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ORIGINAL ARTICLE

Exercise training reduces inflammatory metabolic activity of visceral fat assessed by ^{18}F-FDG PET/CT in obese women

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Abstract

Objectives: Obesity plays pivotal roles in the increased risk of cardiometabolic disease via induction of the inflammatory reaction from macrophages in visceral adipose tissue (VAT), which may elevate the inflammatory activity of VAT. This prospective study aimed to evaluate whether the inflammatory activity of VAT existed in association with systemic inflammation, and whether exercise could ameliorate the inflammatory activity of VAT assessed by ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in obese women.

Design and Patients: A total of 23 obese women who participated in an exercise program were included. Subjects underwent ^{18}F-FDG PET/CT before the start of the exercise program (baseline) and after the completion of the 3-month exercise program. For the assessment of VAT metabolic activity, the maximum standardized uptake value (SUVmax) and the mean standardized uptake value (SUVmean) were measured. The SUVmax of spleen, bone marrow (BM) and the high-sensitivity C-reactive protein (hsCRP) were used as a surrogate marker for systemic inflammation.

Results: Baseline SUVmax of VAT was positively correlated with the SUVmax of spleen, BM and hsCRP, whereas VAT SUVmean was not correlated. Exercise reduced SUVmax of VAT in addition to adiposity, the SUVmax of spleen, BM and hsCRP. However, VAT SUVmean was not significantly changed. Furthermore, the association of SUVmax of VAT, and the SUVmax of spleen, BM and hsCRP was no longer relevant after exercise.

Conclusion: In obese women, the SUVmax of VAT assessed by ^{18}F-FDG PET/CT was associated with systemic inflammation and exercise reduced the SUVmax of VAT and abrogated its association with systemic inflammation.

KEYWORDS

exercise, inflammation, obesity, positron emission tomography, visceral fat

1 | INTRODUCTION

Obesity is an important public health concern worldwide with a continuously increasing prevalence.[1] Furthermore, it has been considered an important risk factor for cardiometabolic disease, which is responsible for approximately 3 million deaths per year globally.[1,2]

Body fat tissue is classically distributed to the visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). VAT, unlike SAT, is a well-known key player in obesity-induced cardiometabolic disease; it not only stores lipids but also is a metabolically active endocrine and paracrine organ.[3,4] In addition, altered body fat distribution, which is related to abdominal obesity, seems to contribute to the shifting of VAT toward metabolically active status, although the detailed mechanism

remains unclear.[3,4] Metabolically active VAT secretes cytokines and bioactive mediators, thereby promoting inflammatory process [3,4] which can increase insulin resistance and aggravate atherosclerotic plaque vulnerability, which eventually leads to higher risks of cardiometabolic diseases.[5-7] Thus, inflammatory activity in metabolically active VAT is a crucial mechanism in obesity-induced cardiometabolic disease.

Considering the relationship between VAT and cardiometabolic disease, increased visceral adiposity has been regarded as a risk factor due to increasing inflammatory activity.[8,9] However, measurement of visceral adiposity alone is insufficient to reflect the inflammatory activity of VAT.[10,11] This conventional measurement can only reflect the structural area of VAT instead of functional properties. During the inflammation, glucose uptake is increased in the immune cells such as macrophages.[12] This basic physiology of glucose metabolism in inflammatory process is the underlying key principle in ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) to assess inflammatory activity of inflamed tissue, especially atherosclerotic plaques.[13] As macrophages are also increased in metabolically active VAT,[3,4] we postulated that ^{18}F-FDG PET/CT could reflect the inflammatory activity in metabolically active VAT.

Exercise confers significant health benefits and reduces the risk of cardiometabolic disease, partly because of its anti-inflammatory effect, which could be attributed to the reduction in VAT mass with a reduction in pro-inflammatory activity of preexisted macrophages and subsequent production of inflammatory cytokines in VAT.[14] Numerous previous studies have been reported that exercise can reduce VAT mass which is measured by CT or magnetic resonance image (MRI).[15,16] However, there is a lack of non-invasive imaging study which can directly reflects the functional change of VAT inflammatory activity by exercise intervention, thereby supporting the use of exercise as an intervention in reducing inflammation in obese population.

