected when LCHF diet is applied (p<0.001).

On the other hand, regardless of patients' diet, seventeen from 18 (94%) diabetic and 102 from 196 (52%) non-diabetic patients revealed absent myocardial ¹⁸F-FDG uptake favoring less frequency of ¹⁸F-FDG uptake in diabetic cases (p<0.001). Other non-diabetic cases show a pattern of myocardial ¹⁸F-FDG activity including diffuse in 42 (21.5%), locoregional in 40 (20%) and heterogenous or multifocal uptake in 11 (6%) cases.

Table 1: Baseline characteristics of patients in two groups.

Patients' Characteristics		Total	Diet groups		Sig. of difference
			RD	LCHFD	P value
Demographic	Age (yrs) *	47.5±15.6	47.7±15.7	47±15.6	0.089
	Gender (female %)	50	48.6	51.4	0.785
Clinical situation	Smoking	9.3	12.1	6.5	0.240
	Diabetes mellitus	8.4	8.4	8.4	1.000
	Hypertension	14	15	13.1	0.844
	Hyperlipidemia	10.3	10.3	10.3	1.000
	Cardiac disease	6.5	6.5	6.5	1.000
	Hypothyroid state	10.3	9.3	11.2	0.822
Body texture	Body mass index*	25.4±4.5	25.7±4.3	25.4±4.9	0.328
	Heart to chest diameter ratio*	0.47±0.1	0.48±0.1	0.46±0.05	0.055
Treatment- related factors	Cardiac radiation exposure	7.9	6.5	9.3	0.614
	Cardiotoxic chemotherapy	78	78.5	77.6	1.000
	Noncardiotoxic chemotherapy	6.5	8.4	4.7	0.408
Patient' condition at the time of PET study	Heart rate (beat/min) *	80.7±9.1	80.4±9.2	80.7±9.1	0.794
	Injected dose ofFDG (mCi) *	10.7±1.7	10.6±1.8	10.7±1.7	0.652
	Systolic Blood pressure (mmHg) *	116.9±13.9	120±15.7	116.9±13.9	0.129
	Diastolic Blood pressure(mmHg) *	77.5±7	79.1±8.8	77.5±7.9	0.182
	Blood sugar (mg/dL)*	93.7±17	95.2±18.8	93.7±17.1	0.539
Drugs	Oral anti-diabetic agent	7	6.5	7.5	1.000
	Insulin	2.3	1.9	2.8	1.000
	Beta-blockers	13.1	14	12.1	0.420
	L-Thyroxin	9.3	8.4	10.3	0.815
	Bone marrow stimulating factors	8.4	11.2	5.6	0.018
	Steroids	5.6	6.5	4.7	0.768
	Benzodiazepines	8.9	12.1	5.6	0.148

*Numeric data has been expressed as mean ± standard deviation; RD: routine diet; LCHFD: low carbohydrate, high fat diet.

On the basis of intra-group analysis, the difference was also detected in OD group while is not confirmed in the cases with LCHF diet.

In OD group, in addition to diabetes mellitus, other significant predicting factors of cardiac ^{18}F-FDG uptake were gender and cardiotoxic chemotherapy, whereas all other assumed variables were not shown to be significant. In this group, ^{18}F-FDG uptake was more frequent among men than women (83.6% vs. 59.6%, p<0.001). The most frequent pattern of uptake in both genders is diffuse uptake (45.4% in men and 34.6% in women) and the least frequent pattern is heterogeneous uptake (9.1% in men and 1.9% in women) representing different patterns in male vs. female patients (p=0.028). In OD group patients with history of previous cardiotoxic chemotherapy (84

cases), the frequencies of diffuse, locoregional and heterogeneous uptake were 34 (40.5%), 21 (25%) and 3 (3.5%), respectively, which was significantly different from 9 cases with noncardiotoxic chemotherapy, i.e. 2 (22%), 1 (11%) and 3 (33%), respectively, or 14 patients with no history of chemotherapy, i.e. 7 (50%), 6 (43%) and 0 (0%), respectively. Thus, cardiotoxic chemotherapy drugs show significant influence on the pattern of ^{18}F-FDG cardiac uptake just when routine diet is applied for the preparation of patients (p<0.001). Conversely, none of the studied factors was confirmed to have statistically significant effect on the pattern of myocardial ^{18}F-FDG uptake in LCHF group.

