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The association between high-sensitivity C-reactive protein concentration and diabetic nephropathy: a meta-analysis

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Abstract. – OBJECTIVE: To explore the association between high-sensitivity C-reactive protein (hs-CRP) concentration and diabetic nephropathy (DN).

MATERIALS AND METHODS: We systematically searched Pubmed, Medline and Embase databases up to September, 2014 for the relevant studies. Heterogeneity across studies was evaluated by Cochran's Q test and I^2 statistic. The standard mean difference (SMD) and the corresponding 95% confidence interval (CI) were combined to evaluate the effect size. Sensitivity analysis was also performed by omitting each study to evaluate the stability of the results. In addition, publication bias was tested by Egger's test.

RESULTS: A total of 11 studies containing 1 331 cases and 1 779 controls were included in this study. Significant heterogeneities were observed in our results. The result of meta-analysis showed that the hs-CRP concentrations in DN patients were significantly higher than that in controls of healthy people and diabetes mellitus (DM) patients without nephropathy. In addition, the hs-CRP concentration in macroalbuminuria (D3) group was significantly higher than that in microalbuminuria (D2) group and non-albuminuria group (D1). Sensitivity analysis revealed that the results were stable. As well, no publication bias was observed in our results.

CONCLUSIONS: We suggest that hs-CRP concentration can be an indicator of DN in DM patients.

Key Words:
High-sensitivity C-reactive protein, Diabetic nephropathy, Meta-analysis.

Introduction

Diabetic nephropathy (DN) is a major microvascular complication of diabetes mellitus (DM)[1]. DN is a primary cause of morbidity and mortality in DM subjects and has become the leading cause of end-stage renal disease worldwide[2,3]. Many factors including hyperglycemia, hypertension, hereditary, sedentary lifestyle, obesity, smoking, and advancing age contribute to the development of DN[4,5]. Inflammation plays an important role in the pathogenesis of DN. Leukocytes, macrophages and monocytes all involve in the process of DN[6,7], and proinflammatory cytokines and inflammatory markers are strongly associated with the development of DN[8,9].

High-sensitivity C-reactive protein (hs-CRP), a marker of inflammation, has been reported to be associated with development of DN[10,11]. Albuminuria is one of the first asymptomatic clinical features of micro-vascular damage in DM. It has been shown that the microalbuminuria and macroalbuminuria are associated with progressive renal function loss[12]. Circulating hs-CRP levels may predict the development of albuminuria in some longitudinal studies of type 1 and type 2 DM patients[11,13]. However, the adverse views persisted no association between hs-CRP levels and diabetic complications[14].

The association between hs-CRP levels and the development of DN remains unclear. Thus, we systematically reviewed the relevant published studies and performed a meta-analysis to evaluate the correlation between hs-CRP levels and risk of DN. We anticipant that our result can provide an insight for developing diagnostic tools of DN.

Materials and Methods

Search Strategy

Pubmed, Medline and Embase databases were systematically searched up to September, 2014 for the relevant studies. The search terms were:

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"high-sensitivity C-reactive protein" or "hs-CRP" and "diabetic nephropathy" or "DN" or "diabetic nephropathies".

Inclusion and Exclusion Criteria

Some definitions should be explained firstly. DM was diagnosed on the basis of the World Health Organization criteria [15]. According to urinary albumin excretion rate (UAER), the DM patients were divided into 3 groups: D1 = normoalbuminuria (UAER of creatinine: < 30 mg/d or < 20 μg/min), D2 = microalbuminuria (UAER of creatinine: 30-300 mg/d or 20-200 μg/min) and D3 = macroalbuminuria (UAER of creatinine: ≥ 300 mg/d or > 200 μg/min). Patients in D2 and D3 groups were considered as DN (case group), while in D1 group were considered as control group.

The following studies were included: (1) the design of the study was case-control or prospective cohort study; (2) the case group was DN patients, and the control group was healthy people (those who had no hypertension, metabolic, hepatic or renal disease) or/and DM patients without nephropathy (DM patients in D1 group); (3) the studies reported the association between hs-CRP and DN; (4) the number of cases and controls was provided; (5) the mean values ± standard deviation (SD) of hs-CRP were given.

Reviews, reports, comments and letters were excluded. In addition, the studies published in a language other than English were excluded.

Data Extraction and Quality Assessment

The following data were extracted independently by two reviewers from the included studies: name of the first author, publication year, study year, region of the participants, type of study, measurement method of hs-CRP, number of the cases and controls, age, BMI, gender distribution (male/female), mean duration of DM and concentration of hs-CRP. The discrepancy was resolved by discussion with a third reviewer.

The quality of the included studies was assessed by Newcastle-Ottawa Scale (NOS)[16]. This scale contains 8 items, and the total score was 9. The studies scoring 0-4 represent low quality, and 5-9 represent high quality[17].

Statistical Analysis

When the hs-CRP concentration was marked by a median and range, two simple formulas could estimate the mean value using the median value, range and the sample size. Median can be considered as mean when the sample size is larger than 25. For moderately sized samples ($15 < n \leq 70$), the range/4 is the best estimator for the SD (variance). For large samples ($n > 70$), the range/6 gives the best estimator for the SD (variance)[18].

Meta-analysis was performed by using R 3.10 software. Heterogeneity across studies was evaluated by Cochran's Q test[19] and I^2 statistic. $p < 0.05$ and $I^2 > 50\%$ was considered as a significant heterogeneity. According to the heterogeneity, the estimates of standard mean difference (SMD) and the corresponding 95% confidence interval (CI) were combined by a random-effects model (Dersimonian-Laird method) or a fixed-effect model (Mantel-Haenszel method), when appropriate[20]. Sensitivity analyses were performed by omitting each study. Finally, Egger's test were used to evaluate publication bias [21], $p < 0.05$ was considered as statistically significant.

