Effect modification of the association between plasma glucose and diabetic kidney disease by hypersensitive C-reactive protein in patients with diabetes mellitus

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Abstract

Background

Prior studies showed activation inflammatory biomarkers, e.g., hypersensitive C-reactive protein (hs-CRP), were associated with diabetic kidney disease (DKD) susceptibility; inflammatory gene expression profiles in the diabetic mice might be critical features determining susceptibility of DKD. The aim of this investigation was to explore effect modification of hs-CRP on the association between hyperglycemia and DKD in type 2 diabetes mellitus (T2DM).

Methods

We consecutively collected 812 patients with T2DM in a cross-sectional study. Multivariable logistic regression models was used to estimate odd ratios and 95% confidence intervals of plasma glucose for DKD, with adjustment for the potential confounders. Interaction between plasma glucose and hs-CRP was tested by likelihood ratio tests.

Results

The median age of the participants was 54 years (interquartile: 46–63), 58% were male and 26.2% experienced DKD. There seemed to be a nonlinear effect modification on the association between fast plasma glucose (FPG) and DKD by hs-CRP (*P* for linear interaction = 0.052). For participants with hs-CRP value lower than 3 mg/L, there no existed an interaction effect ($P_{interaction}$ = 0.3). In contrast, a significant interaction effect was noted among individuals with hs-CRP value higher than 3 mg/L ($P_{interaction}$ = 0.003).The marginal effect, i.e., log (odds), of FPG on DKD linearly rose with hs-CRP level increasing among these subjects. In terms of effect modification on the relationship between 2-hour plasma glucose (2 h-PG) and DKD by hs-CRP, it appeared to be linear. The higher the hs-CRP value, the stronger the strength of their associations. Johnson-Neyman plot showed when hs-CRP level was lower than 2.4 mg/L the marginal effect of 2 h-PG on DKD was nonsignificant (boundary of 95% confidence interval included zero) and it became significant as hs-CRP level higher than 2.4 mg/L (boundary of 95% confidence interval excluded zero) .

Conclusions

The associations of 2 h-PG as well as FPG with DKD were modified by hs-CRP in individuals with T2DM. It appeared when hs-CRP level was higher than 3 mg/L in these patients, the association strength of both FPG and 2 h-PG with DKD linearly rose with hs-CRP level increasing. A prospective study is warranted to confirm this finding.

Background

The prevalence and incidence of diabetes mellitus (DM) has increased significantly worldwide. Globally, more than 400 million people currently have DM and about 600 million may be affected by 2035[1]. Approximately 20% of patients with diabetes are complicated with diabetic kidney disease (DKD)[2], which is associated with increased risks of morbidity and mortality and is the leading cause of end-stage renal disease (ESRD)[3, 4].

Understanding risk factors for DKD development can help with early prevention and intervention for DKD. Of the established risk factors, hyperglycemic burden has been proved to be the most important for DKD. However, not everyone with poor glycemic controls develops renal disease[5]. In clinical practice, hypoglycemic treatment is the essential step for patients with DM. Nevertheless, hypoglycemia is often present in the process of hypoglycemic treatment and is associated with both macrovascular and microvascular endpoints in type 2 diabetes[6]. Given these conditions, identifying individuals whose hyperglycemic exposure significantly correlates with DKD is of importance in terms of accurate prevention and control DKD during glycemic control in patients with type 2 diabetes mellitus (T2DM).

In one animal experiment, there existed a marked triggering of immune and inflammatory gene expression profiles in the diabetic mice that developed DKD; by contrast, these pathways were coordinately down-regulated in the counterparts protected from kidney injury, suggesting inflammation and immune responsiveness may be critical features determining susceptibility of DKD[7, 8]. Several clinical studies also showed activation inflammatory biomarkers, i.e. hypersensitive C-reactive protein (hs-CRP) and TNF-α, were associated with DKD susceptibility[9, 10]. Therefore, we hypothesized hs-CRP, an inflammatory marker, might modify the association of hyperglycemia with DKD. We investigated the effect modification of hs-CRP on the association between hyperglycemia and DKD in T2DM in this study.

Methods

Study design and Participants

We consecutively enrolled 812 T2DM hospitalized in Beijing Chaoyang Hospital affiliated to Capital University of Medical Sciences from September 2017 to March 2018 in the cross-sectional study. The inclusion criteria were age > 18 years and diagnosis of T2DM. The study was approved by ethics committee of Chaoyang Hospital and all and all participants provided written informed consent.

