Observational Study

Relationship between inflammatory markers and visceral obesity in obese and overweight Korean adults

An observational study

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Abstract

Obesity is now considered a state of chronic low-grade inflammation. We investigated the relationship between several inflammatory markers and body composition for identifying patients with an increased risk of visceral obesity and compared the predictive values of inflammatory indices in visceral obesity.

Six hundred individuals who received health checkups for obesity-related risk factors in Severance Hospital between January 2008 and March 2017 were included in our study. Serum inflammatory markers, such as white blood cell (WBC), high-sensitivity C-reactive protein (hsCRP), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) levels were assessed. Intra-abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) areas were measured with computed tomography. We performed analysis of covariance, trend analysis, Steiger’s Z tests, and multiple linear regression analysis to investigate associations between abdominal adiposity indices and inflammatory markers.

Pearson’s correlation analysis revealed a stronger association of VAT with WBC counts (r = 0.157, P < .001) than with levels of NLR (r = 0.108, P = .11; Steiger’s Z test, P = .04) and PLR (r = 0.036, P = .39; Steiger’s Z test, P = .003). WBC and hsCRP levels linearly increased with VAT area (overall P < .001 and trend P < .001) and VAT/SAT ratio (overall P < .001 and trend P < .002; overall P < .001 and trend P < .001, respectively) but linearly decreased with SAT (overall P = .02 and trend P = .17; overall P = .03 and trend P = .01, respectively). Visceral adipose tissue area was more highly associated with WBC and hsCRP levels than with NLR and PLR. Only VAT area was significantly associated with WBC, hsCRP, and NLR levels after adjusting for confounding variables.

We found that VAT, but not SAT area is independently associated with several inflammatory markers. WBC and hsCRP are more strongly correlated with VAT compared with NLR and PLR. Thus, WBC and hsCRP could be useful parameters for identifying individuals at risk for visceral obesity and cardiometabolic diseases.

Abbreviations: BMI = body mass index, HDL = high-density lipoprotein, hsCRP = high-sensitivity C-reactive protein, LDL = low-density lipoprotein, MS = metabolic syndrome, NLR = neutrophil-lymphocyte ratio, PLR = platelet-lymphocyte ratio, SAT = subcutaneous adipose tissue, TG = triglycerides, VAT = visceral adipose tissue, V/S ratio = VAT/SAT ratio, WBC = white blood cells, WC = waist circumference.

Keywords: hsCRP, inflammatory marker, visceral fat, WBC

1. Introduction

Chronic low-grade inflammation has been documented to play regulatory roles in various metabolic diseases and cardiovascular disease (CVD) under both physiological and pathophysiological conditions. Obesity is an important cause of chronic diseases and is also considered a state of chronic low-grade inflammation. The excessive accumulation of fat in adipose tissue recruits macrophages and leads to increased production of many pro-inflammatory cytokines and chemokines, including tumor necrosis factor-α, monocyte-chemoattractant protein 1, and interleukin-6 that can attract inflammatory cells. Finally, this obesity-mediated adipose tissue remodeling causes metabolic dysfunction such as insulin resistance and obesity-related systemic diseases. Therefore, the evaluation of an individual’s inflammatory status could be helpful for predicting obesity-related health problems and decrease chronic disease burden in this population.

Several inflammatory biomarkers, such as high-sensitivity C-reactive protein (hsCRP) and white blood cell (WBC) count, have been used to predict the risk of coronary heart disease and other age-related degenerative diseases. These markers are also associated with the degree of obesity expressed as body mass index (BMI), waist circumference (WC), and waist-
However, these body composition variables cannot distinguish visceral adipose tissue (VAT) from subcutaneous adipose tissue (SAT) and are limited for predicting CVD. Visceral adipose tissue area has a stronger association with cardiometabolic risk than SAT area, and although the pathological mechanisms linking VAT with its comorbidities are multifactorial, altered secretion of pro-inflammatory adipokines and a succession of inflammatory processes in VAT are considered primary contributing factors for CVD.

Recently, neutrophil-lymphocyte and platelet-lymphocyte ratios (NLR and PLR) have emerged as reliable prognostic parameters in many cancers and inflammatory diseases. However, there has been controversy about the relationship between NLR, PLR, and body composition and more studies are required.

