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Serum CD14 concentration is associated with obesity and insulin resistance in non-diabetic individuals

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Abstract

Objective: CD14 is a lipopolysaccharide-binding protein that serves as a marker of monocytes. The role of circulating CD14 in patients with obesity without diabetes remains unknown. Here, we characterized the relationships between serum CD14 concentration and metabolic parameters related to diabetes and obesity.

Methods: We performed an observational, prospective case–control study. Eighty participants were evaluated: 26 drug-naïve patients with type 2 diabetes mellitus and 54 healthy individuals. We compared the circulating CD14 concentration and metabolic parameters of the participants with and without diabetes.

Results: The circulating CD14 concentration did not significantly differ between the two groups, but was lower in participants with obesity than in lean controls. No significant associations existed between CD14 concentration and metabolic parameters in the participants with diabetes, but in those without diabetes, the circulating CD14 concentration significantly negatively correlated with body mass index; waist circumference; the concentrations of fasting insulin, 2-hour post-load glucose, 2-h post-load insulin, and low-density lipoprotein-cholesterol; homeostasis model of assessment (HOMA) of insulin resistance; and HOMA beta-cell function.

Conclusions: This is the first study to show associations of serum CD14 concentration with metabolic parameters in non-diabetic individuals. Circulating CD14 may represent a useful biomarker of metabolic dysfunction in non-diabetic individuals.

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Introduction

CD14, a 55-kDa glycoprotein, is a multifunctional receptor that is constitutively expressed at high levels on the surfaces of mature monocytes, macrophages, and neutrophils, but also in a range of non-myeloid tissues, and binds to lipopolysaccharides (LPSs) and other bacterial wall components.[1,2] The receptor is anchored to the plasma membrane *via* a glycosylphosphatidylinositol moiety, but is also detectable in serum as a soluble form that lacks the membrane-anchoring component.[3] Stimulation of monocytes and macrophages by LPS induces the overexpression of certain cytokines and inflammatory mediators that amplify and diversify the LPS signal.[3] The soluble form of CD14 (sCD14) is abundant in serum and is derived both from the secretion of CD14 and from the enzymatic cleavage of glycosyl-phosphatidylinositol-anchored tissue CD14.[4] The results of several studies have suggested that sCD14 plays a key role in the signal transduction of LPS-related proinflammatory cascades by toll-like receptors.[5,6] sCD14 is an acute-phase reactant, and it has various effects on LPS-related inflammatory signaling.[2] It potentiates the LPS-related inflammatory response in cells with or without membrane-bound CD14,[2] but a high concentration of sCD14 buffers LPS by promoting its transfer to lipoprotein particles, thereby preventing its binding to monocyte and macrophage membranes.[7]

Recent studies have shown associations between sCD14 and various human diseases. A high sCD14 concentration was shown to be associated with incident cardiovascular disease and mortality in older adults.[8] In addition, a recent study showed that a high exosomal CD14 protein concentration is associated with metabolic syndrome.[9] The relationship between the sCD14 concentration and insulin resistance has been evaluated in several clinical studies, which showed an inverse relationship,[10] a relationship that differed according to the presence or absence of morbid obesity,[11] or no association.[12] Thus, the findings to date are conflicting, and the role of circulating CD14 in healthy individuals has not been investigated.

We hypothesized that circulating CD14 might play a pivotal role in the metabolic homeostasis of non-diabetic individuals with obesity. To address this hypothesis, we compared the insulin resistance, metabolic parameters, sCD14 concentration, obesity, and waist circumference of a group of healthy individuals and a group of drug-naïve patients with type 2 diabetes.

Methods

Participants

We performed an observational, prospective case–control study, which is reported according to the STROBE guidelines.[13] The study was conducted in accordance with the Declaration of Helsinki, as revised in 2013, and the study protocol was approved by the Institutional Review Board of Chungnam National University Hospital (approval number: CNUH 2014-12-013).

Written informed consent was obtained from each of the participants before their enrollment. Between January 2016 and December 2017, we enrolled consecutive outpatients at the Department of Endocrine Metabolism of Chungnam National University Hospital. To reduce the influence of acute systemic factors that affect sCD14 concentration, we used inclusion criteria of age >18 years, systolic and diastolic blood pressure <140 and <100 mm Hg, respectively, an absence of alcohol or substance abuse, an absence of clinical signs of infection or inflammation, and an absence of pregnancy.

