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*Original Article*

# Novel technique of detecting inflammatory and osseous changes in the glenohumeral joint associated with patient age and weight using FDG- and NaF-PET imaging

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**Abstract:** Objective: The glenohumeral (GH) joint is a classic ball-and-socket joint of the shoulder subject to various pathologies including osteoarthritis (OA). Degenerative changes of the OA evident on traditional imaging are proceeded by molecular changes, which if detected early could enhance disease prevention and treatment. In this study, we use $^{18}$F-FluoroDeoxyGlucose (FDG) and $^{18}$F-sodium-fluoride (NaF)-PET/CT to investigate the effects limb laterality, age, and BMI on the inflammation and bone turnover of the GH shoulder joint. Methods: FDG and NaF-PET/CT scans of 41 females (mean age of 43.9 ± 14.2 years) and 45 males (mean age of 44.5 ± 13.8 years) were analyzed with a semi-quantitative technique based on predefined region of interest. Results: There was greater FDG uptake in the left side of the GH joint compared to the right in both females (left: 0.79 ± 0.17, right: 0.71 ± 0.2; $P < 0.0001$) and males (left: 0.76 ± 0.19, right: 0.57 ± 0.18; $P < 0.0001$). We also observed a strong positive association between BMI and FDG uptakes in females (left: $P < 0.0001$, r = 0.71, right: $P < 0.0001$, r = 0.58) and males (left: $P < 0.0001$, r = 0.56, right: $P < 0.0001$, r = 0.64). Association between BMI and NaF uptake were found in males as well (left: $P = 0.004$, r = 0.42, right: $P = 0.02$, r = 0.35). Conclusion: Our study demonstrates the varying effect of limb laterality and BMI on FDG and NaF uptake at the GH joint. Adoption of molecular imaging will require future studies that correlate tracer uptake with relevant medical and illness history as well as degenerative change evident on traditional imaging.

**Keywords:** Glenohumeral joint, aging, BMI, limb laterality, FDG, NaF, PET, arthritis

## Introduction

The glenohumeral (GH) or shoulder joint is a ball-and-socket joint formed by the articulation between glenoid fossa of the scapula and head of the humerus, acting as one of the most flexible joints of the body. Osteoarthritis (OA) is a previously underrecognized disease affecting the GH joint present in a significant number of patients as it can lead to chronic pain, reduced function, and decreased overall quality of life [1-3]. Multiple risk factors including increased age and obesity influence the occurrence of OA [4]. At the cellular level, OA is characterized by cartilage inflammation, joint space narrowing, subchondral bone degeneration, and osteophyte formation [5]. Currently, imaging of choice for the shoulder bone are primarily plain radiographs followed by computed tomography (CT) or magnetic resonance imaging (MRI), but they only detect macroscopic changes evidence at later stages of the disease progression [6]. As such, molecular imaging modalities capable of detecting early cellular alterations may be key in the early detection, intervention, and even therapy response monitoring of GH joint arthritis.

$^{18}$F-FluoroDeoxyGlucose (FDG) and $^{18}$F-sodium-fluoride (NaF) positron emission tomography/

computed tomography (PET/CT) are imaging modalities with potential roles for management of GH joint OA by the detection and visualization of early inflammation and bone turnover, respectively. FDG is a radioactive glucose tracer taken up by metabolically active cells such as macrophage and tumor cells regularly used in oncology [7]. Meanwhile, NaF is a tracer taken up in tissues with high osteoblastic activity and bone turnover traditionally used for osteoblastic metastases to the bone such as prostate cancer [8, 9]. Recently, the role of FDG and NaF PET/CT beyond cancers in the detection and monitoring of therapy response in joint and bone disorders such as OA, osteoporosis, rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis has been emerging and gaining traction in the literature [10-16].

In our study, we investigate the potential of FDG and NaF-PET/CT in measuring the inflammatory and metabolic effects of limb laterality, age, and BMI on the GH joint with a semi-quantitative PET approach in an adult population of diverse age and BMI range. We hypothesize that factors that increase inflammation, such as obesity, will be associated with increased FDG uptake while factors associated with osseous degeneration such as aging will increase focal NaF uptake. Additionally, we correlate structural changes of osteoarthritis (OA) with FDG or NaF avidity in a subset of subjects with OA to determine the degenerative changes associated with tracer uptake at the GH joint.

## Material and methods

This retrospective cross-sectional study explores the application of FDG and NaF-PET/CT in the analysis of GH joints. We analyzed healthy volunteer subjects from the Cardiovascular Molecular Calcification Assessed by $^{18}$F-NaF PET CT (CAMONA) study performed at the Odense University Hospital (OUH) in Denmark (NCT01724749). The CAMONA study has been described previously [17].

