Association of Baseline Subject Characteristics with Changes in Coronary Calcification Assessed by 18F-Sodium Fluoride PET/CT

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Introduction

Plaque macrocalcification and microcalcification are associated with atherosclerosis. Atherosclerosis often does not have symptoms, but when severe it can lead to a heart attack or stroke. Macrocalcification can lead to plaque stability, but microcalcification can lead to plaque vulnerability and increase the potential for the rupture that causes cardiovascular events [1-3].

While CT imaging is capable of measuring macrocalcification in the coronary arteries it cannot detect microcalcification [1]. 18F-Sodium Fluoride (NaF) is a radiopharmaceutical with affinity of fluoride to hydroxyapatite. For this reason, it is appealing for bone imaging. Recent studies have shown that NaF could also be used to detect calcified micro-deposits within coronary plaque [1, 2, 4-8]. NaF PET/CT is the only noninvasive imaging technique currently capable of distinguishing between macro- and microcalcification [2]. NaF is able to distinguish between areas of micro and macrocalcifcation because the extent of fluoride absorption depends on surface area, making it more likely to bind to microcalcification but unable to penetrate deeper into areas of macrocalcifcation [2]. The method of using NaF PET/CT scans to detect microcalcification has been shown to be repeatable and reproducible [8].

Fluoride uptake has been shown to correlate with cardiovascular disease risk and have a direct link to myocardial infarction [4, 5, 9]. Many individuals with coronary artery disease are asymptomatic. One study of middle aged Western asymptomatic subjects found that a majority had scans indicating coronary artery disease [10]. NaF imaging has been shown to be feasible even in healthy patients [11]. The disease is often a silent killer, leading to abrupt deaths due to myocardial infarction, but NaF is associated with such events. In a study of 40 patients with myocardial infarction, the highest coronary NaF uptake was seen on culprit plaque [5], revealing the power of the radiotracer to indicate potential risk areas. In addition to being able to identify areas of myocardial infarction, NaF has been shown to be able to provide an independent prediction of whether myocardial infarction will be fatal or nonfatal [6].

With NaF being a reliable indicator of microcalcification, progression of atherosclerosis, and the possibility of coronary events, it becomes a powerful tool to study what impacts these occurrences and how to prevent them. Prior studies have examined the factors that uptake of NaF correlates with, including age, BMI, hypertension, and male sex [7, 12, 13]. Our study examined the rate of change of calcification over a two year period in individuals. Understanding what factors relate to increase in microcalcification can help improve the predictive power of NaF imaging in healthy patients. The primary purpose of our study was to test which baseline subject characteristics are associated with the changes in coronary microcalcification over a two year period as assessed by NaF PET/CT standard uptake values (SUV).

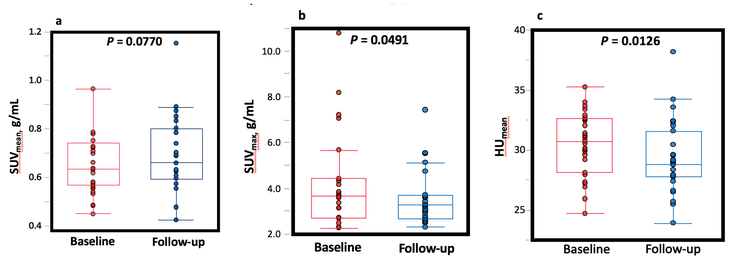

Fig. 2 Boxplots of baseline and follow-up values of all subjects for **a** SUV_{mean}, **b** SUV_{max}, and **c** HU. P values are derived from nonparametric paired signed rank tests.

Methods and Materials

The participants of this prospective study were taken form a larger prospective Cardiovascular Molecular Calcification Assessed by NaF PET/CT (CAMONA) study. The study was conducted by Odense University Hospital and approved by the DanishNational Health Committee on Health Research Ethics.

Our study included healthy patients from the CAMONA study that came in for PET/CT scans two years apart. 23 individuals (female, N = 8, 52 ± 10 years, BMI 24 ± 1.7 kg/m^2; male, N = 15, age 50 ± 10 years, BMI 27 ± 2.9 kg/m^2) in the study had two year follow-up data with consistent dosages, and were used to examine the change in SUVmean, SUVmax, and HUmean over time, as well as the relationship between these changes and age, BMI, cardiovascular risk factors, and blood chemistry

Hybrid PET/CT machines were used to create NaF PET/CT imaging.

All participants had BMI, age, coronary calcium score, cardiovascular risk factors, blood chemistry, and Framingham HeartSCORE determined at the time of their baseline scan.

The operator guided software PMOD (PMOD Technologies LLC, Switzerland) was used to calculate SUV by creating volumes of interest around subjects' hearts.

Nonparametric statistical analyses were performed to determine significant results.

