Fluorodeoxyglucose-positron emission tomography (FDG-PET) of carotid arteries and non-alcoholic fatty liver disease (NAFLD): An analytical cross-sectional study from a teaching hospital, Kerala, South India

Sameer Rane¹, RajeshThachathodiyl², Shanmuga S. Palaniswamy³, Jaideep C. Menon⁴, Remya Sudevan⁵

¹Department of Cardiology, Consultant Cardiologist (EP), Mumbai Heart Clinic, Chembur, Mumbai, Maharashtra, ²Department of Cardiology, Amrita Institute of Medical Sciences and Research Centre, Amrita Vishwa Vidyapeetham, Kochi, Kerala, ³Department of Nuclear Medicine, ⁴Department of Cardiology, Consultant Cardiologist, ⁵Department of Cardiology, Consultant Clinical Epidemiologist, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India

ABSTRACT

Introduction: Evidence related to carotid artery F-fluorodeoxyglucose-positron emission tomography (FDG-PET) and non-alcoholic fatty liver disease (NAFLD) is limited from a low-resource setting. The present study aims to examine the association between FDG-PET uptakes by the carotid arteries in patients having different grades of NAFLD.

Materials and Methods: An analytical cross-sectional study was done in a tertiary care center in South India for 1 year. Sonographically confirmed NAFLD patients of the age group 18 years and above were consecutively enrolled for the study after getting informed consent. Anthropometric measurements, ultrasonography for identifying the grades of fatty liver and FDG-PET were performed in the study participants. The data for the study were collected by the research personnel and entered in Microsoft Excel. The data were analyzed in the IBM SPSS version 20.0 software.

Results: A total of 24 patients were in the final analysis. The mean age of patients in this study was 56.79 (11.26) years. Among the 24 patients, 95.83% (n = 23) were males. The mean FDG-PET uptake in the carotids was 1.75 (0.42) units. The FDG uptake was higher in the moderate NAFLD group (1.46 [0.40] vs 2.04 [0.14]) and the difference was statistically significant with \( P < 0.001 \). The FDG uptake between the coronary artery disease (CAD) with NAFLD and non CAD with NAFLD groups was not statistically significant (1.60 [0.46] vs 1.86 [0.36], \( P = 0.17 \)). The FDG uptake in CAD patients with mild and moderate NAFLD had no statistical significance between the two groups (1.43 [0.45] vs 2.00 [0.00], \( P = 0.06 \)).

Conclusion: The findings of this study showed increased uptake of FDG-PET in carotids in subjects with moderate fatty liver when compared with those with mild fatty liver.

Keywords: Carotid arteries, coronary artery disease (CAD), and resource-limited setting, F-fluorodeoxyglucose-positron emission tomography (FDG-PET), non-alcoholic fatty liver disease (NAFLD)

Address for correspondence: Dr. Remya Sudevan, Consultant Clinical Epidemiologist, Departments of Health Sciences Research and Cardiology, Amrita Institute of Medical Sciences and Research Centre, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India. E-mail: drremyasudevan27@gmail.com

Received: 24-11-2021 | Revised: 11-02-2022 | Accepted: 23-02-2022 | Published: 22-07-2022

How to cite this article: Rane S, Thachathodiyl R, Palaniswamy SS, Menon JC, Sudevan R. Fluorodeoxyglucose-positron emission tomography (FDG-PET) of carotid arteries and non-alcoholic fatty liver disease (NAFLD): An analytical cross-sectional study from a teaching hospital, Kerala, South India. J Family Med Prim Care 2022;11:3766-70.
in cardiovascular disease genesis. The major cardiovascular disease (CVD) risk factors seen in NAFLD patients are dyslipidemia, abdominal obesity, insulin resistance, and chronic inflammatory state. The association between pathophysiology with the emergence of CVD in NAFLD patients is indefinite. Nevertheless, evidence indicates chronic inflammation leads to atherosclerotic plaque formation, which subsequently leads to CVD. Atherosclerosis is an unresolved inflammatory condition, lacking the switch from the pro-inflammatory to the pro-resolving phase, the latter characterized by the termination of inflammatory cell recruitment, removal of inflammatory cells from the site of inflammation by apoptosis, and dead cell clearance, reprogramming of macrophages toward an anti-inflammatory, regenerative phenotype, and finally egress of effector cells and tissue regeneration.

