



# Elevated Levels of hs-CRP Are Associated With High Prevalence of Depression in Japanese Patients With Type 2 Diabetes: The Diabetes Distress and Care Registry at Tenri (DDCRT 6)

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## OBJECTIVE

Because of the absence of data on the direct association between inflammation and depression in patients with diabetes, we examined the association between hs-CRP levels and the high prevalence of depression in adult patients with type 2 diabetes.

## RESEARCH DESIGN AND METHODS

Cross-sectional data were obtained from 3,573 patients with type 2 diabetes recruited from a Japanese diabetes registry. A multiple logistic regression analysis adjusted for potential confounders was used to assess independent associations between hs-CRP levels and major depression, as defined by the Patient Health Questionnaire-9.

## RESULTS

Mean age, BMI, and HbA<sub>1c</sub> levels were 66.0 years, 24.6 kg/m<sup>2</sup>, and 7.4% (57.8 mmol/mol), respectively, and 122 patients (3.4%) suffered from major depression. In the age- and sex-adjusted model, the odds ratio (OR) for major depression was 1.86 (95% CI 1.01–3.42; *P* = 0.045) in the highest CRP quintile compared with that in the 3rd CRP quintile; however, this association disappeared after adjustment for other possible confounders (OR 1.58 [95% CI 0.85–2.94]; *P* = 0.148). Among patients with a BMI of ≥25 kg/m<sup>2</sup>, a significant association was observed between the highest hs-CRP quintile and major depression (multivariable-adjusted OR 2.69 [95% CI 1.09–7.08]; *P* = 0.032).

## CONCLUSIONS

We observed a significant positive association between high hs-CRP levels and depression in patients with diabetes who had a high BMI.

In the last decade, several studies have been published that suggest a close association between diabetes and depression. Patients with diabetes have a high prevalence of depression (1), particularly that associated with poor treatment adherence and glycemic control (1,2), and a high prevalence of complications (3). In addition, depression is associated with mortality in these patients (4).

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Because of this strong association, several recent studies have suggested the possibility of a common biological pathway such as inflammation as an underlying mechanism of the association between depression and diabetes (5). However, few studies have examined the clinical role of inflammation and depression as biological correlates in patients with diabetes. Moreover, some studies have failed to determine the association of depression with diabetes in very young patients (6). Many studies have suggested the role of increased immune system activity and inflammation in both diabetes and depression (7–9). Multiple mechanisms are involved in the association between diabetes and inflammation, including modulation of lipolysis, alteration of glucose uptake by adipose tissue, and an indirect mechanism involving an increase in free fatty acid levels blocking the insulin signaling pathway (10). Psychological stress can also cause inflammation via innervation of cytokine-producing cells and activation of the sympathetic nervous systems and adrenergic receptors on macrophages (11). Depression enhances the production of inflammatory cytokines (12–14). Overproduction of inflammatory cytokines may stimulate corticotropin-releasing hormone production, a mechanism that leads to hypothalamic-pituitary axis activity. Conversely, cytokines induce depressive-like behaviors; in studies where healthy participants were given endotoxin infusions to trigger cytokine release, the participants developed classic depressive symptoms (15). Based on this evidence, it could be hypothesized that inflammation is the common biological pathway underlying the association between diabetes and depression. Recently, Doyle et al. (16) examined the association between inflammation and elevated depressive symptoms, and they found that higher C-reactive protein (CRP) levels were observed in patients with diabetes with depression than in those without. However, in this study, the subjects are relatively obese, and thus this study did not answer the question of whether the association between CRP levels and depression in patients with diabetes could be applicable to the relatively lean population. In addition, the study included a small sample of patients with diabetes and depression

( $n = 14$  for CRP analysis), so the robustness of the results needs to be tested in a larger study population.

In this study, we hypothesized that high CRP levels were associated with the high prevalence of depression in patients with diabetes and that this association may be modified by obesity or glycemic control. The large sample size of our study enabled us to examine the association between hs-CRP levels and the prevalence of depression in adult patients with type 2 diabetes stratified by obesity or glycemic control.

