Serum Chemerin Levels Are Associated with Abdominal Visceral Fat in Type 2 Diabetes

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INTRODUCTION

In type 2 diabetes (T2DM), the pattern of adipose tissue distribution is significantly different from individuals without diabetes. Subjects with T2DM have more visceral adipose tissue and lesser subcutaneous adipose tissue than in healthy control subjects (1). Most studies have found that visceral adipose tissue is strongly related to insulin resistance in T2DM. Visceral fat accumulation has a significant negative impact on glycemic control through a decrease in peripheral insulin sensitivity and an enhancement of gluconeogenesis (2) and it is associated with the development of coronary heart disease (3).

T2DM seems to be closely related to the endocrine activity of adipose tissue. Adipose tissue is known to express and secrete a variety of adipokines, such as leptin, adiponectin, resistin, chemerin, retinol binding protein-4 (RBP-4), omentin and adipocyte fatty acid-binding protein (A-FABP). The release of adipokines by adipocytes can lead to a chronic inflammatory state that could play a central role in the development of insulin resistance and T2DM and is associated with the risk of cardiovascular disease (4). However, among these adipokines, the potential role of chemerin on T2DM and adiposity has not been fully examined and remains controversial.

Chemerin is a recently identified adipokine suggested to play a role in obesity and its metabolic complications. The relationship between visceral obesity and serum chemerin levels in type 2 diabetes (T2DM) is unknown and may differ from that of subjects without diabetes. Therefore, we evaluated whether serum chemerin was associated with visceral abdominal obesity in patients with T2DM. A total of 218 Korean patients with T2DM were enrolled and metabolic parameters, abdominal visceral and subcutaneous fat areas, and serum chemerin levels were measured. Serum chemerin level showed positive correlation with fasting insulin, HOMA-IR, serum triglyceride, serum creatinine, urine albumin/creatinine ratio, high-sensitivity C-reactive protein (hsCRP), fibrinogen, abdominal visceral fat area, visceral to subcutaneous fat area ratio, and negatively correlation with high density lipoprotein cholesterol and creatinine clearance (CCr) after adjusting for age, gender and body mass index. Multiple linear stepwise regression analysis showed that abdominal visceral fat area (β = 0.001, P < 0.001), serum triglyceride (β = 0.001, P < 0.001), CCr (β = −0.003, P = 0.001), hsCRP (β = 0.157, P = 0.001), fibrinogen (β = 0.001, P < 0.001), and BMI (β = 0.02, P = 0.008) independently affected log transformed serum chemerin levels. Higher serum chemerin level was associated with higher level of abdominal visceral fat area, serum triglyceride, hsCRP and fibrinogen and lower level of CCr in patients with T2DM. Serum chemerin may be used as a biomarker of visceral adiposity and chemerin may play a role in inflammation, decreased renal function, and increased cardiovascular risk in T2DM.

Keywords: Chemerin; Abdominal Visceral Fat; Type 2 Diabetes Mellitus

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ever, the relationship between serum chemerin levels and body fat composition, in particular visceral abdominal obesity in people with T2DM has not been well studied and this relationship may be different from those without diabetes. Therefore, we investigated whether circulating chemerin levels might be associated with the degree of visceral obesity and other metabolic parameters in patients with T2DM.

MATERIALS AND METHODS

Study participants
In this study, 218 subjects with T2DM participated from the outpatient clinic of Inha University Hospital Diabetes and Endocrinology Center, Incheon, Korea. Diabetes was defined according to the American Diabetes Association diagnostic criteria (9). Eligible participants were aged 20-75 years with T2DM taking oral hypoglycemic agent, but not on insulin therapy. Participants who had a history of type 1 diabetes, active malignancy, infection and severe renal (serum creatinine level > 2 mg/dL) or hepatic disease (alanine aminotransferase or aspartate aminotransferase level greater than or equal to twofold higher than the upper normal limit), and patients taking an anti-obesity drug or a thiazolidinedione were excluded.

Anthropometric measurement
Body weight, height, waist circumference (WC), and blood pressure were measured. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). WC was measured at the midpoint between the lower borders of the rib cage and the iliac crest. Blood pressure was measured after the subject has been in rest for at least 10 minutes in a sitting position.

Blood collection and biochemical analyses
Blood samples were collected after an overnight fast of at least 8 hours and stored at -80°C for subsequent assays. Serum glucose was measured by a hexokinase method and hemoglobin A1c (HbA1c) values were determined by high-performance liquid chromatography (HLC-723G7, Tosoh, Tokyo, Japan). Insulin was measured by a radioimmunoassay (TFB, Tokyo, Japan). Serum concentrations of triglyceride, total cholesterol, and high density lipoprotein cholesterol (HDL-C) were measured with an automatic chemical analyzer (Hitachi 7600; Tokyo, Japan). Fibrinogen concentrations were measured by a Diagnostica STA analyzer with fibrinogen reagent (STA-fibrinogen). Creatinine clearance (CCr) was calculated by the Cockcroft-Gault equation: [(140-age) × total body weight/(serum creatinine (mg/dL) × 72) (× 0.85 for females). Chemerin (Mesdia, Seoul, Korea), lipocalin-2 (R&D systems, Minneapolis, MN, USA) and omentin-1 (Biovender Laboratory Medicine Inc, Modrice, Czech Republic) levels were measured by ELISA (enzyme-linked immunosorbent assay). The intra assay CVs were 11.3%, 9.4%, and 4.6% respectively. High sensitivity C-reactive protein (hsCRP) was measured by a high-sensitivity latex enhanced, immunephelometric assay method with a chemical analyzer (Hitachi 7600; Tokyo, Japan). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by the following formula: (fasting insulin [IU/mL] × fasting glucose [mmol/L])/22.5.

