FDG PET/CT for evaluating systemic arterial inflammation induced by anthracycline-based chemotherapy of Hodgkin lymphoma
A retrospective cohort study

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Abstract

To evaluate arterial fluorodeoxyglucose (FDG) uptake as a marker of arterial inflammation in multiple vascular beds in patients treated with anthracycline-based chemotherapy for Hodgkin lymphoma (HL).

We used maximum standardized uptake value (SUVmax) and target-to-background ratio (TBR) to quantify arterial FDG uptake in the carotid artery, ascending aorta, abdominal aorta, and femoral artery obtained on positron emission tomography/computed tomography (PET/CT) imaging performed at baseline before chemotherapy and after completion of chemotherapy in patients with HL treated with an anthracycline-containing regimen. We compared the SUVmax and TBR obtained at baseline with that obtained post-chemotherapy for each arterial bed to evaluate the effect of anthracycline-based chemotherapy. We evaluated the effect of cardiovascular risk factors such as human immunodeficiency virus (HIV) infection, smoking, hypertension, and diabetes on the changes in SUVmax and TBR seen in the different arterial beds after anthracycline-based chemotherapy.

Fifty-two patients were included with a mean age of 34.56 ± 10.19 years. There were 33 males, and 18 patients were HIV-infected. The mean interval between completion of chemotherapy and follow-up flourine-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) scan was 65 weeks. We found no significant difference in arterial FDG uptake measured by SUVmax and TBR in all arterial beds between the pre- and post-chemotherapy FDG PET/CT. There was no significant impact of HIV infection, smoking, and hypertension on the changes in arterial FDG uptake following treatment with anthracycline-based chemotherapy.

In patients with HL who were treated with anthracycline-based chemotherapy, we found no significant increase in arterial inflammation measured by FDG PET/CT after an average follow-up period of about 65 weeks since completion of chemotherapy.

Abbreviations: ABVD = adriamycin, bleomycin, vinblastine, dacarbazine, ASCVD = atherosclerotic cardiovascular disease, BMI = body mass index, FDG PET/CT = flourine-18 fluorodeoxyglucose positron emission tomography/computed tomography, HIV = human immunodeficiency virus, HL = Hodgkin lymphoma, SUVmax = maximum standardized uptake value, TBR = target-to-background ratio.

Keywords: arterial inflammation, anthracyclines, FDG PET/CT, Hodgkin lymphoma

1. Introduction

Hodgkin lymphoma (HL) is a malignant disease with an excellent response to therapy. Ten-year overall survival is reported in over 80% of patients treated for HL.[1,2] Over 90% of patients treated for HL in their childhood or adolescence survive into adulthood.[3] Anthracyclines are a group of anti-cancer chemotherapeutic agents that form the backbone of HL treatment. Avoiding them in HL treatment leads to less favorable treatment outcome.[4] Despite their efficacy, anthracyclines increase

cardiovascular mortality and morbidity of patients in the long run. One of the pathogenic mechanisms by which anthracyclines predispose to atherosclerotic cardiovascular disease (ASCVD) is by causing impairment in the repair of endothelial injury. Anthracycline agents cause an increase in the circulating level of functionally incapacitated endothelial progenitor cells,[5] which are responsible for the repair of endothelial injury through the process of re-endothelization after injury.[6] Unrepaired endothelial injury is the bedrock lesion for the formation of vascular atheroma formation.

Long-term survival of patients treated for HL and the negative impact of anthracycline on vascular endothelial function, therefore, expose these patients to significant cardiovascular morbidity and mortality. A recent study with an extended follow-up of 40 years post HL treatment reported a 4- to 7-fold increased risk of coronary artery disease among HL survivors compared with the general population, which translates to 857 excess cardiovascular events per 10,000 person-years.[7]

Inflammation is the hallmark process that drives vascular atheroma formation, progression, and its catastrophic completion.[8] The prominent role played by inflammation in ASCVD has formed the basis for the keen interest in the use of anti-inflammatory agents as a primary and secondary preventive therapeutic intervention in many recent randomized trials.[9,10] Florine-18 fluorodeoxyglucose (FDG) is a radioactive analog of glucose which is trapped by cancer cells and activated inflammatory cells. Photons emitted when FDG undergoes radioactive decay can be imaged using hybrid positron emission tomography and computed tomography (PET/CT) scanner. Flourine-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) has, therefore, emerged in the last 2 decades as a sensitive tool for non-invasive imaging of biological processes, including inflammation, infection, and neoplasm. The intensity of FDG uptake in the vessel has been shown to correlate with the level of vascular macrophage invasion.[11,12] Abdelbaky et al showed, in a longitudinal FDG PET/CT study, that arterial inflammation precedes subsequent calcification in the same location as a marker of plaque progression.[13] The level of inflammation in the vessel in general or in an atherosclerotic lesion in specific correlates with the risk of cardiovascular events in a patient.[14–16] FDG PET/CT is the most accurate imaging modality for the staging and re-staging of HL and is the most commonly used imaging modality for these indications in routine clinical practice.[17,18] FDG PET/CT can, therefore, serve the dual role for evaluating HL and vascular inflammation as a risk for ASCVD in patients treated with anthracycline-based chemotherapy. To our knowledge, no published study has evaluated the clinical utility of FDG PET/CT in characterizing arterial inflammation in the patients treated with anthracycline-based chemotherapy for HL. In this study, we aimed to evaluate arterial FDG uptake as a marker of arterial inflammation in multiple vascular beds of patients treated with anthracycline-based chemotherapy for HL. We hypothesized that arterial FDG uptake would be higher on post-chemotherapy FDG PET/CT compared with pre-therapy FDG PET/CT.