## RESEARCH DESIGN AND METHODS

### Patients

Patient data were derived from the second-year survey of a diabetes registry at Tenri Hospital, a regional tertiary care teaching hospital in Japan. The details of this registry have previously been described (17–19). In brief, this study is a cohort study aiming at evaluating the cross-sectional and prospective association between psychosocioeconomic factors, biomarkers, and the incidence of micro- and macrovascular complications in patients with diabetes. The registry recruited patients diagnosed with diabetes who had visited the outpatient clinic of our hospital between October 2009 and December 2011. The second-year survey was performed from January to December 2011. We excluded patients with prediabetes diagnosed by an oral glucose tolerance test, gestational diabetes mellitus, type 1 diabetes, or diabetes induced by steroid use or other endocrinological diseases, and we finally used data of patients diagnosed with type 2 diabetes. At registration, the attending physician confirmed the diagnosis according to the Classification and Diagnostic Criteria of Diabetes Mellitus by the Japan Diabetes Society. The ethics committee of Tenri Hospital approved this study. In 2011, of all 4,332 eligible patients with diabetes (40.5% female patients with type 1 [4.6%] and type 2 [92.3%] diabetes with mean [SD] age 65.6 [12.1] years), 4,197 provided consent to participate in the study; 3,671 were confirmed to have type 2 diabetes. We excluded 30 patients with missing data of hs-CRP levels and 67 patients who did not complete the Patient Health Questionnaire-9 (PHQ-9). The remaining 3,573 patients who met the inclusion criteria were included in the study.

### Data Collection

On the survey date, patients underwent routine medical history inquiry, physical examinations, and laboratory tests. Clinical research coordinators used patient medical charts to collect information on demographics such as age, sex, body weight, duration of diabetes, medical history including micro- and macrovascular complications, and treatment modalities. Laboratory tests included the evaluation of HbA<sub>1c</sub> and hs-CRP levels. HbA<sub>1c</sub> levels were expressed in accordance with the National Glycohemoglobin Standardization Program as recommended by the Japanese Diabetes Society (20). Physical exercise was measured using the short version of the International Physical Activity Questionnaire (IPAQ), a self-reporting instrument that asks for an estimate of total weekly physical activity (walking/vigorous and moderate-intensity activity) during the previous week. Physical activity levels were categorized into three (low, moderate, and high) categories following the scoring rule of IPAQ (21).

### Assay of hs-CRP Levels

Technicians blinded to the patients' clinical data collected random blood samples on the same day as registration before patients answered the self-administered survey using the PHQ-9. Shortly thereafter, technicians performed measurement of hs-CRP levels with separated serum samples using a latex immunoassay method with the commercial kits LT CRP-HS II (Wako Pure Chemical Industries, Ltd., Osaka, Japan; for sensitivity, when saline is used, the absorbance change should be not more than 0.01 [ $\Delta E/\text{min}$ ]) and Hitachi LABOSPECT 008 automatic analyzer (Hitachi Products, Hitachi City, Japan).

### Depression

The diagnosis of depression at the time of participation in this study was made using the PHQ-9 as a screening tool (22,23). The PHQ-9 has been validated as being appropriate for screening for depression in patients with diabetes (24) and includes nine items assessing nine symptoms of depression as defined by the DSM-IV (25,26). Internal consistency of the PHQ-9 has been shown to be high (Cronbach  $\alpha$  of 0.89) (26). Results from interviews showed that individuals who scored high ( $\geq 10$ ) on the PHQ-9 were between 7 and 13.6

times more likely to be diagnosed with depression by the mental health professional. On the other hand, individuals scoring low ( $\leq 4$ ) on the PHQ-9 had a less than a 1 in 25 chance of having depression. We used the below criteria to define major depression according to the DSM-IV classification. Major depression was diagnosed if five or more of the nine depressive symptom criteria were present for at least “more than half the days” in the past 2 weeks and one of the symptoms was depressed mood or anhedonia (22,23).