Assessments of clinical parameters

All the participants underwent a physical examination on the day they started participating in the study. Their height and body mass were measured in a standing position, while barefoot and wearing light clothing, to the nearest 0.1 cm and 0.1 kg, respectively. Waist circumference was measured in the horizontal plane between the inferior costal margin and iliac crest on the midaxillary line. These measurements were standardized using calibrated devices and performed by trained personnel in our clinics. Body mass index (BMI) was calculated as body mass (kg) divided by height squared (m^2). Systolic and diastolic blood pressure were measured using an Omron IntelliSense Automatic Blood Pressure Monitor (Omron, Kyoto, Japan) after 10 minutes of rest.

Measurements of biochemical parameters

Blood samples were collected into tubes containing EDTA in the morning after an overnight fast of at least 8 hours.[14] The fasting glucose, C-peptide, insulin, triglyceride, total cholesterol, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), apolipoprotein B, urea nitrogen, creatinine, high-sensitivity C-reactive protein, and glycated hemoglobin (HbA1c) concentrations; and the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities were measured. Standard biochemical parameters were measured using a blood chemistry analyzer (Hitachi 747; Hitachi, Tokyo, Japan). HbA1c was measured by high-performance liquid chromatography (Bio-Rad, Hercules, CA, USA). The insulin and C-peptide concentrations were measured by radioimmunoassay (Roche, Penzberg, Germany). Seventy-five-gram oral glucose tolerance testing (OGTT) was also performed, and the homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as follows: fasting insulin concentration ($\mu U/mL$) $\times$ fasting glucose concentration (mmol/L)/22.5. The homeostasis model assessment of β-cell function (HOMA-β) was calculated as follows: fasting insulin concentration ($\mu U/mL$) $\times$ 20/ fasting glucose concentration (mmol/L) – 3.5.[15,16] The serum concentration of CD14 was measured using a commercial sandwich ELISA kit (R&D Systems, Minneapolis, MN, USA; catalog no. DC140).

Definitions of obesity and type 2 diabetes mellitus (T2DM)

Obesity was defined using a body mass index (BMI) $\geq$25 kg/m^2, according to the World Health Organization Asia-Pacific classification guidelines.[17] T2DM was defined using a fasting blood glucose (FBG) of $\geq$7 mmol/L, a 2-h blood glucose level of $\geq$11.1 mmol/L during OGTT, a non-fasting blood glucose level of $\geq$11.1 mmol/L accompanied by classic symptoms of hyperglycemia, or a glycated hemoglobin (HbA1c) level of $\geq$6.5%.[18]

Statistical analysis

Continuous data are summarized as mean ± standard deviation (SD) and were compared between groups using Student's *t*-test or the Mann–Whitney U-test. Categorical data are expressed as percentages and were compared using the chi-square test. We derived Pearson and partial correlations to assess the relationships between sCD14 concentration and other parameters. Two-tailed *P*-values <0.05 were considered to indicate statistical significance. All statistical analyses were performed using SPSS ver. 22.0 (IBM Inc., Armonk, NY, USA).

Results

Serum CD14 concentrations in participants with and without diabetes

We recruited 89 patients, but nine were excluded because of hepatitis (two), malignant tumors (one with prostate cancer and two with thyroid cancer), or clinical signs of infection or inflammation (four). Thus, 80 participants were enrolled in the study, of whom 26 had newly diagnosed T2DM and were drug-naïve and 54 did not have diabetes.

We measured the sCD14 concentration and assessed various clinical parameters in all 80 participants. Their clinical characteristics are listed in Table 1. The participants were 17.5% men, their mean age was 48.2 ± 14.8 years, their mean BMI was 24.7 ± 4.7 kg/m^2, their mean fasting glucose concentration was 6.62 ± 2.83 mmol/L, and the mean HbA1c level was 6.2% ± 0.4%. We compared the sCD14 concentrations of the participants according to the presence or absence of T2DM (Table 1), and found that it did not differ between participants with and without diabetes.