To describe the study briefly, the CAMONA trial included overall of 139 volunteers from a heterogenous population in Denmark between the ages 12 to 80 years who underwent FDG and NaF PET/CT as a part of the study. Eighty-nine of the volunteers were deemed 'healthy' subjects without any history of cardiovascular disease, immunodeficiency, autoimmune diseases, history of alcohol or drug abuse, history of malignant cancer, indication for mental illness, or were pregnant. Information on the history of joint pain, arthritic disease, or occupation was not recorded. The CAMONA study was conducted from 2012 to 2016 in accordance with the Declaration of Helsinki and approved by the Danish National Committee on Health Research Ethics study. All study participants provided written informed consent.

For our study, we examined the FDG and NaF-PET/CT scans of the 86 of the healthy volunteers. We also identified 20 subjects with evidence of OA on CT image for further evaluation of structural degenerate changes and their association with tracer uptake (**Figure 1A**). The analysis of data from 3 healthy volunteers from the 89 could not be performed because their scan files with appropriate time points were not available at our research database. The demographics of the study subjects are described in **Table 1**.

*Study design*

Scans of the subjects were performed on integrated PET/CT scanners (GE Discovery 690, VCT, RX, and STE) at OUH. PET images were acquired 90 minutes after intravenous administration of 2.2 MBq of NaF per kilogram of body weight or 180 minutes after intravenous injection of 4.0 MBq of FDG per kilogram of body weight. FDG was administered after an overnight fast of at least 8 hours, and blood glucose levels were measured to ensure that it was below 8 mmol/L. NaF PET/CT scans were performed within two weeks of FDG PET/CT scan on average. The age and body mass index (BMI) of the subjects were recorded as a design of the investigation. Our imaging protocol was performed in accordance with the practice guidelines of the Society of Nuclear Medicine [18].

*Image analysis*

Analysis was performed retrospectively and blindly. We first generated regions of the interest (ROIs) in the GH joints with fused PET/CT image and calculated the global mean standardized uptake values (global SUVmean) reflecting NaF and FDG uptakes with a Hounsfield unit (HU) threshold-based segmentation algorithm on the OsiriX software version 12.0 (Pixmeo, Bernex, Switzerland). The 3D

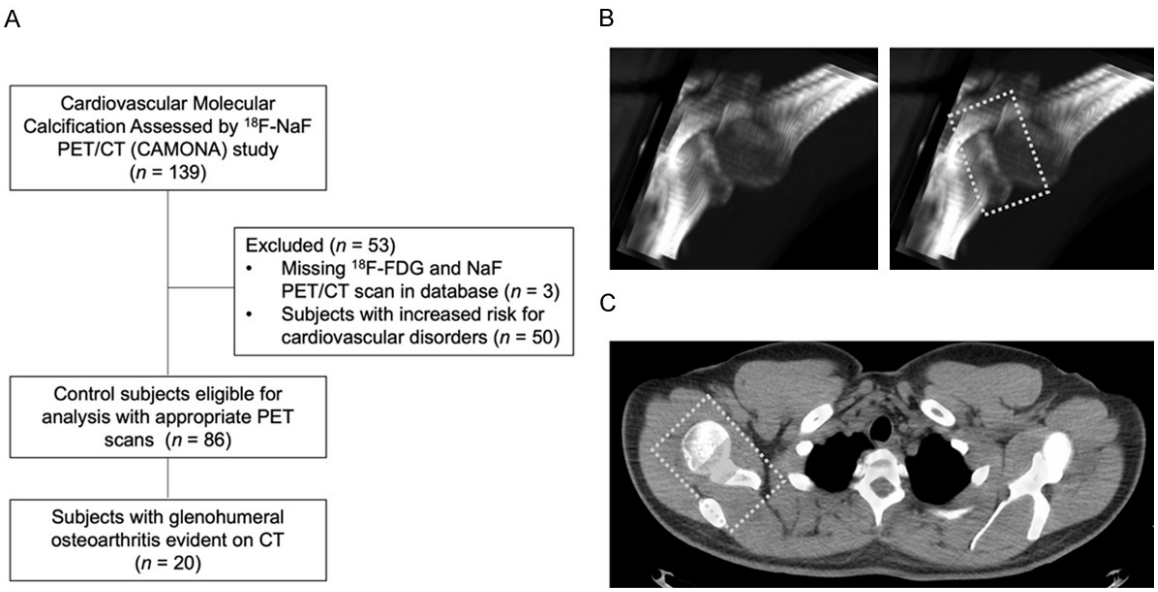


**Figure 1.** Study design and methodology. (A) Diagram outlining the selection of subjects analyzed in the study. (B) 3D Maximum Intensity Projection (MIP) of CT scan delineating the ROI in the right GH joint in gray rectangle and (C) Transverse view of the GH joint with ROI highlighted in gray.

