Glucose metabolism of visceral adipose tissue measured by $^{18}$F-FDG PET/CT is related to the presence of colonic adenoma

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This study investigated the relationships between the area and metabolic activity of adipose tissue and the presence of colorectal adenoma (CRA). Our institutional review board approved the study and waived informed consent. A total of 212 subjects who underwent fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) and colonoscopy for routine health check-ups were enrolled. The volumetric parameters of areas of visceral (VAT$_{av}$), subcutaneous (SAT$_{av}$), and total adipose tissue (TAT$_{av}$) and calculated visceral-to-subcutaneous adipose tissue ratio (VSR) and visceral-to-total adipose tissue ratio (VAR) were considered. Metabolic parameters of standardized uptake value (SUV) of visceral ($c_{SUV}_{max}$, $c_{SUV}_{mean}$), subcutaneous ($sc_{SUV}_{max}$, $sc_{SUV}_{mean}$), and calculated visceral-to-subcutaneous adipose tissue ratio ($VSR_{max}$, $VSR_{mean}$) were considered. Anthropometric data of height, weight, body mass index (BMI), waist circumference (WC), body fat mass (BFM), skeletal muscle mass (SMM), and diverse laboratory data were also considered as variables. Sixty-six subjects were placed in the CRA group and 146 subjects in the non-CRA group. The presence of CRA was significantly correlated with older age ($P = .001$), male sex ($P = .041$), higher BMI ($P = .004$), higher WC ($P = .001$), higher BFM ($P = .024$), higher VAT$_{av}$ ($P < .001$), higher TAT$_{av}$ ($P = .004$), higher VAR ($P < .001$), higher VSR ($P < .001$), lower $c_{SUV}_{max}$ ($P = .002$), lower $sc_{SUV}_{max}$ ($P < .001$), and lower $VSR_{mean}$ ($P = .002$). On multiple regression analysis, $c_{SUV}_{max}$ and $vc_{SUV}_{max}$ were independently associated with the presence of CRA ($P = .009$ and $P = .045$). Lower glucose metabolism of visceral adipose tissue was related to the presence of CRA. Our findings identify the value of visceral metabolic dysfunction as a potential surrogate marker of elevated risk for CRA.

**Abbreviations:** BFM = body fat mass, BMI = body mass index, CRA = colorectal adenoma, CT = computed tomography, DBP = diastolic blood pressure, DM = diabetes mellitus, HTN = hypertension, IL = interleukin, ILP = insulin-like peptide, MAO = metabolically abnormal obese, MHO = metabolically healthy obese, PET = positron emission tomography, ROI = region of interest, SAT$_{av}$ = average subcutaneous adipose tissue area, SBP = systolic blood pressure, $c_{SUV}_{max}$ = average SUV of SAT, SMM = skeletal muscle mass, $sc_{SUV}_{max}$ = average SUV of SAT, TAT$_{av}$ = average total adipose tissue area, VAR = visceral-to-total adipose tissue ratio, VAT$_{av}$ = average visceral adipose tissue area, VSR = visceral-to-subcutaneous adipose tissue ratio, $VSR_{max}$ = visceral-to-subcutaneous SUV ratio, $VSR_{mean}$ = visceral-to-subcutaneous SUV ratio, $vc_{SUV}_{max}$ = average SUV of VAT, $vs_{SUV}_{mean}$ = average SUV of VAT, WC = waist circumference, WHR = waist to hip ratio.

**Keywords:** colonic adenoma, fluorodeoxyglucose positron emission tomography/computed tomography, glucose metabolism, visceral adipose tissue

1. Introduction

Colorectal cancer (CRC) is the third most frequently diagnosed cancer in men and the second in women worldwide. In Asian countries, the incidence of CRC is still increasing, probably due to the westernization of diet and dramatic increase in obesity. The link between obesity and cancer risk has received considerable attention recently. Of all cancer types, strong relationships...
between CRC and colorectal adenoma (CRA), a precursor of cancer, with obesity have been reported by epidemiological studies.\[1,3\]