Measurement of abdominal adipose tissue
Intra-abdominal adipose tissue area was measured by a computed tomography (CT) scan (Lightspeed VCT 64 Rows, GE Healthcare, Waukesha, WI, USA). A 5 mm CT slice scan was acquired at the L4-L5 level with the subject supine. The adipose tissue area was determined electronically by setting the attenuation values for a region of interest within a range of -250 to -50 Hounsfield unit (HU). The subcutaneous fat area was derived by subtracting the visceral fat area from the total abdominal fat area. The visceral to subcutaneous fat area ratio (V/S ratio) was also calculated.

Measurement of brachial ankle pulse wave velocity (baPWV)
baPWV was measured using model BP-203RPE II volume-plethysmographic apparatus (Colin, Komaki, Japan). Each participant rested in the supine position for 10 minutes, and was examined with electrocardiographic electrodes placed on both wrists and cuffs wrapped around both brachia and ankles. Transmission time was calculated as the time for the waveform to travel between the right arm and both ankles, and the transmission distance between the right brachium and ankle was automatically calculated based on the height of the participant. In the present study, the means of right and left baPWV were used for analysis.

Definition of diabetic retinopathy
Diabetic retinopathy was diagnosed by ophthalmologists according to the international classification of diabetic retinopathy as previously described (10).

Statistical analysis
All calculations and statistical analyses were performed using the SPSS for Windows software (version 19.0, Chicago, IL, USA). Data are expressed as the mean ± SD. Baseline comparisons and characteristics according to presence of diabetic retinopathy were assessed by t-test, Wilcoxon rank sum test and χ² test as appropriate. Partial Spearman’s correlation analysis was used to examine the association between serum chemerin levels and other metabolic variables. To establish the independent factors associated with chemerin levels, multiple linear stepwise regression analysis was used. Chemerin was log transformed and independent variables in the multiple stepwise regression analysis were age, gender, BMI, fasting insulin, HOMA-IR, HDL cholesterol, triglyceride, serum creatinine, CCr, urine albumin/
cr ratio, hsCRP, fibrinogen, visceral fat area, and V/S ratio. Results were considered statistically significant if the P value was < 0.05.

Ethics statement
This study was approved by the institutional review board at Inha University Hospital (IRB 2006-67) and all participants provided written informed consent to participate in the study.

RESULTS

A total of 218 subjects (131 men and 87 women) participated in the study. Baseline clinical characteristics of this study subjects are summarized in Table 1. Mean age was 52.2 ± 7.5 years, BMI 25.3 ± 2.9 kg/m², HbA1c 7.5% ± 1.3%, visceral abdominal fat area 111.7 ± 48.9 cm², subcutaneous abdominal fat area 153.1 ± 66.6 cm², and serum chemerin 80.3 ± 22.3 ng/mL. Serum chemerin level was positively correlated with BMI, WC, abdominal subcutaneous fat area, abdominal visceral fat area, V/S ratio, blood pressure, fasting insulin, HOMA-IR, triglyceride, urine albumin/creatinine ratio, hsCRP, fibrinogen, and negatively correlated with HDL-C. However, after adjusting for age, gender and BMI, serum chemerin level was positively correlated with fasting insulin (r = 0.25, P < 0.001), HOMA-IR (r = 0.19, P = 0.006), triglyceride (r = 0.36, P < 0.001), serum creatinine (r = 0.21, P = 0.002), urine albumin/creatinine ratio (r = 0.25, P < 0.001), hsCRP (r = 0.31, P < 0.001), fibrinogen (r = 0.32, P < 0.001), abdominal visceral fat area (r = 0.28, P < 0.001), and V/S ratio (r = 0.30, P < 0.001), and negatively correlated with HDL-C (r = -0.19, P = 0.005) and CrCr (r = -0.18, P = 0.009) as shown in Table 2 and Fig. 1. We also examined the association of serum chemerin levels with omentin-1 and lipocalin-2, but no association was observed. Multiple linear stepwise regression analysis showed that abdominal visceral fat area (β = 0.001, P < 0.001), serum triglyceride (β = 0.001,