Serum CD14 concentrations in participants with or without obesity

Next, we compared the sCD14 concentration in participants with and without obesity. The waist circumference, blood pressure, HOMA-β, and ALT activity of the lean participants (BMI <25 kg/m^2) were lower than in those with obesity (BMI ≥ 25 kg/m^2), but neither the blood glucose concentration nor the HbA1c level differed. The HDL-C concentration was significantly higher in the lean group. The sCD14 concentration was 2290.6 ± 475.6 pg/mL in the lean group and 2068.4 ± 459.7 pg/mL in the obesity group, which was significantly different ($p = 0.043$). We also compared the sCD14 concentration of participants with and without obesity according to their T2DM status. In the non-diabetic participants, the sCD14 concentration was significantly higher in the lean than in the obesity group, but this difference was absent in the participants with diabetes (Table 2).

Relationships between circulating CD14 concentration and metabolic parameters

We next assessed the correlations between the sCD14 concentration and various metabolic parameters in patients with T2DM (BMI, fasting glucose, fasting C-peptide, high-sensitivity C-reactive protein, HbA1c, HOMA-IR, HOMA-β, and lipid species) (Table 3), but found no significant relationships. However, in non-diabetic participants, the sCD14 concentration negatively correlated with BMI ($r = -0.278$, $P = 0.042$), fasting insulin ($r = -0.342$, $P = 0.015$), post-load 2-hour glucose ($r = -0.291$, $P = 0.039$), post-load 2-hour insulin ($r = -0.360$, $P = 0.010$), HOMA-IR ($r = -0.334$, $P = 0.018$), HOMA-β ($r = -0.330$, $P = 0.019$), and LDL-C ($r = -0.313$, $P = 0.029$) (Table 4).

Table 1. Comparison of the metabolic parameters and serum CD14 concentration of participants with and without type 2 diabetes mellitus.

Parameter	Full cohort (N = 80)	Non-diabetic participants (N = 54)	Participants with type 2 DM (N = 26)	*P*-value
Age (years)	48.2 ± 14.8	48.2 ± 14.8	51.3 ± 14.9	0.383
Sex (Male/Female)	14/66	7/47	7/19	0.124
BMI (kg/m^2)	24.7 ± 4.7	24.2 ± 4.1	25.9 ± 5.6	0.125
Body mass (kg)	64.8 ± 16.1	62.5 ± 14.2	69.7 ± 18.8	0.059
Waist circumference (cm)	86.8 ± 12.7	83.9 ± 14.6	89.8 ± 10.2	0.229
Systolic blood pressure (mmHg)	126.5 ± 12.9	125.5 ± 12.1	128.4 ± 14.6	0.360
Diastolic blood pressure (mmHg)	77.2 ± 10.1	75.6 ± 9.3	80.4 ± 10.9	0.045
Fasting glucose (mmol/L)	6.62 ± 2.83	5.26 ± 0.50	9.45 ± 3.53	<0.001
Fasting insulin (pmol/L)	14.1 ± 39.8	8.9 ± 4.1	24.1 ± 67.4	0.262
Fasting c-peptide (pmol/L)	0.7 ± 0.4	0.66 ± 0.35	0.83 ± 0.34	0.045
Post-load 2-hour glucose (mmol/L)	9.69 ± 5.97	6.55 ± 1.81	16.34 ± 6.29	<0.001
Post-load 2-hour insulin (pmol/L)	55.8 ± 63.2	48.5 ± 47.0	71.0 ± 87.3	0.246
Post-load C-peptide (pmol/L)	3.0 ± 1.6	3.04 ± 1.40	2.96 ±1.93	0.784
HbA1c (%)	6.2 ± 0.4	5.4 ± 0.4	7.9 ± 2.2	<0.001
HOMA-IR	5.2 ± 19.6	2.1 ± 1.0	11.0 ± 33.1	0.181
HOMA-β	36.0 ± 71.2	30.5 ± 15.3	46.8 ± 122.1	0.513
TG (mmol/L)	1.42 ± 1.04	1.16 ± 0.77	1.92 ± 1.28	0.009
LDL-C (mmol/L)	3.13 ± 0.91	3.01 ± 0.80	3.36 ± 1.07	0.124
HDL-C (mmol/L)	1.47 ± 0.37	1.52 ± 0.34	1.38 ± 0.42	0.134
AST (U/L)	25.8 ± 24.7	21.7 ± 7.6	33.7 ± 40.2	0.146
ALT (U/L)	26.8 ± 26.3	21.5 ± 14.6	36.9 ± 44.6	0.100
hsCRP (mg/L)	1.32 ± 2.36	1.13 ± 1.48	2.02 ± 4.34	0.516
CD14(pg/ml)	2207.3 ± 479.1	2200.9 ± 07.6	2220.5 ± 423.0	0.865

Data are presented as mean ± SD.