In addition to the presence and pattern of ^{18}F-FDG uptake, the factors associated with the intensity of ^{18}F-FDG uptake were also evaluated. Estimated SUV_{max} in the group with LCHF diet (2.88±1.01) was much lower than that of patients with routine diet (8.77±6.3). Thus, the diet is significantly associated with the intensity of cardiac ^{18}F-FDG uptake (p<0.001). On the basis of univariate analyses, other factors associations with the intensity of ^{18}F-FDG uptake were also evaluated. As shown in Figure 2, there is a positive correlation between increased cardiac diameter and higher myocardial SUV_{max} in all patients (p=0.001) but not in each group using separate analyses. In addition, correlation analysis reveals that myocardial SUV_{max} is in association with age only in the LCHF diet group (Figure 3, p=0.009) and not in the OD group.

The associations of other factors are summarized in Table 2. As noted in this table, diabetic patients revealed a significantly lower intensity of uptake just in OD group. In addition, lower SUV_{max} is associated with lower diastolic blood pressure (dBP<100mmHg vs. >=100mmHg) when pooled data of all patients is considered, while no significant association is observed between SUVmax and dBP in the intra-group analysis of patients after considering the diet. In the group with routine diet, female gender (p=0.009) was also found to be associated with lower myocardial SUV_{max} while this association was not found in LCHF diet group. On the other hand, in the group with LCHF diet, the factors associated with higher myocardial SUV_{max} were BMI and serum glucose (Table 2). In addition, consumption of benzodiazepine (p=0.001), corticosteroid (p= 0.006) and βblockers (p=0.006) were associated with higher myocardial SUV_{max} in this group (Table 3). Due to the low frequency of cases and suboptimal analytic power, the effects of some drugs such as anti-hyperlipidemic drugs were not investigated.

All univariately significant factors were also evaluated by multivariate logistic regression analysis. The binary dependent variable was defined by the comparison of cardiac uptake with mediastinal blood

pool. Patients with cardiac SUVmax equal or less than mediastinal blood pool background were assigned in "low cardiac uptake" and those with higher cardiac SUVmax were assigned in "high cardiac uptake" category. Multivariate analysis revealed that among all of the univariately significant variables, the diet is the only predictive factor that is independently associated with myocardial ^{18}F-FDG uptake (p<0.001).
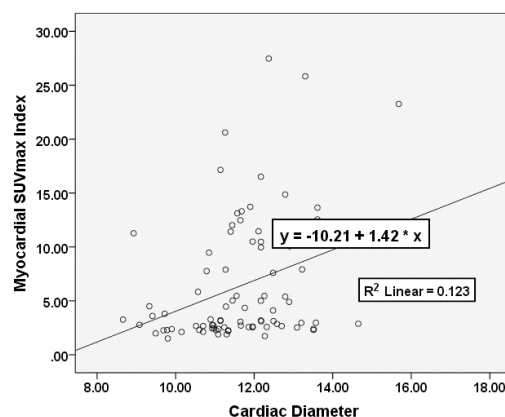

Fig 2. Correlation between cardiac diameter (cm) and myocardial SUV_{max} in all studied patients
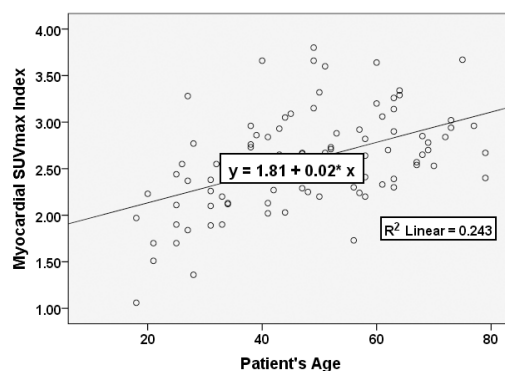

Fig 3. Correlation between age (years) and myocardial SUV_{max} in the low carbohydrate high fat diet group

DISCUSSION

The aim of the present study was to assess predicting factors affecting the pattern and amount of myocardial ^{18}F-FDG uptake. ^{18}F-FDG PET scan of the mediastinum could be influenced by intense myocardial ^{18}F-FDG uptake. Furthermore, high myocardial activity may affect the interpretation of cardiac and paracardiac abnormalities resulting in false positive or false negative findings [5, 9].