In this prospective study, we aimed to evaluate whether the metabolic activity of VAT assessed by ^{18}F-FDG PET/CT exists in association with systemic inflammation, and whether exercise training could ameliorate the inflammatory metabolic activity of VAT in obese women.

2 | MATERIALS AND METHODS

2.1 | Subjects

Subjects included obese women prospectively recruited from a local community health centre between June 2008 and March 2009. Obesity is defined as a body mass index (BMI) ≥25 kg/m^2, according to the clinical guideline for obesity in Korea.[17] Subjects with cardiovascular disease, uncontrolled diabetes mellitus, hypertension (≥stage 2), malignancy, and severe hepatic or renal disease and those receiving hormone replacement therapy or treated with any medications that could affect inflammatory condition within 6 months of the study were excluded. A total of 23 obese women were enrolled in this study. The institutional review board of Korea University Guro Hospital (approval no. GR0888-005) approved the study design, and all subjects provided written informed consent.

2.2 | Study design

Subjects participated in an exercise training program under supervision 5 days per week for 3 months without diet restriction. All anthropometric and clinical laboratory measurements were performed before the start of the exercise training program (baseline) and after the completion of the 3-month exercise training program (post-exercise). ^{18}F-FDG PET/CT was also performed at baseline and post-exercise.

2.3 | Exercise protocol

The exercise training program consisted of aerobic exercise and subsequent muscle-resistant training, recommended by the American College of Sports Medicine (ACSM) and the American Heart Association (AHA) to promote and maintain health.[18] In each day, during aerobic exercise, subjects took 30 minutes of moderate-intensity activity (walking at very brisk pace; 4 mph) followed by 20 minutes of vigorous intensity (running at 7 mph). Intensity was determined based on metabolic equivalents (METs). Moderate intensity was defined as between 3 and 6 METs whereas vigorous intensity was defined as above 6 METs.[18] Muscle-resistant training was designed to perform 8-10 exercises involving the major muscle groups with 8-12 repetitions.[18]

2.4 | Anthropometric and clinical laboratory measurements

BMI was calculated as weight (kg) divided by height squared (m^2). Waist circumference was measured at the midpoint between the lower border of the rib cage and the iliac crest. Hip circumference was measured at the widest circumference over the buttocks in standing position.

All blood samples were acquired after 12-hour overnight fasting. Levels of total cholesterol, triglyceride, high-density lipoprotein cholesterol, aspartate transaminase and alanine aminotransferase were measured using a chemistry analyzer (Hitachi 747, Hitachi). The high-sensitivity C-reactive protein (hsCRP) levels were measured by using Dade Behring BNII analyzer (Siemens). Lipid profiles including total cholesterol, triglycerides, low-density lipoprotein and high-density lipoprotein cholesterol were measured by standard enzymatic methods after 8 hours of fasting. Fasting glucose level was measured using the glucose oxidase method. Brachial blood pressure was measured using an automatic oscillometric device (OMRON M10-IT, OMRON Healthcare).

2.5 | ^{18}F-FDG PET/CT protocol

All subjects were fasted for at least 6 hours before undergoing ^{18}F-FDG PET/CT to maintain a blood glucose level of <180 mg/dL. PET/CT scan was started 1 hour after the injection of 5.29 MBq/kg (0.14 mCi/kg) ^{18}F-FDG using an integrated PET/CT scanner (GEMINI TF, Philips Medical

Systems, Cleveland, OH, USA). CT scan (120 kVp, 50 mA, 4-mm slice thickness) was performed for attenuation correction, followed by PET scan. The PET unit had 18-cm axial field of view and 4.4-mm spatial resolution. PET images were reconstructed using an iterative algorithm (three-dimensional row-action maximum likelihood algorithm).

