Is ^{18}F-FDG PET/CT a valuable diagnostic tool for verifying accelerated atherosclerosis secondary to diabetes mellitus on insulin in the aortic segments and large arteries?

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Abstract

Objective: Fluorine-18 fluorodeoxylglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has a well-established role for detection and quantification of atherosclerotic inflammatory disease using standardized uptake value (SUV) measurements. Our aim was to compare the inflammatory and macroscopic calcification processes of atherosclerosis in the aortic segments and large arteries of subjects with insulin dependent diametes mellitus (IDDM) compared to those of age-matched controls via ^{18}F-FDG PET/CT. **Subjects and Methods:** A hundred and ten subjects who underwent ^{18}F-FDG PET/CT imaging for oncological diseases were retrospectively studied. Fifty five were diabetics on insulin and 55 were age-matched controls. Average SUVmax and SUVmean for four segments of aorta and for common iliac arteries and femoral arteries were measured and compared between subject groups. Presence or absence of macroscopic calcification on CT images for each arterial segment was also noted and compared between these groups. **Results:** Average SUVmax and SUVmean were statistically significantly greater in subjects with IDDM compared to controls in all arterial segments (P≤0.001). Presence of calcification on CT was more frequently encountered in 6 of the 8 segments in subjects with IDDM, and there was statistically significantly difference for the descending aorta and abdominal aorta. **Conclusion:** Our results show that inflammatory component of atherosclerosis was more severe in all aortic segments in subjects with IDDM compared to those of controls. Presence of macroscopic calcification also detected to be more frequently encountered in the descending thoracic and abdominal aorta in subjects with IDDM. Fluorine-18-FDG PET/CT is a valuable diagnostic tool for detecting and semi-quantifying accelerated atherosclerotic inflammatory and calcific changes secondary to diabetes mellitus treated with insulin in the aortic segments and large arteries.

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Introduction

Atherosclerosis is the leading cause of mortality worldwide. It is a cardiovascular disease marked by inflammation, plaque formation, and calcification within the arterial walls. Atherosclerosis can involve all arterial vascular beds in the body. Atherosclerotic plaques are mainly composed of lipids, calcium, and inflammatory cells including macrophages. Fluorine-18-FDG PET/CT imaging has the potential both for detection of atherosclerotic and inflammatory disease [1, 2]. The reason for ^{18}F-FDG avidity in atherosclerotic plaques is the inflammatory cells, mainly macrophages [3]. It is possible to determine the severity of the inflammatory process in the atherosclerotic plaques using SUV values.

Atherosclerotic lesions frequently become calcified. The process begins early and accelerates as the disease progresses [4]. Determination of the presence or absence of visible macroscopic arterial atherosclerotic calcification is also feasible via the CT portion of PET/CT [5].

Diabetes mellitus (DM) is a well-known risk factor for atherosclerosis [6, 7]. Diabetes mellitus exacerbates the mechanisms underlying atherosclerosis, and worsens the prognosis in the setting of acute coronary syndrome [7, 8]. Therefore, inflammatory changes and atherosclerotic calcification are expected to be accelerated in subjects with DM treated with insulin compared to normal controls. Positron emission tomography/CT could be used to evaluate both processes. There have been only a few studies investigating the ^{18}F-FDG PET uptake in relation to diabetes [9, 10] in these significantly higher ^{18}F-FDG PET uptake was found in diabetic patients as compared to nondiabetics. No data is yet available in the literature evaluating both inflammation and calcification in subjevts with DM under the insulin treatment.

Our aim was to compare the inflammatory atherosclerosis in the aorta and large arteries using SUV measurements between diabetic subjects on insulin to age-matched controls with no history of DM or other cardiovascular risk factors. In addition, we aimed to compare macroscopic calcifications noted on the CT part of the PET/CT in the aorta and large arteries of subjects for the two above mentioned groups in a series of patients who were referred for PET/CT for tumor imaging.

