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ORIGINAL ARTICLE

Influence of atherosclerosis-related risk factors on serum high-sensitivity C-reactive protein levels in patients with type 2 diabetes: Comparison of their influence in obese and non-obese patients

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ABSTRACT

Aims/Introduction: Increased levels of high-sensitivity C-reactive protein (hs-CRP) likely leads to the development of atherosclerosis. Therefore, it is very important to know which factors largely influence hs-CRP levels. In the present study, we examined the influence of various atherosclerosis-related factors on hs-CRP levels in patients with type 2 diabetes.

Materials and Methods: A total of 275 patients (176 men, 99 women) were enrolled in this study. We tested the relationship between the number of risk factors reaching a desired value and hs-CRP levels. The Mann–Whitney *U*-test was used to compare two groups. The Kruskal–Wallis test was used to carry out overall group comparisons, and the Steel–Dwass test was used to carry out between-group comparisons. Spearman's rank correlation was carried out to study the correlation between hs-CRP levels and clinical parameters. Multivariate regression method was used to analyze the factors independently contributing to hs-CRP levels.

Results: Hs-CRP levels were lower in patients with a larger number of risk factors reaching a desired value. In particular, triglyceride and body mass index (BMI) were independent risk factors determining hs-CRP levels in a multivariate regression analysis. Furthermore, we compared the influence of various factors on hs-CRP levels in both obese (BMI ≥25 kg/m^2) and non-obese patients with type 2 diabetes (BMI <25 kg/m^2). In obese groups, BMI and urinary albumin were independent risk factors determining hs-CRP levels, whereas triglyceride and statin were independent risk factors in non-obese patients.

Conclusions: There is some difference in the factors responsible for hs-CRP levels in obese and non-obese patients with type 2 diabetes.

INTRODUCTION

It is well known that atherosclerosis is an inflammatory disease. Indeed, during the development of atherosclerosis, activated macrophages produce a variety of inflammatory cytokines and growth factors[1,2]. Clustering of atherosclerosis-related risk factors increases the incidence of cardiovascular disease in patients with diabetes, and thus it is important to comprehensively manage such multiple risk factors from the clinical point of view[3,4]. An increase of serum high-sensitivity C-reactive protein (hs-CRP) level likely leads to the development of atherosclerosis. Indeed, it has been reported that hs-CRP level

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is associated with carotid atherosclerosis in patients with type 2 diabetes mellitus[5–8], suggesting that hs-CRP is a useful marker to predict an accelerated atherosclerotic process. It has also been shown that elevated hs-CRP levels are associated with increased cardiovascular risk[9–12].

Some *in vitro* studies have reported that: (i) CRP binds to diverse unmodified and modified forms of low-density lipoprotein (LDL)[13–15]; (ii) CRP inosculates to and signals through Fcγ receptors[16–19]; and (iii) LDL-bound CRP is taken up by macrophages through FcγR-dependent and FcγR-independent pathways[20]. In short, the colocalization of CRP and macrophages in the lesion, high expression levels of FcγRs on macrophages, and CRP-mediated LDL uptake into macrophages suggest that CRP opsonizes LDL for macrophages. In consequence, CRP could be strongly responsible for foam cell formation in atherogenesis[20]. Furthermore, the Centers for Disease Control and Prevention and the American Heart Association gave the guidelines that we should use to measure hs-CRP levels in patients who have cardiovascular risks[21]. Various new pharmacological approaches have been introduced to reduce hs-CRP levels[22–26]. In order to assess the factors that largely influence hs-CRP levels, here we examined how the accumulation of various atherosclerosis-related risk factors influences serum hs-CRP levels, and also tested which factors strongly influence hs-CRP levels in patients with type 2 diabetes. Furthermore, we compared the influence of various factors on hs-CRP levels between obese and non-obese patients with type 2 diabetes.