2.6 | Image analysis

Images were reviewed by two experienced nuclear medicine physicians (KP and SK) using a dedicated commercially available workstation (Extended Brilliance Workspace version 3.5, Philips Healthcare, Eindhoven, Netherlands). For the measurement of VAT area, cross-sectional CT images at the L4-L5 vertebral disc space were used.[19] On CT images, fat regions including VAT were identified based on the predefined Hounsfield units (ranging from −70 to −110), as previously described.[20-22] VAT area was manually delineated as intra-abdominal fat surrounded by abdominal and oblique muscular walls excluding the vertebral columns and paraspinal muscles.

For the assessment of metabolic activity of VAT and SAT, regions of interest (ROIs) were placed on the targeted region, and standardized uptake value (SUV) was calculated as follows:

$$\text{SUV} = \text{Tracer activity (ROI) (MBq/mL)} / \text{Injected dose (MBq)} / \text{Total body weight (g)}$$

For the evaluation of metabolic activity of VAT, a total of 10 ROIs were placed on VAT area and manually adjusted to exclude overspill ^{18}F-FDG uptake in the vessel, intestine, and/or muscle, as previously described.[20-22] Averaged SUVmax and SUVmean of these 10 ROIs were determined and defined as VAT SUVmax and VAT SUVmean, respectively. For the evaluation of functional activity of SAT, 10 ROIs were located on the buttock area or subcutaneous anterior abdominal wall. Averaged SUVmax and SUVmean of these 10 ROIs were determined and defined as SAT SUVmax and SAT SUVmean, respectively.

2.7 | Measurement of systemic inflammatory surrogate markers

In addition to hsCRP, both spleen SUVmax and bone marrow (BM) SUVmax can also be used as surrogate markers for reflecting systemic inflammation.[23] For the assessment of metabolic activity of spleen and BM, the SUVmax of spleen and BM were measured as previously described.[23] ROIs were placed on the spleen and the third to fifth lumbar vertebrae. Averaged SUVmax from all transaxial slices was used as representative SUVmax for the entire organ.

2.8 | Statistical analysis

All data were presented as mean ± standard deviation. Normality was tested using the Shapiro-Wilk test. Paired *t* test or Wilcoxon signed-rank test was used to compare baseline and post-exercise. Differences between the two groups were analysed using Student's *t* test or the Mann-Whitney *U* test. Pearson's or Spearman's correlation coefficient and multiple linear regression analyses were also performed. SPSS version 17.0 (SPSS Inc) and MedCalc version 18.5 (MedCalc, Mariakerke, Belgium) were used for data analysis. A *P*-value of <.05 was considered statistically significant.

TABLE 1 Baseline characteristics of subjects

Baseline characteristics	n = 23
Age (years)	46 ± 8.0
Height (cm)	156.8 ± 5.5
Smoking (current), n (%)	0 (0)
Alcohol drinking, n (%)	8 (34.8)
Menopause, n (%)	12 (52.2)
Hypertension (stage 1), n (%)	4 (17.4)
Diabetes, n (%)	0 (0)
Dyslipidaemia, n (%)	7 (30.4)
Medication, n (%)	0 (0)

Note: Age and height were presented as mean ± standard deviation.

TABLE 2 Changes in body composition and clinical laboratory measures after 3-month exercise training