The imaging modalities used contemporarily, such as intima-media thickness (IMT), coronary artery calcification scores (CAC), and X-ray angiography, can quantify atherosclerosis; however, they are unable to determine the degree of inflammation of plaque and its vulnerability to rupture. Positron emission tomography (PET) scanning using a metabolic marker namely F-fluorodeoxyglucose (FDG) is an effective imaging technique to detect macrophage infiltration in atherosclerotic plaques, arterial inflammation, and probability to rupture. Unstable inflammatory plaques have increased FDG uptake in atherosclerotic vessels and endarterectomy tissues demonstrating that these areas correlate with infiltrating macrophages. The contribution of inflammation in cerebrovascular events is by aiding the progression of vulnerable plaques and causing their instability. As such, arterial inflammation is closely associated with cardio-cerebrovascular events. Studies have been able to successfully demonstrate inflammatory cell infiltration in coronary and carotid plaques of patients with acute coronary syndrome or stroke. Accordingly, biomarkers of inflammation are being targeted as cerebroindicators of cardiovascular prognosis. These findings indicate that FDG-PET has the ability to monitor the inflammatory component of atherosclerotic plaques and suggest a non-invasive role for predicting future vascular events.

NAFLD is the enhanced state of oxidative stress and hence it is a pro-atherogenic characteristic. This is believed to play a role in the progression from hepatic steatosis to steatohepatitis, fibrosis, and cirrhosis. Reactive oxygen species derived from steatosis-stimulated fatty acid oxidation, attendant hepatocyte injury and cytokine release, and the ensuing inflammatory milieu are likely to perpetuate the liver disease of NAFLD and add additional atherogenic stimuli to the already high oxidative/inflammatory status associated with Metabolic equivalent of task (Mets) and epitomized by an elevated C-reactive protein (CRP) serum level.

Laboratory levels of inflammation are strongly associated with adiposity measures and insulin resistance. CRP was also associated with Alanine Transaminase (ALT), the best serum marker of hepatic inflammation. Together, these findings suggest that hepatic injury contributed to the inflammatory status in NAFLD.

Carotid artery FDG uptake is significantly associated with clinical risk factors that can eventually lead to chronic diseases such as coronary artery disease (CAD) and NAFLD. Multiple study analysis shows that triglyceride levels, diabetes, and metabolic syndrome were independent determinants of high FDG-PET uptake. Early detection of NAFLD through FDG-PET can provide proper evidence to primary care physicians for the right diagnosis, early intervention, and appropriate treatment for NAFLD. Evidence related to carotid artery FDG-PET and NAFLD is limited from our setting. The present study aims to examine the association between FDG-PET uptake by the carotid arteries in patients having different grades of NAFLD.

Materials and Methods

Study design: Analytical cross-sectional study

Study Population: Patients with NAFLD under care in study institution (Amrita Institute of Medical Sciences and Research Center, Kochi, Kerala, Tertiary Care Center and Medical College).

Inclusion criteria: Sonographically confirmed NAFLD patients of age group 18 years and above.

Exclusion criteria: Alcoholic liver disease, renal failure (defined as an estimated GFR of <50), and pregnancy.

Study Period: September 2015 to October 2016.

Conduct of study: The study was conducted with the approval from the institutional ethics committee. The study participants were consecutively recruited according to the inclusion/exclusion criteria. Informed consent was taken from the participants. All study patients underwent anthropometric measurements for height, weight, blood pressure (BP), and waist circumference (WC). Body mass index (BMI) was calculated from weight (kg)/height²(m²). The variables selected for the study were age group, BMI, grades of NAFLD, CAD categorized with grades of NAFLD, and statin dose. The data were collected by the research personnel in the study proforma and entered in Microsoft Excel for analysis.

Ultrasonography for fatty liver assessment

Abdominal ultrasonography was performed using a SEQUOIA-512 (Siemens, Mountain View, California), LOGIQ 700 Expert (GE Healthcare, Milwaukee, Wisconsin), or LOGIQ E9 (GE Healthcare) device. The presence of NAFLD and severity of fatty liver infiltration were determined as follows. Mild NAFLD was defined as mildly increased liver echogenicity and a clear depiction of hepatic and portal vein walls. Moderate NAFLD increased echogenicity, obscuring the hepatic and portal vein walls.
Positron emission tomography/CT imaging

All subjects were instructed to fast for 6 h before the FDG-PET/computed tomography (CT) study and blood glucose levels were <150 mg/dL at the time of FDG injection. Imaging was performed on a GE Discovery PET/CT scanner (GE Healthcare). The CT images were acquired first at 45 min after FDG (370 MBq) injection using an 8-slice (140 keV, 40-120 mAs adjusted to body weight; section width of 5 mm). No intravenous or oral contrast materials were used. Emission PET images of the head, neck, and thorax were then acquired for 4 min/frame in a two-dimensional mode. Attenuation-corrected PET images (voxel size, 4.3 × 4.3 × 3.9 mm³) were reconstructed using CT data using an ordered-subsets expectation-maximization algorithm (28 subsets, 2 iterations).