2. Materials and methods

2.1. Patients

We performed a retrospective review of FDG PET/CT scans of patients referred to the Department of Nuclear Medicine at Steve Biko Academic Hospital, Pretoria, between August 2015 and September 2019 for baseline staging and post-chemotherapy assessment of HL. We included patients who were aged 18 years and older and were treated with a standard course of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD). We excluded patients in whom arterial FDG uptake could not be quantified without interference from adjacent lymphoma. Other exclusion criteria were renal failure (estimated glomerular filtration rate of $<60\,mL/min/m^2$), treatment with chemotherapy regime other than ABVD, additional radiotherapy, technically inadequate scans, ongoing use of steroid or other anti-inflammatory medications, and suspected or confirmed vasculitis. We reviewed the patients' hospital records to obtain their demographic information, the associated co-morbidities, and social history. Patients were defined as smokers if they smoke at least a stick of cigarette per day. Patients were classified as hypertensive or diabetic if they self-identify as such based on previous hospital diagnosis or they are on treatment for these chronic medical conditions. Our institutional review board approved the study and waived the need for patients' consent due to the retrospective design of this study.

2.2. FDG PET/CT scan imaging

FDG PET/CT scan imaging was performed as previously described and according to published guidelines.[19,20] Briefly, all patients had a minimum of 4 hours of fasting. The blood sugar level was less than 11.1 mmol/L in all patients at the time of FDG injection. The activity of FDG administered was adjusted for patient weight. Imaging commenced 60 minutes after the intravenous administration of FDG. Imaging was acquired on a Biograph 40 Truepoint hybrid PET/CT scanner (Siemens Medical Solution, Illinois). Imaging was acquired from vertex to mid-thigh. PET imaging was acquired in 3D mode at 3 minutes per bed position with a 50% overlap. We performed image reconstruction using the ordered subset expectation maximization algorithm (4 iterations and 8 subsets) with a Gaussian filter applied at full-width half-maximum of 5.0 mm.

2.3. Image analysis

We performed image analysis on a dedicated workstation equipped with a Syngo.via software. We used the maximum standardized uptake value (SUVmax) and the target-to-background ratio (TBR) as the parameters for arterial FDG uptake quantification following the recommendation of the Cardiovascular Committee of the European Association of Nuclear Medicine (EANM).[21] To evaluate systemic arterial inflammation using vascular FDG uptake, we selected the distal common carotid artery, the ascending aorta, the infra-renal abdominal aorta, and the proximal femoral artery as the representative arterial beds on both the baseline and post-chemotherapy FDG PET/CT scans. We determined SUVmax and TBR at these arterial beds. For SUVmax, we drew multiple regions of interest (ROI) around the arterial bed of interest and obtained the mean of the SUVmax measurements obtained from each ROI. For TBR (target-to-background ratio), the target represents the mean SUVmax obtained in the arterial bed of interest, while background represents the mean of SUVmean obtained from multiple ROI drawn in the lumen of the vein adjacent to the arterial bed of interest. For the common carotid artery, venous SUVmean was obtained from the adjacent internal jugular vein,

superior vena cava for the ascending aorta, the inferior vena cava for the abdominal aorta, and the femoral vein for the femoral artery. TBR was obtained by dividing the mean arterial SUVmax by the mean venous SUVmean. In patients who had multiple FDG PET/CT scans after completion of chemotherapy, the analysis was done on the latest scan to obtain the maximum interval between completion of chemotherapy and follow-up FDG PET/CT.

2.4. Statistical analysis

We expressed continuous variables as mean ± standard deviation (SD). We expressed categorical data as proportions (percentages). We used the paired samples T test to compare SUVmax and TBR obtained at the 4 arterial beds of interest between the pre-chemotherapy and post-chemotherapy FDG PET/CT scans. We also compared the patients' parameters such as fasting blood sugar, the activity of FDG administered for PET/CT scan, patients' weight, and patients' body mass index between the pre- and post-chemotherapy FDG PET/CT scans. We performed sub-group analysis in patients with human immunodeficiency virus (HIV) infection by comparing pre- and post-chemotherapy variables using independent samples T test. We evaluated the impact of specific cardiovascular risk factors, including smoking, hypertension, and diabetes mellitus, on the changes in arterial FDG uptake in response to chemotherapy. All statistical analyses were two-tailed, and P-value <.05 was considered statistically significant. We performed statistical analyses using the IBM SPSS Statistics 21.0 (IBM Corp, Armonk, New York).