P-values are the results of the unpaired *t*-test for continuous parametric data and the Mann–Whitney U-test for non-parametric data.

DM, diabetes mellitus; BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance: HOMA-β, homeostasis model assessment of beta-cell function; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; AST, aspartate aminotransferase activity; ALT, alanine aminotransferase activity; hsCRP, high-sensitivity C-reactive protein.

Comparisons of metabolic parameters between the low- and high-CD14 sub-groups of participants without diabetes

We next compared the metabolic data between non-diabetic participants with low- or high-CD14 concentration, according to the median value (Table 5). The BMI, waist circumference, fasting insulin, post-load 2-hour insulin, HOMA-IR, and HOMA-β were significantly higher in the low- than in the high-CD14 group. Conversely, the LDL-C concentration was significantly higher in the low- than in the high-CD14 group.

Discussion

To the best of our knowledge, this is the first study to show an association between

Table 2. Comparison of the metabolic data and serum CD14 concentration of the participants, according to their BMI.

	Full cohort			Participants without diabetes			Participants with diabetes		
Parameter	Lean group (BMI < 25 kg/m^2) (N = 50)	Obesity group (BMI ≥ 25 kg/m^2) (N = 30)	*P*-value	Lean group (BMI < 25 kg/m^2) (N = 37)	Obesity group (BMI ≥ 25 kg/m^2) (N = 17)	*P*-value	Lean group (BMI < 25 kg/m^2) (N = 13)	Obesity group (BMI ≥ 25 kg/m^2) (N = 13)	*P*-value
Age (years)	49.4 ± 14.0	48.9 ± 16.3	0.885	48.5 ± 13.8	47.5 ± 17.2	0.823	51.9 ± 14.8	50.7 ± 15.6	0.838
Sex (Male/Female)	7/43	7/23	0.287	4/33	3/14	0.487	3/10	4/9	0.658
BMI (kg/m^2)	22.0 ± 2.2	29.2 ± 4.2	<0.001	22.0 ± 2.2	28.9 ± 3.3	<0.001	22.2 ± 2.4	29.5 ± 5.5	<0.001
Waist circumference (cm)	78.5 ± 9.0	95.1 ± 10.3	<0.001	76.2 ± 6.9	97.8 ± 14.8	0.027	82.8 ± 11.5	93.6 ± 7.5	0.052
Systolic blood pressure (mmHg)	123.9 ± 12.7	130.7 ± 12.4	0.023	122.8 ± 11.9	131.4 ± 10.7	0.014	127.1 ± 14.8	129.7 ± 14.8	0.656
Diastolic blood pressure (mmHg)	75.2 ± 9.6	80.5 ± 10.1	0.021	73.5 ± 9.0	80.1 ± 8.6	0.014	19.9 ± 10.1	80.9 ± 12.1	0.807
Fasting glucose (mmol/L)	6.29 ± 2.58	7.17 ± 3.17	0.205	5.19 ± 0.53	5.41 ± 0.42	0.158	9.41 ± 3.47	9.48 ± 3.73	0.962
Fasting insulin (pmol/L)	7.9 ± 3.2	24.7 ± 64.7	0.075	7.4 ± 2.8	12.6 ± 4.5	0.001	9.5 ± 3.9	38.8 ± 94.9	0.276
Fasting C-peptide (pmol/L)	0.56 ± 0.22	1.00 ± 0.39	<0.001	0.51 ± 0.14	1.00 ± 0.46	0.001	0.69 ± 0.32	0.99 ± 0.30	0.023
Post-load 2-hour glucose (mmol/L)	8.79 ± 5.60	11.21 ± 6.37	0.090	6.19 ± 1.68	7.34 ± 1.90	0.034	16.34 ± 6.23	16.36 ± 6.64	0.996
Post-load 2-hour insulin (pmol/L)	40.7 ± 35.5	82.1 ± 88.7	0.027	38.8 ± 29.6	71.2 ± 69.3	0.024	46.4 ± 50.0	95.6 ± 110.2	0.173
Post-load C-peptide (pmol/L)	2.73 ± 1.46	3.50 ± 1.69	0.049	2.75 ± 1.15	3.73 ± 1.72	0.026	2.77 ± 2.18	3.21 ± 1.67	0.514
HbA1c (%)	6.1 ± 1.7	6.5 ± 1.8	0.300	5.4 ± 0.4	5.5 ± 0.4	0.254	7.95 ± 2.34	7.77 ± 2.10	0.834
HOMA-IR	2.3 ± 1.5	10.1 ± 32.0	0.211	1.7 ± 0.6	3.0 ± 1.2	0.001	3.9 ± 2.0	18.2 ± 46.6	0.281
HOMA-β	23.6 ± 12.4	57.2 ± 115.6	0.136	25.0 ± 11.2	43.3 ± 16.1	0.001	19.6 ± 14.9	73.3 ± 171.1	0.271
TG (mmol/L)	1.34 ± 1.12	1.57 ± 0.87	0.353	1.00 ± 0.66	1.55 ± 0.90	0.022	2.24 ± 1.55	1.59 ± 0.88	0.321
LDL-C (mmol/L)	3.02 ± 0.86	3.33 ± 0.98	0.151	2.86 ± 0.74	3.41 ± 0.85	0.027	3.48 ± 0.03	3.25 ± 1.12	0.199
HDL-C (mmol/L)	1.59 ± 0.38	1.26 ± 0.26	<0.001	1.59 ± 0.33	1.31 ± 0.28	0.007	1.56 ± 0.51	1.20 ± 0.23	0.039
AST (U/L)	21.2 ± 11.2	33.8 ± 37.0	0.090	20.2 ± 6.9	25.4 ± 8.3	0.025	23.9 ± 18.6	43.4 ± 53.0	0.224
ALT (U/L)	17.7 ± 10.3	42.4 ± 42.4	0.005	16.9 ± 10.7	32.5 ± 17.0	0.004	19.9 ± 9.0	53.8 ± 58.6	0.061
hsCRP (mg/L)	0.94 ± 1.35	1.98 ± 3.42	0.218	0.99 ± 1.41	1.54 ± 1.65	0.297	0.5 ± 0.3	2.6 ± 5.1	0.504
CD14 (pg/ml)	2290.6 ± 475.6	2068.4 ± 459.7	0.043	2268.8 ± 350.8	2043.1 ± 429.0	0.029	2352.6 ± 399.37	2088.5 ± 419.0	0.113