Table 1. Clinical characteristics of the study subjects

| Characteristics | Men (n = 131) | Women (n = 87) | Total (n = 218) | P value |
|-----------------|--------------|---------------|----------------|---------|
| Age, yr         | 51.6 ± 7.9   | 53.2 ± 7.0    | 52.2 ± 7.5     | 0.14    |
| Duration, yr    | 6.0 ± 5.3    | 5.7 ± 5.2     | 5.9 ± 5.3      | 0.75    |
| Medication      |              |               |                |         |
| Sulfonylurea, % | 41.2         | 47.1          | 43.6           | 0.41    |
| Metformin, %    | 76.3         | 83.9          | 79.4           | 0.23    |
| Hypertension medication, % | 32.8 | 26.4 | 30.3 | 0.37 |
| Statin, %       | 35.1         | 48.3          | 40.4           | 0.07    |
| Diabetic retinopathy, % | 23.7 | 13.8 | 19.7 | 0.08 |
| BMI, kg/m²      | 25.3 ± 3.0   | 25.1 ± 3.0    | 25.3 ± 2.9     | 0.64    |
| Waist circumference, cm | 87.6 ± 7.9 | 84 ± 6.7 | 86.1 ± 7.6 | 0.001 |
| Total Abdominal fat area, cm² | 242 ± 92.1 | 299.2 ± 88.5 | 264.8 ± 94.7 | < 0.001 |
| Visceral fat area, cm² | 113.7 ± 52.0 | 108.6 ± 44.1 | 111.7 ± 48.9 | 0.46 |
| Subcutaneous fat area, cm² | 128.3 ± 56.4 | 190.6 ± 63.3 | 153.1 ± 66.6 | < 0.001 |
| V/S ratio       | 0.05 ± 0.5   | 0.02 ± 0.4    | 0.08 ± 0.5     | < 0.001 |
| Systolic BP, mmHg | 125.3 ± 14.1 | 124.4 ± 13.9 | 124.9 ± 14.0  | 0.67    |
| Diastolic BP, mmHg | 81.4 ± 10.8 | 77.2 ± 10.4  | 79.7 ± 10.8    | 0.005   |
| Fasting plasma glucose, mM | 8.3 ± 2.2 | 7.9 ± 2.4 | 8.1 ± 2.3 | 0.26 |
| HbA1c, %        | 7.5 ± 1.4    | 7.4 ± 1.1     | 7.5 ± 1.3      | 0.36    |
| HbA1c, mmol/mol | 59.0 ± 15.4  | 57.2 ± 12.0   | 58.3 ± 14.1    | 0.36    |
| HOMA-IR         | 3.2 ± 2.2    | 3.7 ± 2.5     | 3.4 ± 2.4      | 0.1     |
| Fasting insulin, pM | 8.8 ± 6.1 | 10.7 ± 6.8 | 9.6 ± 6.4 | 0.03 |
| Total cholesterol, mmol/L | 4.3 ± 0.9 | 4.3 ± 1.0 | 4.3 ± 0.9 | 0.87 |
| HDL cholesterol, mmol/L | 1.3 ± 0.3 | 1.3 ± 0.3 | 1.3 ± 0.3 | 0.09 |
| Triglyceride, mmol/L | 1.9 ± 1.3 | 1.7 ± 0.9 | 1.8 ± 1.2 | 0.16 |
| LDL cholesterol, mmol/L | 2.2 ± 0.9 | 2.2 ± 0.8 | 2.2 ± 0.8 | 0.81 |
| Serum creatinine, mg/dL | 1.05 ± 0.1 | 0.81 ± 0.1 | 0.95 ± 0.2 | < 0.001 |
| CrCr, mg/dl      | 87.4 ± 26.9  | 78.4 ± 14.9   | 83.8 ± 23.3    | 0.002   |
| Albumin/Cr Ratio, μg/mgCr | 55.6 ± 196.6 | 29.4 ± 37.5 | 45.1 ± 154.5 | 0.14 |
| hs CRP, mg/dL    | 0.2 ± 0.4    | 0.2 ± 0.4     | 0.17 ± 0.4     | 0.01 |
| Fibrinogen, mg/dL | 303.2 ± 63.9 | 320.4 ± 76.9 | 310 ± 69.7 | 0.08 |
| PWV mean, m/sec | 15.0 ± 2.5   | 15.0 ± 2.4    | 14.9 ± 2.4     | 0.63    |
| Chemerin, ng/mL | 78.6 ± 22.0  | 82.9 ± 22.6   | 80.3 ± 22.3    | 0.16    |
| Omentin-1, ng/mL | 427.7 ± 140.2 | 462.6 ± 154.9 | 441.7 ± 146.9 | 0.08 |
| Lipocalin, ng/mL | 73.9 ± 21.2  | 65.6 ± 22.8   | 70.7 ± 1.5     | 0.01    |

Data were expressed as the mean ± SD. The Wilcoxon rank sum test, t-test and χ² test were used to compare the baseline characteristics as appropriate.