MATERIALS AND METHODS

Study Population and Patient Preparation

Patients with type 2 diabetes who visited the outpatient clinic of diabetes at Kawasaki Medical School Hospital in Kurashiki, Japan, and whose hs-CRP was <0.3 mg/dL were eligible to participate in the present study. In order to avoid patients with acute inflammatory diseases, such as influenza, we limited the hs-CRP value to <0.3 mg/dL. In addition, we excluded patients with the following diseases: acute inflammatory disease, autoimmune disease, malignancy, severe liver dysfunction, severe renal dysfunction (male: creatinine [Cre] ≥1.2 mg/dL; female: Cre ≥1.0 mg/dL), severe hypertriglyceridemia (triglyceride [TG] ≥400 mg/dL), using steroid and/or immunosuppressive agents. We enrolled all outpatients with type 2 diabetes in line with inclusion criteria and exclusion criteria in the present study. The Kawasaki Medical School and hospital ethics committee approved the study protocol (No. 1940), and informed consent was obtained from each patient by showing it on our homepage after a full explanation of the study.

Clinical Procedures

The diagnosis of the occurrence of ischemic heart disease was carried out by cardiologists based on the clinical symptoms, characteristic electrocardiogram changes, cardiac enzyme levels and the findings in coronary angiography and/or echocardiography, according to established guidelines. Stroke was defined as a validated definite or probable hospitalized cerebral infarction, cerebral hemorrhage and subarachnoid hemorrhage diagnosed by neurosurgical experts based on clinical symptoms and neuroimaging findings, according to established guidelines. Diabetic neuropathy was defined as having subjective and/or objective symptoms. The presence of diabetic retinopathy was defined as having simple diabetic retinopathy or more severe retinopathy, which was diagnosed by ophthalmologists based on the findings of funduscopy. The presence of diabetic nephropathy was defined as having albuminuria (urinary albumin excretion ≥30 mg/g.Cre). The best possible treatment was carried out for diabetes, hypertension and dyslipidemia.

Desired Value of Various Atherosclerosis-Related Risk Factors

The desired value of various atherosclerosis-related risk factors was defined as follows: obesity BMI <25 kg/m^2; diabetes, glycated hemoglobin (HbA1c) <7.0% (53 mmol/mol); hypertension, systolic blood pressure <130 mmHg and diastolic blood pressure <80 mmHg; dyslipidemia, LDL cholesterol <120 mg/dL (in case with ischemic heart disease, LDL cholesterol <100 mg/dL), high-density lipoprotein (HDL) cholesterol ≥40 mg/dL and TG <150 mg/dL, which was based on the Japan Atherosclerosis Society guidelines.

Statistical Analysis

The Mann–Whitney *U*-test was used to compare two groups. The Kruskal–Wallis test was used to carry out overall group comparisons, and the Steel–Dwass test was used to carry out between-group comparisons. Spearman's rank correlation was carried out to study the correlation between hs-CRP levels and clinical parameters. Multivariate regression method was used to analyze the factors independently contributing to serum hs-CRP levels.

RESULTS

Characteristics of the Study Participants

A total of 275 patients (176 men, 99 women) were enrolled in the present study. Supplemental Table 1 shows the baseline characteristics of the study participants (age 64.4 ± 10.2 years, BMI 24.7 ± 4.2 kg/m^2, bodyweight 64.3 ± 13.1 kg, duration of diabetes 13.6 ± 8.4 years, HbA1c 6.9 ± 0.9% [52 ± 9.8 mmol/mol], fasting plasma glucose 125 ± 29 mg/dL, fasting plasma insulin 6.99 ± 9.04 μU/mL, homeostatic model assessment of insulin resistance 1.81 ± 2.56, systolic blood pressure 126 ± 16 mmHg, diastolic blood pressure 70 ± 11 mmHg, LDL cholesterol 110 ± 27 mg/dL, HDL cholesterol 55 ± 13 mg/dL, TG 114 ± 51 mg/dL, total cholesterol 188 ± 30 mg/dL, Cre 0.76 ± 0.17 mg/dL, hs-CRP 0.07 ± 0.06 mg/dL and urinary albumin 85.2 ± 247.2 mg/g.Cre. In addition, 114 patients (41%) had diabetic neuropathy, 74 (27%) had diabetic retinopathy, 67 (24%) had diabetic nephropathy, and 55 (20%) had ischemic heart disease and/or stroke.

