Efficacy of ^{18}F-FDG and ^{18}F-NaF PET/CT imaging: A novel semi-quantitative assessment of the effects of age and obesity on hip joint inflammation and bone degeneration

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Abstract

Objective: Osteoarthritis (OA) is characterized by synovial tissue inflammation and underlying bone degeneration in the joints. Aging and obesity are among the major risk factors. This study evaluated the effects of aging and body mass index (BMI) on hip joint inflammation and bone degeneration using fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) and fluorine-18 sodium fluoride (^{18}F-NaF) PET/CT imaging, respectively. **Subjects and Methods:** In this retrospective study, a total of 116 subjects (58 males and 58 females) who had undergone both ^{18}F-FDG and ^{18}F-NaF PET/CT imaging were analyzed. The mean age of these subjects was 48.6±14.5 with an age range of 21-75 years. Fluorine-18-FDG and ^{18}F-NaF PET/CT imaging was conducted 180min and 90min (respectively) after intravenous administration of the appropriate tracer. The hip joint was segmented on fused PET/CT images using OsiriX MD v.9.5 (DICOM viewer and image-analysis program, Pixmeo SARL; Bernex, Switzerland). The region of interest (ROI) for the hip joint was indicated by using a 3D-growing region algorithm with upper/lower Hounsfield Units (HU) followed by a morphological closing algorithm. The metabolic activity for the left and right side of the joint was measured and correlated with age and BMI. **Results:** Fluorine-18-FDG uptake in the hip was 0.83±0.22 (right side: 0.83±0.23, left side: 0.83±0.22, P=0.82). Fluorine-18-NaF uptake in the hip was 3.20±1.07 (right side: 3.25±1.14, left side: 3.15±1.04, P= 0.02). Body mass index positively correlated with both ^{18}F-FDG (r=0.29, P=0.001) and NaF (r=0.26, P=0.005) uptake. No significant correlation was seen between age and either ^{18}F-FDG (r=0.12, P=0.19) or ^{18}F-NaF (r= 0.03, P=0.78) uptake. **Conclusion:** Body mass index had a significant impact on ^{18}F-FDG and ^{18}F-NaF uptake, whereas age had no correlation with either tracer uptake. Obesity increases the mechanical forces applied on weight-bearing joints such as the hip. Body mass index was related to increased joint inflammation and bone degeneration. These findings further support the studies explaining the role of adipose tissue in promoting OA.

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Introduction

The hip joint, also known as the acetabulofemoral joint, is comprised of the femoral head and the acetabulum, which is a concave surface of the pelvis that is composed of portions of the ilium, ischium, and pubis [1]. The primary function of the hip joint is to support the body's weight and allow movement in all three principal axes: transverse, longitudinal, and sagittal. Stability in the joint arises from both the shape of the acetabulum and the fibrocartilage ring known as the acetabular labrum. The labrum forms a ring around the acetabulum, which increases its depth and therefore increases the surface area and strength of the joint [1].

Osteoarthritis (OA) is a chronic disease that involves degeneration of the articular cartilage and underlying bone, leading to pain, stiffness, and loss of motion [2, 3]. It is one of the primary causes of disability in people over 65 in the United States [2, 3]. Osteoarthritis can result from a combination of risk factors, such as obesity, age and genetics and it mostly affects the joints in the hands, hips and knees [2]. The hip joint is of particular importance because about 5% of the population over age 65 have OA of the hips. With hips being a weight-bearing joint, risk factors include not only age and obesity, but also participation in weight-bearing activities such as standing, lifting, playing sports and moving objects [3].

The aim of this study was to use fluorine-18-fluorodeoxyglucose (^{18}F-FDG) and fluorine-18 sodium fluoride positron emission tomography/computed tomography (^{18}F-NaF PET/CT) imaging to assess inflammation and bone degeneration, respectively, using a novel semi-quantification technique. Tracer uptake was quantified using the stan-

dard uptake value (SUV) and compared with age and obesity to assess the effects of these widely studied risk factors on OA. This is a unique study that investigates the hip joint quantitatively with both ^{18}F-FDG and ^{18}F-NaF PET/CT imaging and correlates tracer uptake with the age and body mass index (BMI) of the subjects. Utilizing PET/CT imaging can help in identifying early onset of OA and may assist in delaying OA into the later years of life.