**Table 1.** Study group demographics

| | Female (n = 41) | Male (n = 45) | *p* value | Total (n = 86) |
|---|---|---|---|---|
| Age group (years), mean ± SD | 43.9 ± 14.2 | 44.5 ± 13.8 | 0.85 | 44.2 ± 13.9 |
| BMI (kg/m$^2$), mean ± SD | 25.6 ± 3.19 | 27.6 ± 5.18 | 0.04 | 26.6 ± 4.43 |
| BP (mm Hg), mean ± SD | | | | |
| Systolic | 129.5 ± 17.6 | 130.8 ± 17.9 | 0.74 | 130.2 ± 17.7 |
| Diastolic | 77.3 ± 9.1 | 78.3 ± 9.2 | 0.65 | 77.8 ± 9.2 |
| Smokers (n) | | | | |
| None | 15 | 26 | | 41 |
| Former | 21 | 16 | | 37 |
| Current | 5 | 3 | | 8 |

Characteristics of the subjects in the study including age and body mass index (BMI), Blood Pressure (BP), smoker status, and their standard deviations (SD).

Maximum Intensity Projection (MIP) of CT-scan coronal view was projected to identify the GH joint. ROI was defined as the region including the head of the humerus and glenoid fossa of the scapula 1 cm away from the GH joint (**Figure 1B** and **1C**). Areas outside of the ROI were deleted using the scissor tool. Global mean standardized uptake value (SUVmean) was calculated as the average standardized uptake value (SUV) of all voxels included in each ROI. Maximum SUV (SUVmax) was calculated as the average of maximal SUV within each slice of the ROI.

For the assessment of OA at the GH joint, transverse and coronal CT scans were evaluated for presence of osteophytes, subchondral cysts, and subchondral sclerosis, which are components incorporated in various OA scales such as the Kellgren and Lawrence system [19-21].

*Statistical analysis*

Statistical tests and graphs were performed and made using GraphPad Prism 8 (San Diego, CA, USA). In the graphs and results, error bars and plus-minus signs represent standard deviations (SD). To compare the global SUVmean of FDG or NaF uptake between the left and right sides, Wilcoxon matched pairs signed rank test was performed. Lastly, Spearman correlation test was performed to determine the linear

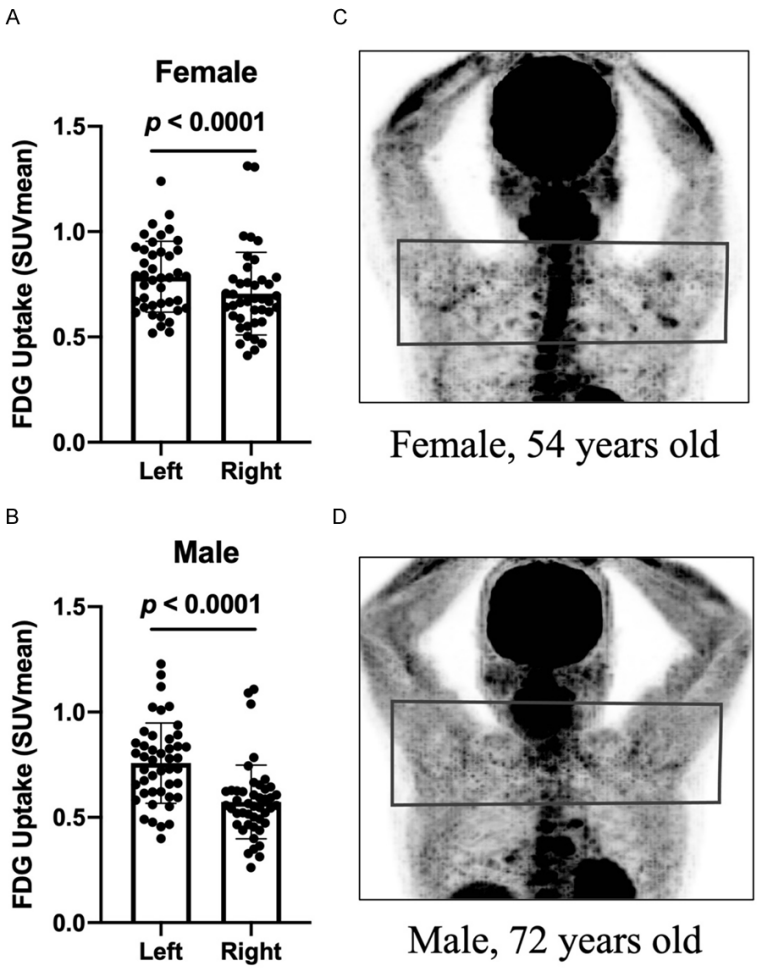


**Figure 2.** Asymmetrical FDG uptake in the GH joint. The left GH joint demonstrates greater FDG uptake than the left in both (A) females and (B) males. Representative Maximum Intensity Projection (MIP) images of NaF-PET scan from (C) female and (D) male subjects. Black rectangle encompasses the GH joint.

association between global SUVmean, age, BMI as well as that between FDG and NaF. We defined *P*-value less than 0.05 ($P < 0.05$) as statistically significant.