### Statistical Analysis

Continuous variables were expressed as mean (SD). Intergroup differences were evaluated using the unpaired Student *t* test for normally distributed variables, the Mann-Whitney *U* test for variables with skewed distribution, and  $\chi^2$  analysis for categorical variables. Because the distribution of CRP levels was right skewed, CRP levels were categorized into quintiles. A logistic regression analysis was used to estimate the odds ratio (OR) (95% CI) for major depression with a reference category of CRP levels of the third quintile. The two following statistical models were used: model 1 was an age- and sex-adjusted model; model 2 was adjusted for age, sex, and exercise (low, moderate, and high); variables in model 3, selected using backward stepwise selection, were used with an entry probability of 0.05 and removal probabilities of 0.2. The initial model for backward stepwise selection was comprised of age; sex; duration of diabetes; type of diabetes therapy; smoking; BMI; HbA<sub>1c</sub> levels; history of cardiovascular disease, cancer, and arthritis (osteoarthritis or collagen vascular disease including rheumatoid arthritis); nonsteroidal anti-inflammatory drug use; diabetic retinopathy; and diabetic nephropathy.

Subsequently, we examined the stratified analysis by BMI or glycemic control. In the stratified analysis by BMI, we divided patients based on BMI into two categories (BMI of  $< 25$  or  $\geq 25$  kg/m<sup>2</sup>), and the logistic regression model used was model 3 (described above). We selected the cutoff point of BMI as 25 kg/m<sup>2</sup> because the Japan Society for the Study of Obesity defines obesity in this manner. In the stratified analysis by glycemic control, we divided patients based on HbA<sub>1c</sub> levels into the two following

categories: those with HbA<sub>1c</sub> levels of  $< 7.5$  or  $\geq 7.5\%$  ( $< 58$  or  $\geq 58$  mmol/mol), and the logistic regression model used was model 2. The cutoff point of HbA<sub>1c</sub> levels was determined based on the Japan Diabetes Association recommendation and the National Institute for Health and Clinical Excellence criteria for excellent glycemic control (27). We tested for statistical interaction by adding interaction terms between CRP category and BMI or HbA<sub>1c</sub> category to a multivariable-adjusted logistic regression model. All *P* values were two-sided; *P* values of  $< 0.05$  were considered statistically significant, except those for interaction analyses where we used  $P < 0.10$ . All analyses were performed using Stata/SE, version 12.1 (Stata Corporation, College Station, TX).

## RESULTS

### Patient Characteristics

Table 1 shows the demographic characteristics and laboratory data of patients according to the presence or absence of major depression. Overall, mean age, HbA<sub>1c</sub> level, and BMI were 66.0 years, 7.4% (57.8 mmol/mol), and 24.6 kg/m<sup>2</sup>, respectively. Patients with major depression tended to be relatively young ( $P < 0.001$ ) and female ( $P < 0.001$ ) with a high BMI ( $P < 0.001$ ), high HbA<sub>1c</sub> levels ( $P < 0.001$ ), and high hs-CRP levels ( $P = 0.0098$ ); had more diabetic nephropathy ( $P = 0.043$ ), required more insulin therapy ( $P = 0.001$ ), and exercised less ( $P < 0.001$ ); and the distribution of smoking category was statistically different between two groups ( $P < 0.001$ ).

The ORs for the association between CRP quintile and major depression are shown in Table 2. In the age- and sex-adjusted model (model 1), the OR for major depression was 1.86 (95% CI 1.01–3.42;  $P = 0.045$ ) in the highest CRP quintile compared with that in the reference category of CRP levels (third quintile). However, this association diminished after adding exercise to the model (OR 1.70 [95% CI 0.92–3.13];  $P = 0.089$ ). Further adjustment (model 3) disappeared this association (OR 1.58 [95% CI 0.85–2.94];  $P = 0.148$ ) in the highest CRP quintile.