3. Results

A total of 52 patients were included with a mean age of 34.56 ± 10.19 years. There were 33 males, and 18 patients were HIV-infected. The mean duration between the pre- and post-chemotherapy FDG PET/CT scan was 24.06 months, while the average interval between completion of chemotherapy and follow-up FDG PET/CT was 65 weeks. Table 1 shows the baseline clinical and demographic characteristics of the patients included.

Patients' weight and, consequently, their body mass index (BMI) were significantly higher at the time of post-chemotherapy FDG PET/CT compared with pre-chemotherapy FDG PET/CT. Fasting blood sugar at the time of FDG administration was similar between pre- and post-chemotherapy FDG PET/CT scans. Similarly, the activity of FDG administered for both pre- and post-chemotherapy scans was comparable. We found no significant difference in the SUVmax and TBR measured in the carotid artery, ascending aorta, abdominal aorta, and femoral artery between the pre- and post-chemotherapy FDG PET/CT scans. Table 2 shows a detailed comparison between pre- and post-chemotherapy FDG PET/CT scans.

We compared HIV-infected patients, and those without regarding changes in baseline characteristics and PET-derived variables. There was no significant difference in the weight and BMI of HIV-infected patients and those who were not. Similarly, there was no significant difference in the activity of FDG administered for PET/CT scan and the blood sugar levels at the time of FDG administration between HIV-infected patients versus HIV-uninfected patients. Table 3 shows comparative data between HIV-infected and HIV-uninfected patients regarding changes in patients' and PET-derived variables between pre- and post-chemotherapy variables.

Table 1

Baseline clinical and demographic characteristics of the patients.

Variable	Frequency	Percent (%)
Age (yr)		
Mean ± SD		34.56 ± 10.19
Range		18–60
Gender		
Male	33	63.5
Female	19	36.5
HIV		
Yes	18	34.6
No	34	65.4
Smoking		
Yes	15	28.8
No	37	71.2
HTN		
Yes	3	5.8
No	49	94.2
DM		
Yes	2	3.8
No	50	96.2
Weight (kg)		
Mean ± SD		70.62 ± 17.90
BMI (kg/m²)		
Mean ± SD		25.23 ± 5.98
CD4 (cells/μL)		
Mean ± SD		282.44 ± 131.94
Interval between the 2 PET scans (mo)		
Mean ± SD		24.06 ± 21.53
Interval between completion of chemotherapy and post-chemo-PET scan (wk)		
Mean ± SD		64.67 ± 88.41

BMI: body mass index; CD4: cluster of differentiation 4; DM: diabetes mellitus; HIV: human immunodeficiency virus; HTN: systemic hypertension; PET: positron emission tomography.

Table 2

Comparison of parameters obtained at pre-chemotherapy and post-chemotherapy FDG PET/CT scans.

Variable	Pre-chemo Mean ± SD	Post-chemo Mean ± SD	t	P
Weight (kg)	70.62 ± 17.90	74.51 ± 14.38	−3.092	.003[*]
BMI (kg/m²)	25.23 ± 5.98	26.73 ± 5.25	−3.230	.002[*]
FBS (mmol/L)	5.94 ± 1.66	5.54 ± 1.20	1.461	.150
Administered FDG (mCi)	8.78 ± 2.32	9.05 ± 2.15	−1.281	.206
Ascending aorta				
SUVmax	2.67 ± 0.75	2.66 ± 0.65	0.144	.886
TBR	1.77 ± 0.38	1.83 ± 0.48	−0.765	.448
Carotid artery				
SUVmax	2.02 ± 0.59	2.01 ± 0.53	0.039	.969
TBR	1.44 ± 0.35	1.45 ± 0.41	−0.076	.940
Abdominal aorta				
SUVmax	2.63 ± 0.81	2.47 ± 0.61	1.363	.179
TBR	1.81 ± 0.46	1.69 ± 0.35	1.410	.164
Femoral artery				
SUVmax	1.48 ± 0.49	1.50 ± 0.47	−0.314	.755
TBR	1.28 ± 0.31	1.38 ± 0.36	−1.390	.171

BMI: body mass index; FBS: fasting blood sugar; FDG: fluorodeoxyglucose; FDG PET/CT: flourine-18 fluorodeoxyglucose positron emission tomography/computed tomography; SUVmax: maximum standardized uptake value; t: paired samples T test; TBR: target-to-background ratio.
[*] $P < .05$.

Table 3

Comparison of the change in parameters between the 2 FDG PET/CT scans according to patients' HIV serostatus.