Characteristics	Baseline	Post-exercise	*P*
Body weight (kg)	65.3 ± 7.5	62.4 ± 8	<.001
BMI (kg/m^2)	27.5 ± 2.2	25.3 ± 2.5	<.001
Waist circumference (cm)	83.2 ± 5.5	81.3 ± 5.9	.05
Hip circumference (cm)	98.6 ± 5.1	95.4 ± 4.6	<.001
AST (IU/L)	12.3 ± 3.9	11.7 ± 5.1	.47
ALT (IU/L)	21 ± 3.9	21 ± 4.2	.69
Triglyceride (mg/dL)	105.7 ± 47.3	112.1 ± 46.6	.26
Total cholesterol (mg/dL)	177.4 ± 30.6	178.3 ± 30	.89
HDL-C (mg/dL)	49.9 ± 11.3	49.9 ± 9.2	.71
LDL-C (mg/dL)	106.3 ± 29.5	101.3 ± 37.9	.77
Glucose (mg/dL)	89 ± 8.3	88 ± 9.6	.47
SBP (mm Hg)	123.7 ± 16.4	116.4 ± 10.3	.002
DBP (mm Hg)	75 ± 11	71.6 ± 8	.009
VAT area (cm^2)	154.4 ± 32.7	142.3 ± 37.5	.007
hsCRP (mg/L)	1.98 ± 3.42	0.86 ± 1.34	.006

Note: All data were presented as mean ± standard deviation.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SAT, subcutaneous adipose tissue; SBP, systolic blood pressure; VAT, visceral adipose tissue.

TABLE 3 Correlations between metabolic parameters of adipose tissue, VAT area, and systemic inflammatory parameters, the basal state and state after exercise training

		VAT		SAT	
Status	**Parameters**	**SUVmax**	**SUVmean**	**SUVmax**	**SUVmean**
Baseline	VAT area (cm^2)	0.31	−0.54*	−0.14	−0.06
	Spleen SUVmax	0.67**	−0.32	−0.19	−0.09
	BM SUVmax	0.43*	−0.1	−0.31	−0.09
	hsCRP	0.62**	−0.17	−0.28	−0.16
Post-exercise	VAT area (cm^2)	0.25	0.06	0.01	0.06
	Spleen SUVmax	-0.02	−0.22	0.36	0.1
	BM SUVmax	0.31	0.36	−0.02	0.09
	hsCRP	0.33	0.12	0.07	−0.08

Note: Data were correlation coefficients from correlation analysis.

Abbreviations: –, not significant; BM, bone marrow; hsCRP, high-sensitivity C-reactive protein; SAT, subcutaneous adipose tissue; SUVmax, maximum standardized uptake value; SUVmean, mean standardized uptake value; VAT, visceral adipose tissue.

*$P < .05$.

**$P < .01$.

3 | RESULTS

The baseline characteristics of all subjects are presented in Table 1. All subjects completed the scheduled exercise training program. As shown in Table 2, a 3-month exercise training significantly reduced body adiposity, blood pressure, and decreased the level of hsCRP.

3.1 | Correlation between body adiposity, metabolic activity of adipose tissue and systemic inflammatory activity at baseline

As shown in Table 3, at baseline, VAT SUVmax was positively correlated with the systemic inflammatory surrogate markers including spleen SUVmax, BM SUVmax and hsCRP, but not with the VAT area; in contrast, VAT SUVmean showed no significant correlation with spleen SUVmax, BM SUVmax and hsCRP, but with negatively correlated with VAT area. All metabolic parameters of SAT exhibited no correlation with VAT area and systemic inflammatory surrogate markers. In multiple linear regression analysis in Table 4, unlike to VAT SUVmean, only VAT SUVmax was associated with the spleen and BM SUVmax and BMI. These results reveal that VAT SUVmax could reflect the systemic inflammatory activity in obese women at baseline.

3.2 | The effect of exercise training on metabolic activity of adipose tissue, and systemic inflammatory surrogate markers

Exercise training significantly reduced VAT SUVmax ($P < .001$) (Figures 1 and 2A), whereas SAT SUVmax was not significantly affected ($P = .25$) (Figures 1 and 2B). VAT SUVmax was significantly higher than SAT SUVmax at both baseline ($P < .001$) and post-exercise ($P < .001$) (Figure 2C,D). On the other hand, both VAT SUVmean and SAT SUVmean were not changed by exercise training intervention ($P = .57$ and $P = .24$, respectively) (Supplementary Figure S1A,B). However, VAT SUVmean was also significantly higher than SAT SUVmean at both baseline ($P < .001$) and post-exercise ($P < .001$) (Supplementary Figure S1C,D). Furthermore, consistent with the effect of exercise on hsCRP, exercise training also significantly reduced both spleen and BM SUVmax (1.73 ± 0.28 to 1.6 ± 0.21, $P = .004$; 1.55 ± 0.26 to 1.43 ± 0.22, $P = .018$).