Table 1 | Correlation of serum hs-CRP and a variety of clinical parameters and multivariate regression analysis to determine the independent factors contributing to hs-CRP levels in all subjects

	Univariate		Multivariate	Model 1	Multivariate	Model 2	Multivariate	Model 3
	ρ	*P*	*t*	*P*	*t*	*P*	*t*	*P*
Triglyceride	0.262	<0.0001	3.03	0.0028	3.01	0.0031	2.97	0.0035
BMI	0.253	<0.0001	2.18	0.0303	2.20	0.0290	2.20	0.0290
HDL-cholesterol	−0.232	0.0001	−1.16	n.s.	−1.15	n.s.	−1.29	n.s
Body weight	0.207	0.0005						
Insulin	0.238	0.0009	1.21	n.s.	1.03	n.s.	0.93	n.s
Urinary albumin	0.216	0.001	1.47	n.s.	1.25	n.s.	1.24	n.s
HbA1c	0.169	0.005	1.11	n.s.	0.94	n.s.	1.05	n.s
Fasting plasma glucose	0.158	0.009						
Duration of diabetes	−0.158	n.s.						
Age	0.142	n.s.			0.02	n.s.	0.26	n.s
HOMA-IR	−0.162	n.s.						
Creatinine	−0.095	n.s.						
Diastolic BP	0.079	n.s.						
LDL-cholesterol	0.068	n.s.						
Total cholesterol	0.055	n.s.						
Systolic BP	0.042	n.s.						
Gender (male 1, female 2)					2.05	0.0421	2.30	0.0229
TZD use							0.06	n.s
Statin use							−1.34	n.s
ARB/ACEi use							−0.61	n.s

Model 1: triglyceride, BMI, HDL cholesterol, insulin, urinary albumin and HbA1c were included as independent variables. Model 2: age and gender as well as triglyceride, BMI, HDL-cholesterol, insulin, urinary albumin and HbA1c were included as independent variables. Model 3: TZD use, Statin use, ARB/ACEi use in addition to the factors of Model 2 were included as independent variables. hs-CRP, high-sense C-reactive protein; BMI, body mass index; HOMA-IR, homeostasis model assessment for insulin resistance; LDL, Low-density lipoprotein; HDL, high-density lipoprotein; BP, blood pressure; TZD, thiazolidinedione; ARB, angiotensin II receptor blocker; ACEi, angiotensin-converting enzyme inhibitor; n.s., not significant.

Influence of Various Atherosclerosis-Related Risk Factors on Serum hs-CRP Levels in Patients with Type 2 Diabetes

The desired value of various atherosclerosis-related factors was defined as follows: obesity, BMI <25 kg/m^2; diabetes, HbA1c <7.0% (53 mmol/mol); hypertension, systolic blood pressure <130 mmHg and diastolic blood pressure <80 mmHg; and dyslipidemia, LDL cholesterol <120 mg/dL (in case without ischemic heart disease), LDL cholesterol <100 mg/dL (in case with ischemic heart disease), HDL cholesterol ≥40 mg/dL and TG <150 mg/dl. As the results, in a total of 275 patients, 155 patients (56.4%) achieved BMI <25 kg/m^2, 170 (60.7%) achieved HbA1c <7.0% (53 mmol/mol), 158 (57.5%) reached a desired value for hypertension and 75 (27.3%) reached a desired value for dyslipidemia. As shown in Figure 1, hs-CRP levels were lower in participants with a larger number of risk factors reaching a desired value (overall trend, $P < 0.01$). Indeed, hs-CRP levels in patients with three risk factors reaching a desired value were significantly lower than those in patients with zero or one risk factor reaching a desired value. In addition, hs-CRP levels in patients with four risk factors reaching a desired value were lower than those in patients with zero or one risk factor reaching a desired value, although it did not reach a statistical significance. Similar findings that hs-CRP levels were lower in patients with a larger number of risk factors reaching a desired value were obtained in each obese (BMI ≥25 kg/m^2) and non-obese group (BMI <25 kg/m^2), but it did not reach a statistical significance, presumably because of the small number of patients in each group (data not shown).

Influence of Various Clinical Parameters on Serum Hs-CRP Levels in Patients with Type 2 Diabetes

To examine which clinical parameters largely influence serum hs-CRP levels, we estimated their influence in patients with type 2 diabetes using a univariate and multivariate analysis. As shown in Table 1, in a univariate analysis, TG, BMI, bodyweight, insulin, homeostatic model assessment of insulin resistance, urinary albumin, HbA1c and fasting plasma glucose were significantly positively correlated with hs-CRP levels. In contrast, HDL cholesterol was negatively correlated with hs-CRP levels. To determine the independent factors contributing to serum hs-CRP levels, we carried out a multivariate regression analysis using TG, BMI, HDL cholesterol, insulin, urinary albumin and HbA1c as independent variables (model 1), all of which were significantly associated with hs-CRP in a univariate analysis (Table 1). We excluded bodyweight and fasting plasma glucose in this analysis, because they are thought to be confounding factors. As shown in Table 1, TG and BMI were independent factors determining hs-CRP levels. In addition, a