	HIV			
	Mean ± SD	Mean ± SD		
Change in parameters	Yes (n=18)	No (n=34)	t	P
Weight (kg)	2.77 ± 5.92	4.49 ± 10.41	−0.648	.520
BMI (kg/m²)	1.03 ± 2.10	1.75 ± 3.86	−0.738	.464
FBS (mmol/L)	0.05 ± 1.2	−0.63 ± 2.21	1.203	.235
Administered FDG (mCi)	−0.26 ± 1.37	0.55 ± 1.55	−1.875	.067
Ascending aorta				
SUVmax	0.02 ± 0.81	−0.04 ± 0.94	0.208	.836
TBR	0.07 ± 0.42	0.05 ± 0.61	0.085	.933
Carotid artery				
SUVmax	−0.13 ± 0.59	0.06 ± 0.92	−0.803	.426
TBR	0.01 ± 0.46	0.00 ± 0.57	0.087	.931
Abdominal aorta				
SUVmax	−0.18 ± 1.08	−0.15 ± 0.72	−0.122	.904
TBR	−0.06 ± 0.66	−0.16 ± 0.62	0.519	.606
Femoral artery				
SUVmax	−0.10 ± 0.36	0.09 ± 0.63	−1.166	.249
TBR	−0.05 ± 0.45	0.18 ± 0.53	−1.548	.128

BMI: body mass index; FBS: fasting blood sugar; FDG: fluorodeoxyglucose; FDG PET/CT: flourine-18 fluorodeoxyglucose positron emission tomography/computed tomography; HIV: human immunodeficiency virus; SUVmax: maximum standardized uptake value; t: independent samples T test; TBR: target-to-background ratio.

We evaluated the effects of the presence of certain ASCVD risk factors on the differences in FDG PET-derived variables between the 2 scans. We found no significant difference between patients who were smokers versus those who were not (Table 4). Regarding systemic hypertension, we did not find any significant difference between hypertensive and normotensive patients (Table 5). Among patients who were diabetic, there was a mean decline in patients' weight of 10.10 kg between pre- and post-chemotherapy FDG PET/CT scan while weight increased by a mean of 4.46 kg among non-diabetic patients (P=.025). Consequently, there was a significant difference in weight and BMI between patients grouped based on a history of diabetes mellitus between the 2 FDG PET/CT scans. We found no significant difference in the activity of FDG administered and the blood sugar level between patients who were diabetic and those who were not (Table 6). Among the changes in PET-derived variables between the pre- and post-therapy FDG PET/CT, patients who were diabetic, had a decline in SUVmax measured at the ascending aorta while non-diabetic patients had an increase in the same parameter (P=.035). In the femoral artery, diabetic patients had a significant rise in TBR compared with non-diabetic patients, P=.002 (Table 6). The rest of the quantitative parameters were not significantly different between diabetics and non-diabetics.

In order to determine the trends in arterial FDG uptake after anthracycline-based chemotherapy, we grouped patients accord-

Table 4

Comparison between patients grouped according to smoking history.

	Smoking			
	Yes	No		
Change in parameters	Mean ± SD	Mean ± SD	t	P
Weight (kg)	2.97 ± 12.93	4.27 ± 7.17	−0.462	.646
BMI (kg/m²)	1.21 ± 4.65	1.62 ± 2.73	−0.398	.692
FBS (mmol/L)	−0.51 ± 2.28	−0.35 ± 1.83	−0.263	.794
Administered FDG (mCi)	0.33 ± 1.93	0.25 ± 1.36	0.185	.854
Ascending aorta				
SUVmax	0.08 ± 0.79	−0.06 ± 0.94	0.482	.632
TBR	0.08 ± 0.79	−0.06 ± 0.94	0.180	.858
Carotid artery				
SUVmax	−0.19 ± 0.81	0.07 ± 0.82	−1.065	.292
TBR	−0.21 ± 0.57	0.09 ± 0.49	−1.951	.057
Abdominal aorta				
SUVmax	−0.10 ± 0.88	−0.18 ± 0.85	0.302	.764
TBR	−0.22 ± 0.62	−0.08 ± 0.63	−0.684	.497
Femoral artery				
SUVmax	0.13 ± 0.49	−0.02 ± 0.58	0.850	.399
TBR	0.16 ± 0.72	0.07 ± 0.40	0.534	.596

BMI: body mass index; FBS: fasting blood sugar; FDG: fluorodeoxyglucose; SUVmax: maximum standardized uptake value; t: independent samples T test; TBR: target-to-background ratio.

Table 5

Comparison between patients grouped according to the history of systemic hypertension.

| | Hypertension | | | |
| | Yes | No | | |
Change in parameters	Mean ± SD	Mean ± SD	t	P
Weight (kg)	4.33 ± 9.95	3.87 ± 9.14	0.085	.932
BMI (kg/m^2)	1.71 ± 3.74	1.49 ± 3.37	0.108	.915
FBS (mmol/L)	1.30 ± 2.08	−0.50 ± 1.91	1.576	.121
Administered FDG (mCi)	1.27 ± 1.27	0.21 ± 1.53	1.168	.248
Ascending aorta				
SUVmax	0.51 ± 1.15	−0.05 ± 0.88	1.049	.299
TBR	−0.45 ± 0.31	0.09 ± 0.55	−1.680	.099
Carotid artery				
SUVmax	0.55 ± 1.41	−0.04 ± 0.78	1.210	.232
TBR	0.09 ± 0.23	0.00 ± 0.54	0.281	.780
Abdominal aorta				
SUVmax	0.51 ± 1.13	−0.20 ± 0.83	1.411	.164
TBR	−0.01 ± 0.15	−0.13 ± 0.64	0.327	.745
Femoral artery				
SUVmax	0.40 ± 0.85	0.00 ± 0.53	1.219	.288
TBR	0.13 ± 0.07	0/.10 ± 0.52	0.112	.911