Subjects and Methods

This retrospective study was performed after the ethical committee approval from our institute. Clinical and imaging data of subjects who had undergone ^{18}F-FDG PET/CT imaging between October 2014 and October 2016 were reviewed. A total of 110 subjects were included. Fifty five subjects were insulin dependent diabetics (IDDM) (29 male and 26 female) who comprised the first study group. The other 55 were age-matched controls (44 male and 11 female) who had no history of DM or other known cardiovascular risk factors according to available clinical and laboratory data. The mean age and SD for subjects with IDDM was 61.5±10 years old and the mean age and SD for controls was 61.2±10 years old (P=ns) (Table 1). The first group were subjects with several different cancers referred for initial staging or restaging. The control group had subjects for solitary pulmonary nodule characterization, initial staging of lung cancer or esophageal cancer.

Table 1. *Demographics of patient population being compared*

	Diabetic Subjects on Insulin	Controls	P
Mean age±SD years	61.5±10	61.2±10	ns
Mean blood glucose at the time of injeciton (mg/dL)	142±32	97±17	P<0.005
Number of male/female	29/26	44/11	P<0.05

Exclusion crtieria in both groups were the presence of non-arterial ^{18}F-FDG uptake that interfered with arterial wall ^{18}F-FDG uptake measurement in any of the arterial segments, and the presence of extensive pathological ^{18}F-FDG uptake that overlapped with any of the arterial sites assessed in this study.

The PET/CT scans were acquired after patients had fasted for at least 4 hours and had blood glucose levels less than 200mg/dL. Image acquisition occurred 1 hour after injection of 0.37MBq/kg of ^{18}F-FDG using a General Electric Discovery 710 PET/CT scanner (GE Medical Systems, Waukesha, WI, USA). The low-dose CT image acquisition was performed without injection of iodinated contrast material, followed by PET image acquisition using 3 minutes per bed position, extending from the skull vertex to the proximal thighs.

Imaging Analysis

Image analysis was performed on a dedicated workstation (ADW 4.6, GE Medical Systems, Waukesha, WI, USA).

Averages of the maximum standardized uptake value (SUVmax) and mean standardized uptake value (SUVmean) for four segments of the aorta (ascending, arch, descending, abdominal) and for the right and left common iliac arteries and the right and left common femoral arteries were measured and compared between subject groups (Figure 1) using axial slices of PET images of ^{18}F-FDG PET/CT.

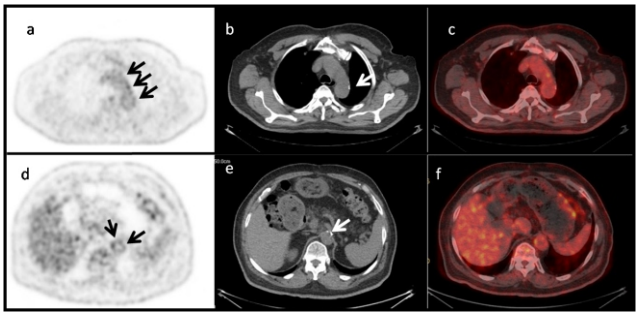

Figure 1. A 72 years old man with IDDM who underwent ^{18}F-FDG PET/CT imaging. PET images (a, d) and fusion PET/CT images (c, f) show increased ^{18}F-FDG uptake (black arrows) in walls of aortic arch and abdominal aorta due to atherosclerotic inflammation. Macroscopic atherosclerotic calcification (white arrows) in walls of aortic arch and abdominal aorta was also visually detected using axial low-dose CT images (b, e). SUVmax and SUVmean were 2.9 and 2.2 for aortic arch, and 2.6 and 2.4 for abdominal aorta, respectively.

For SUV measurements, the ^{18}F-FDG uptake in the wall of each arterial segment was first evaluated visually. Fusion PET/CT images were used to confirm that the uptake was indeed within the arterial wall (Figure 1). The areas with the highest ^{18}F-FDG uptake in any particular arterial segment on axial ^{18}F-FDG PET images were enlarged to the whole screen. A small square region of interest (ROI) was placed over each highest uptake region without extending beyond the area of uptake or arterial wall. For each segment we recorded the highest SUVmax and SUVmean among all measurements. Standarized uptake value measurements for ascending, arch, descending, abdominal aorta, right and left common iliac arteries, and right and left common femoral arterial segments were measured in both IDDM and control subject groups.