Data are presented as mean ± SD.

P-values were derived from the unpaired *t*-test for continuous parametric data and the Mann–Whitney U-test for non-parametric data.

BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance: HOMA-β, homeostasis model assessment of beta-cell function; TG, triglycerides; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; AST, aspartate aminotransferase activity; ALT, alanine aminotransferase activity; hsCRP, high-sensitivity C-reactive protein.

Table 3. Correlation analysis for the relationships between serum CD14 concentration and metabolic parameters in participants with type 2 diabetes mellitus.

Parameter	Coefficient (r)[a]	*P* value
BMI (kg/m^2)	−0.268	0.186
Waist circumference (cm)	0.121	0.680
Fasting glucose (mmol/L)	0.131	0.523
Fasting insulin (mIU/L)	−0.006	0.975
Fasting C-peptide (mIU/L)	0.179	0.392
Post-load 2-hour glucose (mmol/L)	−0.027	0.900
Post-load 2-hour insulin (mIU/L)	−0.088	0.683
Post-load 2-hr C-peptide (pmol/L)	0.054	0.805
HbA1c (%)	0.046	0.823
HOMA-IR	0.035	0.867
HOMA-β	−0.048	0.818
TG (mmol/L)	−0.248	0.223
LDL-C (mmol/L)	0.131	0.532
hsCRP (pmol/L)	0.037	0.913

N = 80.

[a]Coefficients (r) were calculated using Spearman's method.

BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance: HOMA-β, homeostasis model assessment of beta-cell function; TG, triglycerides; LDL-C, low-density lipoprotein-cholesterol; hsCRP, high-sensitivity C-reactive protein.

the sCD14 concentration and obesity/insulin resistance in non-diabetic individuals. Consequently, we explored whether circulating CD14 might protect against metabolic stress. CD14 is a component of the innate immune system,[19] and one form is anchored to membranes *via* a glycosylphosphatidylinositol tail, whereas sCD14 lacks the tail and is secreted from vesicles.[20] sCD14 promotes the binding of LPS to toll-like receptor 4 (TLR4),[21,22] which has been shown to activate the nuclear factor kappa B and mitogen-activated protein kinase pro-inflammatory signaling cascades.[23] However, other studies have made the opposite findings. CD14 was shown to reduce inflammation *via* Grp78-mediated TLR4 internalization.[24] sCD14 has also been shown to increase LPS neutralization in reconstituted lipoprotein particles by >30-fold.[25,26] Furthermore, CD14 deficiency was shown to exacerbate both mild and severe inflammation, to reduce or increase immune cell recruitment, and affect the outcomes of stroke.[27] Thus, CD14 may be an important regulator of inflammation. CD14-induced signaling have complex effects on the development and outcomes of inflammation that depend on tissue type, the expression level, the CD14 ligand involved, and the cross-talk that occurs among CD14-activated pathways.[28]

Greulich *et al.* reported that epicardial biopsies from patients with T2DM are characterized by clusters of CD14-positive monocytes and CD68-positive macrophages.[29] Moreover, obese mice lacking CD14 exhibited lower circulating lipid concentrations and macrophage infiltration of adipose tissue and the liver than wild-type mice,[5,30] along with superior glucose tolerance. A recent study showed that CD14 expression in resident adipose tissue cells directly promotes inflammation and

Table 4. Correlation analysis of the relationships between serum CD14 concentration and metabolic parameters in non-diabetic participants.

Parameter	Coefficient (r)[a]	*P* value
BMI (kg/m^2)	−0.278	0.042
Waist circumference (cm)	−0.623	0.017
Systolic blood pressure	−0.039	0.731
Diastolic blood pressure	−0.111	0.328
Fasting glucose (mmol/L)	−0.086	0.539
Fasting insulin (mIU/L)	−0.342	0.015
Fasting C-peptide (mIU/L)	−0.188	0.201
Post-load 2-hour glucose (mmol/L)	−0.291	0.039
Post-load 2-hour insulin (mIU/L)	−0.360	0.010
Post-load 2-hour C-peptide (mIU/L)	−0.243	0.096
HbA1c (%)	0.042	0.774
HOMA-IR	−0.334	0.018
HOMA-β	−0.330	0.019
TG (mmol/L)	0.044	0.765
LDL-C (mmol/L)	−0.313	0.029
hsCRP (pmol/L)	0.267	0.092

N = 80.

[a]Coefficients (r) were calculated using Spearman's method.

BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance: HOMA-β, homeostasis model assessment of beta-cell function; TG, triglycerides; LDL-C, low-density lipoprotein-cholesterol; hsCRP, high-sensitivity C-reactive protein.

stimulates the proliferation of macrophages and adipocyte progenitor cells.[6] Thus, CD14 may be involved in the metabolic complications of obesity, and CD14-associated inflammation may be important for body mass gain and insulin resistance.

sCD14 is secreted from vesicles in individuals with metabolic disease.[28] The concentration of sCD14 in conditioned medium derived from cultures of epicardial adipose tissue (EAT) biopsies from patients with T2DM was higher than that derived from non-diabetic individuals.[29] sCD14 increases cardiomyocyte inflammation by increasing the activities of p38 kinase and extracellular signal-regulated kinase. sCD14 also impairs cardiomyocyte function and insulin sensitivity, suggesting that greater sCD14 release from the EAT of patients with T2DM may contribute to the pathogenesis of the cardiometabolic complications of diabetes.[31] CD14 released from the EAT impairs insulin signaling in an LPS-independent manner.[31] Therefore, many researchers now consider that sCD14 plays a number of other roles, in addition to its role as an LPS receptor.[2] One previous study revealed associations between the serum sCD14 concentration and clinical parameters. It was found to negatively correlate with the fasting insulin concentration, HOMA-IR, and the systolic and diastolic blood pressure, but the study was relatively small. In another study, non-obese participants were found to have lower circulating sCD14 concentrations than participants with obesity, and the sCD14 concentration of participants with morbid obesity was found to be positively associated with their body fat percentage and waist circumference,[11] suggesting that circulating sCD14 plays a compensatory (in individuals

Table 5. Comparison of the metabolic parameters in participants without diabetes, categorized according to circulating CD14.