Table 2: The associations between different factors and intensity of ^{18}F-FDG uptake on the basis of univariate analyses.

Factor	State	Maximum heart standard uptake value (SUV max)					
		Total		Routine diet		LCHF diet	
		mean± SD	p Value	mean± SD	p Value	mean± SD	p Value
Gender	Female	5.04±4.6	0.052	7.34±5.8	0.009	2.86±0.98	0.890
	Male	6.61±5.9		10.12±6.5		2.90±1.0	
Diabetes mellitus	Yes	3.30±2.0	0.105	3.83±2.8	0.002	2.78±0.3	0.590
	No	6.07±5.5		9.22±6.4		2.89±1.0	
Smoking	Yes	6.99±5.6	0.229	9.34±5.6	0.454	2.63±0.65	0.743
	No	5.70±5.4		8.69±6.4		2.90±1.0	
Physical activity	Regular	8.71±8.1	0.531	6.47±3.6	0.198	2.87±0.7	0.811
	Irregular	4.45±3.1		14.55±7.9		2.63±0.5	
	No	5.87±5.4		8.18±6.4		2.91±1.0	
BMI	< 30 Kg/m2	5.79±5.4	0.199	8.95±6.3	0.417	2.80±0.9	0.008
	> 30 Kg/m2	6.02±5.3		7.92±6.3		3.43±1.1	
Diastolic BP	< 89 mmHg	5.52±5.1	0.032	8.38±6.1	0.156	2.89±1.0	0.533
	> 90 mmHg	8.50±7.1		11.18±7.2		2.76±0.2	
Systolic BP	< 99 mmHg	4.33±3.8	0.256	7.30±5.4	0.618	2.85±1.6	0.537
	100-139 mmHg	5.88±5.4		8.96±6.4		2.90±0.9	
	> 140 mmHg	6.21±5.8		8.00±6.5		2.62±0.3	
Blood sugar	< 99 mg/dl	5.78±5.4	0.391	8.75±6.3	0.900	2.77±0.9	0.022
	> 100 mg/dl	5.93±5.4		8.82±6.5		3.13±1.0	

LCHF: Low carbohydrate high fat; BMI: Body mass index; SD: Standard deviation; BP: Blood pressure

Table 3: Association of medications with maximum myocardial standard uptake value.

Drugs	State	Maximum heart standard uptake value (SUV max)					
		Total		Routine diet		LCHF diet	
		mean±SD	p value	mean±SD	p value	mean±SD	p value
Benzodiazepine	Yes	6.54±4.4	0.036	7.57±5.1	0.587	4.32±1.0	0.001
	No	5.75±5.5		8.94±6.5		2.79±0.9	
Beta blocker	Yes	4.98±3.4	0.630	6.10±4.2	0.067	3.69±1.3	0.005
	No	5.95±5.6		9.21±6.5		2.77±0.9	
Steroid	Yes	6.07±4.5	0.390	7.02±5.8	0.326	4.75±1.7	0.006
	No	5.81±5.4		8.89±6.4		2.79±0.8	

LCHF: Low carbohydrate high fat; SD: Standard deviation

In this study, the effect of independent clinical variables and imaging factors on myocardial ^{18}F-FDG uptake was evaluated in a group of 214 patients with proven or suspected malignancy. As diet was the only independent variable which could be effectively handled, the patients were divided randomly into two diet groups; a routine or ordinary diet (OD group) and a LCHF diet (LCHF group) each contains 107 patients. Our study showed a statistically significant association between gender and myocardial ^{18}F-FDG uptake pattern as well as myocardial uptake intensity in patients prepared with ordinary diet. Male cases revealed significantly higher myocardial ^{18}F-FDG uptake than females in OD group. Israel et al.

reported that higher myocardial ^{18}F-FDG uptake cannot be attributed to the larger size of the male heart [10]. It is mainly because the heart volume was considered in their SUV_{mean} based analysis. Gender-dependent differences of fat metabolism may support these results. In female patients, myocardial fatty acid metabolism is higher than male cases as estrogen increases fatty acid oxidation in the liver and skeletal muscles while decreases GLUT4 expression, glucose oxidation, gluconeogenesis and glycogenesis [11], resulting in lower myocardial uptake in females. On the other hand, no association was found between gender and cardiac activity in the case of LCHF diet in our study. A logical reason for this event is that in the group prepared by LCHF diet, the metabolism of fatty acid, as an available and common myocardial substrate, is increased in both genders leading to a diminished gender-based difference in myocardial metabolism.

