Serum High-Sensitivity C-Reactive Protein Levels Are Associated With High Risk of Development, Not Progression, of Diabetic Nephropathy Among Japanese Type 2 Diabetic Patients: A Prospective Cohort Study (Diabetes Distress and Care Registry at Tenri [DDCRT7])

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OBJECTIVE

To assess the prospective association between baseline serum hs-CRP concentration and the subsequent risk of development or progression of diabetic nephropathy.

RESEARCH DESIGN AND METHODS

Longitudinal data were obtained from 2,518 patients with type 2 diabetes registered in a Japanese diabetes registry. To assess the independent correlations between serum baseline hs-CRP and either the development or progression of diabetic nephropathy 1 year later, the Cox proportional hazards model was used and adjusted for potential confounders.

RESULTS

The mean patient age, BMI, and HbA_{1c} level were 66.1 years, 24.6 kg/m^2, and 7.5% (57.6 mmol/mol), respectively. Baseline serum hs-CRP levels were significantly associated with the urinary albumin-to-creatinine ratio at baseline ($P < 0.001$). Multivariable adjusted hazard ratio for the development from normoalbuminuria to microalbuminuria was 1.31 (95% CI 0.80–2.17; $P = 0.286$), 1.55 (1.16–2.08; $P = 0.003$), and 1.57 (1.22–2.03; $P = 0.001$), respectively, for the second, third, and fourth quartiles of serum hs-CRP levels, showing a statistically significant linear trend across categories ($P < 0.001$). We did not observe a significant association between hs-CRP levels and the subsequent risk of diabetic nephropathy progression (P for trend = 0.575).

CONCLUSIONS

Serum hs-CRP levels, independent of possible confounders, were associated with a subsequent risk of developing, not progressing, diabetic nephropathy in type 2 diabetic patients. Serum hs-CRP may be useful for predicting the future risk of developing diabetic nephropathy.

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**A complete list of the members of the Diabetes Distress and Care Registry at Tenri Study Group can be found in the Supplementary Data online.*

Diabetic nephropathy is a common complication of diabetes and the leading cause of end-stage renal disease in developed countries (1,2). Several studies have reported that diabetic nephropathy is related to the onset of cardiovascular disease, which worsens the overall prognosis (3,4). An understanding of the clinical characteristics and risk factors associated with the development and progression of diabetic nephropathy is useful for establishing effective therapeutic strategies to prevent the progression and the onset of cardiovascular complications.

A number of risk factors have been suggested in the pathogenesis of diabetic nephropathy, including low birth weight, endothelial dysfunction, smoking, renin-angiotensin system stimulation, obesity, hyperglycemia, and high blood pressure (5,6). Recent basic science studies suggest that proinflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor play a role in the pathogenesis of diabetic nephropathy (7). Several human studies support these findings, and several cross-sectional studies have reported that high levels of inflammatory markers, such as IL-6, fibrinogen, or C-reactive protein (CRP), are associated with diabetic nephropathy in patients with diabetes. However, because of the nature of a cross-sectional study, the direct causality between high levels of inflammatory markers and diabetic nephropathy is unknown. A previous study reported that baseline CRP levels were associated with a subsequent increment of urinary albumin excretion in patients with type 2 diabetes (8); however, this study did not examine if either progression or development of diabetic nephropathy was associated with high levels of CRP. Further, this study did not adjust for the use of medications, such as ACE inhibitor (ACE-I), angiotensin II receptor blocker (ARB), or nonsteroidal anti-inflammatory drugs (NSAIDs), which may influence renal function during follow-ups.

Therefore, we studied a cohort of Japanese patients with type 2 diabetes from a large-scale single-center registry to determine the prospective association between baseline serum hs-CRP concentration and the subsequent risk of development or progression of diabetic nephropathy.

