RESEARCH ARTICLE

Comparison of Visceral Fat Measures with Cardiometabolic Risk Factors in Healthy Adults

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Abstract

We aimed to evaluate the associations of visceral adiposity with cardiometabolic risk factors in normal subjects with integrated 18F-Fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT). A total of 58 normal subjects who underwent 18F-FDG PET/CT scan for cancer screening were included in this study. Volume and average Hounsfield unit (HU) of visceral adipose tissue (VAT) was measured from CT components of integrated PET/CT. Standardized uptake values (SUVmax) of liver, spleen, lumbar spine and ascending aorta (AA) were measured from PET components of integrated PET/CT. Body mass index (coefficient 78.25, p = 0.0259), glucose (37.62, p < 0.0001), insulin (348.90, p = 0.0011), logarithmic transformation of homeostatic model assessment index-insulin resistance (-2118.37, p = 0.0007), and VAT HU (-134.99, p < 0.0001) were independently associated with VAT volume. Glucose (0.1187, p = 0.0098) and VAT volume (-0.004, p < 0.0001) were found to be associated with VAT HU. Both VAT volume and VAT HU of whole abdominal cavity is significantly associated with cardiometabolic risk factors.

Introduction

According to the most recent estimates of the 2013 Korean national health and nutrition examination survey, 37.8% of men and 25.1% of women classified as obese[1]. The prevalence of obesity has increased over the last decade and numerous prospective cohort studies have shown that obese persons, defined by a body mass index (BMI), have an increased risk of hypertension, cardiovascular disease, and all cause mortality [1–4]. Furthermore, the distribution of fat depots, such as visceral abdominal adipose tissue (VAT), independent of overall obesity, has been associated with cardiometabolic risks [5, 6].

Several studies have shown the area of VAT, measured by single-slice computed tomography (CT) image at L4-5 intervertebral space, could reflect the amount of VAT and may be the predictor of cardiometabolic complications [7, 8]. However, using a single slice of CT image to
represent total VAT may not be appropriate for all population because of there are race, sex or age differences in the distribution of VAT across the abdomen [9]. Furthermore, controversy exists which measurement site is the best correlated to not only VAT volumes but also cardiometabolic risk factors [9–11]. Thus, volumetric quantification of whole abdomen is the gold standard to assess amount of VAT [5, 12].

Previous studies suggested CT attenuation of adipose tissue, measured in Hounsfield Units (HU) as a density on x-ray imaging was adopted as a marker of fat quality and lower CT attenuation was associated with higher cardiovascular disease risk, independent of fat volume [13–15]. Although, these studies demonstrated that regional CT imaging allows the assessment of volume and density of adipose tissue, they could not assessed the whole adipose tissue of abdominal cavity.

In the present study, we measured total volume and attenuation of whole VAT of abdominal cavity with integrated 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scans to evaluate the associations between cardiometabolic risks and other variables from PET/CT.

**Materials and Methods**

**Patients**

A total of 58 subjects who underwent 18F-FDG PET/CT scan for cancer screening between February 2011 and September 2014 were included in this study. Study participants with known malignancy or age <18 years were excluded (Fig 1).

This study was designed as a retrospective review of participants’ charts. Participants’ information was anonymized by JG Lee. The consent from participants was not needed according to Institutional Review Board of Pusan National University Hospital (PNUH-2015-07892).

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**Fig 1. Flow diagram of study subjects.**

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Measurement

Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²). Waist circumference was measured at the narrowest point between the lower border of the rib cage and the iliac crest, at the end of a normal expiration of breath and to the nearest 0.1cm. Percentage of body fat and total fat mass was measured by bioelectric impedance analysis (Inbody 3.0, Biospace Co, Ltd, Korea). Fasting plasma glucose was measured by the glucose oxidase method using a Synchon LX20 (Beckman Coulter, Fullerton, CA, USA). Fasting insulin was measured using a radioimmunoassay (Diagnostic Product Corporation, Los Angeles, CA, USA) with antibody-coated tubes. A mercury sphygmomanometer was used for measurement of blood pressure of each subject in sitting position after a 10-min rest. Homeostatic model assessment index-insulin resistance (HOMA-IR) was calculated using the formula for estimation of insulin sensitivity: fasting insulin (IU/mL) x fasting glucose (mg/dL)/405[16]. Lipid profile was measured by an enzymatic colorimetric method using with an autoanalyzer (Hitachi 747; Hitachi Corp., Tokyo, Japan).