## Results

FDG and NaF-PET/CT scans of 41 females (mean age of 43.9 ± 14.2 years) and 45 males (mean age of 44.5 ± 13.8 years) were analyzed in total. No significant differences in the mean age of females and males were found ($P = 0.85$; **Table 1**).

There was greater FDG uptake in the left side of the GH joint compared to the right in both females (left: 0.79 ± 0.17, right: 0.71 ± 0.2; $P < 0.0001$) and males (left: 0.76 ± 0.19, right: 0.57 ± 0.18; $P < 0.0001$; **Figure 2**) as measured by SUVmean. In contrast, no significant differences in laterality were found for NaF uptake in both females (left: 2.22 ± 0.75, right: 2.24 ± 0.84; $P = 0.07$) and males (left: 1.94 ± 0.77, right: 1.98 ± 0.85; $P = 0.38$).

There were no consistent correlations between age and either NaF or FDG uptake (**Table 2**). However, there was also a strong positive association between BMI and FDG uptake in both females (left: $P < 0.0001$, $r = 0.71$, right: $P < 0.0001$, $r = 0.58$) and males (left: $P < 0.0001$, $r = 0.56$, right: $P < 0.0001$, $r = 0.64$; **Figure 3** and **Table 3**). A similar association between BMI and NaF uptake was found in females (left: $P = 0.54$, $r = 0.10$, right: $P = 0.04$, $r = 0.32$) and males (left: $P = 0.004$, $r = 0.42$, right: $P = 0.02$, $r = 0.35$; **Figure 4**) as well.

We also found a positive correlation between FDG and NaF uptake at the GH joint of male subjects (left: $P = 0.002$, $r = 0.45$, right: $P = 0.0006$, $r = 0.49$). A similar positive correlation was found only in the right side for females (left: $P = 0.84$, $r = 0.03$, right: $P = 0.008$, $r = 0.41$; **Figure 5**).

To further assess the relationship between tracer uptake and presence of OA, we evaluated the glenohumeral joint of the patients. Out of all, twenty patients (5 females, 15 males, average age: 53.1) were identified to have GH OA based on the presence of osteophytes, subchondral cysts, or subchondral sclerosis on the CT image (**Table 4**). Of them, 16 right and 14 left joints were categorized to have OA. Most common findings were subchondral cysts (n = 31) followed by subchondral sclerosis (n = 6) and osteophytes (n = 3). For the subchondral cysts, 17 (54.8%) lesions showed only NaF avidity, 7 (22.6%) showed both FDG and NaF

**Table 2.** Correlation between tracer uptake and age

| Variables | Female | *p* value | Spearman R | Male | *p* value | Spearman R |
|---|---|---|---|---|---|---|
| FDG-Left-SUVmean ± SD | 0.79 ± 0.17 | 0.24 | -0.19 | 0.76 ± 0.19 | 0.35 | 0.14 |
| FDG-Right-SUVmean ± SD | 0.71 ± 0.20 | 0.04 | -0.32 | 0.57 ± 0.18 | 0.99 | 0.001 |
| NaF-Left-SUVmean ± SD | 2.22 ± 0.75 | 0.86 | 0.03 | 1.94 ± 0.77 | 0.15 | -0.22 |
| NaF-Right-SUVmean ± SD | 2.24 ± 0.84 | 0.16 | -0.22 | 1.98 ± 0.85 | 0.13 | -0.23 |
| FDG-Left-SUVmax ± SD | 1.50 ± 0.35 | 0.86 | -0.03 | 1.44 ± 0.41 | 0.17 | 0.21 |
| FDG-Right-SUVmax ± SD | 1.40 ± 0.37 | 0.20 | -0.21 | 1.19 ± 0.38 | 0.67 | 0.07 |
| NaF-Left-SUVmax ± SD | 5.21 ± 2.00 | 0.54 | 0.10 | 4.75 ± 2.07 | 0.20 | -0.20 |
| NaF-Right-SUVmax ± SD | 4.67 ± 2.20 | 0.90 | 0.02 | 4.02 ± 2.20 | 0.24 | -0.18 |

Summary of FDG and NaF uptake values and their correlation with age in females and males, including standard deviations (SD).