Results

Study Selection

The flow diagram of the study selection was shown in Figure 1. A total of 249 studies were searched by the initial retrieve. Then, 168 irrele-

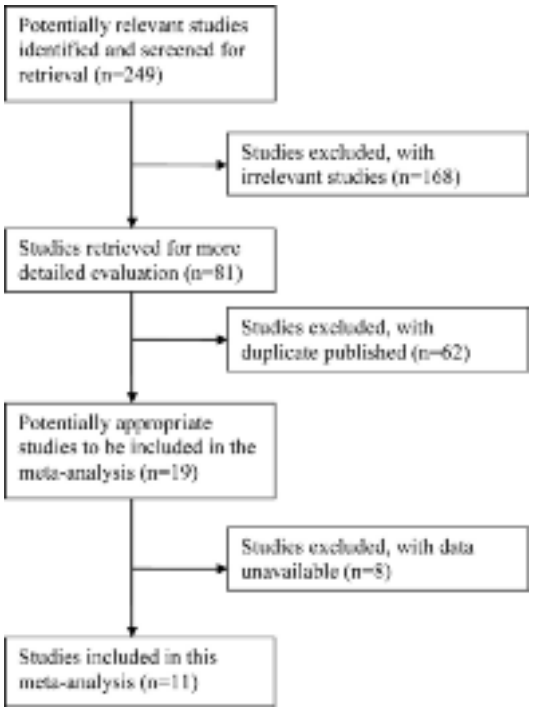

Figure 1. The flow diagram of selection process of the relevant studies.

vant studies and 62 duplicate studies were excluded by browsing titles and abstracts. After full-text review, 8 studies with unavailable data were excluded. Finally, 11 studies were included in this meta-analysis[11,22-31].

The Characteristics of the Included Studies

As shown in Table I, the included studies were published from 2005 to 2014, and contained 1 331 cases and 1 779 controls. No significant differences were found in BMI and age between cases and controls. The included studies were distributed in India, Egypt, Turkey, China, Denmark, Spain and Australia. All of the included studies are case-control studies except the work of Hansen et al[11] which is a prospective cohort study. Moreover, the score of all included studies is more than 4, indicating that these studies are high quality studies.

Meta-Analysis

Comparison of the hs-CRP contents between case group and control group was shown in Figure 2A. Significant heterogeneity (I^2 = 96.6%, p < 0.0001) were observed across studies. Thus, the random-effects model was used to combine the estimates. The result showed that hs-CRP concentrations in case group were significantly higher than those in control group (SMD = 2.14, 95% CI: 1.60-2.68). Sensitivity analysis showed that omitting each study had no effect on the pooled estimates, which indicated that the results of the analysis were stable (Supplemental Table I). Egger's test showed that no publication bias was observed (t =1.95, p = 0.08).

Comparison of the hs-CRP concentrations between case group and D1 group was shown in Figure 2B. As well, random-effects model was used to combine the estimates because of the significant heterogeneity among studies (I^2 = 97.9%, p < 0.0001). The results showed that the hs-CRP concentrations patients of case group were significantly higher than those of D1 group (SMD = 1.18, 95% CI: 0.41-1.95). Sensitive analysis indicated that the results were stable (Supplemental Table II) and no publication bias was observed (t = 2.07, p = 0.08).

Comparison of the hs-CRP concentrations between D3 group and D2 group showed significant heterogeneity (I^2 = 75.5%, p = 0.0026, Figure 2C). The hs-CRP concentration in D3 group was significantly higher than that in D2 group (SMD = 0.68, 95% CI: 0.34-1.03). Sensitivity analysis showed that the result was stable (Supplemental Table III), and Egger's test revealed that there was no publication bias (t = 1.12, p = 0.34).

Comparison of the hs-CRP levels between DN patients in case group and healthy people in control group was shown in Figure 2D. Random-effects model was chosen to combine the estimates because of the high heterogeneity among studies (I^2 = 94.7%, p < 0.0001). As a result, the hs-CRP levels in DN patients were much more than those in healthy people (SMD = 2.68, 95% CI: 1.82-3.53). Sensitivity analysis showed that the result was stable (Supplemental Table IV), and Egger's test revealed that there was no publication bias (t = 1.66, p = 0.15).

Comparison of the hs-CRP levels between D1 and D2 groups was shown in Figure 2E. Random-effects model was used because of high heterogeneity (I^2 = 96.3%, p < 0.0001). The results indicated that the hs-CRP levels in D1 group were significantly lower than those in D2 group (SMD = -1.51, 95% CI: -2.43–-0.59). Sensitive analysis showed the stable results (Supplemental Table V), and Egger's test revealed no publication bias (t = 2.77, p = 0.07).

Comparison of the hs-CRP concentrations between D1 and D3 groups was shown in Figure 2F. Random-effects model was used because of high heterogeneity (I^2 = 87.8%, p < 0.0001). The results indicated that the hs-CRP levels in D1 group were significantly lower than those in D3 group (SMD = -2.20, 95% CI: -2.79–-1.61). Sensitivity analysis did not reverse the results (Supplemental Table VI), and Egger's test revealed no publication bias (t = 0.42, p = 0.70).

Discussion

DN develops as a result of the progression of DM[32]. Chronic endothelial inflammation is a major risk factor in the occurring of diabetic complications and has a pathogenic role in the progression of DN[33]. CRP measurements have been used to be one of inflammation markers. The serum hs-CRP levels in DM patients are known to be higher than that in healthy populations[10,34]. In this study, we included 11 studies which containing 1 331 cases and 1 779 controls to evaluate the relationship between hs-CRP levels and DN. Our result showed that hs-CRP concentrations in DN patients were significantly higher than that in healthy populations and in DM patients without nephropathy. As well, hs-CRP

Table I. The characteristics of the included studies.