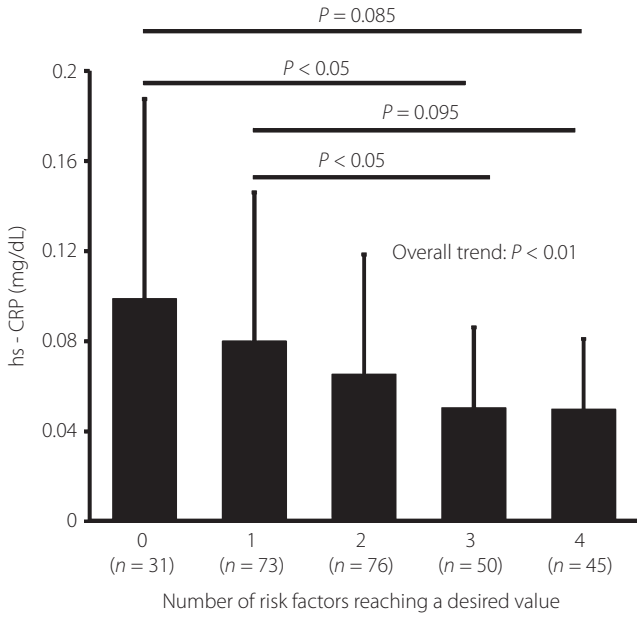

Figure 1 | Influence of the number of risk factors reaching a desired value on serum high-sensitivity C-reactive protein (hs-CRP) in patients with type 2 diabetes.

multivariate regression analysis including age and sex, as well as TG, BMI, HDL cholesterol, insulin, urinary albumin and HbA1c as independent variables (Table 1, model 2), showed that TG, BMI and sex were independent factors determining hs-CRP levels. These results show that low TG and low BMI are closely associated with low serum hs-CRP levels in patients with type 2 diabetes. In addition, as it is possible that several kinds of medication, such as angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), thiazolidinedione (TZD) and statins, influence hs-CRP levels, we examined the influence of such medication on hs-CRP levels. First, 150 patients (54%) had taken ACEi and/or ARB. In the analysis according to those administration, there was no difference in the hs-CRP value (ACEi/ARB (+) *vs* ACEi/ARB (–); 0.07 ± 0.07 mg/dl *vs* 0.07 ± 0.06 mg/dL, $P = 0.56$). Second, 150 patients (54%) had taken TZD. There was no difference in the hs-CRP value (TZD [+] vs TZD [–]; 0.07 ± 0.07 mg/dL *vs* 0.07 ± 0.07 mg/dL, $P = 0.77$). Finally, 151 patients (55%) had taken statin. There was no difference in the hs-CRP value (statin [+] vs statin (–); 0.07 ± 0.07 mg/dL vs 0.07 ± 0.06 mg/dL, $P = 0.99$). The regression analysis, which included the medications in addition to the factors in model 2 as independent variables, also showed the same results (Table 1, model 3).

To examine the correlation between BMI and serum hs-CRP levels, we divided the participants into four groups (group 1: BMI <20, $n = 27$; group 2: BMI 20–25, $n = 128$; group 3: BMI 25–30, $n = 89$; group 4: BMI ≥30, $n = 31$). As shown in Figure 2a, serum hs-CRP levels were higher in patients with higher BMI (overall trend, $P < 0.0005$). Indeed, hs-CRP levels in patients with BMI ≥30 were significantly higher compared