RESEARCH DESIGN AND METHODS

Patients

Patient data were derived from the 2nd-year survey of a diabetes registry at Tenri Hospital, a regional tertiary-care teaching hospital in Japan. The details of this registry can be found elsewhere (9–11). In brief, this study is a cohort study aimed 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 2nd-year survey was performed from January to December 2011. We excluded patients with prediabetes diagnosed by an oral glucose tolerance test, gestational diabetes, 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 by the Japan Diabetes Society. For this analysis, we only included patients if all of their baseline hs-CRP data and baseline and follow-up urinary albumin-to-creatinine ratio (UACR) data were available. On registration, the attending physician confirmed the diagnosis according to the classification and diagnostic criteria of diabetes by the Japan Diabetes Society. The ethics committee of Tenri Hospital approved this study.

Data Collection

On the survey date, patients underwent a routine medical history inquiry, physical examination, and laboratory tests. Clinical research coordinators used patient medical charts to collect information on demographics, including age, sex, body weight, duration of diabetes, past medical history including micro- and macrovascular complications, and treatment modalities. Laboratory tests included evaluation of HbA_{1c} levels, hs-CRP levels, and the UACR from a spot urine sample. HbA_{1c} levels were expressed in accordance with the National Glycohemoglobin Standardization Program (NGSP) as recommended by the Japanese Diabetes Society (12), and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units. The glomerular filtration rate was estimated (eGFR) using an equation proposed by the Japanese Society of Nephrology (13). Physical exercise was measured using the short version of the International Physical Activity Questionnaire (IPAQ), a self-reported 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 categories (low, moderate, and high) according to the scoring rule of IPAQ (14).

Outcomes

One year after registration, we evaluated the following outcomes: the transition from normoalbuminuria to microalbuminuria or macroalbuminuria (defined as the development of diabetic nephropathy) and the transition from microalbuminuria to macroalbuminuria (defined as the progression of diabetic nephropathy). Based on the UACR, we classified the stages of diabetic nephropathy as normoalbuminuria (UACR $<$3.4 mg/mmol), microalbuminuria (UACR 3.4–33.9 mg/mmol), and macroalbuminuria (UACR $\geq$33.9 mg/mmol) (15). Because Japan Diabetes Society uses eGFR criteria "equal to or more than 30 mL/min/1.73 m^2" to define normoalbuminuria or microalbuminuria stages in addition to UACR levels (16), we excluded patients with eGFR levels $<$30 mL/min/1.73 m^2.

hs-CRP Assay

Technicians blinded to patient clinical data collected a random blood sample on the same day as the registration before the patients answered a self-administered survey. Soon after, technicians carried out the test for hs-CRP using separated serum. The latex immunoassay method was performed using commercial kits LT CRP-HS II (Wako Pure Chemical Industries, Ltd., Chuo-ku, Osaka, Japan; sensitivity: when saline is used, the absorbance change is not $>$0.01 [ΔE/min]) and a Hitachi LABOSPECT 008 automatic analyzer (Hitachi Products, Hitachi City, Japan).

Statistical Analysis

Continuous variables were expressed as the mean (SD). Intergroup differences

were evaluated using the one-way ANOVA test. Because the distribution of hs-CRP was right skewed, hs-CRP was categorized into quartiles for the analysis. The association between hs-CRP quartiles and the outcomes were analyzed using the Cox proportional hazards model considering clustering within the attending physician. Person-time was calculated as the registration date until the day the outcome was confirmed, or the end of follow-up, whichever occurred first. The hazard ratio (HR) (95% CI) was estimated for the outcome in comparison with a reference category of hs-CRP (first quartile). Proportional hazard assumptions were confirmed with visual inspection, where the survival function versus the survival time resulted in a graph with parallel curves, and similarly, the log[−log(survival)] versus the log of survival time graph resulted in parallel lines, as previously performed and described (17). In addition, we used natural log–transformed hs-CRP levels as a covariate to estimate HR (95% CI) per 1 unit increment of ln (hs-CRP). Three statistical models were used. The first model was the crude model; the second model was the age- and sex-adjusted model; and the third model was adjusted for age, sex, BMI, exercise, smoking, systolic blood pressure, diastolic blood pressure, HDL, LDL, triglyceride, serum creatinine, eGFR, serum uric acid, ACE-I use, ARB use, statin use, HbA_{1c} levels, past history of cardiovascular disease, past history of cancer, history of arthritis (osteoarthritis or collagen vascular disease including rheumatoid arthritis), NSAID use, and diabetic retinopathy. We selected these covariates because these are known to be or considered to be associated with hs-CRP levels and diabetic nephropathy. All *P* values were two-sided. *P* values of <0.05 were considered statistically significant. All analyses were performed using Stata/SE version 13.0 (Stata Corporation, College Station, TX).