BMI: body mass index; FBS: fasting blood sugar; FDG: fluorodeoxyglucose; SUVmax: maximum standardized uptake value; t: independent samples T test; TBR: target-to-background ratio.

ing to the interval between completion of chemotherapy and the time of follow-up FDG PET/CT (at increments of 4 weeks). We plotted SUVmax and TBR obtained on pre- and post-chemotherapy for each arterial bed. At most time points, SUVmax and TBR were lower on the post-chemotherapy FDG PET/CT compared with the pre-chemotherapy scan. In patients who had their post-chemotherapy FDG PET/CT at 24 weeks or more after completion of chemotherapy, SUVmax, and TBR obtained at this follow-up scan were similar or higher than baseline pre-chemotherapy SUVmax and TBR. Figures 1 and 2 show the trends over time of SUVmax and TBR in patients grouped according to the interval between completion of chemotherapy and the follow-up FDG PET/CT scan. Figure 3 shows how TBR and SUVmax were computed.

4. Discussion

We evaluated systemic arterial inflammation in patients treated with anthracycline-based chemotherapy for HL and found no significant difference in the pre- and post-chemotherapy arterial FDG uptake. We selected 4 arterial beds; carotid artery in the neck, ascending aorta in the chest, infra-renal abdominal aorta in the abdomen, and the proximal femoral artery in the proximal lower limbs; for a holistic evaluation of the effect of anthracycline-based chemotherapy on the systemic arterial vascular wall. Several observational studies have reported a higher incidence of cardiac morbidity and mortality contributed by ASCVD in patients treated with anthracycline-based chemotherapy for HL.[7,22,23] Invasion of the arterial wall by inflammatory cells is one of the earliest events in the formation

Table 6

Comparison between patients grouped according to the history of diabetes mellitus.

| | Diabetes mellitus | | | |
| | Yes | No | | |
Change in parameters	Mean ± SD	Mean ± SD	t	P
Weight (kg)	−10.10 ± 2.69	4.46 ± 8.79	−2.315	.025[*]
BMI (kg/m^2)	−3.39 ± 0.93	1.69 ± 3.27	−2.183	.034[*]
FBS (mmol/L)	−0.10 ± 3.68	−0.41 ± 1.91	0.216	.830
Administered FDG (mCi)	−0.95 ± 0.21	0.32 ± 1.54	−1.158	.252
Ascending aorta				
SUVmax	−1.32 ± 0.99	0.03 ± 0.86	−2.170	.035[*]
TBR	0.68 ± 1.02	0.03 ± 0.53	1.660	.103
Carotid artery				
SUVmax	−0.21 ± 0.04	0.00 ± 0.84	−0.349	.728
TBR	−0.11 ± 1.72	0.01 ± 0.48	−0.298	.767
Abdominal aorta				
SUVmax	−0.97 ± 0.79	−0.13 ± 0.85	−1.372	.176
TBR	0.09 ± 0.47	−0.13 ± 0.63	0.474	.637
Femoral artery				
SUVmax	0.48 ± 0.86	0.01 ± 0.54	1.181	.243
TBR	1.16 ± 1.07	0.06 ± 0.44	3.294	.002[*]

