Quantitative PET-MR Imaging of Bone Remodeling and Muscle Composition Across Age, Sex, and BMI

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INTRODUCTION: Subchondral bone activity is increasingly recognized as a therapeutic target for disease-modifying osteoarthritis drugs (DMOADs) and as a marker of mechanical stress within the joint [1]. In parallel, muscle decline and sarcopenia have gained traction for their role in osteoarthritis development, sharing many of the same risk factors, including aging, obesity, and altered biomechanics [2]. Sodium fluoride ([^{18}F]NaF) PET uniquely enables in vivo assessment of bone remodeling activity; hybrid PET-MRI allows simultaneous evaluation of multiple musculoskeletal processes, including bone metabolism and muscle composition, providing a comprehensive method to study early joint health. In this study, we investigated how key osteoarthritis risk factors, including age, sex, and body mass index (BMI), affect subchondral bone remodeling as well as muscle quantity and quality in an asymptomatic population. We hypothesized that smaller muscle size and greater fat infiltration, which are considered hallmarks of muscle decline, would be associated with higher subchondral bone turnover (SUVmean/SUVmax), and that these relationships would vary according to age, sex, and BMI.

METHODS: 53 asymptomatic subjects (20-80 years old, 24 female) with no history of knee injury or symptomatic arthritis underwent bilateral knee imaging on a 3T GE PET-MRI scanner. Dynamic [18F]NaF PET scans were acquired before and after a stair-climbing exercise (2.5mCi dose/injection) and were used to quantify standardized uptake value measures (SUVmean, SUVmax) and their exercise-induced change: ΔSUVmean, ΔSUVmax. Femoral, tibial and patellar subchondral bone regions were segmented using an automated pipeline [3]. IDEAL (Dixon) MRI Fat- and Water -only scans of the bilateral thighs were also acquired and used compute muscle fat fraction. The quadriceps, hip adductors, and hamstrings were segmented using an automated pipeline (MuscleMap) [4] and maximum muscle cross-sectional area (CSA) and fat fraction were calculated for each muscle.
Statistical analysis included a linear mixed effects model for each tissue outcome (bone and muscle metrics), where sex (male vs. female), age (years) and BMI (kg/m²) and their interactions were included as fixed-effect predictors, and random intercepts for within-individual correlation. To look at whether bone and muscle values are linked beyond age, sex, and BMI, adjusted Spearman correlations between metrics were calculated. Significance was set to $p<0.05$.

RESULTS: For asymptomatic adults, both age and BMI were consistently associated with higher baseline bone SUV/SUVmax. Exercise-induced bone uptake (ΔSUV, ΔSUVmax) was more strongly modulated by BMI and sex, with males showing reduced responses. Age was associated with decreased maximum muscle CSA as well as increased fat fraction. BMI was strongly linked to increased CSA and fat fraction. Males had significantly larger CSA, but similar fat fraction compared to females. BMI emerged as the strongest and most consistent predictor across all bone and muscle metrics. Age showed divergent effects (positive for bone uptake, negative for muscle size, positive for fat infiltration) as expected. Sex differences were more pronounced in muscle CSA and post-exercise bone response. For cross-tissue analysis, significant associations were observed between subregional bone SUVmax and muscle composition. For SUVmax vs muscle CSA, negative correlations were strongest in the femoral and patellar regions, including the lateral central femur (hamstrings r= -0.34, hip adductors r= -0.35, both p<0.05) and patella (hamstrings r= -0.33, quadriceps r= -0.28, both p<0.05). With exercise-induced change in SUVmax, similar negative relationships persisted, mostly in the trochlea (quadriceps r= -0.30, p<0.05) and lateral central femur (quadriceps r= -0.28, p<0.05). In contrast, SUVmax vs fat fraction revealed positive associations, particularly in the medial posterior femur with hamstrings (r=0.41, p<0.01) and hip adductors (r=0.29, p<0.05), and in the lateral central femur with hamstrings (r=0.29, p<0.05). For change in SUVmax vs fat fraction, associations were weaker but remained significant in the medial posterior femur with hamstrings (r=0.35, p<0.01).