RESULTS

Patient Characteristics

In 2011, of the 4,330 eligible patients with diabetes (mean age [SD], 65.6 years [12.1]; 40.5% female; 4.6% type 1 diabetes; 92.3% type 2 diabetes), 4,191 provided consent to participate in the study and 3,717 were confirmed with type 2 diabetes. Further, 37 patients were excluded because of missing hs-CRP levels, 255 patients because of missing baseline UACR data, and 463 patients because of missing follow-up UACR data. We further excluded 444 patients whose baseline UACR levels were >33.9 mg/mmol, or baseline eGFR levels were <30 mL/min/1.73 m^2. The remaining 2,518 patients were included in the study. Table 1 displays the demographic characteristics and laboratory data of patients according to the presence or absence of major depression. Overall, the mean age, HbA_{1c} level, and BMI were 66.1 years, 7.5% (57.6 mmol/mol), and 24.6 kg/m^2, respectively (Table 1). Patients with higher hs-CRP levels tended to have lower HDL levels ($P < 0.001$); higher LDL and triglyceride levels ($P < 0.001$); lower eGFR levels ($P = 0.019$); higher uric acid ($P < 0.001$), HbA_{1c} ($P < 0.001$), and UACR ($P < 0.001$) levels; less exercise ($P < 0.001$); and more NSAID ($P = 0.007$) and ARB ($P = 0.016$) use.

Over the median follow-up of 0.94 years, we observed 197 case subjects who developed diabetic nephropathy (incidence ratio 155.4/1,000 person-years [95% CI 135.1–178.7]) (Table 2). The HRs for the association between CRP quartile and development of diabetic nephropathy are shown in Table 3. In the crude model, we observed a significant association between baseline hs-CRP quartiles and the subsequent risk of developing diabetic nephropathy (*P* for trend <0.001). This association did not change after adjusting for age and sex (*P* for trend <0.001) and was slightly attenuated by adjusting for other possible confounders but, nonetheless, remained a significant association. The multivariable-adjusted HRs for developing diabetic nephropathy were 1.31 (95% CI 0.80–2.17; $P = 0.286$), 1.55 (1.16–2.08; $P = 0.003$), and 1.57 (1.22–2.03; $P = 0.001$), respectively, for the second to fourth quartiles as compared with the first quartile of hs-CRP (*P* for trend <0.001). We also observed a significant association between log-transformed hs-CRP levels and the subsequent risk of developing diabetic nephropathy (multivariable-adjusted HR per 1 unit increment of ln[hs-CRP] = 1.10 [95% CI 1.10–1.17]; $P = 0.001$) (Supplementary Table 1).

Further, we looked at the association between baseline hs-CRP quartiles and the risk of progression of diabetic nephropathy (Table 4). Over the median follow-up of 0.94 years, we observed 109 case subjects whose diabetic nephropathy progressed (incidence ratio 92.4/1,000 person-years [95% CI 75.7–112.7]) (Table 2). We did not observe a significant association between baseline hs-CRP quartiles and the subsequent risk of diabetic nephropathy progression both in the crude model (*P* for trend = 0.404) and multivariable-adjusted model (*P* for trend = 0.575). The multivariable-adjusted HRs for developing diabetic nephropathy were 0.59 (95% CI 0.33–1.47; $P = 0.071$), 1.14 (0.69–1.91; $P = 0.609$), and 1.03 (0.55–1.91; $P = 0.931$), respectively, for the second to fourth quartiles as compared with the first quartile of hs-CRP. We did not observe a significant association between log-transformed hs-CRP levels and the subsequent risk of developing diabetic nephropathy (multivariable-adjusted HR per 1 unit increment of ln [hs-CRP] = 1.03 [95% CI 0.87–1.22]; $P = 0.734$) (Supplementary Table 1).