To evaluate the relationship between CRC and obesity, diverse anthropometric methods, such as body mass index (BMI), waist to hip ratio (WHR), and waist circumference (WC), have been used as indices of obesity.\[6–8\] However, such anthropometric indices can be skewed by muscle mass or measurement error. By using computed tomography (CT) or magnetic resonance imaging (MRI), an accurate measurement of fat volume is possible.\[9,10\] Moreover, such cross-sectional imaging modalities can provide fine distinction of adipose tissue compartments, thereby supporting a stronger relationship of visceral adipose tissue (VAT) than subcutaneous adipose tissue (SAT) with the risk of CRC and CRA.\[11–14\]

Different physiologic and molecular characteristics between the 2 adipose tissue compartments might contribute to their different relationships with CRC. Fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) is a functional molecular imaging method that can noninvasively evaluate in vivo glucose metabolism. Although FDG PET was initially developed for tumor imaging, applications for this modality are now being expanded to nontumor pathophysiology.\[15,16\] The glucose metabolism of adipose tissue has been investigated by several groups, and differential glucose utilization between VAT and SAT has been consistently suggested.\[17,18\] However, no existing studies have evaluated the direct relationship between glucose utilization in the 2 adipose tissue compartments and the presence of CRA.

Therefore, the present study aimed to evaluate the association of glucose metabolism in adipose tissue with the presence of CRA in healthy subjects. Metabolic activity of VAT and SAT were separately measured, and relationships with CRA were investigated along with other previously reported anthropometric and CT-based parameters.\[9,19\]

2. Materials and methods

2.1. Study subjects

We conducted a retrospective review of the FDG PET/CT database of the Health Promotion Center. Our institutional review board (IRB) approved this study. All procedures involving human participants were performed according to the ethical standards of the IRB and the Declaration of Helsinki. Informed consent was waived by the IRB for all patients, and we anonymized all of the data before analysis. Among 835 subjects who underwent FDG PET/CT for routine health check-ups between January 2011 and February 2015, medical records of a screening colonoscopy were available in 269 subjects. There were no patients with a history of CRC or other malignancies. Among the 269 subjects, 146 were classified in the non-CRA group after excluding 43 subjects with inflammatory bowel disease (e.g., ulcerative colitis, Crohn disease) or other benign lesions (e.g., hyperplastic or inflammatory polyps and diverticula). Thus, the final statistical analysis was performed with a total of 212 subjects (66 CRA vs 146 non-CRA, Fig. 1).

2.2. Data collection

Social history of smoking habit or alcohol intake and history of diabetes mellitus (DM) or hypertension (HTN) were checked by Health Promotion Center chart review. Anthropometric data of height, weight, BMI, WC, body fat mass (BFM), and skeletal muscle mass (SMM) were retrieved. A trained nurse measured height and weight using standardized procedures, and BMI was calculated as weight (kg) divided by height (m) squared. WC was measured at the umbilicus level using a nonstretchable measuring tape. BFM and SMM were automatically measured using a whole-body bioelectric impedance analysis system (InBody, Co Ltd, Seoul, Korea). Systolic and diastolic blood pressure were measured in a sitting position using an automatic oscillometric device. At the time of the Health Promotion Center visit, blood was obtained from all the subjects in the morning after an overnight fast to perform standard laboratory tests. Levels of triglycerides, cholesterol, glycated hemoglobin (HbA1c), and C-reactive protein and erythrocyte sedimentation rate (ESR) were measured.

2.3. $^{18}$F-FDG PET/CT

All subjects were evaluated with FDG PET/CT for routine health check-ups. Before the FDG injection, subjects were instructed to fast for at least 6 hours. Blood glucose level was measured and confirmed to be <140 mg/dL. Each subject was injected with an FDG dose of 3.18 MBq/kg. After the injection, patients were instructed to rest for 1 hour before the scan. For PET/CT, a noncontrast CT was obtained first, after which an emission PET scan was performed from the skull base to the thigh using an integrated Siemens Biograph mCT with 128 slice CT (Siemens Medical Solutions, Erlangen, Germany). The emission PET images were acquired for 2 minutes scan/bed position with 3D mode. Then, PET images were reconstructed with 3.0 mm slice thickness using a 3D OSEM iterative algorithm.