3.3 | Correlation between body adiposity, metabolic activity of adipose tissue and systemic inflammatory activity after exercise training

As shown in Table 3, at post-exercise, the correlations between VAT SUVmax and spleen SUVmax, BM SUVmax, and hsCRP were disappeared, nor with the VAT area or those of SAT. In multiple linear regression analysis in Table 4, the associations between VAT SUVmax and spleen SUVmax, BM SUVmax, and hsCRP were also disappeared after completion of 3-month exercise training. Therefore, VAT SUVmax was reduced and became subsequently not to be related to systemic inflammation with exercise training for 3 months in obese women.

4 | DISCUSSION

To the best of our knowledge, this is the first prospective study to investigate the anti-inflammatory effect of exercise training on functional metabolic activity using ^{18}F-FDG PET/CT. In this present study, we clearly identified that VAT SUVmax measured by ^{18}F-FDG PET/CT was associated with systemic inflammation in obese women, and exercise training for 3 months reduced VAT SUVmax and its association with systemic inflammation became disappeared.

TABLE 4 Multiple linear regression analysis using metabolic parameters of VAT as dependent variables

Variable		Baseline		Post-exercise	
Dependent	**Independent**	***β***	***P***	***β***	***P***
VAT SUVmax	BMI[a]	0.042	.007	0.05	<.001
	BMI[b]	0.046	.001	0.051	<.001
	VAT area[a]	0	.606	0	.804
	VAT area[b]	0	.585	0	.818
	Spleen SUVmax[a]	0.309	.001	−0.152	.184
	Spleen SUVmax[b]	0.305	.001	−0.127	.251
	BM SUVmax[a]	0.196	.024	0.199	.147
	BM SUVmax[b]	0.196	.021	0.127	.259
	hsCRP[a]	0.004	.575	−0.024	.333
VAT SUVmean	BMI[a]	−0.001	.848	0.008	.271
	BMI[b]	−0.003	.536	0.009	.239
	VAT area[a]	−0.001	.056	0	.373
	VAT area[b]	−0.001	.055	0	.367
	Spleen SUVmax[a]	−0.045	.222	−0.192	.028
	Spleen SUVmax[b]	−0.044	.226	−0.182	.027
	BM SUVmax[a]	0.014	.692	0.186	.066
	BM SUVmax[b]	0.014	.689	0.159	.056
	hsCRP[a]	−0.002	.572	−0.009	.603

Abbreviations: BM, bone marrow; BMI, body mass index;hsCRP, high-sensitivity C-reactive protein; SUVmax, maximum standardized uptake value; SUVmean, mean standardized uptake value; VAT, visceral adipose tissue.

[a]After adjustment for age, body weight, waist circumference, hip circumference, smoking, alcohol drinking, menopause, hypertension and dyslipidaemia.

[b]After adjustment for the above covariates and hsCRP.

In our study, VAT SUVmax was found to be closely associated with systemic inflammatory status in contrast to VAT SUVmean in obese women. Interestingly, recent previous studies report that VAT SUVmean was lower in obese subjects than in metabolically healthy lean subjects.[24,25] Thus, considering the coupling relationship between the inflammatory activity of VAT and obesity, the use of VAT SUVmean instead of VAT SUVmax seems to be limited to reflect the inflammatory metabolic activity of VAT in obese population. Although the detailed underlying mechanism remains unclear, the different result between VAT SUVmax and VAT SUVmean in obese population can be explained by the different glucose metabolism of adipocytes and inflammatory cells which are primarily involved in VAT inflammation.[26]