CONCLUSIONS

Serum CRP levels are well studied as sensitive circulating markers of inflammation, as CRP is independently associated with an increased risk of cardiovascular disease and diabetes (18–22). In addition to these previous associations, our study identifies new information regarding CRP and disease outcomes. There is a temporal association between elevated levels of hs-CRP and the subsequent risk of developing, not progressing, diabetic nephropathy in a large registry of patients with diabetes, even after adjusting for possible confounders, including medication use, which may influence the natural course of renal function. Our study has also demonstrated that elevated levels of hs-CRP are associated with the development of nephropathy but not associated with the progression of nephropathy.

In 2002, Stehouwer et al. (8) reported for the first time that CRP levels were associated with a subsequent increment in urinary microalbumin levels in patients with diabetes. In a cohort of 328 patients with type 2 diabetes, urinary albumin levels increased by 1.02 mg/24 h (95% CI 1.01–1.27) for each increase in CRP of 1 mg/L over 10 years of follow-up. Using a linear regression

Table 1—Participant baseline characteristics based on total serum hs-CRP concentration quartiles

		hs-CRP quartiles				
	All	First quartile	Second quartile	Third quartile	Fourth quartile	
	n = 2,518	*n* = 819	*n* = 454	*n* = 650	*n* = 595	*P* value
hs-CRP (nmol/L)†	6.6 (1.0–15.2)	1.0 (1.0–1.0)	5.7 (4.8–6.7)	10.5 (8.6–12.4)	30.5 (21.0–54.3)	
Age (years)	66.1 (10.9)	66.7 (10.1)	66.7 (10.6)	65.4 (10.8)	65.8 (12.2)	0.0725
Female (%)	37.5	36.4	34.6	38.3	40.5	0.208
BMI (kg/m^2)	24.6 (4.0)	23.2 (3.4)	24.4 (3.4)	25.2 (3.8)	25.9 (4.9)	<0.001
Systolic blood pressure (mmHg)	137.7 (17.9)	137.8 (18.1)	139.2 (17.4)	138.0 (17.7)	136.3 (17.9)	0.0743
Diastolic blood pressure (mmHg)	73.4 (12.0)	72.2 (11.7)	74.1 (11.3)	73.9 (12.3)	73.8 (12.5)	0.0063
HDL (mmol/L)	1.44 (0.40)	1.55 (0.39)	1.42 (0.38)	1.39 (0.38)	1.37 (0.39)	<0.001
LDL (mmol/L)	2.65 (0.72)	2.57 (0.69)	2.62 (0.69)	2.72 (0.75)	2.70 (0.74)	<0.001
Triglyceride (mmol/L)	1.73 (1.14)	1.46 (0.86)	1.82 (1.16)	1.86 (1.07)	1.88 (1.43)	<0.001
Creatinine (μmol/L)	67.6 (19.7)	65.9 (18.3)	68.4 (19.7)	67.7 (19.9)	69.2 (21.3)	0.012
eGFR (mL/min/1.73 m^2)	75.2 (22)	76.9 (21.4)	75.2 (21)	75.2 (21.6)	72.9 (23.6)	0.019
Uric acid (μmol/L)	325.6 (64.1)	303.3 (84.9)	310.8 (81.7)	316.0 (81.7)	325.6 (84.1)	<0.001
HbA_{1c}						
NGSP (%)	7.5 (1.1)	7.2 (1.0)	7.5 (1.1)	7.6 (1.2)	7.6 (1.3)	<0.001
IFCC (mmol/mol)	57.6 (12.1)	55.3 (10.7)	58.0 (11.8)	58.7 (12.2)	59.2 (13.3)	<0.001
UACR (mg/mmol)	5.81 (6.8)	5.17 (6.20)	5.50 (6.36)	6.00 (6.90)	6.74 (7.50)	<0.001
Smoking (%)						0.296
Never	42.6	43.7	41.7	43.5	40.8	
Past	40.7	41.4	39.5	38.1	43.7	
Current	16.7	14.9	18.8	18.5	15.5	
Exercise (IPAQ category) (%)						<0.001
Low	36.4	29.9	35.5	37.2	45.0	
Moderate	31.2	34.5	32.9	28.9	27.6	
High	32.5	35.6	31.6	33.9	27.4	
Past history of cardiovascular disease (%)	15.8	16.2	13.7	14.3	18.4	0.130
Past history of cancer (%)	9.7	10.1	8.6	9.4	10.1	0.804
Past history of arthritis (%)	0.28	0.12	0.44	0.31	0.34	0.743
Diabetic retinopathy (%)	48.5	50.1	46.8	46.7	49.3	0.500
NSAID use (%)	23.2	21.6	20.9	21.9	28.4	0.007
ACE-I use (%)	5.9	6.6	5.6	6.0	4.9	0.605
ARB use (%)	36.7	32.5	36.8	39.4	39.5	0.016
Statin use (%)	44.1	45.4	43.0	45.7	41.5	0.376