Author	Public year	Study year	Location	Study type	Measurement method of hs-CRP	The diagnosis of disease	Disease type	N	BMI (kg/m²)	Age (years)	Males/ Females	Mean duration of diabetes (years)	hs-CRP (mg/L)	Score (NOS)
Ahluwalia et al.	2009	NA	India	Case-control study	ELISA study	WHO criteria	T2-DN T2-DM	240 255	27.8±2.9 23.95±2.95	60.12±6.2 58.1±8.0	94/146 105/150	16.3±3.3 15.6±5.3	2.7±1.2 1.9±1.1	5
Avci et al.	2014	NA	Turkey	Case-control study	Commercial kit with nephelometric	Clinical examination	Healthy DM DN	30 30 30	NA NA NA	54.1±6.4 59.8±10.5 61.7±11.3	16/14 22/8 22/8	- 1-6 >1	0.9±0.4 4.0±0.9 3.3±1.0	6
Chen et al.	2013	2011.9-2012.9	China	Case-control study	A quantitative sandwich ELISA	WHO criteria	Healthy D1 D2 D3	86 112 93 56	26.5 ± 3.1 26.3 ± 3.7 26.2 ± 2.9 26.8 ± 3.7	55.2±12.4 54.9± 13.1 53.7± 12.5 62.6± 11.4	45/41 136/125	- 8.9±1.3 9.9±1.7 11.8±2.4	1.0±0.9 2.4±1.1 4.0±1.2 4.5±1.9	8
Choudhary and Ahlawat	2008	NA	India	Case-control study	An ultrasensitive solid-phase EIA	Clinical examination	Healthy D1 D2 D3	20 20 20 20	23.74 ± 3.42 23.69 ± 2.74	55.5 ± 7.57 54.08 ± 7.94	10/10 10/10 10/10 10/10	- 10.2 ±3.5	1.3 ± 0.4 2.7 ± 0.7 5.1 ± 2.2 5.9 ± 2.2	7
Eyileten et al.	2010 2006	2003–	Turkey	Case-control study	Commercial ELISA kits	Clinical examination	Healthy T2-DN	33 32	26.7± 2.4 26.8 ± 2.3	49 ± 5 51± 6	NA NA	NA NA	2.5 ±0.6 10.8 ±2.7	6
Hansen et al.	2010	NA	Denmark	Prospective cohort	An ultrasensitive kit	Clinical examination	D1 D2 D3	1010 236 318	24.6±3.2 25.2±3.3 25.7±3.9	34.0±11.5 36.7±12.1 40.0±9.5	492/518 150/86 184/134	18.1±11.1 24.9±10.6 28.6±7.8	1.7 (1.1-2.9) 2.0 (1.2-3.5) 2.43(1.6-4.4)	6
Navarro et al.	2006	NA	Spain	Case-control study	Ultrasensitive competitive immunoassay	Clinical examination	Healthy D1 D2 D3	32 25 60 75	NA NA NA NA	60±8 60±6 59±8 64±9	17/15 13/12 29/36 26/33	- 8.3±1.7 12.2±3.4 11.9±3.8	1.9(0.2-3.6) 2.0 (0.8-4.0) 5.1 (1.1-8.0) 5.8(3.0-9.3)	7
Nelson et al.	2005	NA	Australia	Case-control study	Nephelometry with available kits	Clinical examination	Healthy T1-DN	51 46	26.8±0.5 30.0±1.2	42.7±1.7 40.1±1.9	38/13 18/28	NA NA	1.6±0.3 4.1±0.6	7
Roopakala et al.	2012	NA	India	Case-control study	A latexenhanced immune-	Clinical examination	Healthy T2-DN	25 55	NA NA	NA 50-65	NA NA	NA NA	2.8 ± 2.6 4.6 ± 4.0	5
Shelbaya et al.	2012	NA	Egypt	Case-control study	nephelometer ELISA	Clinical history and Clinical examination	Healthy D1 D2 D3	10 10 15 15	NA NA NA NA	NA 25.25 ±3.896 25.25 ±3.896 25.8± 5.0	5/5 5/5 8/7 9/6	NA 9.45 ±1.9 10.5 ±1.9 15.2 ±2.0	1.3±0.4 2.5±0.9 4.1±0.8 5.9±2.1	6
Taslipinar et al.	2011	NA	Turkey	Case-control study	The BN ProSpec nephelometer	Clinical examination	T2-DN T2-DM	20 30	30.2 ± 2.0 29.7± 2.2	49.8 ± 4.5 50.6 ± 5.5	10/10 20/10	4.6±1.0 4.0±0.4	16.0(7.0 -24.0) 7.0(5.0-10.0)	6

hs-CRP: high-sensitivity C-reactive protein; DM: diabetes mellitus without nephropathy; DN: diabetic nephropathy; WHO: World Health Organization; ELISA: enzyme-linked immunosorbent assay; EIA: Enzyme immunometric assay; D1: normoalbuminuria; D2: microalbuminuria; D3: macroalbuminuria; T1- or T2-: type 1 or type 1; NA: not application.
Values are means ± standard deviation or median (range).
No significant differences were found in BMI and age between cases and controls.