BMI, body mass index; BP , blood pressure; HOMA-IR, homeostasis model assessment-insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; CrCr, creatinine clearance; PWV, pulse wave velocity; V/S ratio, ratio of visceral to subcutaneous fat.
We report for the first time that serum chemerin levels are positively associated with abdominal visceral fat area using CT and fibrinogen was a definite factor associated with serum chemerin levels in patients with T2DM. In a previous study, chemerin level was significantly associated with visceral fat accumulation in subjects without diabetes (8), and other studies reported that chemerin gene expression was significantly higher in visceral adipose tissue compared with subcutaneous adipose tissue in animals (5). However, the relationship between serum chemerin levels and abdominal fat area, especially subcutaneous and visceral fat in T2DM has not been well studied. In our previous study, a 12-week intensive lifestyle intervention significantly

**DISCUSSION**

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**Table 2.** The correlation between serum chemerin levels and abdominal fat area, metabolic variables

| Variables                        | Unadjusted     | Age, gender, BMI adjusted |
|----------------------------------|----------------|----------------------------|
|                                  | \( r \) | \( P \) | \( r \) | \( P \) |
| Gender                           | 0.11 | 0.09 | 0.03 | 0.63 |
| Age, yr                          | 0.03 | 0.63 | 0.03 | 0.63 |
| BMI, kg/m²                       | 0.29 | < 0.001 | 0.29 | < 0.001 |
| Waist circumference, cm          | 0.24 | < 0.001 | 0.08 | 0.26 |
| Total Adiposity area, cm²        | 0.34 | < 0.001 | 0.16 | 0.02 |
| Visceral fat area, cm²            | 0.39 | < 0.001 | 0.28 | < 0.001 |
| Subcutaneous fat area, cm²       | 0.21 | 0.002 | -0.04 | 0.55 |
| V/S ratio                        | 0.22 | 0.001 | 0.30 | < 0.001 |
| Systolic BP, mmHg                | 0.16 | 0.02 | 0.11 | 0.11 |
| Diastolic BP, mmHg               | 0.15 | 0.03 | 0.13 | 0.07 |
| Fasting plasma glucose, mM       | 0.01 | 0.91 | 0.02 | 0.79 |
| HbAtc, %                         | -0.04 | 0.59 | -0.04 | 0.52 |
| Fasting insulin, pM              | 0.36 | < 0.001 | 0.25 | < 0.001 |
| HOMA-IR                          | 0.29 | < 0.001 | 0.19 | 0.006 |
| Total cholesterol, mmol/L        | -0.05 | 0.50 | -0.05 | 0.51 |
| HDL cholesterol, mmol/L          | -0.18 | 0.009 | -0.19 | 0.005 |
| Triglyceride, mmol/L             | 0.38 | < 0.001 | 0.36 | < 0.001 |
| Serum creatinine, mg/dL          | 0.07 | 0.28 | 0.21 | 0.002 |
| Ccr, mg/dL                       | -0.31 | 0.65 | -0.18 | 0.009 |
| Albumin/Cr Ratio, μg/mgCr        | 0.28 | < 0.001 | 0.25 | < 0.001 |
| hs CPP, mg/dL                    | 0.33 | < 0.001 | 0.31 | < 0.001 |
| Fibrinogen, mg/dL                | 0.33 | < 0.001 | 0.32 | < 0.001 |
| PWV mean, m/sec                  | 0.11 | 0.11 | 0.12 | 0.08 |
| Omentin-1, ng/mL                 | -0.41 | 0.55 | -0.01 | 0.91 |
| Lipocalin, ng/mL                 | 0.11 | 0.12 | 0.10 | 0.13 |

Correlation coefficients \( r \) and \( P \) values were calculated by the partial Spearman’s correlation model.

BMI, body mass index; BP, blood pressure; HOMA-IR, homeostasis model of assessment - insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; Ccr, creatinine clearance; PWV, pulse wave velocity; V/S ratio, ratio of visceral to subcutaneous fat.

\( P < 0.001 \), Ccr (\( \beta = -0.003, P = 0.001 \)), hsCRP (\( \beta = 0.157, P = 0.001 \)), fibrinogen (\( \beta = 0.001, P < 0.001 \)), and BMI (\( \beta = 0.02, P = 0.008 \)) independently affected log transformed serum chemerin levels

(Tables 3). When clinical characteristics were compared according to the presence and absence of diabetic retinopathy, there were no significant differences in most parameters except for longer duration in those with diabetic retinopathy. Chemerin, omentin, lipocalin levels were not different according to the presence of diabetic retinopathy (Table 4).