Integrated ¹⁸F-FDG PET/CT

Patients were injected intravenously with 5.18MBq/kg of ¹⁸F-FDG, following a fasting period of at least 6 h to achieve a blood glucose level of < 140 mg/kg. PET/CT scans commenced 60 min following injection using integrated PET/CT scanners (Gemini TF, Philips, Milpitas, CA, USA). During image acquisition, a CT scan was obtained first for attenuation correction with a slice thickness of 4mm (120kV), and an emission scan was obtained consecutively from the skull base to the proximal thigh with a field-of-view of 576mm. PET images were reconstructed using an iterative algorithm (ordered-subset expectation maximization, iteration: 3, subsets: 33) with an image matrix size of 144 x 144. Two nuclear physicians, blinded to clinical data, reviewed retrospectively PET/CT datasets.

Image analysis

¹⁸F-FDG PET/CT images were reviewed by 2 experienced nuclear physicians with pmod version 3.2 (PMOD Technologies Ltd, Zürich, Switzerland).

a. PET. Standardized uptake values (SUV) were calculated as the tissue concentration of radioactivity (kBq/mL) divided by the injected dose per weight (kBq/g). A circular region of interest with a diameter of 2cm was placed in the right lobe of the liver (Liver SUV) and center of spleen (Spleen SUV), avoiding vessels, bile ducts, calcifications, and artifacts to measure maximum SUV (SUVmax). SUVmax of each lumbar spine was measured on body of L1-5, was averaged, and defined as lumbar SUV. SUVmax of blood pool was evaluated within the wall of the ascending aorta on every 5 axial image, and the average was defined as AA SUV.

b. CT. Volume (VAT volume, ml) and average Hounsfield unit (VAT HU) of visceral adipose tissue was measured from CT components of integrated PET/CT scans. VAT was delineated as follows: 1) manually outlining VOI of the abdominal muscular wall excluding vertebral column and paraspinal muscles, 2) defining voxels between -195HU and -45HU, making a template atlas, 4) applying a template atlas to CT, and 5) measuring parameters (Fig 2).

Statistical analysis

All continuous variables were expressed as mean±standard deviation. Subjects were divided into 2 groups with median value of VAT volume and VAT HU, analyzed with T-test. D’Agostino-Pearson test was adopted to assess normal distribution. Multiple regression method was used to examine the relationship between VAT volume, VAT HU and other variables after
adj ustment with age and sex. Variables with p value <0.05 were entered into model with enter method. A p value of < 0.05 was considered statistically significant. All statistical analyses were performed using the MedCalc software package (ver. 12.6.0.0, MedCalc, Mariakerke, Belgium).

**Results**

Demographics are summarized in Table 1. The mean age was 48.4±8.3 years with a range between 39 and 73. Thirty-eight subjects were male, 20 were female. The mean VAT volume was 3,285ml and the mean VAT HU was -95.2.

**Comparisons between high and low VAT volume and VAT HU**

Subjects were divided into 2 groups according to VAT volume and VAT HU. In high VAT volume (>3,298ml) and low VAT HU (<-94.7) groups, both systolic and diastolic BP, BMI, waist circumference, insulin, lnHOMA-IR, CRP, AA SUV, lumbar SUV, and spleen SUV were higher. HDL cholesterol was lower in both high VAT volume (p = 0.0049) and low VAT HU (p = 0.0001) groups. Glucose (p = 0.0041), and liver SUV (p<0.0001) were higher in high VAT volume group, while LDL cholesterol (p = 0.0158) was higher in low VAT HU group.

**Univariable and multivariable regression analyses of VAT volume**

In univariable analysis, VAT volume showed positive associations with BMI (coefficient 317.91, p<0.0001), waist circumference (144.58, p<0.0001), glucose (46.42, p = 0.0001), insulin (233.70, p = 0.0003), lnHOMA-IR (1228.11, p = 0.0002), and PET parameters of AA SUV (2218.06, p<0.0001), lumbar SUV (2175.40, p = 0.0001), liver SUV (1701.84, p = 0.0002), and spleen SUV (1973.62, p<0.0001) and negative associations with HDL cholesterol (-37.44, p = 0.0008), and VAT HU (-204.09, p<0.0001). In multivariable analysis, BMI (78.25, p = 0.0259), glucose (37.62, p<0.0001), insulin (348.90, p = 0.0011), lnHOMA-IR (-2118.37, p = 0.0007), and VAT HU (-134.99, p<0.0001) were independently associated with VAT volume. Table 2 shows the results of multivariable regression analyses of VAT volume.