2.4. Measurement of adipose tissue distribution and metabolic activity

The PET/CT data were reviewed by 2 board-certified nuclear medicine physicians who were strictly blinded to other clinical
information using a dedicated Multimodality Workplace (Syngo MMWP Version VE61A; Siemens Medical Solutions). The measurement of adipose tissue area (cm²) was accomplished with volume software (Siemens Medical Solutions). Regions of interest (ROIs) of the VAT and total adipose tissue (TAT) area were determined by manual tracing its contour on each CT slice. To isolate voxels containing fat tissue, a fixed attenuation range from −190 to −30 Hounsfield units was applied to each slice. After the VAT area was subtracted from TAT, the remainder was defined as the SAT area. A total of 11 slices were evaluated; 1 cross-sectional slice at the umbilicus level and 10 additional slices separated by 3.0 mm slice thickness in the top and bottom from the umbilicus level. The SAT, VAT, and TAT areas from 11 different slices were averaged to obtain the average SAT (SAT av), average VAT (VAT av), and average TAT (TAT av), which were used for the final statistical analysis. Furthermore, we calculated visceral-to-subcutaneous adipose tissue ratio (VSR) by dividing VAT by SAT and visceral-to-total adipose tissue ratio (VAR) by dividing VAT by TAT.

The measurement of metabolic activity was accomplished with TrueD software (Siemens Medical Solutions). For VAT, ROIs with a same fixed attenuation range were drawn in each contour of VAT on each CT slice, and the same ROI was automatically applied to each coregistered PET/CT slice. The maximal and mean standardized uptake value $SUV_{\text{max}}$ and $SUV_{\text{mean}}$ were retrieved. For the precise measurement of metabolic activity, the placement of ROI was carefully determined and adjusted to avoid possible spillover uptake from neighboring tissue (e.g., bowel) by simultaneous review of PET and CT slices. For SAT, ROIs were drawn in each contour of SAT on each CT slice, and the same ROI was automatically applied to each coregistered PET/CT slice. The $SUV_{\text{max}}$ and $SUV_{\text{mean}}$ of VAT and SAT areas from 11 different slices were averaged to obtain the average SUV of VAT ($SUV_{\text{VAT}}$ and $SUV_{\text{mean}}$) and SAT ($SUV_{\text{SAT}}$ and $SUV_{\text{mean}}$). Then, visceral-to-subcutaneous $SUV_{\text{max}}$ ratio (VSR$\text{max}$) and visceral-to-subcutaneous $SUV_{\text{mean}}$ ratio (VSR$\text{mean}$) were calculated by dividing $v_{\text{SUV}}$ $SUV_{\text{max}}$ by $s_{\text{SUV}}$ $SUV_{\text{max}}$ and $v_{\text{SUV}}$ $SUV_{\text{mean}}$ by $s_{\text{SUV}}$ $SUV_{\text{mean}}$ respectively.

### 2.5. Colonoscopy and diagnosis

Before undergoing full colonoscopy, patients were instructed to eat a low-residual diet for at least 3 days, and bowel preparations were performed using 4L polyethylene glycol (PEG) or 2L PEG plus ascorbic acid. Colonoscopies were carried out by experienced endoscopists (>500 cases) who thoroughly observed the colon from cecum to rectum during a withdrawal time ≥6 minutes. Bowel preparation grade was assessed according to the Aronchick scale, and a “fair” or higher grade was considered adequate bowel preparation. The size of each polyp was estimated using biopsy forceps. The size, morphology, location, and number of all colorectal lesions were documented immediately after colonoscopy. Resected polyps were histopathologically assessed by specialized pathologists. CRAs were distinguished from benign lesions including hyperplastic or inflammatory polyps (Supplementary Table 1, http://links.lww.com/MD/B739).

### 2.6. Statistical analyses

A value $P<.05$ was regarded as statistically significant. All statistical analyses were carried out using SPSS software version 18.0 (SPSS Inc, Chicago, IL).