Population characteristics

The following characteristics of the study population were collected: age, gender, height, weight, body mass index (BMI; calculated by dividing the weight in kilograms by the height in meters squared), diabetes diagnosis (using the American Diabetes Association criteria) and diabetes duration, smoking status (classified as current smokers vs nonsmokers or previous smokers), blood pressure and

hypertension diagnosis (based on 2018 ESC/ESH Guidelines for the management of arterial hypertension[11]).

Laboratory test

Routine blood laboratory tests were centrally carried out after a 12-hour fasting time. The tests mainly included plasma glucose, glycosylated hemoglobin, blood lipid, serum uric acid, serum creatinine, and serum hypertensive C-reactive protein (hs-CRP). The 2-h plasma glucose (2-h PG) value was also measured from a 75-g glucose tolerance test (OGTT). The serum hs-CRP level was determined by using immunochemical assay, i.e. immunoprecipitation, with hs-CRP ≥ 3 mg/L as a cut-off point for identifying high-risk population[12]. Other blood biochemical indexes, such as plasma glucose, lipid profiles, and serum creatinine, were measured by utilizing Siemens automatic biochemical analyzer ADVIA2400. The estimated glomerular filtration rate (eGFR) was calculated using the modified Modification of Diet in Renal Disease formula[13]. We accurately recorded 8-hour urine volume of these DM patients (from 10:00 p.m. to 6:00 a.m. next day). The concentration of urinary albumin was determined by immunoturbidimetric method (Beckman dxc800, USA) and the urinary albumin excretion rate (UAER) was calculated using urine volume and concentration of urinary albumin. DKD was defined as albuminuria (urinary albumin excretion rate [UAER] > 20 ug/min)[14] and/or eGFR values < 60/mL/min/1.73 m^2[15].

Statistical analysis

All continuous variables were evaluated for normality using Kolmogorov-Smirnoff tests as well as quantile-quantile plot and were reported as the mean SD or median (25th to 75th quantile) as appropriate. Comparison of the continuous variables across two groups were performed using the Student t test for normally distributed variables and Mann-Whitney-Wilcoxon test for non-normally distributed variables. Categorical variables were described as percentage and were compared using X^2 test. We used multivariable logistic regression model to estimate odd ratios (ORs) and corresponding 95% confidence intervals (CIs) of fasting plasma glucose (FPG) as well as 2-h PG for DKD, with adjustment for the following potential confounders: age, sex, serum cholesterol, triglyceride, hypersensitive C-reactive protein (hs-CRP), and uric acid, systolic blood pressure, body mass index (BMI), duration of diabetes and hypertension. Interaction between blood glycose and hs-CRP was tested by likelihood ratio tests. We used an estimation approach, i.e. a binning estimator, to test the linear interaction effect (LIE) assumption. A kernel smoothing estimation strategy was also applied to assess the marginal effect, i.e. log (odds), of FPG or 2-h PG on DKD across the range of the moderator, i.e. hs-CRP[16]. As the LIE assumption regarding the marginal effect of 2-h PG on DKD across the range of hs-CRP was valid, we also used Johnson-Neyman technique to estimate the Johnson-Neyman interval, which tells you the range of values of the moderator in which the slope of the predictor is significant vs. nonsignificant at a specified alpha level[17]. Statistical tests were performed using a two-sided a level of 0.05. All statistical analysis was performed using R 4.0.0 software and “interflex” as well as “interactions” package was used.

Results

Population characteristics

The clinical characteristics of the study population are presented in Table 1. Among the 812 T2DM participants, the mean age was 54 years and 58% (474) were male; 26.2% (213) experienced DKD, which included 180 cases with albuminuria and 62 cases with eGFR values < 60/mL/min/1.73 m^2. Those with DKD had a higher prevalence of hypertension (71% vs 51%) and higher values of FPG (8.46 vs 7.59), 2 h-PG (18.8 vs 18.0), SBP (133 vs 127), hs-CRP (2.2 vs 1.5) and albuminuria (45.8 vs 9.4). The eGFR of DKD patients was lower than non-DKD counterparts (97.6 vs 114.0).