Positron emission tomography/CT image analysis

Transaxial FDG-PET and PET/CT tomographic slices of 3.5 mm thickness were analyzed on a Xeleris workstation. Circular or ellipsoidal regions of interest (ROIs) were manually placed over the carotid arteries on every other tomographic slice beginning from the merging point with the brachiocephalic trunk or aortic arch up to four to six slices above the bifurcation site as previously described.[19] Care was taken to include all arterial outer walls while excluding nonvascular tissue of significant activity. From each arterial ROI, mean and maximum standard uptake values (SUVs) were obtained. The blood-pool activity was measured by placing circular ROIs in the mid-lumen of the inferior vena cava on five different tomographic slices and averaging the values to obtain the background SUV. The maximum SUVs of each arterial segment were averaged for both carotid arteries and then divided by the background SUV to yield the maximum target-to-background ratios (TBRs) for each patient.

Statistical analysis

The statistical analysis was performed using the IBM SPSS version 20.0 software. Categorical variables are expressed using frequency and percentage. The numerical variables are presented using mean and standard deviation (SD). The incidence of carotid artery inflammation amongst NAFLD subjects was calculated as a percentage. To test the statistical association of USG detected fatty liver with CAD, Chi-square test was used. To check the statistically significant difference in mean carotid uptake between different factors, the Mann–Whitney U test was used.

Results

Baseline characteristics of study population

A total of 24 patients were in the final analysis. The mean age of patients in this study was 56.79 (11.26) years. The mean age in the mild fatty liver group was 59.75 (10.57) years, whereas in the moderate group it was 53.83 (11.57) years. Among the 24 patients, 95.83% (n = 23) were males. There were 75% (n = 18) patients with BMI <30, whereas the remaining 25% (n = 6) had BMI >30. There were 50% (n = 12) mild NAFLD and 50% (n = 12) moderate NAFLD patients. There were 79.17% (n = 19) patients on low dose (< 20 mg) and 20.83% (n = 5) on high-dose (>20 mg) statins.

FDG-PET uptake details

The mean FDG-PET uptake in the carotids was 1.75 (0.42) units.

Among the 24 NAFLD patients, there were 41.67% (n = 10) CAD patients. In the 10 CAD patients, 70% (n = 7) had mild NAFLD and the remaining 30% (n = 3) had moderate NAFLD.

The FDG uptake between the two groups was not statistically significant (1.60 [0.46] v/s 1.86 [0.36], P = 0.17).

In the age group categories, 10 subjects were below 55 years of age, and 14 were 55 years or above. There was no statistically significant difference in the FDG uptake between the two groups (1.43 [0.45] v/s 2.00 [0.00], P = 0.06).

The uptake in groups receiving low-dose statins was 1.74 (0.42) and in the high-dose statin group, it was 1.80 (0.44). There was no statistical significance in the mean statin dose between the two groups of statins with P = 0.63.

The FDG-PET uptake in the group with BMI <30 was 1.66 (0.45) and in those with BMI >30 was 2.0 (0.0). There was no statistical difference in the FDG uptake between the two groups of BMI and the P value was 0.07. The details are represented in Table 1.

Discussion

This study was done to see the correlation of carotid artery inflammation in patients with NAFLD. Atherosclerosis being termed as a chronic inflammatory state, FDG-PET uptake would be higher in patients with a greater degree of atherosclerosis (e.g., established CAD) or fatty infiltration of the liver. Studies have shown that FDG-PET of carotid arteries is a diagnostic tool for subclinical atherosclerosis detection. Subclinical atherosclerosis is an early marker and strong determinant of carotid artery disease and NAFLD.[20-22] The primary care physicians and family physicians are the first point of healthcare providers for patients to detect and treat the risk factors related to any type of chronic disease. They can detect the early changes in fatty liver and can correlate the grades of fatty liver with FDG-PET of carotid arteries.
A study done by Moon et al.\(^{18}\) showed FDG-PET uptake of the carotid artery as a better tool for assessing subclinical atherosclerosis when compared to carotid intimal thickness using a Doppler study. They noted a carotid uptake in healthy individuals; however, found to have a normal carotid intimal thickness.

NAFLD is the enhanced state of oxidative stress and hence it is a pro-atherogenic characteristic. This is believed to play a role in the progression from hepatic steatosis to steatohepatitis, fibrosis, and cirrhosis.\(^{21}\)

The carotid artery uptake was significantly higher in individuals with moderate fatty liver when compared with patients in the mild fatty liver group \((P < 0.001)\).