Subjects and Methods

This retrospective study utilized ^{18}F-FDG and ^{18}F-NaF PET/CT scans from the "Cardiovascular Molecular Calcification Assessed by ^{18}F-NaF PET/CT" (CAMONA). CAMONA was a prospective study approved by the Danish National Committee on Biomedical Research Ethics, registered at ClinicalTrials.gov (NCT01724749), and conducted from 2012 to 2016 in accordance with the Declaration of Helsinki [4]. A detailed description of this prospective study was previously published by Blomberg BA et al. (2017) [4].

Subject selection

The CAMONA study consisted of 139 volunteers. Eighty-nine of the volunteers were healthy subjects who did not have a history of cardiovascular disease, oncologic disease, autoimmune disease, immunodeficiency syndromes, alcohol use, illicit drug use, or any prescription medication [5]. The other 50 volunteers were patients with a history of chest pa-in who did not have any history of major cardiovascular events, malignancy, chronic inflammatory disease, illicit drug use, or renal insufficiency. Further details regarding recruitment location and inclusion criteria are included in the study by Blomberg BA et al. (2017) [5].

In this retrospective study, 17 subjects were excluded as either their ^{18}F-FDG or ^{18}F-NaF PET/CT scans were not available in our lab's database. Two subjects whose hip joints were not within the field of imaging were also excluded. Another 3 subjects were excluded due to technical issues that prevented analysis of the scans. One subject was excluded due to having a prosthetic hip joint. A total of 116 subjects, 58 males and 58 females, were included in this study. The mean age of these subjects was 48.6±14.5 with an age range of 21-75 years. The linear correlation between age and BMI was not significant, indicating that these variables can be independently assessed with respect to ^{18}F-FDG and ^{18}F-NaF uptake.

Study design

The imaging protocol for the subjects was previously published by Blomberg BA et al. (2014) [6, 7]. Fluorine-18-FDG PET/CT imaging was performed 180 minutes after intravenous administration of 4.0MBq/kg of the tracer, after an overnight fast of at least 8 hours and a confirmed blood glucose concentration below 8mmol/L. Sodium fluoride PET/CT imaging was performed 90 minutes after intravenous administration of 2.2MBq/kg of the tracer. Sodium fluoride PET/CT imaging was performed no later than 2 weeks after the ^{18}F-FDG PET/CT imaging. The PET images were corrected for attenuation, scatter, scanner dead time, and random coincidences. The effective radiation dosage was approximately 14mSv.

Image analysis

All images were analyzed using OsiriX MD v.9.5 (DICOM viewer and image-analysis program, Pixmeo SARL; Bernex, Switzerland). All subjects were anonymized prior to image analysis. A novel quantitative method was used to obtain the region of interest (ROI) for the acetabulofemoral joint. Using the 3D Maximum Intensity Projection (MIP) in the coronal view, a precise rectangular region was cut with the scissor tool that included only the femoral head, the acetabulum and the articular cartilage (Figure 1). The bottom left border of the rectangular region was defined as the visible distinction between the femoral neck and femoral head of the joint. The top right border was approximately 2 millimeters lateral to the pelvic brim. The top left and bottom right borders are approximately 1 centimeter superior and inferior, respectively, to the edge of the femoral neck. A 3D growing region algorithm with a lower Hounsfield Unit (HU) threshold of 150, followed by a morphological closing algorithm with a structured element radius of 20 units was used to indicate the ROI for the joint (Figure 2).

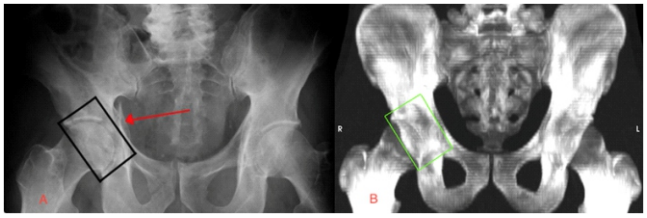

Figure 1. X-ray image of the pelvis (A) in the coronal view with a rectangular region indicating the femoral head, acetabulum and the articular cartilage ("Acetabular fracture as seen on plain X-rays" by James Heilman, MD is licensed under CC BY-SA 3.0/Modified from original). OsiriX 3D MIP (B) in the coronal view with a rectangular region designated with the scissor tool to indicate the hip joint ROI. The X-ray image is shown here as a reference to explain how the boundaries of the rectangular region in the 3D MIP were decided.