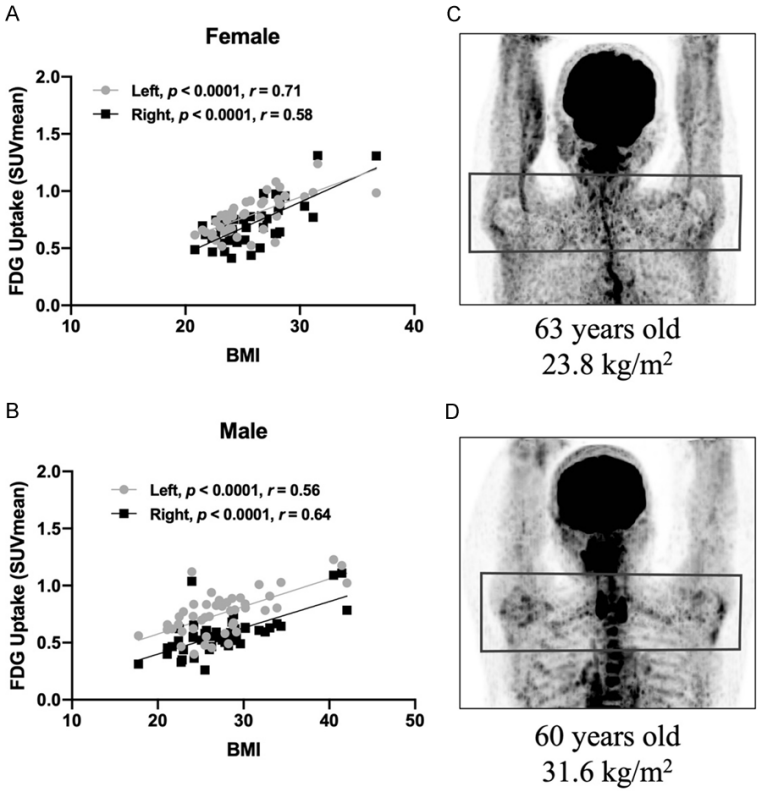


**Figure 3.** Correlation between FDG uptake and BMI at the GH joint. FDG uptake increases with BMI in both (A) females and (B) males. Representative Maximum Intensity Projection (MIP) images of FDG-PET scan from subject with (C) less BMI compared to one with greater BMI (D). Black rectangle encompasses the GH joint.

co-avidity (**Figure 6**), while 7 (22.6%) had no tracer uptake. One out of the 6 (16.7%) sites of subchondral sclerosis showed NaF uptake. On the other hand, none of the osteophyte showed any focal FDG or NaF uptake.

## Discussion

Our study is the first to investigate the inflammatory and metabolic effect of age, BMI, and limb laterality on the GH joint using both NaF and FDG PET/CT on a same study population. Interestingly, we found that the left GH joint had greater FDG uptake compared the right regardless of sex. A study by Schoenfeldt et al. found minimal effect of hand-dominance on the incidence of GH OA suggesting that overuse may not be of significant factor in disease pathogenesis, but rather systemic factors play a greater role [2]. On the other hand, adhesive capsulitis, another pathology affecting the shoulder, have been shown to have greater prevalence in the non-dominant or left arm more than the dominant or right possibly due to hemispheric control of the limb by the brain [22]. Focal FDG uptake in the inferior capsule of the shoulder has been reported in patients with frozen capsulitis, suggesting that FDG uptake of the GH joint in our study population may also correspond to high cellular activity from non-inflammatory cells such as fibroblasts [23, 24]. Instead, OA has been shown to be characterized by circumferential and diffuse FDG uptake in the shoulder, suggesting that deciphering the overall pattern of FDG uptake in the shoulder may be critical for identifying the underlying disease process [25].

We found a significant association between BMI and both FDG and NaF uptake, which is

**Table 3.** Association of tracer uptake with BMI

| Variables | Female | *p* value | Spearman R | Male | *p* value | Spearman R |
|---|---|---|---|---|---|---|
| FDG-Left-SUVmean ± SD | 0.79 ± 0.17 | < 0.0001 | 0.71 | 0.76 ± 0.19 | < 0.0001 | 0.56 |
| FDG-Right-SUVmean ± SD | 0.71 ± 0.20 | < 0.0001 | 0.58 | 0.57 ± 0.18 | < 0.0001 | 0.64 |
| NaF-Left-SUVmean ± SD | 2.22 ± 0.75 | 0.54 | 0.10 | 1.94 ± 0.77 | 0.004 | 0.42 |
| NaF-Right-SUVmean ± SD | 2.24 ± 0.84 | 0.04 | 0.32 | 1.98 ± 0.85 | 0.02 | 0.35 |
| FDG-Left-SUVmax ± SD | 1.50 ± 0.35 | 0.02 | 0.36 | 1.44 ± 0.41 | 0.0003 | 0.51 |
| FDG-Right-SUVmax ± SD | 1.40 ± 0.37 | 0.07 | 0.29 | 1.19 ± 0.38 | 0.0003 | 0.51 |
| NaF-Left-SUVmax ± SD | 5.21 ± 2.00 | 0.98 | 0.003 | 4.75 ± 2.07 | 0.04 | 0.31 |
| NaF-Right-SUVmax ± SD | 4.67 ± 2.20 | 0.33 | 0.15 | 4.02 ± 2.20 | 0.04 | 0.30 |

Summary of FDG and NaF uptake values and their correlation with obesity in females and males, including standard deviations (SD).