Clinical features including anthropometric data, laboratory data, CT-based area, and PET-based metabolic parameters of adipose tissue according to the presence of CRA were compared using the Chi-square test or Fisher exact test for categorical variables or the independent $t$ test for continuous variables. Logistic regression analysis was used to evaluate the association between each clinical feature and the presence of CRA. Multivariate logistic regression analysis was then carried out to determine the factors independently associated with the presence of CRA. Before performing this analysis, factors showing collinearity were omitted. A threshold of $>.7$ for the absolute correlation coefficient was considered to remove collinear variables.$^{[20]}$ Odds ratios with 95% confidence interval and $P$ values are reported. An age- and sex-adjusted Spearman partial correlation analysis was performed to identify the relationships between adipose tissue metabolic parameters and other clinical features.

### 3. Results

A total of 212 subjects (M:F=143:69) were included in the analysis. The baseline and PET/CT-measured features of total subjects are summarized in Table 1.

#### 3.1. Patient baseline characteristics according to the presence of colorectal adenoma

Among all 212 subjects, 66 who had at least 1 adenomatous polyp were classified into the CRA group, whereas 146 normal subjects formed the non-CRA group. Patient characteristics were compared between the CRA and non-CRA groups (Table 1). Older age ($P=.001$), male sex ($P=.041$), higher BMI ($P=.004$), higher WC ($P=.001$), and higher BFMI ($P=.024$) were associated with CRA.

#### 3.2. PET/CT parameters according to the presence of colorectal adenoma

Among CT parameters, VAT av ($P<.001$), TAT av ($P=.004$), VSR ($P<.001$), and VAR ($P<.001$) were significantly higher in the CRA group than the non-CRA group (Fig. 2). Among metabolic PET parameters, $SUV_{\text{max}}$ ($P=.002$), $SUV_{\text{mean}}$ ($P<.001$), and VSR$\text{mean}$ ($P=.002$) were significantly lower in the CRA group than the non-CRA group (Fig. 3).

#### 3.3. Independent relationship of VAT metabolism with the presence of colorectal adenoma

In univariate regression analyses, age ($P=.002$), sex ($P=.042$), weight ($P=.011$), BMI ($P=.006$), WC ($P=.002$), BFMI ($P=.027$), VAT av ($P<.001$), TAT av ($P=.006$), VSR ($P<.001$), VAR ($P<.001$), $SUV_{\text{max}}$ ($P<.003$) $SUV_{\text{mean}}$ ($P<.001$), and VSR$\text{mean}$ ($P=.002$) were significant factors associated with the presence of CRA. Anthropometric SMM and the presence of HTN showed a trend toward significance ($P=.072$ and $P=.089$). The detailed data are presented in Table 2. Before performing multivariate analysis, TAT av and VAT av were found to be collinear; thus, only VAT av was subsequently included in the analysis. In addition, VSR and VAR were found to be collinear, so VAR was subsequently omitted from the multivariate analysis. When a multiple regression analysis was performed using the 11 significant variables on univariate analysis, $SUV_{\text{max}}$ and $SUV_{\text{mean}}$ remained significant independent factors associated with the presence of CRA ($P=.009$ and $P=.045$).
3.4. Correlations between VAT metabolism and other clinical features

To identify the clinical features associated with VAT metabolism, the relationships between VAT SUV and other clinical features were assessed (Table 3). After adjusting for age and sex, \( {}_v\text{SUV}_{\text{max}} \) had a significant negative correlation with VSR (\( R = -0.225, P = .014 \), VAR (\( R = -0.195, P = .034 \)), and serum ESR level (\( R = -0.256, P = .005 \)). \( {}_v\text{SUV}_{\text{mean}} \) had a significant negative correlation with VAT\(_{\text{av}}\) (\( R = -0.430, P < .001 \)), TAT\(_{\text{av}}\) (\( R = -0.242, P = .008 \)), VSR (\( R = -0.394, P < .001 \)), VAR (\( R = -0.422, P < .001 \)), WC (\( R = -0.222, P = .015 \)), BFM (\( R = -0.220, P = .016 \)), and serum ESR level (\( R = -0.202, P = .028 \)).