BMI: body mass index; FBS: fasting blood sugar; FDG: fluorodeoxyglucose; SUVmax: maximum standardized uptake value; t: independent samples T test; TBR: target-to-background ratio.
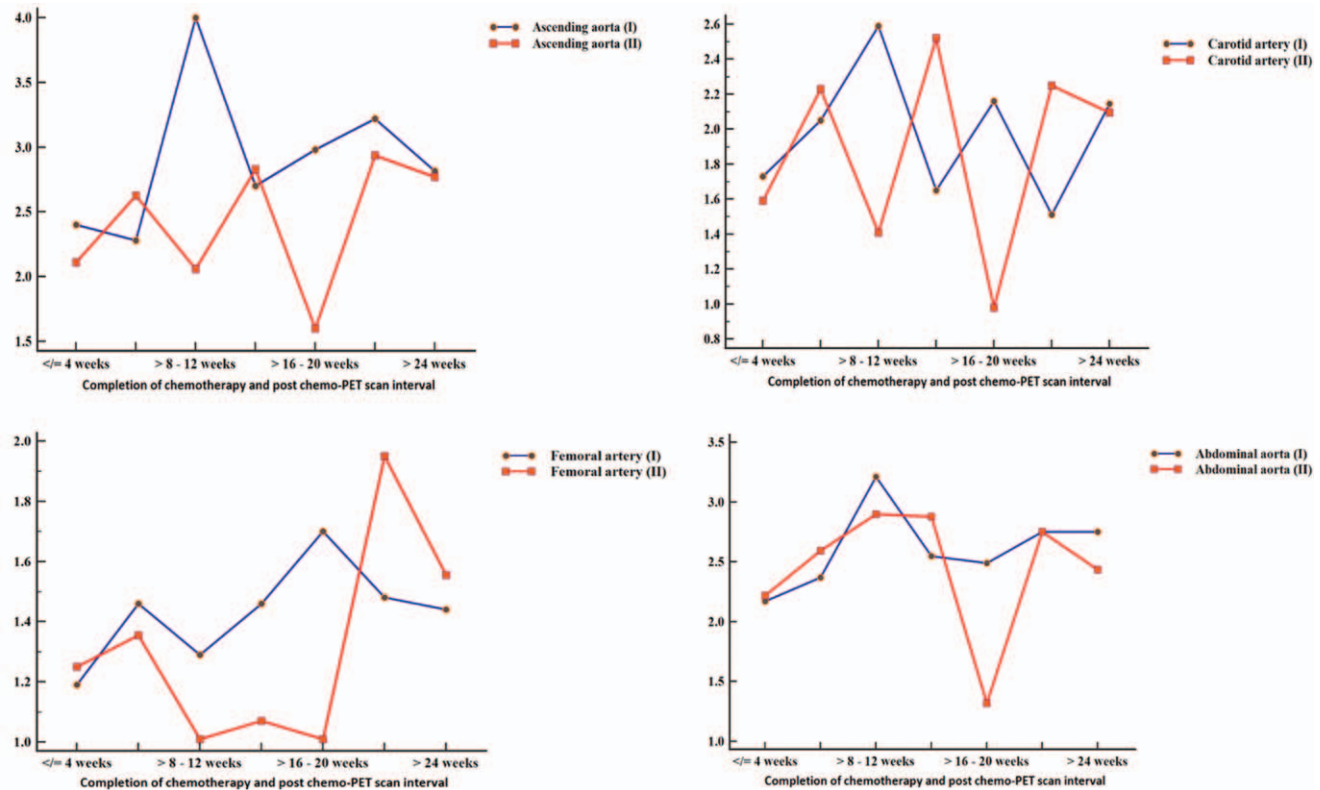[*] P < .05.

Figure 1. Time trend in SUVmax in patients grouped according to the interval between completion of chemotherapy and the time of follow-up FDG PET/CT. The blue curve represents the SUVmax obtained on the pre-chemotherapy FDG PET/CT, while the red curve represents SUVmax obtained in different groups at post-chemotherapy FDG PET/CT. At more than half of the time-points in the 4 arterial beds, SUVmax was lower for the post-therapy FDG PET/CT compared with pre-chemotherapy FDG PET/CT scan. In the group in whom post-chemotherapy FDG PET/CT was obtained more than 24 wk after completion of chemotherapy, SUVmax in the arterials from the post-chemotherapy FDG PET/CT equaled (ascending aorta and carotid artery) or surpassed (femoral artery) that of the pre-chemotherapy FDG PET/CT.

of vascular atheroma, which makes arterial inflammation an early process in ASCVD. Arterial FDG accumulation is a commonly used technique to measure arterial inflammation in cardiovascular risk assessment.[15,24] An increase in arterial FDG accumulation over time is associated with the progression of ASCVD.[25]

In our study, we could not demonstrate an increase in arterial FDG uptake as a marker of arterial inflammation. Many factors could account for this negative result. ASCVD complicating anthracycline treatment occurs after a long latent period. The mean interval between the completion of chemotherapy and follow-up FDG PET/CT in our study was 65 weeks. It may be possible that a more extended follow-up period is necessary for the development of a significant arterial inflammation that will be detectable by FDG PET imaging. Another putative reason for our results may be due to the cytokine-induced by HL itself, causing an accentuated arterial FDG uptake on the baseline pre-chemotherapy FDG PET/CT scan. This may explain why arterial FDG uptake was lower post-chemotherapy compared with pre-chemotherapy in some patients who were imaged earlier than 24 weeks after completion of chemotherapy (Figs. 1 and 2). A recent study found similar levels of circulating dysfunctional endothelial progenitor cells in treatment-naïve HL patients and at 2 years during remission induced by anthracycline-based chemotherapy.[5] Endothelial progenitor cells are responsible for the repair of endothelial damage induced by factors such as diabetes and smoking that predispose to vascular atheroma formation. This suggests that both HL and its treatment with an anthracycline-containing chemotherapy regime increase the risk ASCVD. The primary pathogenic mechanism by which HL and its treatment predispose to ASCVD has been reported to be through impairment in the re-endothelization of damaged vascular endothelium due to dysfunctional endothelial progenitor cells. This pathogenic mechanism will suggest that a long interval is required after HL and its treatment for sufficient endothelial damage to occur in order to have significant arterial inflammation that may progress to ASCVD.