Multiple data are pointing to an association of NAFLD with clinical risk factors for carotid atherosclerosis and other CVD.\(^{12,13}\) Carotid atherosclerosis is an independent risk factor for cardiovascular and cerebrovascular diseases. The influence of NAFLD independently on the atherosclerotic process in these patients was studied. Tahara et al. investigated the relationship between clinical risk factors and increased carotid artery FDG uptake and observed an association of inflammatory carotid atherosclerosis with metabolic syndrome.\(^{14}\)

A study by Lee et al.\(^{23}\) has shown that the carotid artery FDG uptake was significantly associated with clinical cardiovascular risk factors and with the 10-year general cardiovascular risk (assessed using the Framingham Risk Score [FRS]) in an asymptomatic population. As expected, both carotid artery FDG uptake and FRS for CVD were elevated in subjects with metabolic syndrome in our study also. The subjects with metabolic syndrome had a significantly higher hs-CRP levels in the high uptake than the low uptake group.\(^{24}\)

When the two groups were compared in the background of CAD, there was no statistical significance between the two groups \((P = 0.17)\). A possible explanation could be the use of statins as secondary prophylaxis in these patients who had CAD. However, then there was no statistical significance in the patients who were treated with high- and low-dose statins. The high BMI group versus the lesser BMI group failed to show any statistical significance between them \((P = 0.07)\). It can be said that NAFLD causes increased inflammation of the arteries independent of the metabolic state of an individual. However, this needs to be concluded by a study involving a larger sample size.

Advanced age, as per the Framingham criteria, is an established risk factor for CVD\(^{19}\) and is also known to increase FDG uptake in carotid and large arteries.\(^{4,16,17}\) In this study, the effect of age on carotid FDG uptake did not have statistical significance. A study with a larger sample size will be required to determine this relationship.

### Conclusion

The findings of this study showed increased uptake of FDG-PET in carotids in subjects with moderate fatty liver when compared with those with mild fatty liver. The increased uptake is assumed to be due to a chronic inflammatory state and hence higher values were considered as a greater degree of inflammation.

It is expected that a patient with a fatty liver will have high uptake values in the carotid artery, high values in the group with moderate fatty liver, and higher in subsets with coronary artery disease. However, when the mild and moderate fatty liver groups were compared with the presence of coronary artery disease, no statistically significant association was noted.

The majority of the subjects in this study were on statin therapy. The probable explanation is that the statins play a role in modifying the carotid inflammation and hence the carotid uptake of FDG-PET.

It cannot be concluded that a NAFLD diagnosis is associated with subclinical CVD aside from established modifiable cardiovascular risk factors, including obesity, dyslipidemia, hypertension, diabetes, and smoking status.

Future studies with a larger sample size are required to further elucidate the contributory role of the duration of NAFLD on subclinical atherosclerosis, its progression, and subsequent cardio and cerebrovascular events.

Novelty in the study.

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### Table 1: Comparative analysis of FDG-PET* uptake with study variables

| Variables                        | n  | Mean FDG-PET SD** | P     |
|----------------------------------|----|-------------------|-------|
| Grades of NAFLD                  |    |                   |       |
| Mild                             | 12 | 1.46              | 0.40  | <0.001 |
| Moderate                         | 12 | 2.04              | 0.14  |       |
| Patients with and without CAD*** |    |                   |       |
| With CAD                         | 10 | 1.60              | 0.46  | 0.17  |
| Without CAD                      | 14 | 1.86              | 0.36  |       |
| CAD and grades of NAFLD****      |    |                   |       |
| CAD with mild NAFLD              | 7  | 1.43              | 0.45  | 0.06  |
| CAD with moderate NAFLD          | 3  | 2.00              | 0.00  |       |
| Age groups                       |    |                   |       |
| <55                              | 10 | 1.75              | 0.35  | 0.87  |
| ≥55                              | 14 | 1.75              | 0.47  |       |
| Statin dose                      |    |                   |       |
| Low                              | 19 | 1.74              | 0.42  | 0.63  |
| High                             | 5  | 1.80              | 0.45  |       |
| BMI*                             |    |                   |       |
| <30                              | 18 | 1.67              | 0.45  | 0.07  |
| ≥30                              | 6  | 2.00              | 0.00  |       |

*F- fluorodeoxyglucose-positron emission tomography, **Standard deviation, ***Coronary artery disease. ****Non alcoholic fatty liver disease. *Body mass index.
FDG-PET carotid uptake and NAFLD association were studied much in the western population. Our study was done in the Indian population and with resource limitations.

**Limitations**

The study has the following limitations

1. The number of study participants was very low.
2. The study population was almost exclusively male patients.
3. The interpretation of the Ultra-Sonography (USG) parameters and FDG uptake on PET images were entirely observer-dependent.
4. The commonly used laboratory inflammatory markers such as hs-CRP, ESR were not measured to provide parallel information of the baseline inflammatory state.
5. CT of the liver is the imaging modality of choice and has a better predictable value over the USG for characterization of the liver. Because of cost restraints, USG was preferred over CT imaging.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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