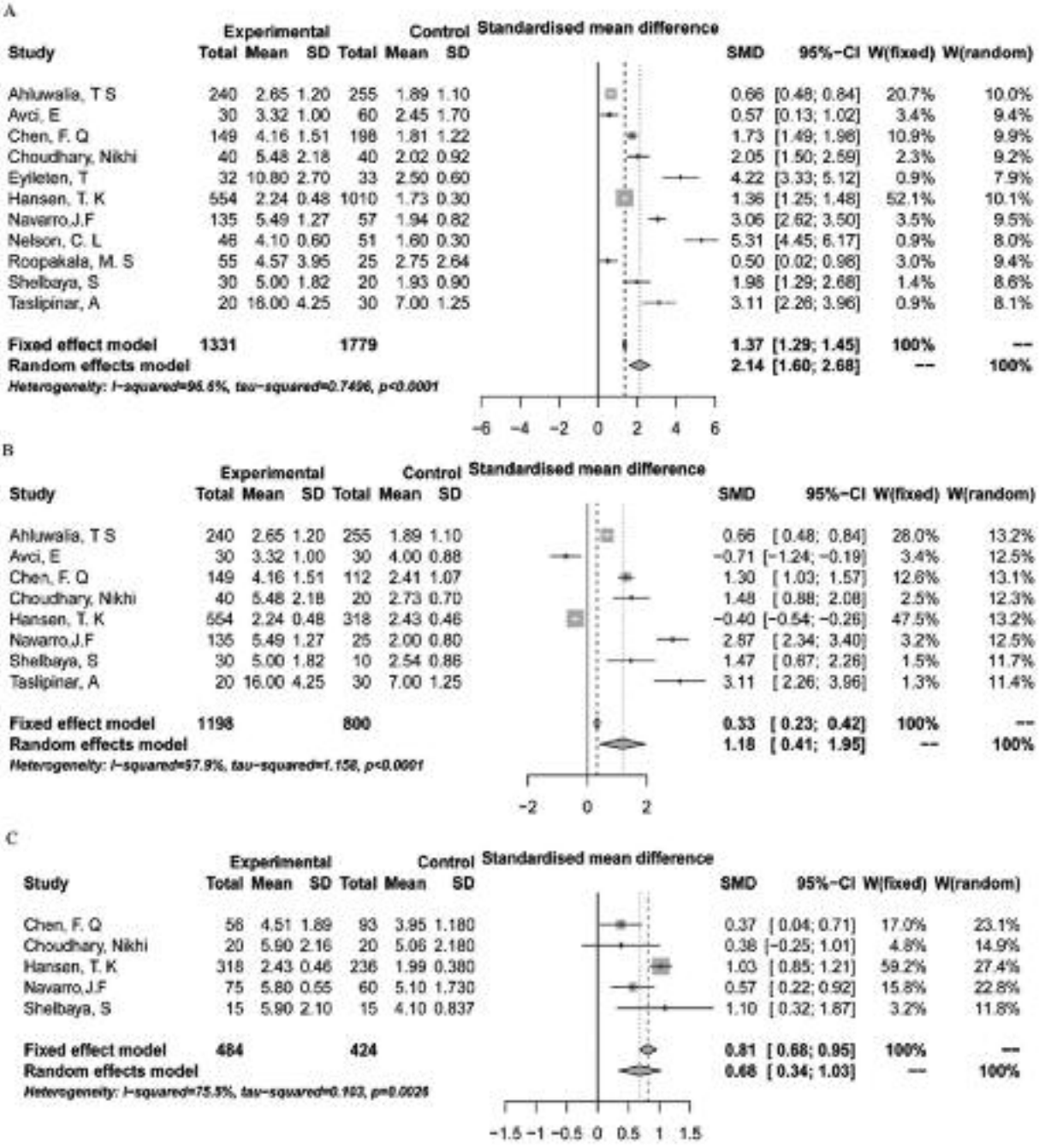

Figure 2. The forest plots of meta-analyses. D1, normoalbuminuria; D2, microalbuminuria; D3, macroalbuminuria; case group, D2 and D3 patients; control group, healthy people and D1 patients. ***A,*** Comparative analysis of the hs-CRP content between case group and control group. ***B,*** Comparative analysis of the hs-CRP concentration between case group and D1 group. ***C,*** Comparative analysis of the hs-CRP concentration between D3 group and D2 group.

Figure continued

concentration in macroalbuminuria group was significantly higher than that in microalbuminuria group and normoalbuminuria group. Our results were stable in sensitivity analysis and no publication bias was observed. These results suggest that hs-CRP concentration can be an indicator of DN in DM patients.

In our study, we found that the increased hs-CRP level may correlate with the severity of DN. The possible mechanisms may be that hs-CRP