Myocardial metabolic response to dobutamine following endurance exercise training is affected by gender in such a way that in males it increases glucose metabolism and decreases fatty acid metabolism while in females it increases both glucose and fatty acid metabolism simultaneously [11].

Age shows statistically significant correlation with intensity of myocardial activity in the group with LCHF diet but not in the group with routine diet. Some investigators revealed that myocardial source of energy may be changed from glucose in embryonal period to fatty acid in adults [12, 13]. However, fatty acid oxidation is expected to decrease again with increasing age due to the injury induced by oxygen free radicals as well as irreversible change of myocardial enzymes and mitochondrial lipid content [14]. Moreover, several clinical studies reported the impairment of cardiac mitochondrial function with age [15, 16]. Preclinical studies have also shown that, myocardial fatty acid metabolism decreases while glucose metabolism increases with aging. In fact, a decline in myocardial fatty acid uptake (MFAU) and myocardial fatty acid oxidation (MFAO) along with increased glucose metabolism occur during human ageing [17]. The influence of ageing became more obvious when the availability of carbohydrate was restricted in our study (LCHF diet group).

In LCHF diet group, obesity has a statistically significant correlation with intensity of myocardial ^{18}F-FDG uptake. Although obese patients show higher cardiac ^{18}F-FDG uptake in our study, it is in contradiction with some literatures reporting that increased BMI and insulin resistance may shift myocardial metabolism to fatty acid [18-20]. Preclinical studies reveal ten days high fat diet reflects the disturbance of insulin signaling in myocardium, increased myocardial fatty acid

availability and decreased glucose utilization [21, 22]. In addition, obesity causes diabetic-like changes in myocardium before hyperglycemic state occurrence [21, 23]. So, other interfering factors were considered carefully to justify the analysis. Despite the initial results of univariate analysis showing the relationship between obesity and higher SUVmax in LCHF-diet group, multivariate analysis indicates BMI does not independently affect myocardial ^{18}F-FDG uptake.

Our results showed that blood sugar level is concordant with increased intensity of myocardial ^{18}F-FDG uptake just in LCHF-diet group (p=0.022). The Randle cycle, also known as the glucose fatty-acid cycle, as a metabolic process involving the competition of glucose and fatty acids for substrates can explain this finding. Higher blood glucose level spares more substrate availability for myocardial glucose metabolism and correspondingly higher ^{18}F-FDG uptake even in the fasted state after a fat-rich meal with restricted sugar. Moreover, increased insulin followed by higher level of blood sugar, causes more GLUT 4 expression. This effect is not significant when a routine diet is used before fasting. Our results showed a good concordance with previous studies [5, 24].

There was a statistically significant association between the presence of diabetes mellitus and pattern/intensity of myocardial ^{18}F-FDG uptake in the group of ordinary diet. In this group, most of diabetic patients showed an absent or negligible myocardial uptake while non-diabetic cases revealed a remarkably higher uptake. Preclinical studies have shown evidences in favor of myocardial metabolic shifting from glucose to fatty acid in both type 1 and 2 of diabetes mellitus [25, 26]. In fact, diabetes increases myocardial fatty acid utilization and decreases glucose consumption as the metabolic substrate [25, 26]. This fact is rationally responsible for difference of myocardial ^{18}F-FDG uptake in diabetic vs. non-diabetic cases. However, this difference fades away when LCHF diet is used. This finding may be described by the difference of ordinary diet in diabetic and non-diabetic cases. Diabetic patients are routinely ordered to eat low carbohydrate food than others. With LCHF diet administration, non-diabetic patients also intake low level of carbohydrate and the substrate availability for myocardial metabolism may be more similar to diabetic patients leading to insignificant difference of myocardial ^{18}F-FDG uptake between diabetic and non-diabetic cases in LCHF-diet group.