![Fig 2. Measurement of whole visceral adipose tissue. (A) Manually outlining volume-of-interest of the abdominal muscular wall, (B) defining voxels between -195HU and -45HU, making a template atlas, and (C) applying a template atlas to CT.](doi:10.1371/journal.pone.0153031.g002)
Table 1. Demographics.

| Characteristic            | All          | High VAT volume | Low VAT volume | p       |
|---------------------------|--------------|-----------------|----------------|---------|
| Age (years)               | 48.4±8.3     | 49.2±8.1        | 47.7±8.5       | 0.4900  |
| Sex (M/F)                 | 38/20        | 26/3            | 12/17          | 0.0002  |
| BMI (kg/m²)               | 25.4±4.9     | 26.2±2.0        | 22.4±2.4       | <0.0001 |
| Waist circumference (cm)  | 84.7±7.6     | 90.4±4.4        | 78.9±5.5       | <0.0001 |
| AST (IU/L)                | 21.7±6.6     | 23.6±6.8        | 19.7±5.9       | 0.0251  |
| ALT (IU/L)                | 22.4±12.3    | 28.1±12.8       | 16.7±8.9       | 0.0002  |
| Hb (g/dL)                 | 14.6±1.5     | 15.2±1.2        | 13.7±1.5       | 0.0001  |
| Hct (%)                   | 42.5±4.0     | 44.3±3.3        | 40.7±3.9       | 0.0004  |
| WBC (x10³/uL)             | 5.7±1.7      | 6.5±1.8         | 4.9±1.1        | 0.0001  |
| Total cholesterol (mg/dL) | 195.4±33.4   | 194.2±33.5      | 196.7±33.9     | 0.7742  |
| LDL cholesterol (mg/dL)   | 125.4±31.8   | 126.8±31.6      | 124.0±32.4     | 0.7411  |
| HDL cholesterol (mg/dL)   | 51.3±14.5    | 46.0±13.8       | 56.6±13.5      | 0.0049  |
| lnTg (mg/dL)              | 4.8±0.5      | 4.9±0.5         | 4.7±0.4        | 0.1340  |
| Glucose (mg/dL)           | 91±14        | 96.0±16.5       | 86.0±7.4       | 0.0041  |
| Insulin (uIU/mL)          | 5.3±2.4      | 6.2±2.9         | 4.4±1.2        | 0.0021  |
| lnHOMA-IR                 | 0.1±0.5      | 0.320.5         | -0.1±0.3       | 0.0012  |
| CRP (mg/dL)               | 0.1±0.1      | 0.11±0.10       | 0.04±0.06      | 0.0016  |
| AA SUV                    | 2.0±0.3      | 2.1±0.3         | 1.8±0.3        | 0.0006  |
| Lumbar SUV                | 1.6±0.3      | 1.7±0.3         | 1.5±0.2        | 0.0045  |
| Liver SUV                 | 2.5±0.3      | 2.6±0.3         | 2.3±0.2        | <0.0001 |
| Spleen SUV                | 1.9±0.3      | 2.0±0.3         | 1.7±0.3        | <0.0001 |
| VAT HU                    | -95.2±5.6    | -99.1±4.0       | -91.4±4.2      | <0.0001 |

VAT, visceral adipose tissue; BMI, body mass index; AST, aspartate transaminase; ALT, alanine transaminase; Hb, hemoglobin; Hct, hematocrit; WBC, white blood cell; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ln, logarithmic transformation; Tg, triglyceride; HOMA-IR, homeostatic model assessment index-insulin resistance; CRP, c-reactive protein; AA, ascending aorta; SUV, standardized uptake value; HU, hounsfield unit.

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Table 2. Multivariable Regression Analyses–VAT volume (adjustment with age and sex).

| Coefficient | t     | p       |
|-------------|-------|---------|
| BMI         | 78.25 | 2.31    | 0.0259  |
| HDL Cholesterol | -10.59 | -1.83   | 0.0747  |
| Glucose     | 37.62 | 5.13    | <0.0001 |
| Insulin     | 348.90| 3.50    | 0.0011  |
| lnHOMA-IR   | -2118.37| -3.63  | 0.0007  |
| AA SUV      | 2.0±0.3 | 1.8±0.3 | 0.0006  |
| Lumbar SUV  | 1.6±0.3 | 1.7±0.3 | 0.0045  |
| Liver SUV   | 2.5±0.3 | 2.6±0.3 | 2.3±0.2 | <0.0001 |
| Spleen SUV  | 1.9±0.3 | 2.0±0.3 | 1.7±0.3 | <0.0001 |
| VAT HU      | -95.2±5.6 | -99.1±4.0 | -91.4±4.2 | <0.0001 |

VAT, visceral adipose tissue; BMI, body mass index; HDL, high-density lipoprotein; ln, logarithmic transformation; HOMA-IR, homeostatic model assessment index-insulin resistance; AA, ascending aorta; SUV, standardized uptake value; HU, hounsfield unit.