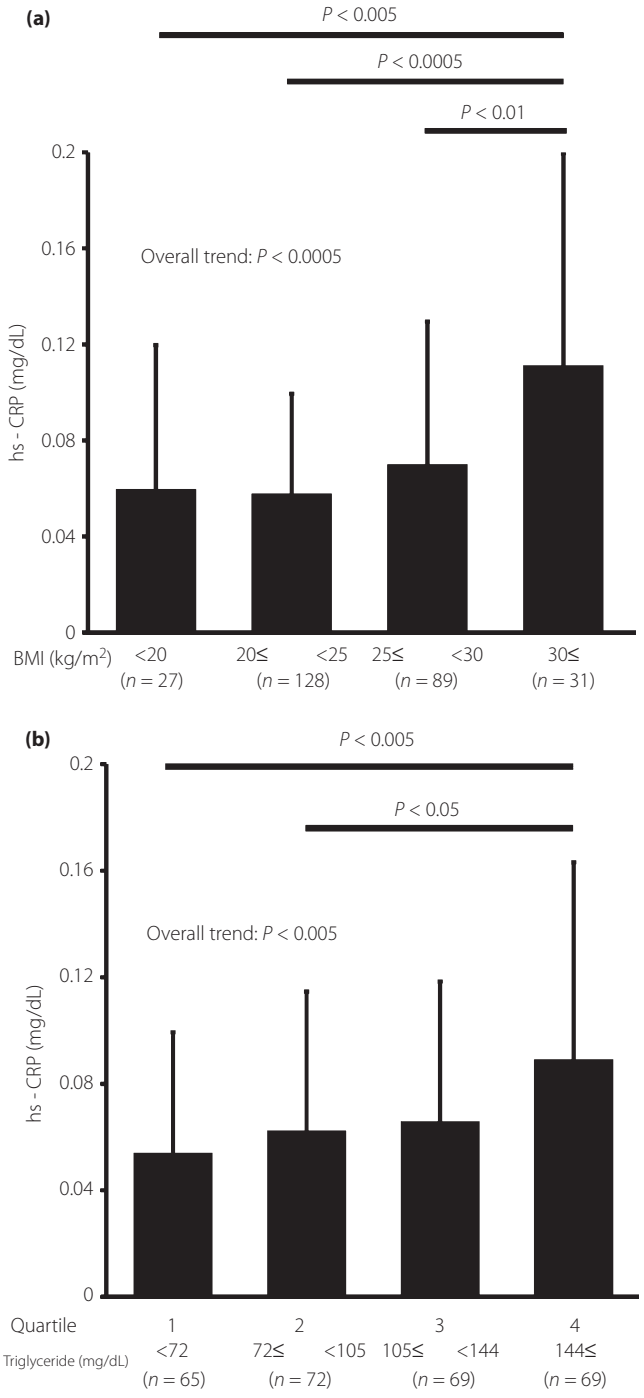

Figure 2 | (a) Correlation of body mass index (BMI) and serum high-sensitivity C-reactive protein (hs-CRP) levels, (b) and correlation of triglyceride and serum hs-CRP levels in patients with type 2 diabetes.

with those with BMI <20, BMI 20–25 or BMI 25–30. However, there was no difference among other groups (BMI <20, BMI 20–25 or BMI 25–30). These results imply that BMI is an important factor determining serum hs-CRP levels, especially in obese patients, but not in non-obese patients. In addition to

BMI, TG was also an independent factor determining serum hs-CRP levels (Table 1). Therefore, to further examine the correlation between TG and serum hs-CRP levels, we divided the patients into four groups (quartile 1: TG <72 mg/dL, $n = 65$; quartile 2: TG 72–105 mg/dL, $n = 72$; quartile 3: TG 105–144 mg/dL, $n = 69$; quartile 4: TG ≥144 mg/dL, $n = 69$). As shown in Figure 2b, serum hs-CRP levels were higher in patients with larger TG levels (overall trend, $P < 0.005$). Indeed, hs-CRP levels in quartile 4 were significantly higher compared with those in quartile 1 or 2.