In OD group, cardiotoxic chemotherapy reveals statistically significant association with myocardial ^{18}F-FDG pattern. The results show that diffuse pattern is more prominent than others. Progressive myocardial injury secondary to cardiotoxic drug

consumption is due to changing myocytes metabolism as well as mitochondrial membrane exposure to oxygen free radicals, apoptosis and necrosis [27, 28]. ^{18}F-FDG PET/CT imaging shows increased myocytes glucose utilization as a result of myocardial adaptive response to mitochondrial injury in cardiotoxic chemotherapy [27]. Globally increased myocardial ^{18}F-FDG uptake, due to direct effect of chemotherapy on glucose metabolism, is also described in previous studies [27].

Our results demonstrated that myocardial SUVmax is higher in benzodiazepine consumers in LCHF-diet group. The result is concordant with the previously published study by Israel et al [10]. Our results also showed a correlation between corticosteroid consumption and higher SUVmax in this group. As to our knowledge, this is the first study in which the effect of corticosteroid consumption on myocardial ^{18}F-FDG uptake has been assessed. Thus, a well-selected larger cohort study would be required to confirm our finding. Due to the low frequency of cases and suboptimal analytic power, the effects of some drugs such as anti-hyperlipidemic drugs were not investigated.

The frequencies of patients consuming levothyroxine, anti-lipid agents, caffeine and G-CSF in our study were not sufficient to reach an optimal statistical power for the analysis of myocardial ^{18}F-FDG uptake in these subgroups of patients. However, a previously published study showed a decrease in myocardial ^{18}F-FDG uptake with consumption of levothyroxine and anti-lipid agents (bezofibrates) [10].

On the other hand, caffeine consumption may increase fatty acid and correspondingly may shift myocardial metabolism from glucose to fatty acid; however, no statistically significant relationship has been found between its consumption with myocardial ^{18}F-FDG uptake [7, 29, 30].

Cardiac diameter shows a statistically significant correlation with SUVmax in all patients. Our hypothesis supports this finding; any increase in cardiac diameter is concomitant with higher incidence of coronary artery disease and heart failure which could adaptively increase myocardial ^{18}F-FDG uptake [31]. As this is the first study in which effect of cardiac diameter on myocardial ^{18}F-FDG uptake was assessed, further investigation is needed to confirm our finding.

Diastolic blood pressure equal or greater than 90 mmHg was concordant with higher SUVmax while the values less than 90 mmHg shows lower SUVmax. Higher diastolic blood pressure may increase cardiac workload and adaptively myocardial ^{18}F-FDG uptake as well. No similar study to date has been found for comparison.

β–blockers increase myocardial SUVmax in LCHF-diet group. Regarding the previous studies, β–blockers may also lead to regional ^{18}F-FDG uptake [32]. Further studies will be needed to demonstrate conclusively the effect of β–blockers on myocardial ^{18}F-FDG uptake.

Thoracic radiotherapy may increase myocardial [18]F-^{18}F-FDG uptake especially in basal segments, so precise monitoring is required to exclude cardiac events. A study by Unal et al. reported that SUVmax values were higher in radiated myocardial segments than non-radiated ones [33]. However, no significant relationship was found between radiotherapy and myocardial ^{18}F-FDG uptake in our study.

In routine diet group, nearly 40% of patients reveal diffuse ^{18}F-FDG uptake while no patient in LCHF-diet group shows this pattern of uptake. Furthermore, 80% of patients in LCHF diet group with only 28% of patients with routine diet reveal no cardiac uptake (absent). Fatty acids are the main source of myocardial metabolism in normal states and supplies up to nearly 60-80% of total myocardial energy for cardiac work states [34, 35]. Plasma free fatty acid level determines the amount of myocardial free fatty acid uptake [34]. Animal studies reveal that high fat diet declines glucose oxidation and di-acyl glycerol retention induces myocardial insulin resistance [34, 36]. Cardiac capacity of fatty acid is restricted by lipotoxicity that leads to apoptosis [34, 37].