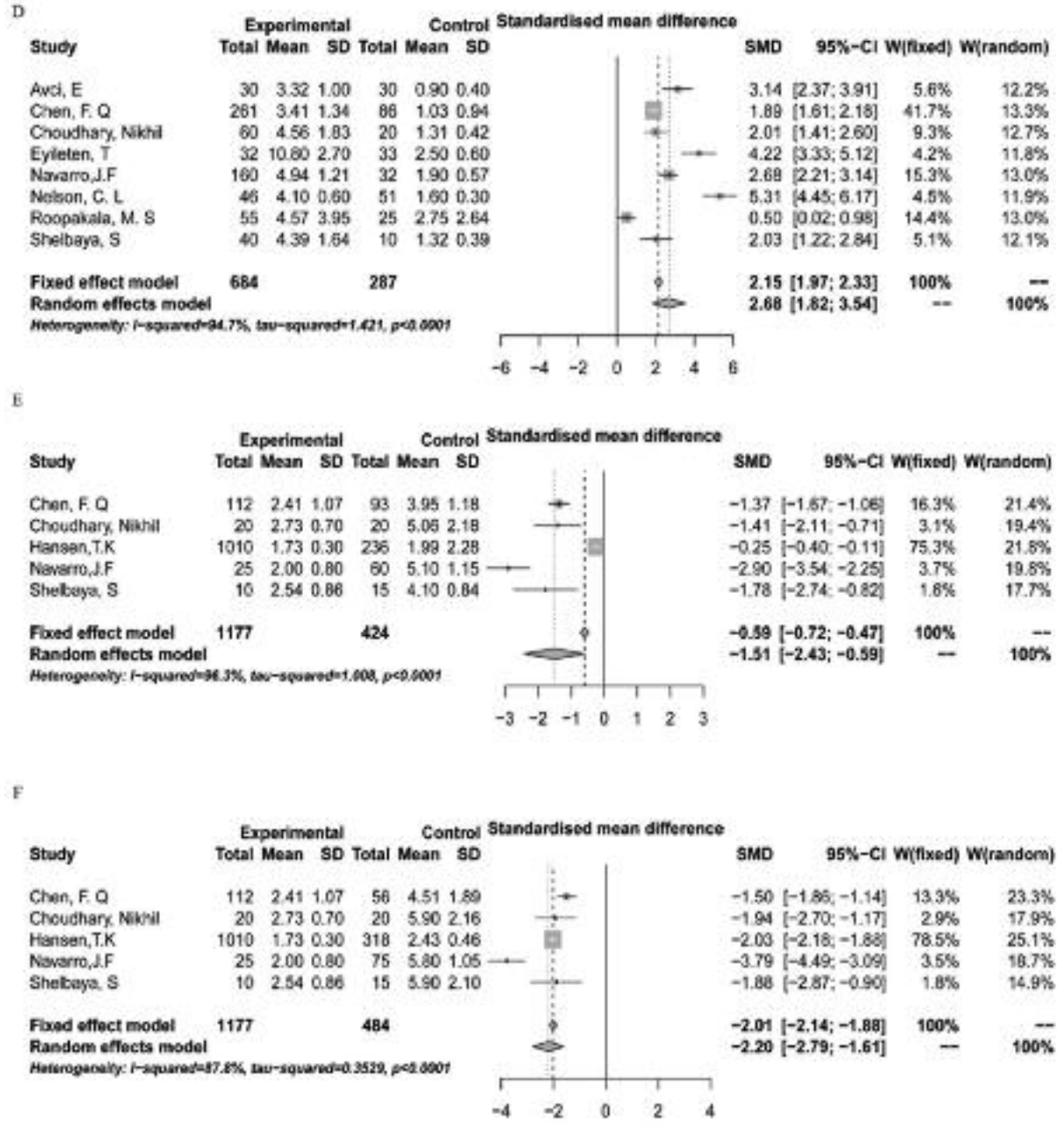

Figure 2. *(Continued).* ***D,*** Comparative analysis of hs-CRP content between DN patients and healthy people. ***E,*** Comparative analysis of hs-CRP content between D1 and D2 group. ***F,*** Comparative analysis of hs-CRP content between D1 and D3 group.

may associate with DN through involving in the renal inflammation. Pro-inflammatory cytokines have been demonstrated as important factors in the development of microvascular diabetic complications, such as nephropathy[35]. As we know, nuclear transcription factor-kappa B (NF-κB) is active in inflammation and immune responses in human cells. NF-κB signaling hs-CRP pathway is reported to be activated in DN and hs-CRP inducing a series of pro-inflammatory cytokines through the NF-κB-dependent mechanism[36,37]. In addition, hs-CRP itself was induced by high level of glucose, which then promoted renal inflammation. These results indicate that hs-CRP may serve as an inflammatory mediator of high glucose levels to promote the diabetic renal inflammation[12].

Suppl. Table I. Sensitivity analysis of the comparative analysis between diabetic nephropathy (DN) patients and the controls (healthy people or/and diabetes mellitus (DM) patients).

	SMD(95%CI)	p	tau²	I²
Omitting Ahluwalia, T S	2.3105 (1.7035-2.9174)	<0.001	0.8668	95.90%
Omitting Avci, E	2.3014 (1.7278-2.8751)	<0.001	0.7702	96.80%
Omitting Chen, F. Q	2.1965 (1.5750-2.8180)	<0.001	0.9139	96.80%
Omitting Choudhary, Nikhi	2.1474 (1.5745-2.7204)	<0.001	0.7706	96.90%
Omitting Eyileten, T	1.9479 (1.4181-2.4777)	<0.001	0.6589	96.50%
Omitting Hansen, T. K	2.2648 (1.5031-3.0264)	<0.001	1.4154	96.90%
Omitting Navarro,J.F	2.0235 (1.4958-2.5513)	<0.001	0.6394	96.20%
Omitting Nelson, C. L	1.8388 (1.3510-2.3266)	<0.001	0.5475	95.80%
Omitting Roopakala, M. S	2.3062 (1.7355-2.8769)	<0.001	0.7622	96.80%
Omitting Shelbaya, S	2.1525 (1.5828-2.7221)	<0.001	0.7654	96.90%
Omitting Taslipinar, A	2.0473 (1.4942-2.6004)	<0.001	0.7226	96.80%
Pooled estimate	2.1361 (1.5968-2.6754)	<0.001	0.7496	96.60%

Sensitivity analysis was performed by omitting each study to evaluate the stability of the results. The pooled estimate was not effected by omitting any of these study, indicating a stable result.

Suppl. Table II. Sensitivity analysis of the comparative analysis between DN patients and the DM patients.

	SMD(95%CI)	p	tau²	I²
Omitting Ahluwalia, T S	1.2788 (0.2204-2.3371)	0.0179	1.9551	98.10%
Omitting Avci, E	1.4564 (0.6258-2.2871)	0.0006	1.182	98.10%
Omitting Chen, F. Q	1.1687 (0.3160-2.0214)	0.0072	1.2416	97.80%
Omitting Choudhary, Nikhi	1.1423 (0.3178-1.9669)	0.0066	1.1671	98.10%
Omitting Hansen, T. K	1.4189 (0.6819-2.1559)	0.0002	0.9052	95.50%
Omitting Navarro,J.F	0.9315 (0.2015-1.6614)	0.0124	0.8971	97.50%
Omitting Shelbaya, S	1.1467 (0.3255-1.9679)	0.0062	1.1659	98.20%
Omitting Taslipinar, A	0.9325 (0.1559-1.7092)	0.0186	1.0394	98.00%
Pooled estimate	1.1838 (0.4145-1.9531)	0.0026	1.1577	97.90%

Sensitivity analysis was performed by omitting each study to evaluate the stability of the results. The pooled estimate was not effected by omitting any of these study, indicating a stable result.