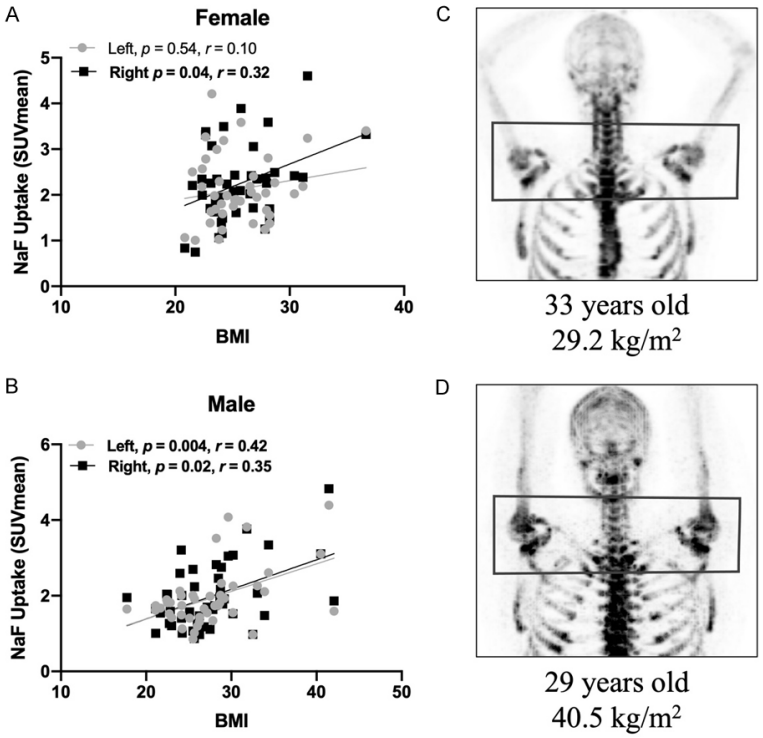


**Figure 4.** Association between NaF uptake and BMI at the GH joint. NaF uptake generally increases with BMI in both (A) females and (B) males. Representative Maximum Intensity Projection (MIP) images of NaF-PET scan comparing subject with (C) less BMI to the to one with greater BMI (D). Black rectangle encompasses the GH joint.

consistent with that obesity remains one of the greatest risk factors for development of OA especially in weight-bearing joints such as the knee [26]. While not weight bearing, the shoulder is hypothesized to be affected by the systemic effects of obesity involving inflammatory cytokines such as adipokines such as leptin and adiponectin [26, 27]. Mechanistically, leptin has been shown to increase the production of matrix metalloproteinases that facilitates degradation of cartilage and pro-inflammatory cytokines such as IL-6 and TNF-α in inflammation [28, 29]. Greater FDG uptake seen in the shoulders of the subjects with greater BMI may precisely correlate to the increased inflammatory environment created by systemic effects of adiposity.

While the interaction of obesity and bone metabolism remains complex, there are several explanations for increased NaF uptake with weight. First is that adipokines increase bone turnover in a similar way to inflammation. In vitro studies demonstrated that leptin could stimulate proliferation and differentiation of osteoblast without affecting the mature osteoclasts [30]. Second is that inflammatory microenvironment associated with obesity has been linked with increased osteoclast formation by the stimulation of the receptor activator of NF-κB (RANK)/RANK ligand pathway, which may increase bone turnover that favors bone degeneration by increasing bone resorption [31]. The increased bone turnover, in turn, could create focal areas NaF uptake despite that there is net overall bone loss. Lastly, changes associated with OA such as subchondral sclerosis and osteophyte for-