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Univariable and multivariable regression analyses of VAT HU

VAT HU was associated positively with HDL cholesterol (0.15, p = 0.0011) and negatively with BMI (-1.12, p < 0.0001), waist circumference (-0.53, p < 0.0001), total cholesterol (-0.04, p = 0.0346), LDL cholesterol (-0.05, p = 0.0104), lnTg (-4.08, p = 0.0040), glucose (-0.12, p = 0.0289), insulin (-0.88, p = 0.0013), lnHOMA-IR (-4.58, p = 0.0012), VAT volume (-0.004, p < 0.0001), and PET parameters of AA SUV (-8.34, p = 0.0001), lumbar SUV (-5.65, p = 0.0192), liver SUV (-5.16, p = 0.0099), and spleen SUV (-6.20, p = 0.0023). In multivariable analysis, glucose (0.1187, p = 0.0098), and VAT volume (-0.004, p < 0.0001) were found to be associated with VAT HU. Table 3 shows the results of multivariable regression analysis of VAT HU.

Table 3. Multivariable Regression Analyses of VAT HU (adjustment with age and sex).

| Variable       | Coefficient | t    | p    |
|----------------|-------------|------|------|
| BMI            | 0.15        | 0.68 | 0.5012|
| Waist circumference | -0.08     | -0.74| 0.4630|
| Total cholesterol | -0.10     | -1.62| 0.1129|
| LDL cholesterol   | 0.06        | 1.05 | 0.2996|
| HDL cholesterol   | 0.06        | 0.91 | 0.3686|
| lnTg             | 1.24        | 0.75 | 0.4595|
| Glucose          | 0.12        | 2.71 | 0.0098|
| Insulin          | 0.95        | 1.65 | 0.1059|
| lnHOMA-IR        | -6.46       | -1.91| 0.0634|
| AA SUV           | -2.08       | -1.44| 0.1580|
| Lumbar SUV       | 2.40        | 1.61 | 0.1144|
| Liver SUV        | 1.31        | 1.02 | 0.3144|
| Spleen SUV       | -0.42       | -0.30| 0.7678|
| CT VAT volume    | -0.004      | -7.15| <0.0001|

VAT, visceral adipose tissue; HU, hounsfield unit; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ln, logarithmic transformation; Tg, triglyceride; HOMA-IR, homeostatic model assessment index-insulin resistance; AA, ascending aorta; SUV, standardized uptake value.

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Discussion

It is well established that visceral adiposity is associated with cardiometabolic risk factors [17]. In this study, both VAT HU and VAT volume were significantly associated with cardiometabolic risk factors. In addition, VAT HU showed a strong association with VAT volume negatively. These results are similar with previous studies with VAT volume (table 4)[14, 15, 18–20]. CT scans were acquired as a substudy of the Framingham Heart Study[14, 15, 18, 19]. In all 4 reports from Framingham Heart Study, 25 contiguous 5-mm thickness CT scan was done in participants[14, 15, 18, 19]. Both volume and HU from VAT and SAT were measured from 25 contiguous 5-mm thickness CT scans. However, 25 contiguous 5-mm thickness CT covers 125 mm of abdomen above S1 level, which is a part of VAT in a subject [13]. In the other study by Tahara et al[20], they adopted PET/CT to measure the metabolic activity of fat tissue. However, 11 contiguous 4-mm thickness CT was included in measuring parameters, covering 44 mm of abdomen, a very small part of the whole abdomen. Until now, measurement of CT-based VAT area is common in a clinical setting. As VAT is distributed in whole abdomen, measuring an area on a single slice at L1 [21], L4/L5 level[22, 23] or several slices from L2 to L5 [24] may not be enough to represent VAT of abdomen. Therefore, we measured a whole
VAT delineating abdominal muscular wall, which might be the most accurate way to estimate VAT.

