Atherosclerosis 268 (2018) 49–54

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Arterial inflammation measured by ^{18}F-FDG-PET-CT to predict coronary events in older subjects

Ryota Iwatsuka [a, b, *], Yuya Matsue [a, c], Taishi Yonetsu [d], Toshihiro O'uchi [e], Akihiko Matsumura [a], Yuji Hashimoto [a], Kenzo Hirao [b]

[a] Department of Cardiology, Kameda Medical Center, Chiba, Japan
[b] Department of Cardiovascular Medicine, Tokyo Medical and Dental University, Tokyo, Japan
[c] Department of Cardiovascular Medicine, Juntendo University School of Medicine, Tokyo, Japan
[d] Division of Cardiovascular Medicine, Tsuchiura Kyodo General Hospital, Ibaraki, Japan
[e] Department of Radiology, Kameda Medical Center, Chiba, Japan

ARTICLE INFO

Article history:
Received 29 September 2017
Received in revised form
10 November 2017
Accepted 16 November 2017
Available online 21 November 2017

Keywords:
Framingham risk score
Coronary heart disease event
Prognosis

ABSTRACT

Background and aims: Although ^{18}F-fluorodeoxyglucose (FDG) uptake has emerged as a sensitive and reliable marker of atherosclerotic inflammation, its additive predictive value for future coronary disease in older subjects is unknown. The aim of this study was to test the prognostic value of aortic inflammation detected via FDG-positron emission tomography (PET)-computed tomography (CT) in older subjects.

Methods: We retrospectively utilized the records of 309 subjects aged over 65 years, without a history of coronary artery disease, who underwent ^{18}F-FDG-PET-CT mostly due to the clinical suspicion of cancer, but eventually turned out to be cancer-free. Target-to-background ratio (TBR) was calculated at the ascending aorta. The endpoint was occurrence of coronary heart disease (CHD) events.

Results: During a median follow-up of 3.9 years, 28 subjects experienced CHD events and 12 patients died due to non-CHD causes. The highest TBR tertile was associated with a high CHD event rate, accounting for death due to non-CHD causes as a competing risk (Gray test, $p = 0.005$). In a Fine and Gray competing risk proportional hazard regression model, TBR was associated with significantly high CHD events independently of FRS, with a hazard ratio (HR) of 1.19 per 0.1 TBR increase ($p < 0.001$). Likewise, a significant increase in the area under the curve (from 0.57 to 0.73, $p = 0.028$) and a significant improvement in net reclassification (0.42, $p = 0.038$) were observed when TBR was added to the model with FRS alone.

Conclusions: In older subjects with no history of malignant disease or overt coronary artery disease, arterial inflammation evaluated by FDG uptake provides information on future occurrence of coronary artery events.

1. Introduction

Atherosclerotic disease remains one of the leading causes of death worldwide, and its prevalence is increasing in the aging population. As life expectancy increases, risk prediction becomes more important because age is a non-modifiable risk factor for atherosclerotic events. Atherosclerotic risk prediction models have been proposed; however, most of these are derived from middle-aged populations. Moreover, a few studies have reported that scores derived from such models do not perform well when applied to relatively older subjects [1–3].

In recent years, it has become apparent that atherosclerotic disease is a systemic disorder and atherosclerotic factors cause endothelial cell damage while subsequently provoking inflammation within the arterial intima [18]. F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) has been used in the diagnosis of malignant diseases, and is a potentially useful imaging tool for the quantitative evaluation of systemic inflammation [4]. In addition, combining images obtained via ^{18}F-FDG-PET with computed tomography (CT) images can provide a better indication of the

* Corresponding author. Department of Cardiology, Kameda Medical Center, 929, Kamogawa City, Chiba, Japan.
E-mail address: ryotaiwtk@gmail.com (R. Iwatsuka).

https://doi.org/10.1016/j.atherosclerosis.2017.11.016
0021-9150/

correct location of vascular inflammation [5]. This implies that ^{18}F-FDG-PET-CT may be able to detect early atherosclerotic changes that cannot be identified otherwise. Indeed, a few studies have shown that FDG uptake may predict future adverse cardiovascular events [6–8]; however, its predictive role for prognosis has not been elucidated in older subjects. Therefore, we hypothesized that vascular inflammation evaluated by ^{18}F-FDG-PET-CT imaging may predict future cardiovascular events in an older population without overt cardiovascular diseases.