DISCUSSION: BMI appears to be a central factor shaping both bone metabolism and muscle composition, with consistent links to higher bone uptake, larger muscle size, and increased fat infiltration. Aging shows a more complex relationship, showing expected age-related declines in muscle quantity and quality alongside elevated bone activity. As expected, sex differences were observed in muscle size, likely due to differences in subject size. However, sex differences were also seen in how bone responds to exercise loading, underscoring biological variation in musculoskeletal adaptation. Moreover, muscle seems to be related to knee subchondral bone metabolism: greater muscle mass is generally associated with lower metabolic demand in bone, whereas lower muscle quality relates to higher bone turnover. As subchondral bone metabolism is linked to mechanical loading, these results suggest that muscle decline may contribute to joint instability, leading to abnormal or focal loading across the joint. Such altered mechanics may heighten subchondral bone remodeling demands and accelerate degeneration of other joint tissues. Collectively, these findings underscore the interdependence of bone and muscle in regulating joint mechanics and metabolism and demonstrate how PET-MRI can capture these interactions as potential early markers of osteoarthritis risk and musculoskeletal decline.

SIGNIFICANCE/CLINICAL RELEVANCE:
Quantitative [^{18}F]NaF PET-MRI enables in vivo assessment of subchondral bone metabolism and muscle composition. Across asymptomatic adults, BMI was consistently linked to higher bone uptake, larger muscle CSA, and greater fat infiltration. Age showed reduced muscle mass and quality as well as increased subchondral bone remodeling, indicative of higher localized bone loading. Sex differences were most evident in exercise-induced bone response. Together, these findings demonstrate age, sex, and BMI influence musculoskeletal biomarkers before clinical symptoms of osteoarthritis appear.

REFERENCES: [1] Roelofs, OandC (2024); [2] Haddock, EJNMMI (2019); [3] Goyal, medRXIV (2025); [4] Github, MuscleMap; [5] Kogan, JMRI (2017).

IMAGES AND TABLES:

Table 1. Linear mixed effects model results for each tissue metric, using a 20-year-old male with BMI 17 kg/m² as baseline. Significant results are bolded and color-coded. Age and BMI are consistently associated with higher bone metabolism and worse muscle quality.

		Predictor	Beta (Estimate)	p-value	95% CI Lower	95% CI Upper
Bone	SUV	**Age**	**0.008**	**0.042**	**0.000**	**0.015**
		BMI	**0.066**	**<0.001**	**0.034**	**0.097**
		Sex[T.M]	-0.239	0.064	-0.492	0.014
	SUVmax	**Age**	**0.012**	**0.001**	**0.005**	**0.019**
		BMI	**0.060**	**<0.001**	**0.029**	**0.090**
		Sex[T.M]	-0.207	0.095	-0.449	0.036
	Exercise-Induced ΔSUV	Age	0.006	0.071	0.000	0.011
		BMI	**0.041**	**0.002**	**0.015**	**0.066**
		Sex[T.M]	**-0.229**	**0.030**	**-0.437**	**-0.022**
	Exercise-Induced ΔSUVmax	**Age**	**0.008**	**0.008**	**0.002**	**0.014**
		BMI	**0.042**	**0.001**	**0.016**	**0.067**
		Sex[T.M]	-0.201	0.055	-0.407	0.004
Muscle	Maximum CSA	**Age**	**-0.003**	**0.020**	**-0.006**	**0.000**
		BMI	**0.026**	**<0.001**	**0.014**	**0.038**
		Sex[T.M]	**0.239**	**<0.001**	**0.153**	**0.325**
	Fat Fraction	**Age**	**0.010**	**<0.001**	**0.006**	**0.013**
		BMI	**0.026**	**0.002**	**0.010**	**0.042**
		Sex[T.M]	-0.004	0.951	-0.120	0.113

Figure 1. Heatmaps display Spearman's correlation coefficients (*r*) between bone PET and muscle measures (max CSA, fat fraction), overlaid on segmentations of the femur (top row), tibia (middle row), and patella (bottom row). * p<0.05, ** p<0.01.