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Clinical significance of serum complement factor 3 in patients with type 2 diabetes mellitus

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ABSTRACT

Aims: Although serum complement factor 3 (C3) is an acute phase reactant mainly synthesized in the liver, several recent studies have shown high C3 gene expression in adipose tissue (AT). However, the relationship between C3 and AT levels has not been fully clarified in type 2 diabetes mellitus (T2DM) patients.

Methods: A total of 164 T2DM patients (109 men and 55 women) participated in this cross-sectional study. A computed tomography scan was performed to measure visceral, subcutaneous, and total AT. The correlation between these factors and C3 levels was examined using Pearson's correlation analysis. A multivariate regression model was used to assess an independent determinant associated with C3 levels after adjusting the explanatory variables (i.e., all ATs [visceral, subcutaneous, and total], and clinical features [sex, age, body mass index, waist circumference, glycated hemoglobin, duration of diabetes, systolic blood pressure, diastolic blood pressure, aspartate aminotransferase levels, alanine aminotransferase levels, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, log (triglyceride levels), estimated glomerular filtration rate, and log(high-sensitivity C-reactive protein levels)]).

Results: Serum C3 levels were correlated with visceral, subcutaneous, and total AT among both men ($r = 0.505$, $p < 0.001$; $r = 0.545$, $p < 0.001$; $r = 0.617$, $p < 0.001$, respectively) and women ($r = 0.396$, $p = 0.003$; $r = 0.517$, $p < 0.001$; $r = 0.548$, $p < 0.001$, respectively). In the multivariate regression model, the association between total AT and C3 levels remained significantly positive ($\beta = 0.490$, $p < 0.001$).

Conclusions: Serum C3 levels are associated with visceral, subcutaneous, and total AT in T2DM patients. Furthermore, C3 levels seem to be a marker for overall adiposity rather than regional adiposity.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by insulin resistance (IR) and impaired insulin secretion. Obesity, especially visceral fat obesity (VFO) along with excess accumulation of visceral adipose tissue (VAT), known to be associated with IR, is an important risk factor for accelerating the development and progression of T2DM as well as related complications [1,2]. The frequency of obesity complicated by T2DM is increasing each year and has become a critical problem worldwide [3].

Levels of complement factor 3 (C3), an acute phase reactant mainly produced in the liver [4], have been reported to be positively associated with body mass index (BMI) [5,6], alanine aminotransferase (ALT) as a surrogate marker of fatty liver disease [7], and the homeostasis model assessment of insulin resistance (HOMA-IR) [5,6]. C3 levels are also linked with development of metabolic syndrome [8] and diabetes [5,6]. Moreover, serum C3 levels have been reported to be correlated with VAT, subcutaneous adipose tissue (SAT), and total adipose tissue (TAT) in both men and women [9], and levels of components of the complement system, including C3, are correlated with measures of adiposity [10–13]. However, as for clinical studies regarding C3 levels, only two have examined adipose tissue (AT) and its composition among the population with T2DM, and both included a small sample size. A study conducted by Koistinen et al. included 12 participants [14], while a study by Samaras et al. included only six [15], although these studies further provided evidence of AT C3 mRNA expression in T2DM.

In clinical practice, T2DM patients are often diagnosed with AT accumulation, liver dysfunction represented by elevated ALT levels, low-grade systemic inflammation, and concurrent hypertension and dyslipidemia with varying durations and levels of control; these factors are intertwined. Therefore, owing to the small sample size in the aforementioned two studies, the results regarding the relationship between C3 and AT in patients with T2DM may not be applicable to the T2DM population in clinical practice; therefore, clinical studies with a larger sample size are required.

Consequently, we examined the relationship between serum C3 levels and AT accumulation as well as sex, age, BMI, waist circumference, blood glucose control as represented by glycated hemoglobin [HbA1c], duration of diabetes, lipid profiles (low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and triglyceride), diastolic and systolic blood pressure, AST (aspartate aminotransferase), ALT, estimated glomerular filtration rate (eGFR), and high-sensitivity C-reactive protein (hs-CRP) in clinical practice. Furthermore, we examined the strength of the relationship of VFO, which is thought to be an important cause of cardiovascular disease, with BMI and C3 levels, respectively, to verify the clinical usefulness of C3 levels as a surrogate marker of VFO in clinical practice.

2. Materials and methods

2.1. Patients

Outpatients with T2DM who attended Eiju General Hospital from September 2015 to March 2016 were eligible for participation in this study. Patients with a malignant or infectious disease, liver cirrhosis, or collagen disease were excluded. Patients with apparently abnormal serum AST or ALT levels (i.e., greater than four times the upper limit of the normal range), severe renal impairment (i.e., eGFR < 30 mL/min per 1.73 m^2 or undergoing renal replacement therapy), moderate or high inflammation (i.e., hs-CRP > 1.5 mg/dL), and pregnant women were excluded. Informed consent was obtained from 176 patients; however, one patient withdrew consent, one patient was excluded based on hs-CRP level, and 10 patients could not be followed before the computed tomography (CT) scan was performed. Finally, 164 patients completed the CT scan and blood sampling. The study was approved by the ethical committee of Eiju General Hospital and performed in accordance with the Declaration of Helsinki.

2.2. Data collection

For this cross-sectional study, basic demographic data, including sex, age, height, weight, waist circumference, duration of diabetes, and self-reported maximum body weight were collected from questionnaires and patient medical records. BMI was calculated as weight (in kg) divided by height (in m) squared. According to the criteria for obesity as recommended by the Japan Society for the Study of Obesity [16], VFO was defined as VAT $\geq$ 100 cm^2 upon arrival at the hospital. All analyses were performed at the Eiju General Hospital Clinical Laboratory using routine methods on an automatic analyzer (LABOSPECT 008, HITACHI Ltd., Tokyo).

Serum AST and ALT levels were measured using an enzymatic method (LSI Medience Corporation, Tokyo), LDL cholesterol and HDL cholesterol were measured using a homogeneous assay, and total cholesterol and triglyceride levels were measured using an enzymatic method (Kyowa Medex Co., Ltd., Tokyo). A latex-enhanced turbidimetric immunoassay (Denka Co., Ltd, Tokyo) was used to measure hs-CRP levels, and a latex agglutination immunoassay (Nittobo Medical Co., Ltd., Tokyo) was used to measure serum C3 levels. The assay systems for C3 and CRP levels were previously standardized for use in Japan with the use of international reference material (EMR-DA470k/IFCC) [17]. HbA1c levels were measured using high-performance liquid chromatography (ARKRAY, Inc., Kyoto), and the values in this paper are expressed according to the National Glycohemoglobin Standardization Program (NGSP) [18], in addition to the International Federation of Clinical Chemistry (IFCC) (mmol/mol) calculated by the following equation: HbA1C-IFCC = 10.93 × HbA1C-NGSP − 23.52 [19].

Estimated GFR was calculated using the formula established by the Japanese Chronic Kidney Disease Initiative Working Group [20] as follows: eGFR (mL/min per 1.73 m^2) = 194 × (serum creatinine)$^{-1.094}$ × (age)$^{-0.287}$ (× 0.739 for women).

The CT measures were taken with a 64-slice CT scanner (GE Healthcare; Optima CT 660 Discovery Edition; 120 kV; rotation time, 0.60 s; 0.516 mm/rot) with patients lying supine with both arms stretched above the head to minimize artifacts. The level chosen for the analysis was the fourth lumbar vertebra corresponding to the umbilical level, aortic bifurcation, and top of the iliac crest, as usually referenced in the literature [21].

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