Subsequently, we proceeded to examine the stratified analysis by BMI or glycemic control (Table 3). In patients with a BMI of  $< 25$  kg/m<sup>2</sup>, no significant association was found between hs-CRP

quintiles and major depression; however, among patients with a BMI of  $\geq 25$  kg/m<sup>2</sup>, a significant association was observed between the highest hs-CRP quintile and major depression (OR 2.69 [95% CI 1.09–7.08];  $P = 0.032$ ) in comparison with the reference category of CRP (third quintile). We did not observe a significant association between hs-CRP and major depression in either of HbA<sub>1c</sub> subgroups.

## CONCLUSIONS

In the nonstratified analysis, the hs-CRP level was associated with a high prevalence of major depression in the age- and sex-adjusted model; however, multivariable adjustment diminished this association. This finding is consistent with that of a previous study in which a crude association between inflammatory markers, including CRP, diminished after adjustment for clinical and demographic covariates in patients with type 1 diabetes (6). In our study, high hs-CRP levels were associated with a high prevalence of major depression in patients with type 2 diabetes if BMI was  $\geq 25$  kg/m<sup>2</sup>. Recently, Doyle et al. (16) examined the association between inflammation and elevated depressive symptoms, and they found that higher CRP levels were observed in patients with diabetes with depression than in those without. Because subjects in this study were an obese population, our results also seem to be consistent with this study. Our results show that the association between hs-CRP and diabetes is valid even in an Asian population, but it might not be extended to nonobese subjects. We did not observe a significant association between hs-CRP and major depression even after stratifying glycemic control levels.

Recent evidence has suggested that depression is a risk factor for developing type 2 diabetes and vice versa (5), and it was speculated that common biological pathways may underlie the association between depression and diabetes (28), one of which is inflammation. A number of prospective studies have suggested that high levels of inflammatory markers predict the incidence of type 2 diabetes (29–31). Several studies have suggested a cross-sectional association between depression and inflammation. Depression has been associated with higher levels of

**Table 1—Baseline characteristics according to depressive status**

	All	Nondepressed	Major depression	P
N	3,573	3,451	122	
Age, years	66.0 (11.4)	66.1 (11.2)	62.4 (14.5)	<0.001
Female, %	38.9	38.3	55.7	<0.001
BMI, kg/m <sup>2</sup>	24.6 (4.2)	24.5 (4.2)	26.0 (5.5)	<0.001
Duration of diabetes, years	14.6 (10.1)	14.6 (10.1)	15.2 (9.5)	0.461
HbA <sub>1c</sub>				<0.001
NSGP, %	7.4 (1.2)	7.4 (1.2)	8.0 (1.7)	
IFCC, mmol/mol	57.8 (13.1)	57.6 (12.8)	63.5 (18.6)	
hs-CRP, mg/dL†	0.08 (0.01–0.17)	0.07 (0.01–0.16)	0.1 (0.01–0.29)	0.0098
Diabetic retinopathy, %	41.9	41.6	49.5	0.128
Diabetic nephropathy, %	54.4	54.1	63.6	0.043
Diabetes therapy, %				0.001
Diet only	14.6	14.9	5.7	
Oral medication only	45.5	45.7	40.2	
Insulin	39.9	39.4	54.1	
Physical activity, %‡				<0.001
Low	39.5	38.7	60.7	
Moderate	29.0	29.2	24.6	
High	31.5	32.1	14.7	
Smoking, %				<0.001
Never	43.3	42.9	54.6	
Past	40.5	41.1	23.1	
Current	16.3	16.2	19.7	
Cardiovascular disease, %	16.5	16.4	20.3	0.313
Cancer, %	9.8	9.9	8.2	0.545
Arthritis, %§	0.22	0.20	0.82	0.157
NSAID use, %	24.1	23.9	39.5	0.155