**DISCUSSION**

We report for the first time that serum chemerin levels are positively associated with abdominal visceral fat area using CT and fibrinogen was a definite factor associated with serum chemerin levels in patients with T2DM. In a previous study, chemerin level was significantly associated with visceral fat accumulation in subjects without diabetes (8), and other studies reported that chemerin gene expression was significantly higher in visceral adipose tissue compared with subcutaneous adipose tissue in animals (5). However, the relationship between serum chemerin levels and abdominal fat area, especially subcutaneous and visceral fat in T2DM has not been well studied. In our previous study, a 12-week intensive lifestyle intervention significantly

**Table 3.** Multiple linear stepwise regression analysis for factors associated with serum chemerin level*

| Factors                        | \( \beta \) | SE | \( P \) | \( R^2 \) |
|--------------------------------|-----------|----|-------|-------|
| Visceral fat area, cm²         | 0.001     | < 0.001 | < 0.001 |       |
| Fibrinogen                     | 0.001     | < 0.001 | 0.001   |       |
| Triglyceride                   | 0.001     | < 0.001 | < 0.001 |       |
| HsCRP                          | 0.157     | 0.045 | 0.001   |       |
| Ccr                            | -0.003    | 0.001 | < 0.001 |       |
| BMI                            | 0.020     | 0.007 | 0.008   | 0.378  |

Independent variables in the multiple stepwise regression analysis were age, gender, body mass index, fasting insulin, HOMA-IR, HDL cholesterol, triglyceride, serum creatinine, Ccr, urine albumin/Cr ratio, hsCRP, fibrinogen, visceral fat area, and V/S ratio. BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; Ccr, creatinine clearance; SE, standard error; \( R^2 \), coefficient of determination.

*Serum chemerin level was log-transformed.

P<0.001)
Table 4. Clinical and laboratory variables according to presence of diabetic retinopathy

| Variables                        | Retinopathy (+) | Retinopathy (-) | P  |
|----------------------------------|-----------------|-----------------|----|
| No. of patients                  | 43              | 175             |    |
| Age, yr                          | 53.9 ± 6.6      | 51.8 ± 7.7      | 0.14|
| Gender (male %)                  | 72.1            | 57.1            | 0.08|
| Duration, yr                     | 8.4 ± 6.6       | 5.3 ± 4.7       | 0.005|
| BMI, kg/m²                       | 25.1 ± 3.5      | 25.3 ± 2.8      | 0.36|
| Waist circumference, cm          | 86.8 ± 9.3      | 86.0 ± 7.2      | 0.94|
| Visceral fat area, cm²           | 101.3 ± 56.2    | 156.9 ± 65.8    | 0.06|
| Subcutaneous fat area, cm²       | 138.0 ± 68.2    | 124.8 ± 14.2    | 0.08|
| V/S ratio                        | 0.81 ± 0.49     | 0.82 ± 0.46     | 0.91|
| Systolic BP, mmHg                | 125.4 ± 13.4    | 79.3 ± 10.1     | 0.78|
| Diastolic BP, mmHg               | 79.1 ± 25.6     | 144.6 ± 38.4    | 0.61|
| Fasting plasma glucose, mM       | 151.6 ± 52.8    | 7.7 ± 1.4       | 0.24|
| HbA1c, %                         | 7.7 ± 1.4       | 7.4 ± 1.2       | 0.20|
| HOMA-IR                          | 2.9 ± 1.9       | 3.5 ± 2.4       | 0.20|
| Total cholesterol, mmol/L        | 174.7 ± 41.9    | 165.3 ± 34.3    | 0.23|
| HDL cholesterol, mmol/L          | 51.7 ± 12.7     | 49.3 ± 11.5     | 0.23|
| Triglyceride, mmol/L             | 166.2 ± 100.7   | 161.3 ± 105.3   | 0.72|
| Serum creatinine, mg/dL          | 1.0 ± 0.2       | 0.9 ± 0.2       | 0.11|
| Ccr, mg/dL                       | 81.4 ± 20.5     | 84.4 ± 23.9     | 0.39|
| Albumin/Cre Ratio                | 45.5 ± 70.8     | 45.0 ± 169.0    | 0.23|
| hs CRP, mg/dL                    | 0.11 ± 0.12     | 0.19 ± 0.42     | 0.54|
| Fibrinogen, mg/dL                | 303.2 ± 61.5    | 317.1 ± 71.7    | 0.47|
| PW mean, m/sec                   | 15.5 ± 3.0      | 14.7 ± 2.8      | 0.23|
| Chemerin, ng/mL                  | 76.3 ± 23.9     | 81.3 ± 21.9     | 0.14|
| Omentin-1, ng/mL                 | 464.7 ± 144.4   | 436.1 ± 147.4   | 0.16|
| Lipocalin, ng/mL                 | 75.1 ± 25.3     | 69.6 ± 21.2     | 0.19|

Data were expressed as the mean ± SD. Wilcoxon rank sum test, t-test and χ² test were used to calculate P values as appropriate.

BMI, body mass index; BP, blood pressure; HOMA-IR, homeostasis model of assessment-insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; Ccr, creatinine clearance; PW, pulse wave velocity; V/S ratio, ratio of visceral to subcutaneous fat.

decreased total body fat content and serum chemerin level (7).

In this study, baseline chemerin level was not associated with visceral abdominal fat and subcutaneous visceral fat. However, the number of participants was too small (n = 35) to explain the association between serum chemerin level and abdominal fat composition, and the participants were limited to only overweight and obese patients with T2DM. Since, there was a possibility that serum chemerin concentration might be associated with abdominal fat area, especially visceral fat compartment in T2DM, we investigated this in a larger number of patients with T2DM and those with a broader range of BMI.