In inflamed VAT, adipocytes become enlarged in size and increase amount of non-esterified fatty acid secretion, which is associated with a down-regulation of glucose transporter-4 (GLUT-4), thereby decreasing glucose uptake.[27] Conversely, macrophages, the predominant inflammatory cell type in VAT, escalate glucose uptake mainly thorough GLUT-1 with increasing degree of VAT inflammation.[28] Thus, as VAT is largely composed of adipocytes, decreased glucose metabolism of adipocytes may contribute to the reduced VAT SUVmean, whereas VAT SUVmax can indicate the maximal inflammatory activity of inflammatory cells, such as macrophages.

Regular exercise is a well-known activity to exhibit anti-inflammatory effect on dysfunctional VAT via inhibition of macrophage infiltration to VAT and prevention of phenotype switching from M2 to M1 macrophages in VAT.[14] In the present study, VAT SUVmax was lowered by exercise training intervention, whereas VAT SUVmean was unchanged. Of course, exercise training reduced the level of hsCRP and the SUVmax of both spleen and BM, which are known to be related to systemic inflammatory activity.[23,29] Regarding this point, the reduction of VAT SUVmax could be explained by the attenuation of the inflammatory activity of VAT, which is related to the anti-inflammatory effects of exercise training. Furthermore, this concept is robustly supported by previous study, which reports that ^{18}F-FDG uptake reflects pro-inflammatory M1 macrophage activity rather than M2 macrophage.[13]

However, despite the robust evidence of simultaneous lowering both systemic inflammatory makers and VAT SUVmax, it is intriguing that the relationship between VAT SUVmax and metabolic activity of systemic immune organs was disappeared after exercise training. We do not know the exact reason. But, in the result of the present study, the VAT SUVmax was decreased with exercise training down to approximately half of the baseline level that might be the intrinsic level of VAT SUVmax in normal population, and this might explain the presence of healthy obesity. Further studies are needed to verify the mechanism of this result.