Data are means (SD) unless otherwise indicated. IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; NSGP, National Glycohemoglobin Standardization Program; NSAIDs, nonsteroidal anti-inflammatory drugs. †Median (interquartile range) is reported. ‡Physical activity levels were categorized into three (low, moderate, high) categories following the scoring rule of the IPAQ (21). §Osteoarthritis or collagen vascular disease including rheumatoid arthritis.

inflammatory markers (white blood cells, CRP, and interleukin [IL]-6) (32,33), and higher depression screen scores were significantly associated with higher CRP levels (34). In addition, the association between depression and inflammation has been shown to be bidirectional. In a cohort of 263 participants, the baseline depression screen score was positively associated with a subsequent increase in IL-6 levels (35).

Conversely, in a cohort of >3,339 participants with >12 years of follow-up, baseline inflammatory marker levels (CRP and IL-6) were associated with a subsequent risk of depression at follow-up (36). However, this association was not observed in patients with type 2 diabetes. A recently conducted meta-analysis revealed that the relative risk of type 2 diabetes was 1.26 (95% CI 1.16–1.37) per 1 log mg/L increment in CRP levels

(37). Hood et al. (6) evaluated the association between numerous inflammatory markers and depression in young patients (mean age 15.2 years) with type 2 diabetes using the Center for Epidemiologic Studies Depression Scale. Even in a crude analysis, they did not identify a significant association between depression and inflammation in patients with diabetes. Although our study was conducted on a different

**Table 2—Association between hs-CRP and major depression**

	hs-CRP quintiles (interquartile range), mg/dL				
	1 (0.01–0.01)	2 (0.05–0.06)	3 (0.07–0.09)	4 (0.12–0.18)	5 (0.31–0.80)
Number of subjects	1,153	443	584	719	674
Number with major depression	33	13	16	26	34
OR (95% CI) for major depression					
Age- and sex-adjusted model (model 1)	1.09 (0.59–2.00)	1.14 (0.54–2.40)	1.00 (Ref.)	1.33 (0.70–2.50)	1.86 (1.01–3.42)
Multivariable-adjusted model (model 2)*	1.16 (0.63–2.13)	1.14 (0.54–2.40)	1.00 (Ref.)	1.26 (0.67–2.39)	1.70 (0.92–3.13)
Multivariable-adjusted model (model 3)†	1.21 (0.66–2.24)	1.14 (0.54–2.43)	1.00 (Ref.)	1.19 (0.63–2.25)	1.58 (0.85–2.94)

\*Model 2 adjusted for age, sex, and exercise. †Model 3 adjusted for age, sex, smoking, type of diabetes therapy, diabetic nephropathy, arthritis, nonsteroidal anti-inflammatory drug use, and exercise (low, middle, and high intensity) (21).

**Table 3—Association between hs-CRP and major depression stratified by BMI or HbA<sub>1c</sub> level\***

	hs-CRP quintiles (interquartile range), mg/dL					P for interaction
	1 (0.01–0.01)	2 (0.05–0.06)	3 (0.07–0.09)	4 (0.12–0.18)	5 (0.31–0.80)	
<b>BMI &lt;25 kg/m<sup>2</sup></b>						
Number of subjects	862	263	324	362	352	0.148
Number with major depression	23	7	10	8	12	
OR (95% CI) for depression (model 3)	0.96 (0.45–2.07)	0.78 (0.28–2.21)	1.00 (Ref.)	0.63 (0.24–1.64)	0.81 (0.32–2.01)	
<b>BMI ≥25 kg/m<sup>2</sup></b>						
Number of subjects	291	180	260	357	322	0.309
Number with major depression	10	7	6	18	24	
OR (95% CI) for depression (model 3)	1.67 (0.59–4.69)	1.95 (0.63–5.98)	1.00 (Ref.)	2.09 (0.81–5.39)	2.69 (1.09–7.08)	
<b>HbA<sub>1c</sub> &lt;7.5% (58 mmol/mol)</b>						
Number of subjects	829	261	347	406	381	0.309
Number with major depression	20	7	11	10	14	
OR (95% CI) for depression (model 3)	0.83 (0.39–1.77)	0.90 (0.34–2.40)	1.00 (Ref.)	0.70 (0.29–1.69)	1.10 (0.49–2.51)	
<b>HbA<sub>1c</sub> ≥7.5% (58 mmol/mol)</b>						
Number of subjects	324	182	237	313	293	0.309
Number with major depression	13	6	5	16	20	
OR (95% CI) for depression (model 3)	1.94 (0.67–5.61)	1.58 (0.47–5.39)	1.00 (Ref.)	2.01 (0.71–5.69)	2.27 (0.81–6.36)	