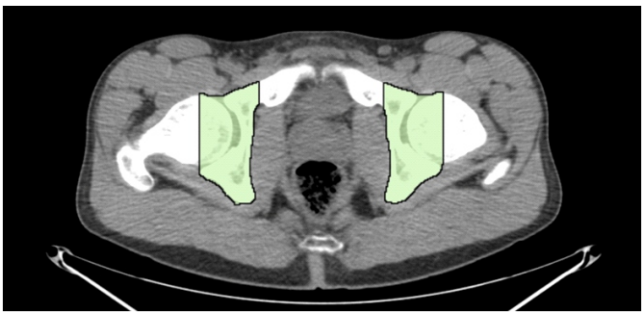

Figure 2. ROI of the hip joint in the axial view of one of the trans-axial slices.

Mean standardized uptake value (SUVmean) and ROIvolume were measured for each trans-axial slice and exported to a CSV file by Osirix. The tracer uptake in each slice was calculated by multiplying the slice SUVmean by the slice ROIvolume. The tra-

cer uptake of all slices was summed up to get the total metabolic activity:

$$\text{Total Metabolic Activity} = \sum (\text{SUVmean} * \text{ROIvolume})$$

take of all slices was summed up to get the total meta-bolic activity:

$$\text{Averaged SUV}_{\text{mean}} = \frac{\text{Total Metabolic Activity}}{\Sigma\,(\text{ROI}_{\text{volume}})}$$

The left and right hip were analyzed and measured separately. The averaged SUVmean for the hip was calculated by taking the mean of the averaged SUVmean values for the left and right hip.

Statistical analysis

Correlations between tracer uptake and both BMI and age were statistically analyzed using linear regression analysis and Pearson's correlation test. Paired t-test was used to analyze the significance of the difference between the left and right hip. Statistical analysis was conducted using IBM SPSS Statistics version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Macintosh, Version 25.0. Armonk, NY: IBM Corp).

Inter-operator agreement

The scans were independently analyzed by two operators. Bland Altman plots were used to assess the inter-operator agreement between the two data sets for both ^{18}F-FDG and ^{18}F-NaF

Results

For ^{18}F-FDG uptake, the mean averaged SUVmean of all the subjects for the hip was 0.83±0.22 (right side: 0.83±0.23, left side: 0.83±0.22, P=0.82). For ^{18}F-NaF uptake, the mean averaged SUVmean for the hip was 3.20±1.07 (right side: 3.25± 1.14, left side: 3.15±1.04, P=0.02). There was a significant positive correlation between BMI and both ^{18}F-FDG (r=0.29, P= 0.001) and ^{18}F-NaF (r=0.26, P=0.005) uptake in the hip joint (Figure 3). There was no significant correlation between age and either ^{18}F-FDG (r=0.12, P=0.19) or ^{18}F-NaF (r=0.03, P=0.78) uptake (Figure 4).

The Bland-Altman plots revealed that the differences in measurements between the two operators were not significant for both ^{18}F-FDG (r=0.06, P=0.53) and ^{18}F-NaF (r=0.05, P= 0.58) uptake in the joint, which indicates a strong inter-operator agreement (Figure 5).

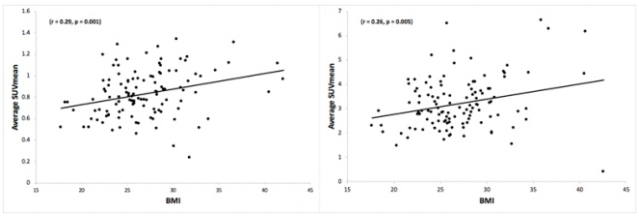

Figure 3. There was a significant positive correlation between BMI and both ^{18}F-FDG (left) and ^{18}F-NaF (right) uptake.

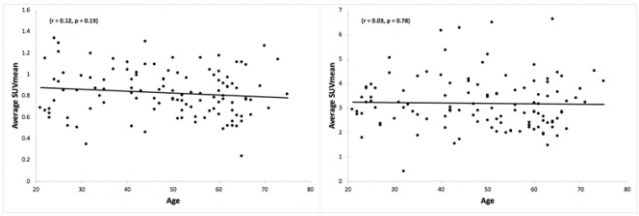

Figure 4. There was no significant correlation between age and either ^{18}F-FDG (left) or ^{18}F-NaF (right) uptake.