Other arterial structural changes occurring soon after anthracycline-based chemotherapy have been reported to contribute anthracycline-induced endothelial dysfunction. Aortic stiffness has been reported within 4 months of treatment with anthracycline-based chemotherapy in a group of oncologic patients.[26] Similar early aortic stiffening (within 6 months of treatment) was confirmed in another study of oncologic patients treated with low dose of anthracycline.[27] Apart from aortic stiffness, flow-mediated dilatation and nitrate-mediated dilatation are 2 sonographic techniques to measure endothelial dysfunction. In a study by Jenei et al, long-term survivors of childhood cancer treated with anthracycline-based chemotherapy experienced marked preclinical vasculopathy characterized by endothelial dysfunction (evaluated by flow-mediated dilatation and nitrate-mediated dilatation) and increased arterial stiff-
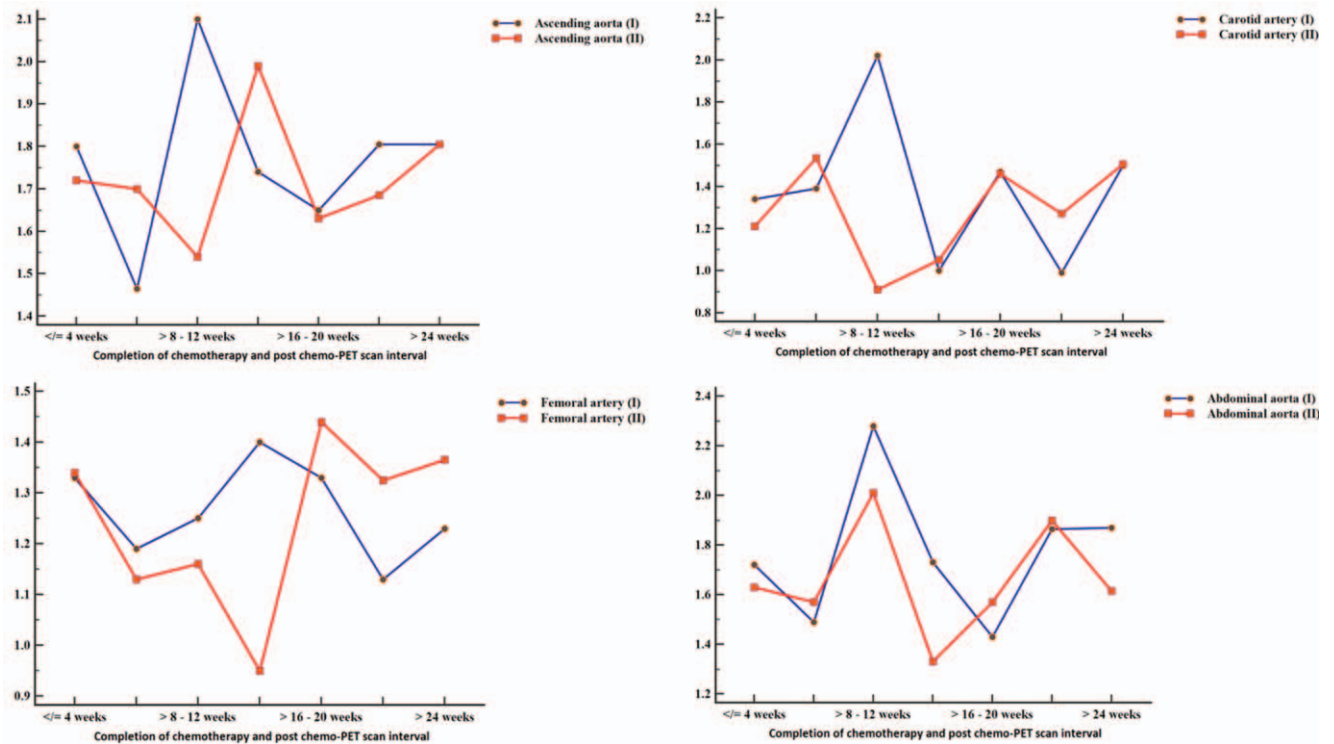
Figure 2. Time trend in TBR in patients grouped according to the interval between completion of chemotherapy and the time of follow-up FDG PET/CT scan. The blue curve represents the TBR obtained on the pre-chemotherapy FDG PET/CT, while the red curve represents TBR obtained in different groups at post-chemotherapy FDG PET/CT. Like for SUVmax shown in Fig. 1, TBR was lower for the post-therapy FDG PET/CT compared with pre-chemotherapy FDG PET/CT in multiple time-points in the trend. In the group in whom post-chemotherapy FDG PET/CT was obtained more than 24 wk after completion of chemotherapy, TBR in the arterials from the post-chemotherapy FDG PET/CT equaled (ascending aorta, carotid artery) or surpassed (femoral artery) that of the pre-chemotherapy FDG PET/CT. TBR of post-chemotherapy FDG PET/CT remained below that of the pre-chemotherapy FDG PET/CT scan in the abdominal aorta.