Obesity, and in particular abdominal obesity, plays a major role in the pathogenesis of several metabolic and cardiovascular problems including T2DM, hypertension, atherosclerosis and coronary artery disease (11). Especially, excess visceral adiposity is associated with impaired glucose tolerance, insulin resistance, and atherogenic dyslipidemia (12). In addition, visceral fat has been associated with coronary stenosis, independent of traditional cardiovascular risk factors, in an asymptomatic population without a history of coronary artery disease (13). Even within the normal range of BMI, accumulation of visceral fat remains to be an independent cardiovascular risk factor (14).

Visceral fat accumulation may also induce secretion of adipocytokines. Oversecretion of pro-inflammatory adipocytokines, such as PAI-1 or tumor necrosis factor-α (TNF-α) and hyposecretion of defensive adipocytokines, such as adiponectin, might be major mechanisms of insulin resistance and T2DM (15). In recent years, several adipocytokines were newly discovered such as retinol binding protein-4 (RBP-4), vaspin, omentin, chemerin and adipocyte fatty acid-binding protein (A-FABP). Among these adipocytokines, this effect of chemerin on the adipose tissue and glucose metabolism remains controversial.

Chemerin is an adipokine which was recently found that has a role in adaptive and innate immunity, and regulates adipocyte differentiation and metabolism by binding to and activating the seven transmembrane-spanning G protein-coupled receptor (GPCR), chemokine-like receptor 1 (CMKLR1) (5). Serum chemerin levels are increased in obesity (5), and the expression is especially higher in visceral adipose tissue compared with subcutaneous adipose tissue in normal glucose tolerance animals (6). In addition, visceral fat mass quantified by magnetic resonance imaging was significantly associated with genetic variations of RARRES2 which encodes chemerin in subjects with an increased risk for T2DM (16). WC is an easily checkable method, however an imprecise measurement of abdominal adiposity because it is the sum of both subcutaneous and visceral adipose tissue compartments. Our results also found that WC was associated with chemerin level, but after adjusting for age, sex and BMI, the correlation of systemic chemerin level with WC was not significant. Therefore, assessment of visceral adipose tissue area requires imaging with radiographic techniques such as CT or magnetic resonance imaging. In this respect, measurement of chemerin levels which is positively associated with visceral obesity, may conveniently provide a more precise information about metabolic risk compared to BMI, WC or radiographic imaging such as CT.

Patients with diabetes have increased prevalence of hypertriglyceridemia. In diabetes, the impaired ability of insulin to inhibit the release of free fatty-acid leads to hypertriglyceridemia (17). There is a controversy whether hypertriglyceridemia is directly related with cardiovascular disease, however, some studies demonstrate that hypertriglyceridemia is associated with cardiovascular disease, especially in patients with insulin resistance or in patient accompanying other type of dyslipidemias (e.g. increased small dense LDL cholesterol and low HDL cholesterol) (17). Recent studies have shown that serum chemerin levels are associated with metabolic risk factors including serum triglyceride (18-20). Takahashi et al. (21) showed that chemerin levels were positively correlated with BMI, total cholesterol, triglyceride levels and negatively correlated with HDL-C in T2DM. Another study showed that chemerin levels were significantly associated with BMI, triglyceride, creatinine, Ccr af-
Our data showed that serum chemerin concentration was significantly associated with serum chemerin levels. In accordance with this finding, CCr and serum creatinine were significantly associated with healthy subjects, suggesting that determinants of renal function that contribute to initiation and progression of inflammation in the obese state by stimulating macrophage adhesion to extracellular matrix proteins and by promoting chemotaxis. Chemerin synthesis is induced by the overexpression of proinflammatory cytokines such as TNF-α and IL-1 which promote atherogenesis. Chemerin may be one of several factors that contribute to cardiovascular disease in T2DM. However, long-term prospective studies of cardiovascular outcome associated with serum chemerin level should be investigated.

Plasma fibrinogen is an acute-phase protein, and is likely to increase with inflammation and has been identified as an independent risk factor for cardiovascular disease and it is associated with traditional cardiovascular risk factors. Plasma fibrinogen may also be increased in T2DM and be associated with a number of components of the metabolic syndrome. These evidences indicate that hyperfibrinogenemia in T2DM could contribute to the excess cardiovascular morbidity and mortality. In the present study, for the first time, we identified that fibrinogen was a definite factor associated with serum chemerin levels in T2DM. In accordance with the above findings, we suggest that serum chemerin levels in T2DM can serve as a predictor of inflammation and cardiovascular disease, like hsCRP and fibrinogen.

Recently, serum chemerin levels were reported to be significantly higher in patients on chronic hemodialysis as compared with healthy subjects, suggesting that determinants of renal function are independently related to serum chemerin levels. In addition, both CCr and serum creatinine were significantly associated with serum chemerin levels. In accordance with these reports, our data showed that serum chemerin concentrations were significantly correlated with serum creatinine and CCr after adjusting age, sex, and BMI. Moreover, CCr was independently associated with serum chemerin levels. These findings indicate that elevated serum chemerin levels could be a marker of low CCr associated with diabetic nephropathy.