†Median and interquartile range.

model incorporating the whole sample irrespective of baseline urinary albumin levels, they assumed that the association between CRP levels and increment of albuminuria did not change in the stages of diabetic nephropathy; however, our study has revealed that the previous assumption was not met. Several other cross-sectional studies support our

Table 2—Baseline serum hs-CRP concentration quartiles and subsequent development or progression of diabetic nephropathy

hs-CRP quartiles	Number of subjects	Person-years	Number of outcomes	Incidence ratio (95% CI)*
Development of diabetic nephropathy				
First quartile	485	445.1	51	114.6 (87.1–150.7)
Second quartile	252	227.0	34	149.8 (107.0–209.6)
Third quartile	357	328.7	63	191.7 (149.7–245.4)
Fourth quartile	291	266.7	49	183.7 (138.9–243.1)
Progression of diabetic nephropathy				
First quartile	334	309.6	27	87.2 (59.8–127.1)
Second quartile	202	188.8	11	58.2 (32.3–105.2)
Third quartile	293	269.9	30	111.1 (77.7–159.0)
Fourth quartile	304	281.5	29	103.0 (71.6–148.3)

*Incidence rate of outcomes per 1,000 person-years.

Table 3—Association between serum hs-CRP concentration and development of diabetic nephropathy (shift from normoalbuminuria to microalbuminuria)

	hs-CRP concentration quartiles				
	1Q	2Q	3Q	4Q	
	n = 486	*n* = 252	*n* = 359	*n* = 293	*P* value for trend
Median of hs-CRP (nmol/L)	1.0	5.7	10.5	30.5	
Interquartile range of hs-CRP (nmol/L)	1.0–1.0	4.8–6.7	8.6–12.4	21.0–54.3	
HR for development (95% CI)					
Crude model	Ref	1.50 (0.98–2.31)	1.70 (1.35–2.14)	1.62 (1.30–2.10)	<0.001
Age- and sex-adjusted model	Ref	1.49 (0.96–2.31)	1.71 (1.38–2.12)	1.61 (1.29–2.00)	<0.001
Multivariable-adjusted model*	Ref	1.31 (0.80–2.17)	1.55 (1.16–2.08)	1.57 (1.22–2.03)	<0.001

*Adjusted for age, sex, BMI, exercise, smoking, systolic blood pressure, diastolic blood pressure, HDL, LDL, triglyceride, serum creatinine, eGFR, serum uric acid, ACE-I use, ARB use, statin use, HbA_{1c} levels, past history of cardiovascular disease, past history of cancer, history of arthritis, NSAID use, and diabetic retinopathy.

results. Navarro et al. (23,24) studied patients with type 2 diabetes and revealed that CRP levels were high in patients with microalbuminuria or mild proteinuria (urinary protein <1 g/day) compared with those with normoalbuminuria. This association was observed even in patients with type 1 diabetes. Saraheimo et al. (25) evaluated the association between CRP levels and diabetic nephropathy in 194 patients with type 1 diabetes and found that CRP was higher in patients with micro- and macroalbuminuria compared with those without. Schalkwijk et al. (26) reported similar results and did not observe a significant difference in CRP levels between those with microalbuminuria and macroalbuminuria, which is consistent with our results. Because of the nature of a cross-sectional study, it is still unknown whether the high levels of CRP cause diabetic nephropathy or vice versa. Our results show that elevated levels of CRP could be upstream of this association.