For the detection of macroscopic atherosclerotic calcification, we qualitatively reviewed the axial low-dose CT images for each of the 8 above-mentioned arterial segments in all subjects. We recorded the presence or absence of any visible calcification within each arterial segment in both IDDM and control subject groups (Figure 1).

Table 2. *^{18}F-FDG PET assessment of atherosclerotic inflammation between diabetes mellitus IDDM and control subject groups.*

Name of arterial segment and measurement type	IDDM subjects SUV (mean±SD)	Control subjects SUV (mean±SD)	P value
Ascending aorta SUVmax	2.62±0.54	2.06±0.39	<0.001
Ascending aorta SUVmean	2.23±0.44	1.78±0.35	«
Aortic arch SUVmax	2.56±0.56	1.99±0.41	«
Aortic arch SUV mean	2.18±0.46	1.69±0.34	«
Descending thoracic aorta SUVmax	2.72±0.58	2.00±0.47	«
Descending thoracic aorta SUV mean	2.33±0.49	1.74±0.44	«
Abdominal aorta SUVmax	2.89±0.64	2.25±0.52	«
Abdominal aorta SUVmean	2.39±0.59	1.90±0.43	«
Right iliac artery SUVmax	2.34±0.51	1.91±0.44	«
Right iliac artery SUVmean	2.06±0.52	1.69±0.39	«
Left iliac artery SUVmax	2.21±0.48	1.82±0.42	«
Left Iliac artery SUVmean	1.95±0.42	1.61±0.37	«
Right femoral artery SUVmax	2.12±0.51	1.74±0.38	«
Right femoral artery SUVmean	1.80±0.45	1.51±0.32	«
Left femoral artery SUVmax	2.04±0.51	1.69±0.42	«
Left femoral artery SUVmean	1.75±0.46	1.42±0.32	«
All segments SUV max	2,43±0,31	1,92±0,18	«
All segments SUV mean	2,01±0,24	1,67±0,15	«

We then compared the average SUVmax and SUVmean for each of the 8 arterial segments and across all arterial segments between IDDM and control subject groups. We also compared the presence or absence of calcification for each of the 8 arterial segments and across all arterial segments between IDDM and control subject groups.

Statistical Analysis

Normality of the distribution of the data was assessed with the Kolmogrov-Smirnov test. Bivariate comparisons were performed using the Mann-Whitney U test for continuous variables, and the chi-square test was used for categorical variables. Statistical analyses were performed using SPSS 21.0 (Windows, Chicago, IL, USA). Data are presented as mean and standard deviation for continuous variables (Table 2) and as numbers and percentages for categorical variables (Table 3).

Results

Average SUVmax and SUVmean measurements were statistically significantly higher in all arterial segments in subjects with IDDM compared to age-matched controls (P≤0.001). The average SUVmax and SUVmean measurements of the four segments of the aorta (ascending, arch, descending, abdominal) and of the common iliac arteries and common femoral arteries are given in Table 1 for both groups. The highest average SUVmax and SUVmean measurements were noted in the abdominal aorta and descending thoracic aorta in both groups.

Macroscopic atherosclerotic calcification was more frequently present in arterial segments of subjects with IDDM compared to age-matched controls in the aortic arch, descending thoracic aorta, abdominal aorta, right iliac artery,

left iliac artery, and right femoral artery. However, the difference in frequency of presence of calcification between two groups was statistically significant only for the abdominal aorta and descending thoracic aorta. The data regarding the frequency of macroscopic calcification for each arterial segment and across all arterial segments in the two study groups are shown in Table 2.