This study has some limitations. First, the study population were Korean subjects with T2DM, therefore the relationship between circulating chemerin level and visceral adipose tissue should be studied further in other populations. Second, we only measured the total form of chemerin. Chemerin is secreted in an inactive form as prochemerin with significantly lower biological activity, and undergoes proteolytic cleavage on the C-terminal by proteases such as neutrophil elastase, cathepsin G and plasmin to become a short form with varying biological activity. Adipocytes express the genes that encode for protease that activate chemerin, such as neutrophil elastase, mast cell tryptase, angiotensin converting enzyme, tPA, uPA, and cathepsin K. C-terminal-truncated chemerin variants display either more chemotactic or anti-inflammatory effects, which is determined by the cleavage at distinct sites by different classes of proteases. Therefore, additional studies are necessary to evaluate the change in chemerin subtypes and the significance of these changes.

In summary, abdominal visceral fat area, BMI, serum triglyceride, hsCRP, fibrinogen, and CCr were independent factors affecting serum chemerin levels in T2DM. Our data suggest that serum chemerin which is associated with many metabolic risk factors can be a predictor of the degree of visceral adiposity and may play an important role in inflammation, diabetic nephropathy, and risk of cardiovascular disease in T2DM. Furthermore, the metabolic complications of obesity in T2DM are not fully predictable based on simple anthropometric measurements. Therefore, clinical utility of chemerin as a biomarker of visceral obesity in T2DM could be useful in early detection of these pathological states, and aid in finding candidates for more intensive lifestyle modification and therapy to prevent their unfavorable consequences.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Study conception and design: Kim SH, Lee SY, Nam MS. Data collection: Lim HA, Shin H, Cho SG, Kim CW, Lee SY. Data analysis and interpretation: Han J, Kim SH, Suh YJ, Lee DH, Nam MS. Writing the first draft: Han J, Kim SH, Nam MS. Review and critical revision: Han J, Kim SH, Suh YJ, Hong S, Kim YS, Nam MS. Final manuscript approval: all authors.
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REFERENCES