Results

Percent change in SUVmean over the two year period correlated BMI and systolic blood pressure. When stratified by gender, males had significant correlations of percent change in SUVmean with BMI ($\rho = 0.85$, $P < 0.0001$) and systolic blood pressure ($\rho = 0.65$, $P = 0.0082$). **(Figure 1)**. However, there were no significant correlations between any female baseline characteristics and percent change in SUVmean.

Paired t-tests in all subjects showed no significant difference between baseline and follow-up values for SUV_{mean} ($P = 0.0770$) and SUV_{max} ($P = 0.0491$). The paired t-test in all subjects for HU showed a significant decrease ($P = 0.0126$). A box plot was derived of the baseline and follow-up values for SUV_{mean}, SUV_{max}, and HU of all subjects **(Figure 2)**.

The change in SUV_{mean} and the change in HU over the two year period for each individual were not correlated (r = 0.31, $P = 0.152$). The change in SUV_{mean} was significantly greater than the change in HU for an individual as determined by a paired t-test ($P = 0.0019$).

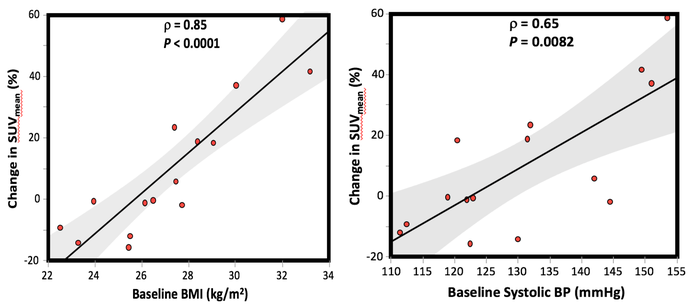

Fig. 1 Change in SUV_{mean} in males over a two year period significantly correlated with BMI and systolic blood pressure

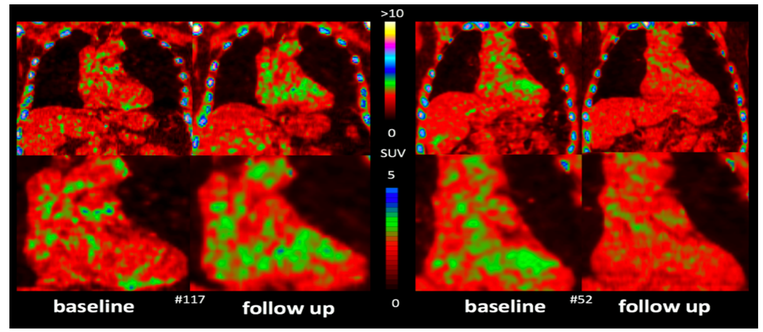

Fig. 3 This figure shows baseline and follow-up PET scans of two individuals. The patient on the left (male, 65-year-old, BMI of 32.0 kg/m^2) shows visibly increased NaF uptake, suggesting atherosclerosis progression, and the patient on the right (male, 60-year-old , BMI of 22.5 kg/m^2) shows decreased NaF uptake, suggesting atherosclerosis regression.

Discussion

Previous studies have shown associations between SUVmean and BMI [7-11]. However, this is the first longitudinal study to show the significant correlation between the percent change in SUVmean over the short term and BMI. This illustrates that not only does the quantity of microcalcification correlate with BMI, but so does the rate of microcalcification. High BMI is a know risk factor for cardiovascular disease [12, 13], and obesity is associated with a shorter lifespan as well as a greater proportion of life lived with cardiovascular disease [14]. Our study included patients whose BMI remained relatively the same, follow-up studies could be done in patients in targeted weight loss programs to see if rate of microcalcification correlates with a change in BMI.

With the strength of the association between change in SUVmean and BMI it is unsurprising that blood pressure significantly correlated with change in SUVmean. NaF emission tomography could be used in the future to see if the use of blood pressure lowering medications or diets could slow the rate of microcalcification.

The correlations in our study were only significant for males. This may be due to the small sample size of females (n = 8). However, an examination of numerous studies provides a conflicting view of how sex impacts NaF uptake, which some suggesting males have more significant uptake and some suggesting females do.

Before analyzing the data for this study, we expected that SUV and HU would have a significant increase over the two year interval as microcalcification progressed but this was not the case. This was likely because subjects had both increases and decreases of SUV and HU over the two year interval, suggesting the possibility of the occurrence of both atherosclerosis progression and regression.

This study was limited by a small sample size (n = 23), especially for females (n = 8). Furthermore, the CAMONA study only had healthy subjecrts with follow-ups, so there were no high risk subjects to compare to.

Further longitudinal studies should be done with larger sample sizes to determine the utility of predicting microcalcification progression using baseline characteristics, as well as to determine the best ways to prevent progression and promote regression of atherosclerosis using this methodology.

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