Table 3. *Low-dose CT assessment of macroscopic atherosclerotic calcification between IDDM and control subject groups.*

Name of arterial segment	IDDM subjects N *(%)	Control subjects N* (%)	P value
Ascending aorta	3(5.5)	3(5.5)	1.000
Aortic arch	30(54.5)	21(38.2)	0.085
Descending thoracic aorta	27(49.1)	14(25.5)	0.010**
Abdominal aorta	49(89.1)	35(63.6)	0.002**
Right iliac artery	43(78.2)	34(61.8)	0.061
Left iliac artery	40(72.7)	31(56.4)	0.073
Right femoral artery	22(40.0)	21(38.2)	0.845
Left femoral artery	18(43.9)	23(56.1)	0.324
Mean±SD of all arterial segments	4.22±2.27	3.31±2.72	0.060

N=numberofsubjectswithcalcificationinthearterialsegmentofinterest,*

***Statisticallysignificant*

Discussion

Fluorine-18-FDG PET/CT a powerful imaging technique for imaging atherosclerosis. Several investigators have studied the feasibility of 18F-FDG PET/CT imaging for detecting and quantifying arterial atherosclerotic lesions in humans. These studies have shown that ^{18}F-FDG PET/CT provides accurate and reproducible measurement of the inflammatory activity of atherosclerotic plaques in large and medium-sized arteries [5, 11-17].

In the current study, we showed evidence of the accelerated atherosclerotic process in subjects with IDDM relative to that in control subjects. In particular, we observed that the average SUV measurements were significantly higher in subjects with IDDM in all arterial segments (P<0.001), which may suggest that the inflammatory component of atherosclerosis measured on ^{18}F-FDG PET/CT is more severe in subjects with IDDM than in controls.

Our findings partially match the observations of a study performed by Pasha AK et al. (2015) [18]. In that study of 76 patients, they compared the SUV measurements from ^{18}F-FDG-PET in the aorta, iliac arteries, and femoral arteries in subjects with at least one risk factor for atherosclerosis to those of normal controls with no risk factors. They observed that average SUVmean measurements were significantly hig-her in the abdominal aorta in subjects with at least one risk factor. In our study, we observed that SUV measurements were higher for all arterial segments including the abdominal aorta. A prior study reported a direct relationship between ^{18}F-FDG uptake and increased cardiovascular risk factors [19]. Another study also reported high levels of ^{18}F-FDG signal in patients with diabetes mellitus [9]. These evaluted only the inflammatory component of atherosclerosis, not macroscopic calcification.

Calcification is also a component of atherosclerotic process, where macroscopic calcification is typically seen later on in the process. Macroscopic atherosclerotic calcification on low-dose CT was more frequently encountered in the aortic arch, descending thoracic aorta, abdominal aorta, iliac arteries, and right femoral artery of subjects with IDDM compared to controls, although with statistical significance only for the abdominal aorta (P=0.002) and descending thoracic aorta (P=0.01). The average SUVmax and SUVmean measurements were the highest in these two arterial segments compared to other segments in both groups, indicating that these were the locations where the most severe atherosclerotic inflammation was taking place. This could be the explanation why the macroscopic calcification was frequent compared to normals in these two segments. The severe the infmammation; there were more areas of macroscopic calcification.

As seen in Figure 1 the visualized macroscopic calcification did not co localize with the visually appreciable areas of ^{18}F-FDG uptake, this is because vascular calcification and vascular metabolic activity rarely overlap, indicating these findings represent different stages in the evolution of atheroma as reported previously [20].

Previous research has shown that the volume of calcification increases in the walls of large arteries with increasing age [21, 22]. In the current study, we only performed a qualitative visual analysis to compare the frequency of calcification between our study groups. Since the subjects in our study were oncological patients we used the standard oncological imaging protocols. We did not perform studies using i,v, contrast, therefore presence of calcium could have been under identified. Also we could not use a calcium scoring programme or calcium volume for better quantification, as calcium scoring programme is not available in the software

of our PET/CT work station. This is a limitation pf our study.