1. Gallagher D, Kelley DE, Yim JE, Spence N, Albu J, Boxt L, Pi-Sunyer FX, Heshka S; MRI Ancillary Study Group of the Look AHEAD Research Group. Adipose tissue distribution is different in type 2 diabetes. Am J Clin Nutr 2009; 89: 807-14.
2. Gastaldelli A, Miyazaki Y, Pettiti M, Matsuda M, Mahankali S, Santini E, DeFronzo RA, Ferrannini E. Metabolic effects of visceral fat accumulation in type 2 diabetes. J Clin Endocrinol Metab 2002; 87: 5098-103.
3. Nakamura T, Tokunaga K, Shimomura I, Nishida M, Yoshida S, Kotani K, Islam AH, Keno Y, Kobatake T, Nagai Y, et al. Contribution of visceral fat accumulation to the development of coronary artery disease in non-obese men. Atherosclerosis 1994; 107: 239-46.
4. Antuna-Puente B, Feve B, Fellahi S, Bastard JP. Adipokines: the missing link between insulin resistance and obesity. Diabetes Metab 2008; 34: 2-11.
5. Goralski KB, McCarthy TC, Hanniman EA, Zabel BA, Butcher EC, Parlee SD, Muruganandan S, Sinal CJ. Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism. J Biol Chem 2007; 282: 28175-80.
6. Bozaoglu K, Bolton K, McVillan J, Zimmet P, Jowett J, Collier G, Walder K, Segal D. Chemerin is a novel adipokine associated with obesity and metabolic syndrome. Endocrinology 2007; 148: 4687-94.
7. Kim SH, Lee SH, Ahn KY, Lee DH, Suh YJ, Cho SG, Choi YI, Lee DH, Lee SY, Hong SB, et al. Effect of lifestyle modification on serum chemerin concentration and its association with insulin sensitivity in overweight and obese adults with type 2 diabetes. Clin Endocrinol (Oxf) 2014; 80: 825-33.
8. Shin HY, Lee DC, Chu SH, Jeon JY, Lee MK, Im JA, Lee JW. Chemerin levels are positively correlated with abdominal visceral fat accumulation. Clin Endocrinol (Oxf) 2012; 77: 47-50.
9. Genuit S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, Kittzmiiller J, Knowler WC, Lebovitz H, Lerman A, et al. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003; 26: 3160-7.
10. Hong SB, Lee JJ, Kim SH, Suh YJ, Han JY, Kim YS, Nam M. The effects of adiponectin and inflammatory cytokines on diabetic vascular complications in obese and non-obese patients with type 2 diabetes mellitus. Diabetes Res Clin Pract. Forthcoming 2016.
11. Hamdy O, Porramatikul S, Al-Ozairi E. Metabolic obesity: the paradox between visceral and subcutaneous fat. Curr Diabetes Rev 2006; 2: 367-73.
12. Poulriot MC, Després JP, Nadeau A, Moorjani S, Prud’Homme D, Lupien PJ, Tremblay A, Bouchard C. Visceral obesity in men. Associations with glucose tolerance, plasma insulin, and lipoprotein levels. Diabetes 1992; 41: 826-34.
13. Kang SJ, Kim D, Park HE, Choi SH, Choi SY, Lee W, Kim JS, Cho SH. Visceral adipose tissue area is associated with coronary stenosis and non-calcified plaques. Int J Obes 2014; 38: 272-8.
14. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. National Institutes of Health. Obes Res 1998; 6 Suppl 2: S15-S295.
15. Matsuzawa Y. The metabolic syndrome and adipokines. FEBS Lett 2006; 580: 2917-21.
16. Müsäig K, Staiger H, Machicaco F, Thamer C, Machann J, Schick F, Clausen CD, Stefan N, Fritsche A, Häring HU, RARRES2, encoding the novel adipokine chemerin, is a genetic determinant of disproportionate regional body fat distribution: a comparative magnetic resonance imaging study. Metabolism 2009; 58: 519-24.
17. Moordadian AD. Dyslipidemia in type 2 diabetes mellitus. Nat Clin Pract Endocrinol Metab 2009; 5: 150-9.
18. Osman MM, El-mageed AI, El-hadiidi E, Shahin RS, Mageed NA. Clinical utility of serum chemerin as a novel marker of metabolic syndrome and type 2 diabetes mellitus. Life Sci 2012; 9: 1098-108.
19. Bozaoglu K, Segal D, Shields KA, Cummings N, Curran JE, Comuzzie AG, Mahaney MC, Rainwater DL, Vandenberg JL, MacCluer JW, et al. Chemerin is associated with metabolic syndrome phenotypes in a Mexican-American population. J Clin Endocrinol Metab 2009; 94: 3085-8.
20. Dong B, Ji W, Zhang Y. Elevated serum chemerin levels are associated with the presence of coronary artery disease in patients with metabolic syndrome. Intern Med 2011; 50: 1093-7.
21. Takahashi M, Inomata S, Okumura Y, Iigaki G, Fukukuda H, Miyake K, Koga D, Akamatsu S, Kasuga M, Takahashi Y. Decreased serum chemerin levels in male Japanese patients with type 2 diabetes: sex dimorphism. Endocr J 2013; 60: 37-44.
22. Hu W, Feng P. Elevated serum chemerin concentrations are associated with renal dysfunction in type 2 diabetic patients. Diabetes Res Clin Pract 2011; 91: 159-63.
23. Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. Circulation 2004; 109: II2-10.
24. Libby P. Inflammation in atherosclerosis. Nature 2002; 420: 868-74.
25. Hart R, Greaves DR. Chemerin contributes to inflammation by promoting macrophage adhesion to VCAM-1 and fibronectin through clustering of VLA-4 and VLA-5. J Immunol 2010; 185: 3728-39.
26. Parlee SD, Ernst MC, Muruganandan S, Sinal CJ, Goralski KB. Serum chemerin levels vary with time of day and are modified by obesity and tumor necrosis factor- [alpha]. Endocrinology 2010; 151: 2590-602.
27. Ernst MC, Sinal CJ. Chemerin: at the crossroads of inflammation and obesity. Trends Endocrinol Metab 2010; 21: 660-7.
28. Weigert J, Neumeier M, Wanninger J, Filarsky M, Bauer S, Wüst R, Farkas S, Scherer MN, Schäffler A, Aslanidis C, et al. Systemic chemerin is related to inflammation rather than obesity in type 2 diabetes. Clin Endocrinol (Oxf) 2010; 72: 342-48.
29. Yan Q, Zhang Y, Hong J, Gu W, Dai M, Shi J, Zhao Y, Wang W, Li X, Ning G. The association of serum chemerin level with risk of coronary artery disease in Chinese adults. Endocrine 2012; 41: 281-8.
30. Barasch E, Benderly M, Graff E, Behar S, Reicher-Reiss H, Caspi A, Pelled B, Reisin L, Roguin N, Goldbourt U. Plasma fibrinogen levels and their correlates in 6457 coronary heart disease patients. The Bezaflibrate Infarction Prevention (BIP) Study. *J Clin Epidemiol* 1995; 48: 757-65.

31. Bembde AS. A study of plasma fibrinogen level in type-2 diabetes mellitus and its relation to glycemic control. *Indian J Hematol Blood Transfus* 2012; 28: 105-8.

32. Pfau D, Bachmann A, Lössner U, Kratzsch J, Blüher M, Stumvoll M, Faßhauer M. Serum levels of the adipokine chemerin in relation to renal function. *Diabetes Care* 2010; 33: 171-3.

33. Parlee SD, McNeil JO, Muruganandan S, Sinal CJ, Goralski KB. Elastase and tryptase govern TNFalpha-mediated production of active chemerin by adipocytes. *PLoS One* 2012; 7: e51072.

34. Du XY, Leung LL. Proteolytic regulatory mechanism of chemerin bioactivity. *Acta Biochim Biophys Sin (Shanghai)* 2009; 41: 973-9.