Suppl. Table III. Sensitivity analysis of the comparative analysis between macroalbuminuria (D3) group and microalbuminuria (D2) group in DN patients.

	SMD(95%CI)	p	tau²	I²
Omitting Chen, F. Q	0.7840 (0.4412-1.1268)	< 0.0001	0.0706	64.00%
Omitting Choudhary, Nikhi	0.7371 (0.3601-1.1141)	0.0001	0.1071	79.20%
Omitting Hansen, T. K	0.5082 (0.2871-0.7293)	< 0.0001	0.0018	3.20%
Omitting Navarro,J.F	0.7145 (0.2768-1.1522)	0.0014	0.141	78.70%
Omitting Shelbaya, S	0.6253 (0.2438-1.0068)	0.0013	0.1156	81.10%
Pooled estimate	0.6836 (0.3410-1.0262)	< 0.0001	0.103	75.50%

Sensitivity analysis was performed by omitting each study to evaluate the stability of the results. The pooled estimate was not effected by omitting any of these study, indicating a stable result.

Confounding factors, such as different types of DM and treatments, may affect the hs-CRP levels. Previous studies have proved that the circulating hs-CRP levels may predict the development of albuminuria in type 1 DM and type 2 DM[11,38]. However, the relationship between hs-CRP levels and glycaemic control is complex. Schaumberg et al[39] found that hs-CRP level may increase with the degree of weight gain during intensified treatment. Other confounders such as

Suppl. Table IV. Sensitivity analysis of the comparative analysis between DN patients and healthy people in control group.

	SMD(95%CI)	p	tau²	I²
Omitting Avci, E	2.6181 (1.6817-3.5544)	< 0.0001	1.4863	95.20%
Omitting Chen, F. Q	2.814 (1.6828-3.9452)	< 0.0001	2.1999	95.30%
Omitting Choudhary, Nikhil	2.7841 (1.7948-3.7735)	< 0.0001	1.6633	95.50%
Omitting Eyileten, T	2.4693 (1.6005-3.3380)	< 0.0001	1.2711	94.60%
Omitting Navarro,J.F	2.6885 (1.6737-3.7034)	< 0.0001	1.7506	95.30%
Omitting Nelson, C. L	2.3081 (1.5728-3.0434)	< 0.0001	0.8805	92.30%
Omitting Roopakala, M. S	2.9933 (2.1899-3.7968)	< 0.0001	1.0522	92.50%
Omitting Shelbaya, S	2.773 (1.8172-3.7287)	< 0.0001	1.555	95.50%
Pooled estimate	2.6796 (1.8204-3.5388)	< 0.0001	1.4209	94.70%

Sensitivity analysis was performed by omitting each study to evaluate the stability of the results. The pooled estimate was not effected by omitting any of these study, indicating a stable result.

Suppl. Table V. Sensitivity analysis of the comparative analysis between D1 and D2 groups.

	SMD(95%CI)	p	tau²	I²
Omitting Chen, F. Q	-1.5637 (-2.9473–-0.1801)	0.0268	1.8761	96.10%
Omitting Choudhary, Nikhil	-1.535 (-2.6025–-0.4676)	0.0048	1.0984	97.00%
Omitting Hansen,T.K	-1.8497 (-2.5950–-1.1045)	< 0.0001	0.4628	83.40%
Omitting Navarro,J.F	-1.1459 (-1.9619–-0.3298)	0.0059	0.6056	94.60%
Omitting Shelbaya, S	-1.4506 (-2.4736–-0.4276)	0.0055	1.0258	97.00%
Pooled estimate	-1.5082 (-2.4288–-0.5875)	0.0013	1.008	96.30%

Sensitivity analysis was performed by omitting each study to evaluate the stability of the results. The pooled estimate was not effected by omitting any of these study, indicating a stable result.

Suppl. Table VI. Sensitivity analysis of the comparative analysis between D1 and D3 groups.

	SMD(95%CI)	p	tau²	I²
Omitting Chen, F. Q	-2.4129 (-3.2459–-1.5799)	< 0.0001	0.5991	87.30%
Omitting Choudhary, Nikhil	-2.2608 (-2.9594–-1.5621)	< 0.0001	0.4198	90.80%
Omitting Hansen,T.K	-2.2712 (-3.3545–-1.1879)	< 0.0001	1.0856	90.80%
Omitting Navarro,J.F	-1.8335 (-2.1716–-1.4954)	< 0.0001	0.0606	58.10%
Omitting Shelbaya, S	-2.257 (-2.9273–-1.5868)	< 0.0001	0.3959	90.80%
Pooled estimate	-2.1965 (-2.7850–-1.6080)	< 0.0001	0.3529	87.80%

Sensitivity analysis was performed by omitting each study to evaluate the stability of the results. The pooled estimate was not effected by omitting any of these study, indicating a stable result.

patients' age, gender and measurements of hs-CRP may also be associated with the hs-CRP level in DM and DN patients. However, due to the limited data, this study did not perform the subgroup studies by these factors. Thus, these relationships need further verify by more studies.

In sensitivity analysis, after omitting each study, our results were stable and not reversed. However, the heterogeneity remains significant. We suggest that several explanations can interpret this. First, we didn't separate the type 1 DM from type 2 DM. These two types of DM have different methods of definition and diagnosis. For example, type 1 DM is dependent on insulin, but type 2 DM is not[40]. Thus, the sensitivity to hs-CRP concentration in the two types of DM may be also different. Second, we didn't adjust the confounders (age, gender, ethnicity, etc.) which might affect the hs-CRP levels. Kang et al[10] suggests that there may be ethnical differences in the serum hs-CRP level. Some other factors, including smoke, hormone replacement therapy and various medications, have been reported to be associated with hs-CRP level[41,42].