Thus, we investigated the relationship between various serum inflammatory markers (hsCRP, WBC, NLR, and PLR) and body composition (VAT and SAT) accurately measured by abdominal computed tomography (CT) scans and compared the predictive values of inflammatory biomarker values in visceral obesity. We also used the VAT area to SAT area ratio (V/S ratio) at the L4–5 level in order to estimate the likelihood of visceral obesity in each subject (visceral V/S ratio ≥0.4; subcutaneous V/S ratio <0.4) and evaluate the correlation with surrogate inflammatory marker levels.

2. Materials and methods

2.1. Study sample

Our study subjects were selected from 474,616 patients who visited the Severance Health promotion center or the Department of Family Medicine in Severance Hospital, in Seoul, South Korea, for health checkups between January 2008 and March 2017. Exclusion criteria were:

1. aged under 19 years or over 65 years;
2. non-Korean;
3. no CT scan to measure abdominal VAT;

(4) diagnosis of hypertension, diabetes, dyslipidemia, thyroid dysfunction, or cancer; and
(5) abnormal values for hsCRP (≥6.0 mg/L) or WBC (≤4,000 or ≥10,000 cells/μL).

After applying these criteria, 600 eligible adults were included in our study (Fig. 1), which complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Severance Hospital.

Hypertension was defined as a history of taking anti-hypertensive medication, a resting systolic blood pressure (BP) ≥140 mm Hg, or a resting diastolic BP ≥90 mm Hg during at least two measurements. Diabetes mellitus was defined as a fasting plasma glucose level ≥126 mg/dL or a history of taking oral hypoglycemic agents or insulin. Dyslipidemia was defined as a total serum cholesterol level ≥240 mg/dL, low-density lipoprotein (LDL) cholesterol ≥160 mg/dL, or a history of taking lipid-lowering drugs.

2.2. Anthropometrics and biochemical variables

Body mass index was defined as body weight divided by the square of body height (kg/m²), and WC (cm) was measured at the umbilicus level at the narrowest point between the lower border of the rib cage and the uppermost border of the iliac crest during normal expiration while the patient was standing. Systolic and diastolic BP (mm Hg) was measured after 10 min of resting in a sitting position and was recorded as the average of three consecutive readings.

Intra-abdominal VAT and SAT areas were measured via fat measurement CT (Tomoscan 350, Philips; Mahwah, NJ, USA) as described previously. Fat measurement CT is an imaging test widely used in clinical studies to assess the visceral and subcutaneous fat most accurately and conveniently with fewer slices and lesser radiation than typical abdomen and pelvis CT (APCT). The VAT and SAT areas were measured at the L4–5 level with 3 mm slice thickness in the supine position. We quantified the VAT area by defining the intra-abdominal cavity at the internal side of the abdominal and oblique muscle walls

Figure 1. Patient selection flow chart. hsCRP = high-sensitivity C-reactive protein, WBC = white blood cell.
surrounding the cavity and the posterior aspect of the vertebral body. The V/S ratio (VAT area to SAT area ratio) at the L4–L5 level was then calculated. All measurements were verified by a skilled radiologist who was blinded to the patient data (see supplement figure, which illustrates the measurement of the VAT area, SAT area, and V/S ratio, http://links.lww.com/MD/C857).

Lifestyle factors, including smoking status (pack-years) and alcohol consumption (average number of drinking days per week within the last year), were self-reported.

Blood samples were collected after an overnight fast (>12 h). Serum levels of glucose, total cholesterol, triglycerides (TG), high-density lipoprotein (HDL) cholesterol, LDL cholesterol, and hsCRP were measured with a Hitachi 7600 Automatic analyzer (High-Technologies Corporation, Hitachi; Tokyo, Japan). Total differential blood counts were recorded with an automatic blood counter system (ADVIA 120, Bayer; Whippney, NJ, USA). Patient NLR and PLR were calculated by dividing the total neutrophil count by the lymphocyte count and the total platelet count by the lymphocyte count, respectively.

Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria. Patients who met at least two of the following four criteria were diagnosed with metabolic syndrome:

1. abdominal obesity (WC >102 cm in men and >88 cm in women);
2. high TG levels (>150 mg/dL) or receiving treatment for dyslipidemia;
3. low HDL levels (<40 mg/dL for men and <50 mg/dL for women); and
4. high BP (systolic >130 mm Hg and/or diastolic >85 mm Hg) or using an anti-hypertensive medication.

### 2.3. Statistical analysis

Data were expressed as means and standard deviations. Normality of the variables was assessed with Kolmogorov–Smirnov tests. To examine the association among surrogate inflammatory markers (WBC, hsCRP, NLR, and PLR), metabolic parameters, and abdominal fat composition, analysis of covariance (ANCOVA) and trend analysis were performed after adjustments for age, sex, BMI. The differences in absolute correlation coefficients between inflammatory markers and abdominal VAT area were determined using Steiger’s Z tests while calculating the dependency for two correlation coefficients.[24] Additionally, multiple linear regression analysis with the Enter method was used to assess independent associations between abdominal adiposity indices and inflammatory markers. Statistical analysis was performed using SPSS version 20 (IBM Corp.; Armonk, NY, USA), and P values less than .05 indicated statistical significance.

### 3. Results

The patients’ demographic and clinical characteristics are shown in Table 1. The mean age was 37.4 years, and mean BMI was 27.9. The mean WBC count was 6400 cells/μL, and mean NLR and PLR were 1.7 and 8.2, respectively. The mean serum hsCRP concentration was 1.5 mg/L.

#### 3.1. Associations between body composition and metabolic parameters

Table 2 shows the relationship between metabolic parameters and abdominal fat composition tertiles by ANCOVA and trend analysis. Diastolic BP, fasting glucose, total cholesterol, TG, HDL, and the mean numbers of metabolic syndrome criteria linearly increased with VAT and V/S values after adjusting covariates (overall P <.05 and trend P <.05). In contrast, HDL levels exhibited an inverse relationship with VAT area (overall P < .001 and trend P < .001) and V/S (overall P <.001 and trend P <.001).

#### 3.2. Associations between abdominal fat composition and inflammatory markers

Figure 2 displays the mean levels of inflammatory markers by abdominal fat composition tertiles after adjusting for age, sex, and BMI. Covariate-adjusted mean WBC and hsCRP levels linearly increased with VAT area (overall P <.001 and trend P <.001) and V/S (overall P =.001 and trend P =.002; overall P <.001 and trend P <.001, respectively). However, covariate-adjusted mean hsCRP levels linearly decreased with SAT area (overall P =.03 and trend P =.01). Mean WBC counts showed similar results (overall P =.02 and
Table 2
Correlations between body composition and metabolic parameters.