Myocardial ^{18}F-FDG uptake is likely the result of randle cycle in which myocardial ^{18}F-FDG DG uptake is decreased as the fatty acid increases [38, 39]. Higher fatty acid level declines GLUT4 and glucose uptake [7, 40]. In this study, LCHF diet administration 24 hours before ^{18}F-FDG injection, shows a significant reduction in myocardial ^{18}F-FDG uptake. In multi-variate analysis, LCHF diet was the only significant factor which strongly affects myocardial ^{18}F-FDG uptake.

Glucose entrance to myocardium is regulated by GLUT1 (insulin independent) and GLUT4 (insulin dependent) [13]. Down-regulation of GLUT4 or decline in myocardial insulin receptors leads to cardiac dysfunction in cardiac hypertrophy [13, 41].

Our results show that LCHF diet administration has suppressive effect on myocardial ^{18}F-FDG uptake in concordance with the result of other studies [7, 35, 42, 43].

Finally, there is no relationship between cardiac ^{18}F-FDG uptake and risk factors for cardiac disease or history of CAD (except for diabetes mellitus) in our study.

CONCLUSION

LCHF diet 24 hours before ^{18}F-FDG injection is effective to suppress myocardial ^{18}F-FDG uptake. In our comprehensive evaluation of clinical and imaging factors affecting myocardial ^{18}F-FDG uptake, LCHF

diet is the only controllable independent powerful factor causing reduction of myocardial ^{18}F-FDG uptake, facilitating interpretation of PET/CT studies.

Acknowledgments

REFERENCES

1. Boellaard R, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W, Verzijlbergen FJ, Barrington SF, Pike LC, Weber WA, Stroobants S, Delbeke D, Donohoe KJ, Holbrook S, Graham MM, Testanera G, Hoekstra OS, Zijlstra J, Visser E, Hoekstra CJ, Pruim J, Willemsen A, Arends B, Kotzerke J, Bockisch A, Beyer T, Chiti A, Krause BJ; European Association of Nuclear Medicine (EANM). FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging. 2015 Feb;42(2):328-54.

2. Abouzied MM, Crawford ES, Nabi HA. 18F-FDG imaging: pitfalls and artifacts. J Nucl Med Technol. 2005 Sep;33(3):145-55; quiz 162-3.

3. Fukuchi K, Ohta H, Matsumura K, Ishida Y. Benign variations and incidental abnormalities of myocardial FDG uptake in the fasting state as encountered during routine oncology positron emission tomography studies. Br J Radiol. 2007 Jan;80(949):3-11.

4. Maurer AH, Burshteyn M, Adler LP, Steiner RM. How to differentiate benign versus malignant cardiac and paracardiac 18F FDG uptake at oncologic PET/CT. Radiographics. 2011 Sep-Oct;31(5):1287-305.

5. Kaneta T, Hakamatsuka T, Takanami K, Yamada T, Takase K, Sato A, Higano S, Kinomura S, Fukuda H, Takahashi S, Yamada S. Evaluation of the relationship between physiological FDG uptake in the heart and age, blood glucose level, fasting period, and hospitalization. Ann Nucl Med. 2006 Apr;20(3):203-8.

6. Williams G, Kolodny GM. Suppression of myocardial 18F-FDG uptake by preparing patients with a high-fat, low-carbohydrate diet. AJR Am J Roentgenol. 2008 Feb;190(2):W151-6.

7. Balink H, Hut E, Pol T, Flokstra FJ, Roef M. Suppression of 18F-FDG Myocardial Uptake Using a Fat-Allowed, Carbohydrate-Restricted Diet. J Nucl Med Technol. 2011 Sep;39(3):185-9.

8. Wykrzykowska J, Lehman S, Williams G, Parker JA, Palmer MR, Varkey S, Kolodny G, Laham R. Imaging of inflamed and vulnerable plaque in coronary arteries with 18F-FDG PET/CT in patients with suppression of myocardial uptake using a low-carbohydrate, high-fat preparation. J Nucl Med. 2009 Apr;50(4):563-8.

9. Williams G, Kolodny GM. Suppression of myocardial 18F-FDG uptake by preparing patients with a high-fat, low-carbohydrate diet. AJR Am J Roentgenol. 2008 Feb;190(2):W151-6.

10. Israel O, Weiler-Sagie M, Rispler S, Bar-Shalom R, Frenkel A, Keidar Z, Bar-Shalev A, Strauss HW. PET/CT quantitation of the effect of patient-related factors on cardiac 18F-FDG uptake. J Nucl Med. 2007 Feb;48(2):234-9.