As shown in Table 1, HbA1c and urinary albumin were significantly associated with serum hs-CRP levels in a univariate analysis, although they were not independent factors to determine hs-CRP levels. Therefore, to further examine the correlation between HbA1c and serum hs-CRP levels, we divided the patients into four groups (quartile 1: HbA1c <6.37% [46.1 mmol/mol], $n = 60$; quartile 2: HbA1c 6.37–6.78% [46.1–50.6 mmol/mol], $n = 74$; quartile 3: HbA1c 6.78–7.29% [50.6–56.2 mmol/mol], $n = 66$; HbA1c ≥7.29% [56.2 mmol/mol], $n = 75$). As shown in supplemental Figure 1a, serum hs-CRP levels were higher in patients with higher HbA1c levels (overall trend, $P < 0.01$). Indeed, hs-CRP levels in quartile 4 were significantly higher compared with those in quartile 1, 2 or 3. These results imply that TG and HbA1c levels are important to determine serum hs-CRP levels, especially in obese patients. Similarly, as shown in supplemental Figure 1b, to examine the correlation between urinary albumin and serum hs-CRP levels, we divided the patients into four groups (quartile 1: urinary albumin <10.1 mg/g.Cre, $n = 57$; quartile 2: urinary albumin 10.1–16.5 mg/g.Cre, $n = 58$; quartile 3: urinary albumin 16.5–37 mg/g.Cre, $n = 58$; urinary albumin ≥37 mg/g.Cre, $n = 58$). As shown in supplemental Figure 1b, serum hs-CRP levels were higher in patients with larger urinary albumin levels (overall trend, $P < 0.01$) and serum hs-CRP levels in quartile 3 or 4 were significantly higher compared with those in quartile 1. These results imply that a small increase of urinary albumin could lead to an increase in serum hs-CRP levels.

Influence of Various Atherosclerosis-Related Factors on Serum Hs-CRP Levels in Patients With Type 2 Diabetes: Comparison of Their Influence Between Obese and Non-Obese Patients

As aforementioned, it seemed that BMI is an important factor determining serum hs-CRP levels only in obese patients, but not in non-obese patients (Figure 2a). Therefore, to further assess the influence of BMI on serum hs-CRP levels, we examined the influence of BMI in obese (BMI ≥25 kg/m^2) and non-obese patients with type 2 diabetes (BMI <25 kg/m^2), separately. As shown in Table 2, in a univariate analysis with

Table 2 | Correlation of hs-CRP and a variety of clinical parameters and multivariate regression analysis to determine the independent factors contributing to hs-CRP levels in subjects with BMI ≥25 kg/m^2

	Univariate ρ	*P*	Multivariate *t*	Model 1 *P*	Multivariate *t*	Model 2 *P*	Multivariate *t*	Model 3 *P*
BMI	0.310	0.0006	4.26	<0.0001	3.39	0.0010	3.53	0.0007
Fasting plasma glucose	0.306	0.0007						
Urinary albumin	0.286	0.0038	2.37	0.0199	2.25	0.0268	1.93	0.0467
HbA1c	0.239	0.0085	1.65	n.s.	1.79	n.s.	1.65	n.s.
Triglyceride	0.220	n.s.						
Creatinine	–0.224	n.s.						
Duration of diabetes	–0.222	n.s.						
HDL-cholesterol	–0.177	n.s.						
Body weight	0.105	n.s.						
Total cholesterol	0.090	n.s.						
LDL-cholesterol	0.083	n.s.						
HOMA-IR	–0.105	n.s.						
Age	–0.073	n.s.			0.51	n.s.	1.20	n.s.
Systolic BP	–0.063	n.s.						
Diastolic BP	0.018	n.s.						
Insulin	0.022	n.s.						
Gender (male 1, female 2)					1.94	n.s.	1.73	n.s.
TZD use							0.07	n.s.
Statin use							0.52	n.s.
ARB/ACEi use							–1.77	n.s.

Model 1: BMI, urinary albumin and HbA1c were included as independent variables. Model 2: age and gender as well as BMI, urinary albumin and HbA1c were included as independent variables. Model 3: TZD use, Statin use, ARB/ACEi use in addition to the factors of Model 2 were included as independent variables. hs-CRP, high-sense C-reactive protein; BMI, body mass index; HOMA-IR, homeostasis model assessment for insulin resistance; LDL, Low-density lipoprotein; HDL, high-density lipoprotein; BP, blood pressure; TZD, thiazolidinedione; ARB, angiotensin II receptor blocker; ACEi, angiotensin-converting enzyme inhibitor; n.s., not significant.

obese patients with type 2 diabetes, BMI, fasting plasma glucose, urinary albumin and HbA1c were significantly correlated with hs-CRP levels. To determine the independent factors contributing to serum hs-CRP levels, we carried out a multivariate regression analysis using BMI, urinary albumin and HbA1c as independent variables (model 1), all of which were significantly associated with hs-CRP in a univariate analysis (Table 2). We excluded fasting plasma glucose in this analysis, because it is thought to be a confounding factor. As shown in Table 2, BMI and urinary albumin were independent factors determining serum hs-CRP levels. In addition, a multivariate regression analysis including age and sex, as well as BMI, urinary albumin and HbA1c as independent variables (Table 2, Model 2), showed the same results; BMI and urinary albumin were independent factors determining hs-CRP levels. These results show that low BMI and low urinary albumin are closely associated with low serum hs-CRP levels in obese patients with type 2 diabetes. The regression analysis, which included the medications in addition to the factors in model 2 as independent variables, also showed the same results (Table 2, model 3).