Nevertheless, it is worth noting that in a comparative analysis between D3 and D2 patients, the heterogeneity was no longer significant after omitting the study of Hansen et al[11]. This may be due to the prospective cohort design of this study. In this meta-analysis, all of other included studies are case-control studies.

Some advantages should be considered in this meta-analysis. Firstly, no publication bias was observed in our results. Secondly, the quality of the included studies was relatively high. Thirdly, our meta-analysis is systematic and comprehensive. Not only hs-CRP levels of DN patients diagnosed according to urinary protein levels were meta-analyzed, but the hs-CRP levels of D3 and D2 patients diagnosed according to UAE were also meta-analyzed.

There are also several criticisms in this meta-analysis. Firstly, significant heterogeneity remains in our results. Secondly, we didn't perform subgroup analysis due to the lack of included studies. Despite these, this study still has guiding significance for deciding that whether hs-CRP can be an indicator of DN in DM patients.

Conclusions

The hs-CRP level was significantly correlated with the development of DN in DM patients. Therefore, we suggest that hs-CRP concentration can be an indicator of DN in DM patients. Our study has a potential value in clinical applications. However, further studies will be needed to explore the function of hs-CRP in the progress of DN. Whatever, hs-CRP can't be the only indicator of DN, and it must be combined with other reliable methods to diagnose DN.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Shiraishi FG, Stringuetta Belik F, Oliveira E Silva VR, Martin LC, Hueb JC, Gonçalves Rde S, Caramori JC, Barreti P, Franco RJ. Inflammation, diabetes, and chronic kidney disease: role of aerobic capacity. Exp Diabetes Res 2012; 2012: 750286.
2) Giunti S, Barit D, Cooper M. Diabetic nephropathy: from mechanisms to rational therapies. Minerva Med 2006; 97: 241-262.
3) Macrae J, Nicastri A, Chen C. Diabetic nephropathy without hyperglycemia. J Diabet Complications 1990; 4: 126-131.
4) Elmarakby AA Sullivan JC. Relationship between oxidative stress and inflammatory cytokines in diabetic nephropathy. Cardiovasc Ther 2012; 30: 49-59.
5) Romero-Aroca P, Mendez-Marin I, Baget-Bernaldiz M, Fernandez-Ballart J, Santos-Blanco E. Review of the relationship between renal and retinal microangiopathy in diabetes mellitus patients. Curr Diabetes Rev 2010; 6: 88-101.
6) Nguyen D, Ping F, Mu W, Hill P, Atkins RC, Chadban SJ. Macrophage accumulation in human progressive diabetic nephropathy. Nephrology (Carlton) 2006; 11: 226-231.
7) Yamamoto Y, Kato I, Doi T, Yonekura H, Ohashi S, Takeuchi M, Watanabe T, Yamagishi S, Sakurai S, Takasawa S, Okamoto H, Yamamoto H. Development and prevention of advanced diabetic nephropathy in RAGE-overexpressing mice. J Clin Invest 2001; 108: 261-268.
8) Saraheimo M, Teppo A-M, Forsblom C, Fagerudd J, Groop PH. Diabetic nephropathy is associated with low-grade inflammation in type 1 diabetic patients. Diabetologia 2003; 46: 1402-1407.
9) Navarro-González JF Mora-Fernández C. The role of inflammatory cytokines in diabetic nephropathy. J Am Soc Nephrol 2008; 19: 433-442.
10) Kang ES, Kim HJ, Ahn CW, Park CW, Cha BS, Lim SK, Kim KR, Lee HC. Relationship of serum high sensitivity C-reactive protein to metabolic syndrome and microvascular complications in type 2 diabetes. Diabetes Res Clin Pract 2005; 69: 151-159.
11) Hansen TK, Forsblom C, Saraheimo M, Thorn L, Waden J, Hoyem P, Ostergaard J, Flyvbjerg A, Groop PH, FinnDiane Study G. Association between mannose-binding lectin, high-sensitivity C-reactive protein and the progression of diabetic nephropathy in type 1 diabetes. Diabetologia 2010; 53: 1517-1524.
12) Ninomiya T, Perkovic V, de Galan BE, Zoungas S, Pillai A, Jardine M, Patel A, Cass A, Neal B, Poulter N. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol 2009; 20: 1813-1821.
13) Stehouwer CD, Gall MA, Twisk JW, Knudsen E, Emeis JJ, Parving HH. Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes progressive, interrelated, and independently associated with risk of death. Diabetes 2002; 51: 1157-1165.
14) Jenkins AJ, Rothen M, Klein RL, Moller K, Eldridge L, Zheng D, Durazo-Arvizu R, McGee D, Lackland D, Thorpe SR, Garvey WT, Lyons TJ; DCCT/EDIC Research Group. Cross-sectional associations of C-reactive protein with vascular risk factors and vascular complications in the DCCT/EDIC cohort. J Diabet Complications 2008; 22: 153-163.

15) Definition W. diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Geneva: World Health Organization, 1999.

16) Wells G, Shea B, O'connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013.

17) Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry 2006; 63: 530-538.

18) Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005; 5: 13.

19) Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997; 127: 820-826.

20) Feng RN, Zhao C, Sun CH, Li Y. Meta-analysis of TNF 308 G/A polymorphism and type 2 diabetes mellitus. PLoS One 2011; 6: e18480.

21) Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Br Med J 1997; 315: 629-634.

22) Ahluwalia TS, Khullar M, Ahuja M, Kohli HS, Bhansali A, Mohan V, Venkatesan R, Rai TS, Sud K, Singal PK. Common variants of inflammatory cytokine genes are associated with risk of nephropathy in type 2 diabetes among Asian Indians. PLoS One 2009; 4: e5168.