Model 3 adjusted for age, sex, smoking, type of diabetes therapy, diabetic nephropathy, arthritis, nonsteroidal anti-inflammatory drug use, and exercise (low, middle, and high) (21).

age-group, our result is consistent with their result with respect to the fact that we did not find a significant association in the nonstratified analysis. Our study determined that several factors such as obesity and glycemic control may modify the association between inflammation and depression. However, it is unclear whether these factors or other unevaluated factors such as insulin insensitivity are the real effect modifiers; thus, further studies are required.

The association between high hs-CRP levels and major depression was attenuated after adjustment for exercise, and the significant association was observed in the high-BMI group, which is an interesting finding. Obesity is strongly associated with chronic inflammation. The association between obesity and inflammation was first reported by Hotamisligil et al. (38), and since then, adipose tissue has been recognized as an important source of a number of cytokines. It is well-known that exercise reduces the risk of developing type 2 diabetes, improves glycemic control in patients with diabetes (39–41), and improves the symptoms of depression (42). Recently, our meta-analysis revealed that long-term exercise reduced CRP levels in patients with diabetes (43). Based on these previous reports, our results suggest that inflammatory cytokines specifically from adipose tissue may play an important role in the association between type 2 diabetes and major depression,

and exercise seems to be a strong confounder in this association between inflammation and depression in these patients.

Some limitations were observed in the current study. The first, most obvious, limitation of the study was its cross-sectional design. Therefore, firm conclusions regarding the directions of the causality of the association between hs-CRP levels and depression in the current analysis cannot be drawn; however, based on biological evidences, we hypothesize a bidirectional association. Second, we used self-reported measures to define major depression, which may have resulted in misclassification. However, this misclassification most likely occurred evenly across hs-CRP categories and resulted in nondifferential misclassification. Nondifferential misclassification inevitably leads to a reduced strength of estimated exposure-disease associations (44). Thus, we may have ultimately underestimated the association between hs-CRP levels and major depression. Third, residual confounders may exist in the association with depression, such as socioeconomic status or marital status; however, we did not have sufficient data on these variables. Fourth, we did not have enough data on whether patients suffered from acute infections, so we could not adjust for that. Despite this, we did not ask patients to participate in the survey if patients had a febrile condition

that day because patients have to be in a good enough condition to answer the self-administered questionnaire; thus, not adjusting for febrile condition might not influence our results so much. Finally, data were derived from the registry of a single diabetes center, thereby raising concerns regarding generalizations derived from the results, particularly for the multi-ethnic North American and European populations.

In conclusion, we observed that hs-CRP levels were associated with a high prevalence of major depression in patients with type 2 diabetes with a BMI of ≥25 kg/m<sup>2</sup>. This association was significant after adjustment for possible confounders. The causality of this association remains unclear and requires evaluation in a future prospective study.

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**Author Contributions.** Y.H. searched the literature, conceived the study, analyzed the data, interpreted the results, wrote the first draft of most sections of the report, obtained funding, collected the data, revised the report, and participated in writing of the report. Y.H. was project coordinator. T.M., S.T., and H.I. organized and supervised the study, interpreted the results, and revised the report. Y.H. and T.M. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

## Appendix

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