As shown in Table 3, in a univariate analysis only with non-obese patients with type 2 diabetes, serum TG, insulin and HDL cholesterol levels were significantly correlated with hs-CRP levels. To determine the independent factors contributing to serum hs-CRP levels, we carried out a multivariate regression analysis using TG, insulin and HDL cholesterol as independent variables (model 1), all of which were significantly associated with hs-CRP in a univariate analysis (Table 3). As shown in Table 3, only TG was an independent factor determining hs-CRP levels. In addition, a multivariate regression analysis including age and sex (Table 3, model 2) showed the same results; only TG was an independent factor determining hs-CRP levels. The regression analysis, which included the medications in addition to the factors in model 2 as independent variables, showed TG and stain use as significant independent factors (Table 3, model 3). These results suggest that low TG and statin use, rather than low BMI, are more closely associated with low serum hs-CRP levels in non-obese patients with type 2 diabetes.

DISCUSSION

It has been thought that serum hs-CRP level leads to the development of atherosclerosis[5–16]. Although various new pharmacological approaches have been introduced to reduce hs-CRP levels[17–26], there are still many cardiovascular diseases all over the world. In the present study, serum hs-CRP levels were lower in patients with a larger number of risk factors reaching a desired value (Fig-

Table 3 | Correlation of hs-CRP and a variety of clinical parameters and multivariate regression analysis to determine the independent factors contributing to hs-CRP levels in subjects with BMI <25 kg/m^2

	Univariate ρ	*P*	Multivariate *t*	Model 1 *P*	Multivariate *t*	Model 2 *P*	Multivariate *t*	Model 3 *P*
Triglyceride	0.228	0.0043	3.32	0.0012	3.55	0.0006	3.63	0.0004
Insulin	0.257	0.0061	0.56	n.s.	0.71	n.s.	0.30	n.s.
HDL-cholesterol	−0.210	0.0086	−1.13	n.s.	−0.89	n.s.	−1.14	n.s.
HOMA-IR	0.219	n.s.						
Age	−0.156	n.s.			−1.39	n.s.	−1.22	n.s.
Urinary albumin	0.152	n.s.						
BMI	0.137	n.s.						
Body weight	0.128	n.s.						
HbA1c	0.093	n.s.						
Duration of diabetes	−0.090	n.s.						
Systolic BP	0.077	n.s.						
Diastolic BP	0.065	n.s.						
Fasting plasma glucose	0.036	n.s.						
Creatinine	−0.019	n.s.						
LDL-cholesterol	0.018	n.s.						
Total cholesterol	−0.002	n.s.						
Gender (male 1, female 2)					−0.02	n.s.	0.41	n.s.
TZD use							−0.53	n.s
Statin use							−2.34	0.0215
ARB/ACEi use							0.87	n.s

Model 1: triglyceride, insulin and HDL-cholesterol were included as independent variables. Model 2: age and gender as well as triglyceride, insulin and HDL-cholesterol were included as independent variables. Model 3: TZD use, Statin use, ARB/ACEi use in addition to the factors of Model 2 were included as independent variables. hs-CRP, high-sense C-reactive protein; BMI, body mass index; HOMA-IR, homeostasis model assessment for insulin resistance; LDL, Low-density lipoprotein; HDL, high-density lipoprotein; BP, blood pressure; TZD, thiazolidinedione; ARB, angiotensin II receptor blocker; ACEi, angiotensin-converting enzyme inhibitor; n.s., not significant.

ure 1). These results suggest an importance of strict management of atherosclerosis-related risk factors (obesity, diabetes, hypertension and dyslipidemia) to reduce serum hs-CRP levels in patients with type 2 diabetes. Multivariate regression analysis showed that TG and BMI were independent risk factors determining hs-CRP levels (Table 1). These results suggest that low TG and low BMI are closely associated with low serum hs-CRP levels in patients with type 2 diabetes.