4. Discussion

We demonstrated here for the first time that glucose metabolism in VAT was correlated with CRA. In this study, subjects with lower glucose metabolism in VAT were more likely to have CRA. Among the considered parameters, \( {}_v\text{SUV}_{\text{max}} \) and \( {}_v\text{SUV}_{\text{mean}} \) which reflect the glucose metabolism of VAT, were independent factors for the presence of CRA, whereas otherwise previously reported anthropometric and CT-measured obesity indices were eliminated in a multivariate analysis.

Obesity increases the risk of CRC, and similar trends exist for CRA.\(^{[15]}\) In particular, VAT accumulation, or visceral obesity, has been found to be of greater importance than SAT.\(^{[11]}\) Obesity increases the risk of CRC, and similar trends exist for CRA.\(^{[15]}\) In particular, VAT accumulation, or visceral obesity, has been found to be of greater importance than SAT.\(^{[11]}\) Although the underlying mechanism linking obesity to CRC is still in a matter of debate, insulin resistance and alteration in levels of proinflammatory cytokines have been suggested as main factors initiating carcinogenesis.\(^{[5,3,21,22]}\) Insulin resistance is a pathological condition characterized by dysregulation of insulin action in peripheral target organs including skeletal muscle, liver, and adipocytes. Hyperinsulinaemia, which is a hallmark of insulin resistance, and increased levels of insulin-like peptides (ILPs) are thought to play a role in the initiation and progression of cancer. ILPs can induce tumor growth directly by stimulating growth factor-dependent cell proliferation and suppression of apoptosis. Impaired insulin action in adipocytes caused by insulin resistance could explain the reduced VAT glucose metabolism observed in the CRA group in this study. Moreover, significant negative correlations between VAT metabolism and diverse obesity indices were found in our data (Table 3), a finding consistent with earlier studies.\(^{[4,5]}\) Furthermore, the lower glucose metabolism in VAT was associated with increased levels of ILPs and decreased levels of insulin-like growth factor-1 (IGF-1), which is a potent mitogen for tumor cells. These findings suggest that VAT metabolism may play a role in the initiation and progression of CRC.
with previous studies. According to a recent study that evaluated FDG uptake in VAT and SAT, metabolically healthy obese (MHO) and metabolically abnormal obese (MAO) have lower VAT FDG uptake than metabolically healthy lean subjects. Those authors also suggested that reduced VAT FDG uptake in MHO and MAO was due to abnormal glucose handling of insulin-resistant adipocytes. Virtanen et al. reported markedly reduced adipose tissue glucose uptake in insulin-resistant obese subjects during insulin stimulation compared with nonobese subjects.

Meanwhile, overproduction of proinflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-1, IL-6, and IL-10 and sustained low-grade subclinical inflammation are recognized as additional links between obesity and carcinogenesis. Cytokine-induced macrophage recruitment into the adipose tissues further enhances the inflammatory reaction. Such an infiltration of macrophages indicates a metabolic increase of adipose tissues in CRA subjects compared with non-CRA subjects. However, our study yielded inconsistent results, despite the link between carcinogenesis and obesity-induced inflammation. Even though inflammatory cells within VAT could augment glucose metabolism in CRA subjects, their contribution to overall glucose metabolism seems to be counterbalanced by the greater mass of insulin-resistant adipocytes. The significant negative correlation shown in our data (Table 3) between VAT metabolism and serum ESR level, a marker of inflammation, supports this hypothesis. Impaired vascularity, perfusion, and capillary density, which are frequently found in obesity, could also participate in the reduced VAT FDG uptake of CRA subjects.