Interestingly, not only VAT volume, but also VAT HU were statistically associated with cardiometabolic risk factors in present study. The mechanisms are not fully clarified, however, a possible explanation is a role of adipocyte hypertrophy. Attenuation of tissue determined by CT is a marker of lipid content and decreased attenuation represents more lipid-dense fat tissue [25]. Cellular lipid contents help to determine adipocyte cell size [26]. Increased adipocyte cell size is associated with reduced number of preadipocytes which is a precursor cells able to differentiate into adipocyte [27]. Impaired adipocyte differentiation is well known to be related with cardiometabolic complications. Furthermore, increased adipocyte size is also correlated with decreased adiponectin concentrations [28]. It has been found that decreased plasma adiponectin concentrations are associated with progression of atherosclerosis and increased incidence of CVD [29]. Taken together, lower attenuation may represents adipocyte hypertrophy, which predicts more adverse cardiometabolic risk. It is certain that, increased amount of VAT is associated with adverse cardiometabolic risk [12]. Numerous studies have demonstrated that the VAT compartment is metabolically active and secreting multiple biologically active molecules such as adipokines, inflammatory markers, vasoactive substances, markers of hemostasis, and growth factors [12, 30, 31]. To assess amount of VAT, the gold standard is the volumetric CT measurement [5, 12]. Because CT is limited by amount of radiation exposure and high cost, waist circumference and BMI, the simple anthropometric markers, commonly used measurement for VAT in the clinical practice and there are data suggesting that these indices are associated with cardiometabolic risk factors [32].

Although PET parameters of AA, lumbar spine, liver, and spleen were associated independently with neither VAT volume nor VAT HU, univariable analysis showed significant associations between PET parameters and both VAT volume and VAT HU. Recent studies reported that FDG uptake could be useful tool for the measurement of inflammation [33]. Histological studies indicated that FDG accumulation was localized within the atherosclerotic plaques [34]. Moreover, FDG uptake of aorta was significantly correlated with LDL-C concentration and atherosclerosis [35]. Tahara et al have presented that FDG uptake of VAT and SAT measured is involved in adipose tissue inflammation [20]. However, misregistration between PET and CT scans can be problematic to measure FDG activity in whole VAT and SAT. VAT and SAT show a faint FDG uptake in a normal subject with SUV less than 1 [36]. Including urine FDG activities from kidney, bladder, or ureter into VAT VOI can lead to increase in metabolic activity in VAT by the mistake. In addition, although VAT is delineated by abdominal muscular layer, SAT is not defined with upper or lower border. Therefore, measuring whole SAT can be subjective and problematic.

This study has several limitations. First, this is a cross sectional study with a small sample size with a retrospective design, thereby precluding inferences of causality or temporality.

### Table 4. Previous studies of VAT volume.

| Author                | Year | Image acquisition      | Level   | Variables       | Parameters of fat |
|-----------------------|------|------------------------|---------|-----------------|-------------------|
| Rosenquist et al.[14] | 2013 | 25 contiguous 5-mm thickness CT | above S1 | VAT and SAT     | Volume and HU     |
| Britton et al.[16]    | 2013 | 25 contiguous 5-mm thickness CT | above S1 | VAT and SAT     | Volume            |
| Alvey et al.[15]      | 2014 | 25 contiguous 5-mm thickness CT | above S1 | VAT and SAT     | Volume and HU     |
| Tahara et al.[20]     | 2015 | 11 contiguous 4-mm thickness CT | umbilicus | VAT and SAT     | Area, HU, and SUV |
| Rosenquist et al.[19] | 2015 | 25 contiguous 5-mm thickness CT | above S1 | VAT and SAT     | Volume and HU     |

VAT, visceral adipose tissue; CT, computed tomography; SAT, subcutaneous adipose tissue; HU, hounsfield unit; SUV, standardized uptake value.

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Second, although FDG-PET/CT imaging was performed and FDG uptake was assessed in the ascending aorta and spleen, we were unable to assess metabolic activity of VAT and SAT because of misregistration. Third, other non-invasive methods for cardiometabolic risks, such as calcium score or carotid intima-media thickness, could not be evaluated.

**Conclusion**

Both VAT volume and VAT HU is significantly associated with cardiometabolic risk factors. This is the first study that measured whole abdominal cavity to estimate VAT.

**Supporting Information**

S1 File. Data of this study.

**Author Contributions**

Conceived and designed the experiments: KP SHL. Performed the experiments: JGL JWS. Analyzed the data: IJK JWS. Contributed reagents/materials/analysis tools: KP JWS. Wrote the paper: KP SHL JWS.

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