11. Wismann J, Willoughby D. Gender differences in carbohydrate metabolism and carbohydrate loading. J Int Soc Sports Nutr. 2006;3:28-34.

12. Doenst T, Pytel G, Schrepper A, Amorim P, Färber G, Shingu Y, Mohr FW, Schwarzer M. Decreased rates of substrate oxidation ex vivo predict the onset of heart failure and contractile dysfunction in rats with pressure overload. Cardiovasc Res. 2010 Jun 1;86(3):461-70.

13. Kolwicz SC Jr, Tian R. Glucose metabolism and cardiac hypertrophy. Cardiovasc Res. 2011 May 1;90(2):194-201.

14. Tarnopolsky M. Gender differences in metabolism: Practical and nutritional implications. Boca Raton: CRC Press; 1999. p. 340.

15. Chaudhary KR, El-Sikhry H, Seubert JM. Mitochondria and the aging heart. J Geriatr Cardiol. 2011 Sep;8(3):159-67.

16. Tocchi A, Quarles EK, Basisty N, Gitari L, Rabinovitch PS. Mitochondrial dysfunction in cardiac aging. Biochim Biophys Acta. 2015 Nov;1847(11):1424-33.

17. Henkin RE. Nuclear medicine. 2nd ed. Philadelphia: Mosby Elsevier; 2006.

18. Aasum E, Hafstad AD, Severson DL, Larsen TS. Age-dependent changes in metabolism, contractile function, and ischemic sensitivity in hearts from db/db mice. Diabetes. 2003 Feb;52(2):434-41.

19. Peterson LR, Herrero P, Schechtman KB, Racette SB, Waggoner AD, Kisrieva-Ware Z, Dence C, Klein S, Marsala J, Meyer T, Gropler RJ. Effect of obesity and insulin resistance on myocardial substrate metabolism and efficiency in young women. Circulation. 2004 May 11;109(18):2191-6.

20. Zhou YT, Grayburn P, Karim A, Shimabukuro M, Higa M, Baetens D, Orci L, Unger RH. Lipotoxic heart disease in obese rats: implications for human obesity. Proc Natl Acad Sci U S A. 2000 Feb 15;97(4):1784-9.

21. Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. Physiol Rev. 2008 Apr;88(2):389-419.

22. Park SY, Cho YR, Kim HJ, Higashimori T, Danton C, Lee MK, Dey A, Rothermel B, Kim YB, Kalinowski A, Russell KS, Kim JK. Unraveling the temporal pattern of diet-induced insulin resistance in individual organs and cardiac dysfunction in C57BL/6 mice. Diabetes. 2005 Dec;54(12):3530-40.

23. Coort SL, Hasselbaink DM, Koonen DP, Willems J, Coumans WA, Chabowski A, van der Vusse GJ, Bonen A, Glatz JF, Luiken JJ. Enhanced sarcolemmal FAT/CD36 content and triacylglycerol storage in cardiac myocytes from obese zucker rats. Diabetes. 2004 Jul;53(7):1655-63.

24. Ozguven MA, Karacalioglu AO, Ince S, Emer MO. Altered biodistribution of FDG in patients with type-2 diabetes mellitus. Ann Nucl Med. 2014 Jul;28(6):505-11.

25. Herrero P, Peterson LR, McGill JB, Matthew S, Lesniak D, Dence C, Gropler RJ. Increased myocardial fatty acid metabolism in patients with type 1 diabetes mellitus. J Am Coll Cardiol. 2006 Feb 7;47(3):598-604.

26. Peterson LR, Herrero P, McGill J, Schechtman KB, Kisrieva-Ware Z, Lesniak D, Gropler RJ. Fatty acids and insulin modulate myocardial substrate metabolism in humans with type 1 diabetes. Diabetes. 2008 Jan;57(1):32-40.

27. Borde C, Kand P, Basu S. Enhanced myocardial fluorodeoxyglucose uptake following Adriamycin-based

therapy: Evidence of early chemotherapeutic cardiotoxicity? World J Radiol. 2012 May 28;4(5):220-3.