| VAT tertile | SAT tertile | V/S tertile |
|-------------|-------------|-------------|
| Q1 mean (SE) | Q2 mean (SE) | Q3 mean (SE) | \(P\) value for trend | Q1 mean (SE) | Q2 mean (SE) | Q3 mean (SE) | \(P\) value for trend | Q1 mean (SE) | Q2 mean (SE) | Q3 mean (SE) | \(P\) value for trend |
| **Blood pressure** | | | | | | | | | | | | | |
| SBP | 121.20 (0.93) | 122.22 (0.78) | 122.58 (0.92) | .62 | .36 | 120.60 (0.82) | 122.52 (0.80) | 122.79 (0.88) | .12 | < .001 | 121.75 (0.86) | 122.36 (0.79) | 121.87 (0.88) | .85 | .001 |
| dBP | 71.68 (0.61) | 73.06 (0.51) | 73.30 (0.61) | .03 | .02 | 73.61 (0.59) | 72.96 (0.53) | 72.67 (0.58) | .50 | .72 | 71.40 (0.56) | 73.31 (0.52) | 74.54 (0.56) | .001 | < .001 |
| **Metabolic variables** | | | | | | | | | | | | | |
| Fasting glucose | 89.68 (0.97) | 91.33 (0.82) | 97.81 (0.97) | < .001 | < .001 | 94.93 (0.88) | 91.20 (0.86) | 92.61 (0.95) | .008 | .28 | 89.23 (0.90) | 92.76 (0.83) | 96.75 (0.89) | < .001 | < .001 |
| Total cholesterol | 181.39 (3.08) | 197.23 (2.58) | 194.81 (3.03) | .001 | .008 | 188.16 (2.72) | 194.40 (2.69) | 191.06 (2.95) | .24 | .07 | 182.12 (2.85) | 194.21 (2.93) | 196.97 (2.79) | < .001 | < .001 |
| LDL cholesterol | 107.28 (2.63) | 122.41 (2.21) | 118.87 (2.59) | < .001 | < .001 | 114.15 (2.33) | 119.94 (2.30) | 114.64 (2.33) | .14 | .10 | 107.06 (2.43) | 113.84 (2.21) | 123.01 (2.38) | < .001 | < .001 |
| Smoking | 1.14 (0.40) | 0.56 (0.35) | 1.60 (0.42) | .06 | .34 | 1.83 (0.43) | 1.25 (0.33) | 0.62 (0.38) | .16 | .13 | 1.06 (0.39) | 1.00 (0.33) | 1.56 (0.43) | .57 | .008 |
| Drinking | 0.39 (0.08) | 0.35 (0.07) | 0.47 (0.08) | .51 | .55 | 0.50 (0.09) | 0.39 (0.07) | 0.35 (0.08) | .44 | .45 | 0.36 (0.07) | 0.36 (0.07) | 0.53 (0.09) | .24 | < .001 |
| Number of MS criteria | 1.07 (0.08) | 1.57 (0.07) | 2.03 (0.08) | < .001 | < .001 | 1.19 (0.07) | 1.79 (0.07) | 1.70 (0.08) | < .001 | < .001 | 1.45 (0.08) | 1.63 (0.07) | 1.60 (0.08) | < .001 | < .001 |

Smoking and drinking variables were defined as total smoking pack-years and average number of drinking days per week within the last year. The model was adjusted for sex, age, and BMI. \(P\) values were calculated using analysis of covariance.

BMI = body mass index, dBP = diastolic blood pressure, HDL = high-density lipoprotein, LDL = low-density lipoprotein, MS = metabolic syndrome, SAT = subcutaneous adipose tissue, SBP = systolic blood pressure, SE = standard error, TG = triglycerides, VAT = visceral adipose tissue, V/S = VAT/SAT ratio.

4. Discussion
We found that levels of certain surrogate inflammatory markers (WBC, hCRP, and NLR) were independent associations with VAT, but not with SAT. Moreover, VAT area was more highly associated with WBC, hCRP, and PLR levels (\(P\) = .001) than with levels of NLR (\(P\) = .39) after adjusting for covariates. A large body of evidence indicates that the regional distribution of WBC, hsCRP, and NLR.

3.4. Independent associations of inflammatory markers with abdominal fat compositions using multivariate models from the sex-and BMI-stratified analysis
We performed the comparison using Seeger’s [7] with a model adjusted for age, sex, and BMI. Pearson’s correlation analysis revealed a strong association between SAT and VAT area and NLR and PLR levels in relation to VAT and VS/V ratios. The significant association between VAT and NLR, although no significant differences in trend for P > .17, was not significantly different between SAT and VAT areas.

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have reported that SAT may have more protective function in endocrine and inflammatory aspects than VAT. Further pathophysiological studies are required to elucidate the exact relationship between SAT and inflammatory markers, considering the anatomical division of subcutaneous fat between the superficial (sSAT) and deep (dSAT) layers.

The relationship between chronic low-grade inflammation, insulin resistance, and other obesity-associated metabolic disturbances has become increasingly recognized, and various studies have tried to identify sensitive and reliable biomarkers of oxidative stress and systemic inflammation. Because tests for several serum inflammatory markers are inexpensive, widely available, and easy to interpret, they can serve as simple indicators of systemic inflammation, disease progression, and health outcomes. Levels of WBC and hsCRP are well-known predictors of CVD, and several epidemiological studies have linked these markers to various obesity parameters and cardiovascular risk factors. More recently, NLR and PLR have received attention as emerging inflammatory markers. High neutrophil and low lymphocyte counts represent the human physiologic immune response, and platelet count increases during an acute inflammatory reaction. To this end, NLR has been studied as a potential inflammatory biomarker in cardiac disorders, gastrointestinal diseases, and malignancies.