2. Patients and methods

2.1. Patient selection and follow-up

All patients who underwent ^{18}F-FDG-PET-CT examination at Kameda Medical Center from April 2007 to January 2014 were retrospectively screened for eligibility. Subjects aged ≥65 years without a known history of cancer or cardiovascular disease were considered for inclusion. Patients who were diagnosed with cancer for the first time via the ^{18}F-FDG-PET-CT procedure were excluded. Patients with cerebrovascular disease or inflammatory vascular disease were also excluded, as were those without complete medical records or accompanying laboratory data, and those with imaging data deemed insufficient. Clinical data including age, sex, systolic blood pressure, current smoking status, diabetes, total cholesterol, and high-density lipoprotein cholesterol were collected from the medical records. With regard to prognosis, wherever possible, all relevant information was obtained from medical records, and those with insufficient follow-up data were contacted via the telephone to acquire such data. An independent radiologist blinded to the clinical/prognostic data analyzed all ^{18}F-FDG-PET images. Due to the retrospective and observational nature of the present study, written informed consent was not required under the Japanese law, and we utilized the opt-out method. All participants were notified regarding their eligibility to participate in the study and it was explained that they were free to opt out of the participation at any time. Our study complied with the Declaration of Helsinki and Japanese Ethical Guidelines for Medical and Health Research involving Human Subjects, and the study protocol was approved by the local ethics committee.

2.2. Framingham risk score and outcome events

The present study employed the gender-specific Framingham risk score (FRS) developed by Wilson et al. [9] which includes age, total and high density lipoprotein, cholesterol, blood pressure, presence of diabetes, and smoking status, because the original FRS was derived from a population aged from 30 to 74 years [10]. The predictive capacity of this gender-specific FRS has been evaluated in an older population, and variables included in this score were proven to be the best predictors of coronary heart disease (CHD) events even in an older population in terms of discrimination, despite relatively poor calibration of the score [3]. We defined CHD events as nonfatal myocardial infarction or coronary death (corresponding to "hard" events defined in the original FRS), and/or hospitalization for angina or revascularization based on a previous study [9]. All CHD events were clinically adjudicated by two cardiologists who were blinded to the findings of PET-CT based on clinical records.

2.3. ^{18}F-FDG-PET-CT protocol

All subjects underwent ^{18}F-FDG-PET-CT imaging via a Discover STE PET/CT scanner (General Electric Medical Systems, Milwaukee, WI). This scanner provides 48 planes, a 15.5-cm field of view, and an intrinsic resolution of 3.25 mm. Before imaging, participants were required to fast for at least 6 h and achieve a glucose level of 180 mg/mL or lower. ^{18}F-FDG was administered at a level of approximately 4.3 MBq/kg (maximum dose 350 MBq), intravenously. PET images were obtained in 3D-mode approximately 60 min later. Subjects were imaged in the supine position, and low-dose CT scanning (20 mAs, 140 kV) was conducted before PET imaging. Image analysis was performed on a dedicated workstation (Xeleris; GE Healthcare). PET data were reconstructed iteratively with and without attenuation correction, and then reoriented in axial, sagittal, and coronal slices. A full 3D reconstruction algorithm based on the row-action maximum-likelihood algorithm was applied via the PET-View software.

2.4. Image analysis

An independent radiologist, who was blinded to the clinical and prognosis data, analyzed all the PET-CT images. Measurements were first performed with the ascending aortic root ^{18}F-FDG standardized uptake values (SUVs) as the maximal SUVs using regions of interest. At the same time, SUV was measured as blood-pool SUV in the same superior vena cava mid-lumen slice. The maximal SUV was divided by the blood-pool SUV, yielding a target-to-background ratio (TBR). These measurements were taken on 7 slices every 3.25 mm starting from the ascending aortic root. The average value was calculated, and the degree of inflammation was defined [11,12]. We measured TBR in ascending aorta because this approach was previously demonstrated to be reproducible [11,13], correlating with histological markers of inflammation [14,15], and has been used in several other studies [16–18].

2.5. Statistical analysis

Data were expressed as the mean and standard deviation for normally distributed variables and as the median and interquartile range for non-normally distributed data. Categorical data were expressed as numbers and percentages. The relationships between baseline characteristics and TBR quantiles were compared via One-way analysis of variance, the Kruskal-Wallis test, or the Chi-squared test as appropriate. When necessary, variables were transformed for further analyses.

Cumulative incidence curves for CHD events stratified by TBR tertiles were constructed reflecting time to death due to non-CHD causes and time to CHD events as competing risks, and compared via the Gray test [19]. Univariate and multivariate Fine and Gray competing risk regression models were used to assess the hazard ratios (HR) for CHD events, with non-CHD death considered a competing risk [20].

To assess whether TBR was associated with improved performance of the conventional model for predicting future CHD events, we constructed receiver operating characteristic (ROC) curves for logistic regression models of FRS and FRS plus TBR. ROC curves were constructed for two models, FRS only and FRS plus TBR. Areas under the curves (AUCs) were compared using the DeLong's method [21]. Improvements in continuous net reclassification and integrated discrimination were also calculated to evaluate the additive prognostic value of TBR [22]. Two-tailed p values < 0.05 were considered statistically significant. Statistical analyses were performed using R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria; ISBN 3-900051-07-0, URL http://www.R-project.org).