28. van der Pal HJ, van Dalen EC, Hauptmann M, Kok WE, Caron HN, van den Bos C, Oldenburger F, Koning CC, van Leeuwen FE, Kremer LC. Cardiac function in 5-year survivors of childhood cancer: a long-term follow-up study. Arch Intern Med. 2010 Jul 26;170(14):1247-55.

29. de Swart J, Snoek-Klaver I, Valkema R, Kam BLR, Krenning EP. The influence of caffeine on the uptake of 18-FDG in the myocardium. Eur J Nucl Med Mol Imaging. 2004;31(suppl):S484.

30. Lam MGE, Dekkers EJM, van Dongen AJ, van Isselt JW, van Rijk PP. Does caffeine influence myocardial FDG uptake? Eur J Nucl Med Mol I. 2004;31(suppl):S205.

31. Maurer AH, Burshteyn M, Adler LP, Steiner RM. How to differentiate benign versus malignant cardiac and paracardiac 18F FDG uptake at oncologic PET/CT. Radiographics. 2011 Sep-Oct;31(5):1287-305.

32. Tahara N, Tahara A, Nitta Y, Kodama N, Mizoguchi M, Kaida H, Baba K, Ishibashi M, Hayabuchi N, Narula J, Imaizumi T. Heterogeneous myocardial FDG uptake and the disease activity in cardiac sarcoidosis. JACC Cardiovasc Imaging. 2010 Dec;3(12):1219-28.

33. Unal K, Unlu M, Akdemir O, Akmansu M. 18F-FDG PET/CT findings of radiotherapy-related myocardial changes in patients with thoracic malignancies. Nucl Med Commun. 2013 Sep;34(9):855-9.

34. Abel ED, O'Shea KM, Ramasamy R. Insulin resistance: metabolic mechanisms and consequences in the heart. Arterioscler Thromb Vasc Biol. 2012 Sep;32(9):2068-76.

35. Dirkx E, Schwenk RW, Glatz JF, Luiken JJ, van Eys GJ. High fat diet induced diabetic cardiomyopathy. Prostaglandins Leukot Essent Fatty Acids. 2011 Nov;85(5):219-25.

36. Zhang L, Ussher JR, Oka T, Cadete VJ, Wagg C, Lopaschuk GD. Cardiac diacylglycerol accumulation in high fat-fed mice is associated with impaired insulin-stimulated glucose oxidation. Cardiovasc Res. 2011 Jan 1;89(1):148-56.

37. Unger RH, Orci L. Lipoapoptosis: its mechanism and its diseases. Biochim Biophys Acta. 2002 Dec 30;1585(2-3):202-12.

38. Fine EJ, Miao W, Koba W, Volek JS, Blaufox MD. Chronic effects of dietary carbohydrate variation on [18F]-2-fluoro-2-deoxyglucose uptake in rodent heart. Nucl Med Commun. 2009 Sep;30(9):675-80.

39. Frayn KN. The glucose-fatty acid cycle: a physiological perspective. Biochem Soc Trans. 2003 Dec;31(Pt 6):1115-9.

40. Armoni M, Harel C, Bar-Yoseph F, Milo S, Karnieli E.Free fatty acids repress the GLUT4 gene expression in cardiac muscle via novel response elements. J Biol Chem. 2005 Oct 14;280(41):34786-95.

41. Domenighetti AA, Danes VR, Curl CL, Favaloro JM, Proietto J, Delbridge LM. Targeted GLUT-4 deficiency in the heart induces cardiomyocyte hypertrophy and impaired contractility linked with Ca(2+) and proton flux dysregulation. J Mol Cell Cardiol. 2010 Apr;48(4):663-72.

42. Cussó L, Vaquero JJ, Bacharach S, Desco M. Comparison of methods to reduce myocardial 18F-FDG uptake in mice: calcium channel blockers versus high-fat diets. PLoS One. 2014 Sep 19;9(9):e107999.

43. Tsuchiya K, Tanaka J, Shuiqing Y, Welch CL, DePinho RA, Tabas I, Tall AR, Goldberg IJ, Accili D. FoxOs integrate pleiotropic actions of insulin in vascular endothelium to protect mice from atherosclerosis. Cell Metab. 2012 Mar 7;15(3):372-81.