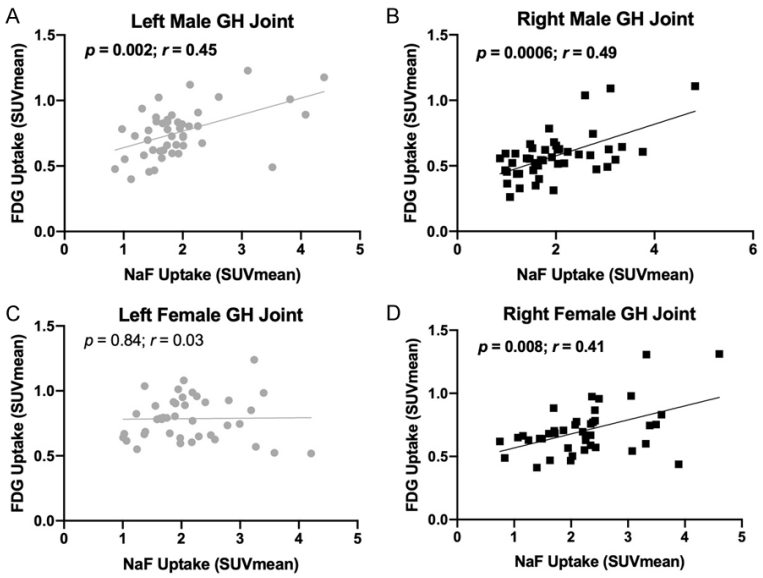


**Figure 5.** Correlation of FDG and NaF uptake in the GH joint. There is a positive correlation between FDG and NaF uptake in both (A) left and (B) right sides of males. Only the (D) right GH joints, not the (C) left, show positive correlation between NaF and FDG uptakes in females.

**Table 4.** Characteristics of subjects with OA

| Variable | OA subjects (n = 20) |
|---|---|
| Mean age (years) | 53.1 ± 11.1 |
| By age group | |
| 20-39 | 2 |
| 40-59 | 10 |
| 60-80 | 8 |
| Sex | |
| Females | 5 |
| Males | 15 |
| Affected side | |
| Right only | 6 |
| Left only | 4 |
| Both | 10 |
| Osteophytes, total | 3 |
| NaF uptake only | 0 |
| FDG uptake only | 0 |
| Both NaF and FDG uptake | 0 |
| No tracer uptake | 3 |
| Subchondral cysts, total | 31 |
| NaF uptake only | 17 |
| FDG uptake only | 0 |
| Both NaF and FDG uptake | 7 |
| No tracer uptake | 7 |
| Subchondral sclerosis, total | 6 |
| NaF uptake only | 1 |
| FDG uptake only | 0 |
| Both NaF and FDG uptake | 0 |
| No tracer uptake | 5 |

Characteristics of subjects with osteoarthritis (OA) by their age group, sex category, affected side, and structural findings including osteophytes, subchondral cysts, and subchondral sclerosis.

mation are osteoblastic in nature, and NaF-PET may be capturing cellular changes associated with them [15, 32].

Our study did not find a consistent correlation between age and FDG or NaF uptake, suggesting that age alone is not a significant influence of tracer uptake at the level of GH joint. A similar finding of no association between aging and tracer uptake at the joint has been previously reported in the knee as well as the acromioclavicular joints [14, 33]. It is possible that aging affects joint inflammation and bone turnover in multifactorial ways that can be in contradictory to one another resulting in insignificant detection of NaF uptake. For instance, aging is associated with increased osteophyte formation that increases NaF uptake, but it also decreases blood flow to the bone decreasing NaF supply and uptake [34]. Hence, aging may theoretically not result in any significant change at a particular region if opposing physiologies are in full equal effect. Another possibility is that the molecular changes associated with OA captured by PET occur early in lifetime and are present in young patients, leading to no difference between younger and older subjects as they both demonstrate some degree of molecular uptake with or without degenerative changes.

We found a positive association between FDG and NaF uptakes in the GH joint, which suggests of coupling between inflammation and bone turnover. Coupling of FDG and NaF uptake has been reported several times in numerous conditions such as rheuma-