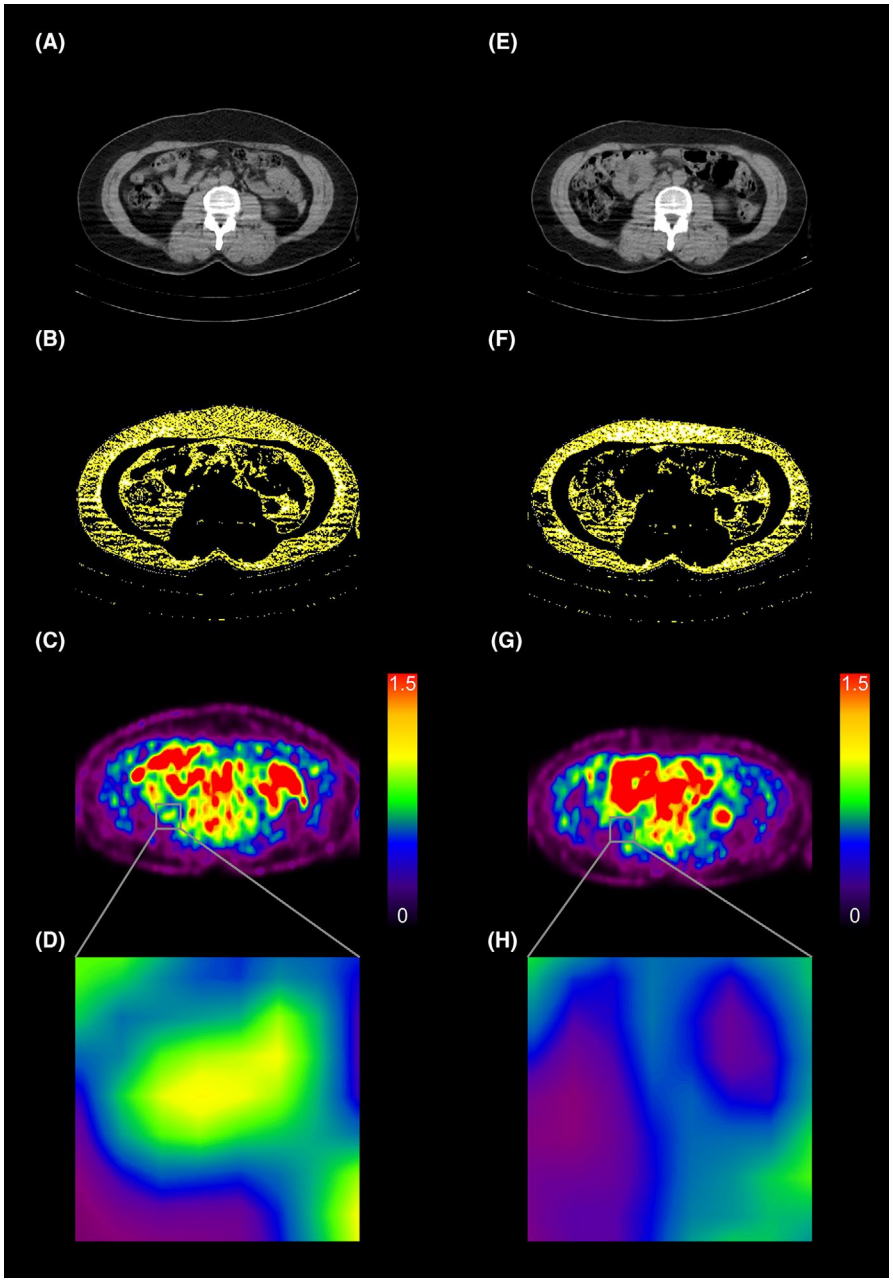

FIGURE 1 Representative images of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) at baseline (A to D) and post-exercise (E to H) on the same participant. Transaxial CT images (A and E). Adipose tissues including visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) were identified using a predefined Hounsfield unit (HU) value for fat tissue ranging from −70 to −110 HU (visualized in yellow colour) (B and F). Transaxial ^{18}F-FDG PET images corresponding to the above transaxial CT images were acquired (C and G). Magnified ^{18}F-FDG PET images of the VAT region at baseline (D) and post-exercise (H). All images were normalized to the same scale of the standardized uptake value (SUV) (1.5)

Recently, several healthcare professional societies concerned with the relationship between obesity and cardiometabolic disease have increasingly focused on the assessment of VAT inflammation for risk stratification and treatment evaluation in the management of overweight and obesity.[30,31] Although tissue biopsy can be regarded as a gold standard to measure VAT inflammation, biopsy procedure is cumbersome and is almost impossible in clinical practice. Thus, it is conceivable that VAT SUVmax assessed by ^{18}F-FDG PET/CT could be a surrogate marker for reflecting VAT inflammation and could play a complement role to current anthropometric measurement in the risk stratification and treatment of obesity-induced cardiometabolic disease.

This study has several limitations. First, despite being a prospective study, it was performed on a relatively small number of cohorts, which might have resulted in various levels of bias. Second, the exercise training program in this study consisted of only one program. Multiple exercise conditions such as training intensity, training period, and exercise type including aerobic and/or muscle-resistant training might have diverse effects on VAT metabolism. Third, we could not control the participant's diet such as glycemic, refined and/or processed food. Fourth, although ^{18}F-FDG PET/CT is a well-known imaging modality for the evaluation of VAT metabolism,[11,20-22,24,25] we could not perform a histopathological analysis of tissue sample from VAT, which could support our findings. Finally, we could not control all the possible factors that might affect FDG uptake such as plasma glucose and insulin levels and the image acquisition time after tracer injection.