In addition, we showed that there is some difference in which factors are important for determining serum hs-CRP levels between obese and non-obese patients (Tables 2 and 3). In a multivariate analysis of obese type 2 diabetes patients, BMI was an independent factor determining serum hs-CRP levels. In contrast, in non-obese patients, BMI was not associated at all with serum hs-CRP levels, even in a univariate analysis, and TG was an independent factor determining hs-CRP levels. These results suggest that in non-obese patients, low TG rather than low bodyweight is more closely associated with low serum hs-CRP levels. In other words, the reduction of BMI is important to decrease serum hs-CRP levels, especially in obese patients with type 2 diabetes. Therefore, in practical medicine, we should focus on reducing bodyweight in obese patients, but focus on reducing TG levels in non-obese patients.

In addition, there have been several reports showing the relationship between hs-CRP levels and albuminuria[27–30], but to the best of our knowledge, this is the first report comparing their relationship between obese and non-obese patients. As shown in Tables 2 and 3, in obese patients, but not in non-obese patients, urinary albumin was significantly associated with serum hs-CRP levels in a univariate analysis, and was an independent factor to determine hs-CRP levels in a multivariate analysis. Therefore, in practical medicine this point would be important, especially for obese patients; although for all patients we should keep in mind the importance of reducing urinary albumin with pharmacological approaches, such as ACE inhibitor or ARB, which would be beneficial for decreasing serum hs-CRP levels and thereby lead to the reduction of cardiovascular diseases.

There are several possibilities with regard to explaining the difference in independent risk factors determining hs-CRP levels, such as BMI, urinary albumin and TG, between obese and non-obese patients. First, in general, hs-CRP shows a high value in obese patients. This might be the reason why BMI was not an independent risk factor in non-obese patients. Furthermore, in the non-obese group, when compared according to median (22 kg/m^2) in regard to BMI, TZD tended to be more often used in the 22–24 kg/m^2 group than in the <22 kg/m^2 group (54% *vs* 38%, $P = 0.075$). TZD also might have affected the present result. Second, the present study showed that urinary albumin was not an independent risk factor for hs-CRP value in non-obese patients. In the non-obese group, when compared according to median (16.5 mg/g.Cre) in regard to urinary albumin, LDL cholesterol value was significantly lower in the over-median group than in under-median group (104 ± 24 mg/dL *vs* 113 ± 23 mg/dL, $P = 0.0164$). The statin was not significantly used in the over-median group than in the under-median group (56% *vs* 49%, $P = 0.385$). Furthermore, ARB or ACE inhibitor tended to be more often used in the over-median group than in the under-median group (56% *vs* 48%, $P = 0.0785$). In short, LDL cholesterol, ARB or ACE inhibitor might be confounding factors in the non-obese group. Finally, although TG was significantly higher in the obese group than in the non-obese group (128 ± 52 mg/dL *vs* 103 ± 48 mg/dL, $P < 0.0001$), the present study showed that TG was not an independent risk factor for hs-CRP value in obese patients. In the obese group, the clinical backgrounds (e.g., drug effect, other clinical parameters) were not significantly different when analyzed according to quartile for TG.

There were several limitations for the interpretation of the present study. First, although we were not taking measures such as the alignment of gender ratio, a large proportion of men were included in the present study. Therefore, it is noted that the data obtained in this study would not be necessarily true when the gender ratio is equivalent or when a large proportion of women are included. Second, because this study was retrospective, we limited the hs-CRP value to less than 0.3 mg/dL in order to avoid the mixture of inflammatory disease cases as much as possible. However, it is possible that CRP exceeds 0.3 mg/dL even in subjects without acute inflammatory disease. Therefore, the data obtained in the present study would not be necessarily true when we set another cut-off level of CRP.

In conclusion, low BMI is closely associated with low hs-CRP, especially in obese patients with type 2 diabetes, whereas low TG is closely associated with hs-CRP, especially in non-obese patients with type 2 diabetes. We should consider this point in practical medicine, and thus the data in the present study results would provide important information from a clinical point of view.

DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 | (a) Correlation of glycated hemoglobin (HbA1c) and serum high-sensitivity protein (hs-CRP) and (b) correlation of urinary albumin and serum hs-CRP levels in patients with type 2 diabetes.

Table S1 | Baseline characteristics of the study participants.