Parameter	Low-CD14 group (CD14 < 2,200 pg/ml) (N = 24)	High-CD14 group (CD14 ≥ 2, 200 pg/ml) (N = 30)	*P*-value
Age (years)	45.9 ± 15.6	50.1 ± 14.1	0.312
Sex (Male/Female)	3/21	4/26	0.543
BMI (kg/m^2)	25.5 ± 4.6	23.1 ± 3.5	0.038
Body mass (kg)	67.7 ± 17.2	58.3 ± 9.7	<0.001
Waist circumference (cm)	98.3 ± 16.6	78.2 ± 9.3	0.013
Systolic blood pressure (mmHg)	125.0 ± 14.4	126.0 ± 10.2	0.782
Diastolic blood pressure (mmHg)	76.5 ± 10.6	74.9 ± 8.3	0.558
Fasting glucose (mmol/L)	5.31 ± 0.56	5.22 ± 0.46	0.539
Fasting insulin (pmol/L)	10.3 ± 4.6	7.8 ± 3.4	0.037
Fasting C-peptide (pmol/L)	0.75 ± 0.43	0.58 ± 0.25	0.133
Post-load 2-hour glucose (mmol/L)	7.12 ± 1.81	6.13 ± 1.72	0.057
Post-load 2-hour insulin (pmol/L)	63.4 ± 58.8	36.9 ± 31.5	0.006
Post-load C-peptide (pmol/L)	3.52 ± 1.49	2.66 ± 1.22	0.061
HbA1c (%)	5.4 ± 0.3	5.5 ± 0.4	0.476
HOMA-IR	2.4 ± 1.2	1.8 ± 0.8	0.041
HOMA-β	35.6 ± 16.7	26.5 ± 12.9	0.041
TG (mmol/L)	1.1 ± 0.8	1.2 ± 0.76	0.638
LDL-C (mmol/L)	3.34 ± 0.90	2.77 ± 0.64	0.019
HDL-C (mmol/L)	1.55 ± 0.30	1.49 ± 0.37	0.549
AST (U/L)	20.2 ± 5.2	23.0 ± 9.0	0.203
ALT (U/L)	21.2 ± 13.3	21.8 ± 15.8	0.893
hsCRP (mg/L)	0.73 ± 0.81	1.39 ± 1.75	0.172
CD14 (pg/ml)	1791.1 ± 407.2	2528.7 ± 298.7	<0.001

Data are presented as mean ± SD.

P-values were derived from the unpaired *t*-test for continuous parametric data and the Mann–Whitney U-test for non-parametric data.

BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance: HOMA-β, homeostasis model assessment of beta-cell function; TG, triglycerides; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; AST, aspartate aminotransferase activity; ALT, alanine aminotransferase activity; hsCRP, high-sensitivity C-reactive protein.

without obesity) or buffering (in individuals with morbid obesity) role. However, the mean BMI of the participants with obesity was approximately 45 kg/m^2, which is much higher than that encountered in Asian people.

The exact role of sCD14 in metabolic regulation requires further study. We found negative correlations of the sCD14 concentration with the BMI, waist circumference, HOMA-IR, and LDL-C concentration of Asian people who do not have diabetes. Participants with obesity had lower CD14 concentrations than those of lean participants. We previously reported significant differences in metabolic parameters between individuals with mild and severe obesity.[15] In contrast to the other studies of sCD14 concentration, the narrow BMI range in our study is more representative of normal populations. Thus, we suggest that sCD14 plays a pivotal regulatory role in the metabolic homeostasis of non-diabetic individuals, more so than in

those with obesity and early metabolic dysfunction.

The present study had some limitations. It was a relatively small observational study; a larger sample size would be necessary to further characterize the relationship between sCD14 and metabolic syndrome. Further studies should also be performed regarding the direct or indirect effects of sCD14 on metabolism and inflammation, and to identify sCD14 receptors in the liver and brown and white adipose tissue, to confirm the role of sCD14 in obesity.

In conclusion, we have identified associations between sCD14 concentration and metabolic parameters in non-diabetic individuals. The present findings suggest that circulating CD14 may represent a biomarker of metabolic dysfunction in people who do not have diabetes.

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Author Contributions

Conception and design: YE Kang, KH Joung, BJ Ku; Provision of study materials or patients: YE Kang, KH Joung, JH Lee, HJ Kim, BJ Ku; Collection and assembly of data: YE Kang, KH Joung, JM Kim, BJ Ku; Data analysis and interpretation: all authors; Manuscript writing: all authors; Final approval of manuscript: all authors.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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