In conclusion, in obese women, VAT SUVmax assessed by ^{18}F-FDG PET/CT could reflect the inflammatory metabolic activity of VAT and exercise training for 3 months decreased VAT SUVmax

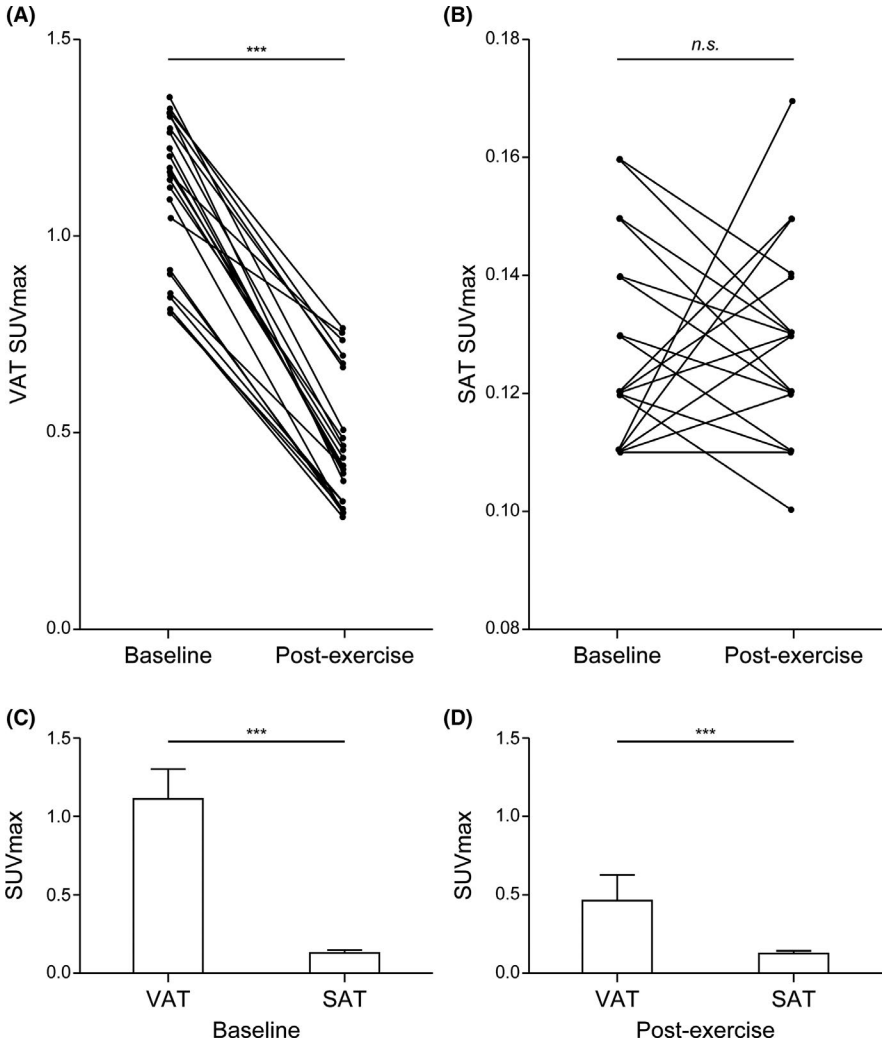

FIGURE 2 Exercise significantly reduced the maximum standardized uptake value of visceral adipose tissue (VAT SUVmax). A, Change in VAT SUVmax at baseline and post-exercise. B, Change in the maximum standardized uptake value of subcutaneous adipose tissue (SAT SUVmax) at baseline and post-exercise. C, Comparison between VAT SUVmax and SAT SUVmax at baseline. D, Comparison between VAT SUVmax and SAT SUVmax at post-exercise. ***$P < .001$; *n.s.*, not significant

and abolished its association with systemic inflammation. Although our data are preliminary, these findings might support that exercise training could be a promising non-pharmacological strategy to reduce inflammatory activity of VAT and ^{18}F-FDG PET/CT could be a surrogate marker for assessing the anti-inflammatory effect of therapeutic intervention targeted to inflamed VAT.

CONFLICT OF INTEREST

The authors declared that no competing interests exist.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restriction.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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