ness.[28] Aortic stiffness increases doing follow-up of patients receiving anthracycline-based chemotherapy.[29] From the foregoing discussion, it is evident by subclinical ASCVD can be assessed by different noninvasive imaging techniques. Arterial changes such as aortic stiffness and endothelial dysfunction measured by magnetic resonance imaging and ultrasound scan show that the vascular changes due to anthracycline chemotherapy occur early after the initiation of treatment. These findings support the data in the literature showing that the incidence of ASCVD starts to rise within 5 years of anthracycline-based

Figure 3. Fused FDG PET/CT images through the chest of a 40-year-old male who had baseline (A) and follow-up imaging post-chemotherapy (B) for Hodgkin lymphoma. This figure depicts how SUVmax and TBR were calculated for each arterial bed using the ascending aorta and the superior vena cava for demonstration. Multiple regions of interests (ROI) are shown encircling the ascending aorta. The mean SUVmax obtained from these ROIs represents the aortic SUVmax. Multiple ROIs are shown within the lumen of the superior vena cava (SVC). The mean of the SUVmean from these ROIs represents the SVC SUVmean. TBR for the ascending aorta was computed by dividing the aortic SUVmax by the SVC SUVmean. Aortic SUVmax and aortic TBR were computed for the baseline and post-chemotherapy FDG PET/CT scans. These parameters were also obtained for the coronary vessels, the abdominal aorta (using the inferior vena cava for background correction), and the femoral vessels.

chemotherapy without plateauing throughout the life cancer survivors.[23,30] While arterial inflammation is a very early step in atherogenesis, our failure to demonstrate significant increased in arterial FDG uptake in our cohort may be due any of several factors including the short-term follow-up and many technical factors that could compromise adequate quantification of arterial FDG uptake.

Patients infected with HIV are at increased risk of ASCVD. Arterial inflammation measured by the intensity of arterial FDG uptake is known to be higher in HIV-infected people compared with age- and gender-matched controls.[15,31] We compared the changes in arterial FDG uptake between HIV-infected and HIV-uninfected patients and found no significant difference in the 2 groups. Similarly, in a sub-group analysis where we compared patients who were smokers and those who were hypertensive versus those who were not, we found no significant difference in the groups based on these 2 variables. An additional factor that may be responsible for the lack of significant differences in these groups relates to the low prevalence of these known cardiovascular risks in our patient population. For example, there were only 15 smokers and 3 patients with systemic hypertension. Our findings regarding sub-group analysis based on the history of diabetes mellitus was a little different. The patients who were diabetic experience significant weight loss and, consequently, a significant decrease in BMI between the pre- and post-chemotherapy FDG PET/CT scans. We found a decline in the SUVmax measured in the ascending aorta between the pre- and post-chemotherapy FDG PET/CT in the diabetic patients while non-diabetic patients experienced a rise in SUVmax of FDG uptake in the ascending aorta. Similarly, we found a significantly higher rise in TBR of FDG uptake in the femoral arterial among diabetic patients compared with non-diabetic patients. We doubt if these significant differences found in 2 of the measured FDG PET parameters are meaningful, especially considering that there were only 2 patients in our study patients who were diabetic at the time of the study.

In this study, we showed the utility of FDG PET/CT obtained for baseline pre-chemotherapy staging and post-chemotherapy re-staging in patients with HL treated with anthracycline-based chemotherapy in the evaluation of arterial inflammation as a risk factor of ASCVD. Evaluation of arterial inflammation in this patient group is essential to evaluate their cardiovascular risk and measure the effectiveness of anti-inflammatory therapy for risk reduction, which has attracted much interest in recent times. Our study has many limitations. Our study population is modest. This is because of the strict selection criteria we applied. Most importantly, we excluded all patients in whom lymphoma involves lymph node groups adjacent to the artery of interest that precluded accurate quantification of arterial FDG uptake without photon spill-over from the lymph nodes. Lymph nodes are generally located around major vessels; hence a large proportion of patients were excluded for this reason. The retrospective design of our study also precludes the application of imaging conditions, including delayed imaging necessary to optimized arterial FDG uptake and improve background activity clearance.[21,32] We failed to demonstrate a significant increase in arterial inflammation following anthracycline-based chemotherapy. We speculate that the short interval between the completion of chemotherapy and the time of follow-up imaging in this study could be a significant contributing factor. Future studies in this area should explore a more extended follow-up interval between the completion of chemotherapy and post-chemotherapy FDG PET/CT.

5. Conclusion

In patients with Hodgkin lymphoma who were treated with anthracycline-based chemotherapy, we found no significant increase in arterial inflammation measured by FDG PET/CT after an average follow-up of about 65 weeks since completion of chemotherapy. The presence of systemic hypertension, diabetes mellitus, and smoking history did not seem to impact on arterial inflammation in our study population.

Author contributions

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