Figure 2. Inflammatory markers according to abdominal fat composition tertiles after adjusting for age, sex, and BMI. Mean (estimated) and standard error (indicated with error bars). P < .05 and P < .01 indicate significant differences among tertiles using analysis of covariance. Trend P < .05; trend P < .01. T, tertile. A, B, C, D: T1 (24.2–78.4), T2 (79.1–117.2), T3 (117.3–411) cm²; E, F, G, H: T1 (33–196.23), T2 (196.6–287.44), T3 (287.5–1189.11) cm²; I, J, K, L: T1 (0.08–0.3), T2 (0.3–0.48), T3 (0.48–10.82). hsCRP = high-sensitivity C-reactive protein, NLR = neutrophil-lymphocyte ratio, PLR = platelet-lymphocyte ratio, SAT = subcutaneous adipose tissue, VAT = visceral adipose tissue, V/S ratio = VAT/SAT ratio; WBC, white blood cell.

### Table 3

|                     | WBC count | hsCRP | NLR | PLR |
|---------------------|-----------|-------|-----|-----|
| **Model 1**         |           |       |     |     |
| VAT (unit100)       | 0.743     | 0.214 | 0.001 | 0.146 |
| SAT (unit100)       | 0.028     | 0.083 | 0.74  | 0.006 |
| **Model 2**         |           |       |     |     |
| V/S ratio (unit1)   | 0.31      | 0.146 | 0.001 | 0.165 |

All variables left in the model are significant at the 0.15 level. No other variable met the 0.15 significance level for entry into the model.

Model 1: adjusted for age, sex, BMI, dBP, HDL, LDL, smoking status.
Model 2: adjusted for age, sex, BMI, dBP, TG, HDL, LDL, smoking status.

BMI = body mass index, dBP = diastolic blood pressure, HDL = high-density lipoprotein, hsCRP = high-sensitivity C-reactive protein, LDL = low-density lipoprotein, NLR = neutrophil-lymphocyte ratio, PLR = platelet-lymphocyte ratio, SAT = subcutaneous adipose tissue, TG = triglycerides, VAT = visceral adipose tissue, V/S = VAT/SAT ratio; WBC = white blood cells.
while PLR has predicted mortality in patients with malignancies and coronary artery disease. However, the relationship between NLR and PLR and adiposity had not been investigated prior to our study. To our knowledge, no previous work has assessed which inflammatory markers are most closely correlated with abdominal visceral adiposity. We found that WBC and hsCRP levels are likely associated with visceral adiposity and are superior to NLR and PLR in this regard.

4.1. Limitations

Our study had several limitations. First, its observational cross-sectional design did not allow us to assess causality or temporality, and we could not exclude possible residual confounding factors. Second, selection bias may have influenced our results because the study sample only included data from a single hospital, which may not be representative of the general population or other races. Third, we did not assess various adipokines or pro-inflammatory mediators to clarify the relationship between visceral adiposity and inflammatory processes. Fourth, we did not distinguish dSAT from sSAT layers in the patients. Despite these limitations, this is the first study to investigate the relationship between multiple inflammatory biomarkers and abdominal adiposity precisely evaluated by CT to predict visceral obesity through comprehensive evaluation using various statistical approaches.

4.2. Future directions

Future investigations should clarify the possible mechanism between inflammatory markers, fat distribution, and chronic inflammation-related diseases. Also, longitudinal studies with larger datasets are needed in order to evaluate the best biomarker visceral obesity.

5. Conclusion

Visceral, but not subcutaneous, adipose tissue area is significantly and independently associated with levels of WBC, hsCRP, and NLR. In addition, VAT is more strongly correlated with WBC and hsCRP than with NLR and PLR.

Author contributions

Data curation: Ju-Yeon Yu, Hye-Sun Lee.

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Methodology: Hye-Sun Lee.

Project administration: Ji-Won Lee.

Supervision: Won-Jun Choi, Hye-Sun Lee, Ji-Won Lee.

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Writing – review & editing: Won-Jun Choi, Hye-Sun Lee, Ji-Won Lee.

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