Because this is an epidemiological study, the biological mechanism behind these results can only be hypothesized. First, high CRP levels may be associated with the development of diabetic nephropathy via exacerbating glycemic control in patients with diabetes, because experimental and clinical studies suggest that CRP is associated with insulin resistance and hyperglycemia (27). However, in our results, we observed a significant association between elevated CRP levels and diabetic nephropathy even after adjusting for glycemic control. Second, it has become increasingly clear that several cytokines/chemokines, such as TNF-α, IL-6, intercellular and vascular cellular adhesion molecules (ICAM-1 and VCAM-1), and monocyte chemoattractant protein-1 (MCP-1), play significant roles in the development of diabetic nephropathy (28); therefore, we may just be observing one aspect of a complex mechanism intermediated by these factors, with high CRP levels acting as a representation of this phenomenon. In that sense, CRP may be a predictor of the early phase of diabetic nephropathy; however, further clinical studies need to be conducted in order to show that CRP itself could be a therapeutic target to prevent diabetic nephropathy.

Some limitations were observed in the current study. First, because this is an epidemiological study, residual confounders may exist in the association with the development of diabetic nephropathy. Second, we evaluated diabetic nephropathy using single UACR measurements at baseline and during follow-up, which may have resulted in misclassification of diabetic nephropathy, leading to erroneous patient classification. However, this misclassification most likely occurred evenly across all hs-CRP level quartile categories, resulting in nondifferential misclassification. Nondifferential exposure misclassification will inevitably lead to decreased strength of estimated exposure/disease correlations (29). Thus, we may have underestimated the correlation between hs-CRP levels and nephropathy progression in our study. Third, the duration of our study is

Table 4—Association between serum hs-CRP concentration and progression of diabetic nephropathy (shift from microalbuminuria to macroalbuminuria)

	hs-CRP concentration quartiles				
	1Q	2Q	3Q	4Q	
	n = 344	*n* = 203	*n* = 301	*n* = 318	*P* value for trend
Median of hs-CRP (nmol/L)	1.0	5.7	10.5	30.5	
Interquartile range of hs-CRP (nmol/L)	1.0–1.0	4.8–6.7	8.6–12.4	21.0–54.3	
HR for development (95% CI)					
Crude model	Ref	0.65 (0.37–1.15)	1.26 (0.72–2.18)	1.18 (0.61–2.26)	0.404
Age- and sex-adjusted model	Ref	0.64 (0.35–1.17)	1.25 (0.68–2.33)	1.18 (0.58–2.39)	0.430
Multivariable-adjusted model*	Ref	0.59 (0.33–1.05)	1.14 (0.69–1.91)	1.03 (0.55–1.91)	0.575

*Adjusted for age, sex, BMI, exercise, smoking, systolic blood pressure, diastolic blood pressure, HDL, LDL, triglyceride, serum creatinine, eGFR, serum uric acid, ACE-I use, ARB use, statin use, HbA_{1c} levels, past history of cardiovascular disease, past history of cancer, history of arthritis, NSAID use, and diabetic retinopathy.

very short, and this might be one reason why we did not find significant association between hs-CRP and progression of diabetic nephropathy. 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 multiethnic North American and European populations.

In conclusion, elevated hs-CRP levels are associated with the subsequent risk of development, but not progression, of diabetic nephropathy in patients with type 2 diabetes. More research is needed to examine if there is an effective strategy to reduce the risk of diabetic nephropathy in a group of patients with diabetes and elevated levels of hs-CRP.

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