23) Shelbaya S, Amer H, Seddik S, Allah A, Sabry I, Mohamed T, El Mosely M. Study of the role of interleukin-6 and highly sensitive C-reactive protein in diabetic nephropathy in type 1 diabetic patients. Eur Rev Med Pharmacol Sci 2012; 16: 176-182.

24) Choudhary N Ahlawat RS. Interleukin-6 and C-reactive protein in pathogenesis of diabetic nephropathy. Iran J Kidney Dis 2008; 2: 73.

25) Roopakala MS, Pawan HR, Krishnamurthy U, Wilma Delphine Silvia CR, Eshwarappa M, Prasanna Kumar KM. Evaluation of high sensitivity C-reactive protein and glycated hemoglobin levels in diabetic nephropathy. Saudi J Kidney Dis Transpl 2012; 23: 286-289.

26) Navarro JF, Mora C, Muros M, Garcia J. Urinary tumour necrosis factor-alpha excretion independently correlates with clinical markers of glomerular and tubulointerstitial injury in type 2 diabetic patients. Nephrol Dial Transplant 2006; 21: 3428-3434.

27) Nelson CL, Karschimkus CS, Dragicevic G, Packham DK, Wilson AM, O'Neal D, Becker GJ, Best JD, Jenkins AJ. Systemic and vascular inflammation is elevated in early IgA and type 1 diabetic nephropathies and relates to vascular disease risk factors and renal function. Nephrol Dial Transplant 2005; 20: 2420-2426.

28) Chen FQ, Wang J, Liu XB, Ma XY, Zhang XB, Huang T, Ma DW, Wang QY. Levels of inflammatory cytokines in type 2 diabetes patients with different urinary albumin excretion rates and their correlation with clinical variables. J Diabetes Res 2013; 2013: 138969.

29) Eyileten T, Sonmez A, Saglam M, Cakir E, Caglar K, Oguz Y, Vural A, Yenicesu M, Yilmaz MI. Effect of renin-angiotensin-aldosterone system (RAAS) blockade on visfatin levels in diabetic nephropathy. Nephrology (Carlton) 2010; 15: 225-229.

30) Avci E, Cakir E, Cevher SC, Yaman H, Agilli M, Bilgi C. Determination of oxidative stress and cellular inflammation in patients with diabetic nephropathy and non-diabetic nephropathy being administered hemodialysis treatment due to chronic renal failure. Ren Fail 2014; 36: 767-773.

31) Taslipinar A, Yaman H, Yilmaz MI, Demirbas S, Saglam M, Taslipinar MY, Agilli M, Kurt YG, Sonmez A, Azal O, Bolu E, Yenicesu M, Kutlu M. The relationship between inflammation, endothelial dysfunction and proteinuria in patients with diabetic nephropathy. Scand J Clin Lab Invest 2011; 71: 606-612.

32) Mastej K Adamiec R. Neutrophil surface expression of CD11b and CD62L in diabetic microangiopathy. Acta Diabetol 2008; 45: 183-190.

33) Schram MT, Chaturvedi N, Schalkwijk C, Giorgino F, Ebeling P, Fuller JH, Stehouwer CD. Vascular risk factors and markers of endothelial function as determinants of inflammatory markers in type 1 diabetes the EURODIAB Prospective complications study. Diabetes Care 2003; 26: 2165-2173.

34) Schalkwijk C, Poland D, Van Dijk W, Kok A, Emeis J, Dräger A, Doni A, Van Hinsbergh V, Stehouwer C. Plasma concentration of C-reactive protein is increased in type I diabetic patients without clinical macroangiopathy and correlates with markers of endothelial dysfunction: evidence for chronic inflammation. Diabetologia 1999; 42: 351-357.

35) Rivero A, Mora C, Muros M, Garcia J, Herrera H, Navarro-Gonzalez J. Pathogenic perspectives for the role of inflammation in diabetic nephropathy. Clin Sci 2009; 116: 479-492.

36) Liang YJ, Shyu KG, Wang BW, Lai LP. C-reactive protein activates the nuclear factor-κB pathway and induces vascular cell adhesion molecule-1 expression through CD32 in human umbilical vein endothelial cells and aortic endothelial cells. J Mol Cell Cardiol 2006; 40: 412-420.

37) Hanriot D, Bello G, Ropars A, Seguin-Devaux C, Poitevin G, Grosjean S, Latger-Cannard V, Devaux Y, Zannad F, Regnault V. C-reactive protein induces pro-and anti-inflammatory effects, including activation of the liver X receptor α, on human monocytes. Thromb Haemost 2008; 99: 558-569.

38) Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR. Risk factors for renal dysfunction in type 2 diabetes UK Prospective Diabetes Study 74. Diabetes 2006; 55: 1832-1839.

39) Schaumberg DA, Glynn RJ, Jenkins AJ, Lyons TJ, Rifai N, Manson JE, Ridker PM, Nathan DM. Effect of intensive glycemic control on levels of markers of inflammation in type 1 diabetes mellitus in the diabetes control and complications trial. Circulation 2005; 111: 2446-2453.

40) DeFronzo R, Simonson D, Ferrannini E. Hepatic and peripheral insulin resistance: a common feature of type 2 (non-insulin-dependent) and type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1982; 23: 313-319.

41) Sesmilo G, Biller BM, Llevadot J, Hayden D, Hanson G, Rifai N, Klibanski A. Effects of growth hormone administration on inflammatory and other cardiovascular risk markers in men with growth hormone deficiencyA randomized, controlled clinical trial. Ann Intern Med 2000; 133: 111-122.

42) Takeda T, Hoshida S, Nishino M, Tanouchi J, Otsu K, Hori M. Relationship between effects of statins, aspirin and angiotensin II modulators on high-sensitive C-reactive protein levels. Atherosclerosis 2003; 169: 155-158.