Physiologic and molecular differences between VAT and SAT have long been a subject of interest. A number of studies have suggested different secretion of inflammatory mediators, gene expression, and metabolism between VAT and SAT. Different implications of 2 distinct adipose tissues in the risk of CRC have been demonstrated using anthropometric profiles such as WC and WHR, both of which are surrogate markers of obesity.
Table 2
Relationship of visceral adipose tissue metabolism with the presence of colorectal adenoma.

| Variable            | Univariate Coefficient | OR (95% CI) | P    | Multivariate Coefficient | OR (95% CI) | P    |
|---------------------|------------------------|-------------|------|--------------------------|-------------|------|
| Age                 | .062                   | 1.064 (1.024–1.105) | .002  | .008                     | 1.008 (0.947–1.072) | .807 |
| Sex                 | .691                   | 1.906 (1.025–3.887) | .042  | .611                     | 1.842 (0.454–7.479) | .393 |
| Cigarette           | .618                   | 1.854 (0.824–4.171) | .135  |                          |              |      |
| Alcohol             | .141                   | 1.152 (0.578–2.933) | .688  |                          |              |      |
| HTN                 | .647                   | 1.009 (0.964–1.024) | .089  |                          |              |      |
| DM                  | .819                   | 2.629 (0.86–8.374)  | .120  |                          |              |      |
| Height              | .019                   | 1.019 (0.980–1.060) | .343  |                          |              |      |
| Weight              | .036                   | 1.037 (1.006–1.066) | .011  |                          |              |      |
| BMI                 | .148                   | 1.160 (0.944–1.437) | .005  | .003                     | 1.003 (0.984–1.022) | .739 |
| WC                  | .056                   | 1.058 (1.021–1.097) | .002  | .006                     | 1.006 (0.980–1.033) | .646 |
| SMM                 | .038                   | 1.038 (0.997–1.082) | .072  |                          |              |      |
| BFMI                | .664                   | 1.066 (1.007–1.118) | .027  |                          |              |      |
| SBP                 | .012                   | 1.012 (0.987–1.037) | .348  |                          |              |      |
| DBP                 | .018                   | 1.018 (0.984–1.054) | .304  |                          |              |      |
| HbA1c               | .019                   | 1.019 (0.652–9.519) | .935  |                          |              |      |
| Triglyceride        | .000                   | 1.000 (0.997–1.003) | .998  |                          |              |      |
| Cholesterol         | .005                   | 0.995 (0.986–1.003) | .243  |                          |              |      |
| CRP                 | .156                   | 1.042 (0.825–1.302) | .006  |                          |              |      |
| ESR                 | .008                   | 1.009 (0.957–1.063) | .751  |                          |              |      |
| VAT<sub>av</sub>    | .018                   | 1.018 (1.011–1.026) | <.001 | <.004                    | 0.996 (0.977–1.016) | .674 |
| SAT<sub>av</sub>    | .001                   | 1.001 (0.997–1.005) | .672  |                          |              |      |
| VAT<sub>var</sub>   | .008                   | 1.005 (1.001–1.008) | <.001 |                          |              |      |
| VSR                 | 2.181                  | 8.853 (3.014–26.008) | <.001 | 2.163                    | 8.699 (0.538–140.713) | .128 |
| VAR                 | .067                   | 1.069 (1.035–1.105) | <.001 | <.001                    | 7.454 (0.358–171.973) | .107 |
| VAT<sub>SUV<sub>mean</sub></sub> | .991 | 0.371 (0.192–0.718) | <.001 | 2.097                    | 0.121 (0.026–0.587) | .009  |
| SAT<sub>SUV<sub>mean</sub></sub> | .920 | 0.022 (0.003–0.121) | <.001 | 3.778                    | 0.023 (0.001–0.919) | .007  |
| VAT<sub>mean</sub>  | .151                   | 1.531 (0.859–2.748) | .673  |                          |              |      |
| VSR<sub>mean</sub>  | 1.309                  | 9.158 (0.004–6.473) | .330  |                          |              |      |
| VSR<sup>max</sup>   | .005                   | 1.091 (0.789–1.505) | .195  |                          |              |      |
| VSR<sub>mean</sub>  | .523                   | 0.593 (0.423–0.830) | <.001 | 2.02                     | 1.224 (0.689–2.174) | .490 |
serum inflammatory marker and diverse obesity indices. The results indicate that metabolic derangement induced by visceral obesity tends to be associated with an increased risk of CRA. The results also indicate the smaller importance of subcutaneous adiposity to the pathogenesis of CRA compared to visceral adiposity.

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