Assessment of the calcification volumes may be a better parameter for quantifying accelerated atherosclerosis due to IDDM or other atherosclerotic risk factors, and may be able show differences in macroscopic atherosclerotic calcification in other arterial segmetns as well.

Another method that is useful to assess atherosclerotic calcification at the molecular level is sodium ^{18}F-fluoride (Na-^{18}F) PET/CT imaging. In a recent study by Bloomberg et al. (2017), the relationship between cardiovascular disease risk and arterial inflammation via ^{18}F-FDG PET/CT imaging, arterial molecular calcification via Na-^{18}F PET/CT imaging, and arterial macroscopic calcification via CT imaging of the thoracic aorta in a population at low cardiovascular risk was assessed [23]. The investigators concluded that thoracic aorta molecular calcification via NaF PET/CT, but not inflammation, is associated with increased cardiovascular disease risk. Future larger scale study of the potential role of Na-^{18}F PET/CT imaging in the setting of DM or other atherosclerotic risk factors may be of interest [22].

Aging is a well-known risk factor for atherosclerosis. Several studies have shown that inflammatory atherosclerotic activity in the large arteries increases with increasing age [5, 13, 21, 22]. Age could be a confounding factor, and therefore we made sure that our two subject groups were age-matched.

We did not perform a gender and race match in these groups, in one of our prior studies we had observed that there was no significant difference in the inflammatory component of arterial atherosclerosis between genders [24]. Also all subjects were the same race/ethnicity.

Different methods have been proposed to quantify ^{18}F-FDG uptake in atherosclerosis: vessel wall-to-blood ratio, whole vessel-to-blood ratio, differential uptake ratio, blood pool ratio, and SUV [25], which is the decay-corrected tissue concentration of ^{18}F-FDG (in kBq/g), corrected for injected ^{18}F-FDG dose and lean body mass is a widely accepted method. Derlin et al. (2012) [26] recently reported that additional correction by division with blood pool SUV might lead to an over-correction, and concluded that there is no reason to prefer this approach over SUVmax for the semi-quantification of radiotracer uptake [25, 26]. We measured both SUVmax and SUVmean, and observed a statistically significant difference for all arterial segments.

The blood glucose levels for the two groups were different and significantly higher in subjects with IDDM. We did not perform a correction for glucose as there is conflicting data for the usefulness of correcting for blood glucose: some studies have found a benefit in normalizing SUV by blood glucose [27-29], others have found no benefit [30-32]. A high patient serum glucose level before imaging can substantially decrease any SUV measurements. If we had performed this correction the corrected SUV for IDDM subjects would have been much more higher than the controls. The difference would have been more significant.

Studies in humans with atherosclerosis have demonstrated that the degree of vascular ^{18}F-FDG uptake relates to cardiovascular risk factors [33, 34]. One limitation of the study is the potential presence of other risk factors/behavior other than IDDM in both study groups. We did not exclude them from the first group, as these may also be accelerating factors of inflammation in atherosclerosis. In the control group, we eliminated the ones with known risk factors using clinical data, but this was a retrospective data, and some of these subjects had very limited clinical data and follow-up.

One other limitation is the potential presence of inflammation associated with the underlying malignancy itself in both groups, or inflammation caused by cancer treatment in subjects with IDDM could have contributed to the arterial inflammation, and therefore our findings may not be solely attributed to the presence of IDDM.

The detection of sub clinical atherosclerosis by imaging can help to refine risk estimates [35, 36], especially by using SUV measurements. Comparison of different risk factors to normal controls, in prospective controlled trials, with no history of underlying malignancy and detecting the factor causing the highest SUV measurements may indicate which risk factor plays the most important role in the disease process. Thus, the clinician can plan a more effective treatment strategy.

In conclusion, ^{18}F-FDG PET/CT can detect accelerated atherosclerotic inflammatory changes and macroscopic atherosclerotic calcification likely secondary to diabetes mellitus in the aortic segments and large arteries. Thus, it may play future role for the assessment of the impact of different atherosclerotic risk factors on arterial inflammation.

The authors of this study declare no conflicts of interest

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