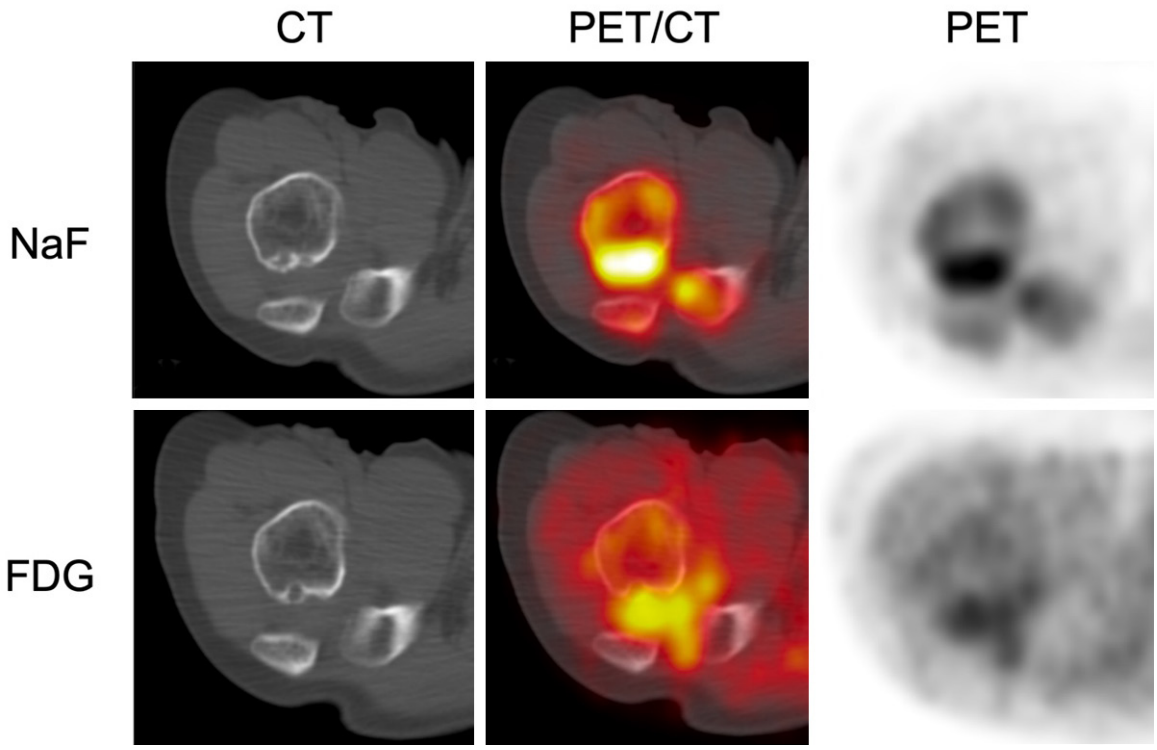


**Figure 6.** Degenerative changes of the GH joint. CT, fused PET/CT, and PET images of right GH joint of a 61-year-old subject with osteoarthritis and subchondral cyst demonstrating both NaF and FDG avidity.

toid arthritis, osseous metastases, and even atherosclerosis [13, 35, 36]. This may not be a surprising finding considering that inflammation and cytokines has a direct role in stimulating both bone metabolism and arterial calcification [37, 38]. However, FDG and NaF uptake may not necessarily overlap spatially. Simoncic et al. for instance NaF and FDG uptakes in the osseous metastases were spatially dislocated, with overlap in the range from 0% to 80% [36]. Further histological or molecular characterization of the coupled regions could be instrumental for determining the pathophysiology of interplay between FDG and NaF.

Our study primarily uses SUVmean instead of SUVmax to evaluate for association of tracer uptake with respect to age, BMI, and laterality. Both SUVmean and SUVmax have been validated in the setting of osteoarthritis [15, 39-41]. SUVmax allows for specific quantitative measurement of a single lesion with the highest uptake, while SUVmean can reflect more comprehensive NaF uptake value if the ROI contains multiple tracer avid lesions. In our study, SUVmean demonstrated more consistent correlation with BMI and age compared to SUVmax. Since degenerative changes are often heterogenous and can occur in multiples within a single voxel of the ROI, we primarily use SUVmean to report the data.

In the 20 patients with evidence of OA by CT, subchondral cyst exhibited the most focal NaF uptake. This finding is supported by previous study by Kogan et al. demonstrating that focal MRI abnormalities in the subchondral bone termed bone marrow lesions, which are known to develop into subchondral cyst like lesions, had significantly higher NaF uptake than osteophytes and sclerosis [42, 43]. Additionally, the study showed that small grade osteophytes did not exhibit NaF avidity, similar to our results. It is possible that since NaF uptake demonstrates early molecular changes, the osteophytes evident on CT have already completed molecular turnover and therefore did not take any new NaF.

Some subchondral cysts also exhibited both FDG and NaF co-avidity, suggesting interplay of inflammation and bone turnover in these

lesions. In terms of pathophysiology, the degradation of bone by osteoclasts and macrophages and subsequent encapsulating bone formation by osteoblast have been implicated in the creation of subchondral bone cysts [44]. As such, FDG uptake may reflect metabolically active macrophage while NaF uptake reflects reactive osteoblastic activity. Previous study has shown that FDG uptake as measured by SUV correlated with clinical severity score for OA [41]. As such, it may be of interest to symptoms related to lesions demonstrating co-avidity to FDG and NaF versus those without.

Our study has some limitations. First is that by retrospective design, we do not have pertinent information on handedness or previous medical history of the subject's shoulder pain, injury, or previous musculoskeletal conditions, which could influence tracer uptakes at the GH joint. Another limitation is that we use CT to examine for findings of OA; the use of MRI and radiographs for OA grading has been much more established in practice and literature [45]. We also did not specifically evaluate for PET avid lesions that do not have degenerative changes evident on CT; these lesions may reflect early molecular, substructural changes of OA. It would be of interest to follow these lesions prospectively and confirm if they lead to actual degenerative changes or cause symptoms.

## Conclusion

Our study demonstrates that limb laterality and obesity could primarily influence FDG and NaF tracer uptake at the GH joint. FDG and NaF-PET/CT may be of valuable tool in assessing various pathologies of the shoulder by detecting inflammation and bone turnover. Future studies incorporating relevant medical history, tracer pattern, and degenerative changes could be of value in adoption of FDG and NaF-PET/CT into the clinical setting.

## Disclosure of conflict of interest

None.

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