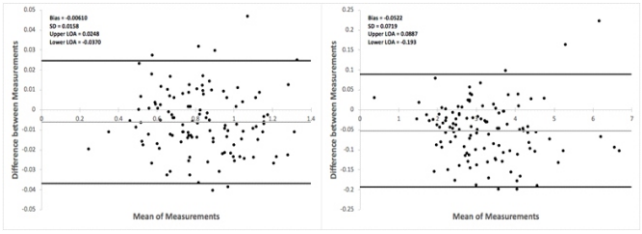

Figure 5. Bland-Altman plots show no significant differences in measurements between the two operators for ^{18}F-FDG (left) and ^{18}F-NaF (right) uptake.

Discussion

Based on the methodology we used, and the data generated from this study, BMI had a significant positive impact on ^{18}F-FDG and ^{18}F-NaF uptake in the hip joint. No significant difference was found in the metabolic activity between the sides of the joint.

Articular cartilage is composed of tissue fluid, type II collagen and proteoglycans. Type II collagen and other minor forms of collagen are embedded in the negatively charged proteoglycans like a gel meshwork which increases tensile strength. This allows for proper joint functioning and mobility. Maturation of the articular cartilage along with minimal turnover of matrix components occurs as the collagen network is crosslinked.

The insult in OA first starts at the molecular level and hence the cartilage is still intact. In an attempt to repair the cartilage, chondrocytes which have minimal regenerative capacity increase matrix synthesis and other proliferative processes [9]. A study by Guilak F et al. (2011) suggests that mechanoreceptors at the surface of chondrocytes sense mechanical stress and can initiate the process of inflammation in OA [10]. Increased expression of COX-2 and IL-1beta and increased synthesis of PGE-2 in fibroblast-like synoviocytes is seen with the mechanical stress. This further increases the synthesis of MMP-2 in the joint cavity and furthers cartilage damage [11]. A study by Sanchez C et al. (2012) showed that there is increased expression of genes coding for IL-6, cyclooxygenase 2,

RANKL, FGF-2 and IL-8, MMP-3, -9 and -13 with compressive forces [12]. These abnormal compressive forces in the form of obesity, immobilization, trauma, and joint instability increase the risk of OA. Mechanical forces cause proliferation and increase differentiation of osteoblasts and osteocytes, escalating bone turnover [13-16]. Studies have shown that weight loss can greatly help in delaying the progression of OA [17]. Thus, increased weight places more force upon the joint causing cartilage changes that can progress the onset of OA.

Adipose tissue in obesity leads to increased synthesis of IL-1, IL-6, tumor necrosis factor alpha (TNF-a), leptin, and adiponectin, which are the proinflammatory cytokines collectively called "adipokines" that are implicated in obesity related OA [18, 19]. In one study, higher BMI in people with OA was significantly correlated with an increased risk of having hip replacement surgery [20]. According to the National Center for Health Statistics, the number and rate of total hip replacements among inpatients aged 45 and over showed an upward trend: 138,700 to 310,800 hip replacements occurred between 2000 and 2010 with a rate of 142.2 to 257.0 replacements per 100,000 inpatients [21]. Interestingly, the percentage of total hip replacements (THR) increased for the younger age groups and decreased for the older age groups between 2000 and 2010 [21]. A strong association was found between obesity and need for (THR) in younger populations (patient mean age 51) in a study by Harma S et al. (2007) [22].

There was no significant correlation between age and either ^{18}F-FDG and ^{18}F-NaF uptake. This could be attributed to the decline in bone mass density with aging, which reduces binding sites of hydroxyl-apatite for ^{18}F-NaF. Conversely, there is increased uptake of the tracer in new bone growth (osteophytes) which is characteristic of OA. However, these two processes negate each other and result in absence of correlation between age and ^{18}F-NaF uptake [23]. The uptake of ^{18}F-FDG is dependent on the amount of GLUT receptors which are significantly higher in the inflammatory cells. This results in increased uptake with inflammation. The section of the joint in this study mainly consisted of bone as compared to soft tissue, which has more inflammatory cells [24]. This could have led to an insignificant correlation of age with ^{18}F-FDG uptake.

The primary limitation of the study was the lack of any patient records with clinical information on the subjects' history of hip problems such as fractures, lesions, and disorders. However, the main purpose of this research was to develop an analysis scheme for semi-quantifying hip disorders with PET. This study presents a methodology to segment the hip joint to assess various hip pathologies, aid in achieving an earlier disease diagnosis, and provide an objective tool to follow disease activity as well as treatment response. Overall, PET/CT is a sensitive imaging modality that can be used to help predict the onset of OA and may have diagnostic and therapeutic implications in musculoskeletal disorders.

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The authors declare that they have no conflicts of interest.

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