Table 1
Baseline clinical characteristics of the study participants

Variables	Total (n = 812)	Non-DKD (n = 599)	DKD (n = 213)	*P*
Age, Mean ± SD	54 ± 13	53 ± 12	58 ± 13	< 0.001
Gender, n (%)				0.766
Male	474 (58)	352 (59)	122 (57)	
Femal	338 (42)	247 (41)	91 (43)	
Smoke, n (%)				0.523
No	471 (58)	343 (57)	128 (60)	
Yes	341 (42)	256 (43)	85 (40)	
HBP, n (%)				< 0.001
No	355 (44)	293 (49)	62 (29)	
Yes	457 (56)	306 (51)	151 (71)	
2 h-PG, Median (IQR)	18.2 (15.4, 20.8)	18.0 (15.4, 20.6)	18.8 (15.9, 21.3)	0.015
FPG, Median (IQR)	7.8 (6.5, 9.5)	7.6 (6.4, 9.2)	8.5 (6.8, 10.5)	< 0.001
HbA1c, Median (IQR)	9.5 (7.7, 11.4)	9.6 (7.7, 11.4)	9.5 (7.8, 11.5)	0.705
hs-CRP, Median (IQR)	1.7 (0.7, 3.7)	1.5 (0.6, 3.4)	2.2 (0.9, 5)	< 0.001
SBP, Mean ± SD	128 ± 17	127 ± 15.5	133 ± 19	< 0.001
DBP, Mean ± SD	79 ± 10	78 ± 9	79 ± 11	0.211
BMI, Mean ± SD	25.9 ± 3.6	25.7 ± 3.5	26.3 ± 3.8	0.063
UA, Median (IQR)	309.7 (256.9, 366.2)	301 (255, 355.5)	329 (273, 386)	< 0.001
Cr, Median (IQR)	64 (53.6, 74.6)	62.1 (52.5, 72.5)	69.8 (59.6, 85)	< 0.001

HBP: hypertension; 2 h-PG: 2-hour plasma glucose measured from a 75-g glucose tolerance test (OGTT); FPG: fasting plasma glucose; HbA1c: glycosylated hemoglobin; hs-CRP: serum hypertensive C-reactive protein; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; UA: serum uric acid; Cr: serum creatinine; Ccr: serum creatinine clearance rate; ABUA: albuminuria; HDLC: high-density lipoprotein cholesterol; DM: diabetes mellitus; LP(a): lipoprotein A; TC: total cholesterol; LDLC: low density cholesterol; TG: triglyceride.

Variables	Total (n = 812)	Non-DKD (n = 599)	DKD (n = 213)	*P*
Ccr, Median (IQR)	110.4 (85.8, 136.7)	114.1 (91.3, 137.9)	97.6 (58.2, 131.6)	< 0.001
ABUA, Median (IQR)	10.6 (7.8, 17.7)	9.38 (6.8, 12.5)	45.8 (22.5, 187.5)	< 0.001
HDLC, Median (IQR)	1.2 (1.0, 1.5)	1.23 (1.0, 1.5)	1.14 (0.9, 1.4)	0.002
DM duration, Median (IQR)	4 (0.5, 10)	3 (0.5, 9)	6 (1, 11)	< 0.001
LP(a), Median (IQR)	20.3 (13.7, 30.6)	20.2 (13.5, 29.9)	21.5 (14.4, 32.2)	0.135
TC, Median (IQR)	4.9 (4.4, 5.7)	4.9 (4.4, 5.7)	5.0 (4.3, 5.9)	0.44
LDLC, Mean ± SD	2.9 ± 1.0	2.9 ± 1.0	3.1 ± 1.0	0.233
TG, Median (IQR)	1.5 (1.0, 2.3)	1.4 (1, 2.2)	1.6 (1.1, 2.6)	< 0.001

HBP: hypertension; 2 h-PG: 2-hour plasma glucose measured from a 75-g glucose tolerance test (OGTT); FPG: fasting plasma glucose; HbA1c: glycosylated hemoglobin; hs-CRP: serum hypertensive C-reactive protein; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; UA: serum uric acid; Cr: serum creatinine; Ccr: serum creatinine clearance rate; ABUA: albuminuria; HDLC: high-density lipoprotein cholesterol; DM: diabetes mellitus; LP(a): lipoprotein A; TC: total cholesterol; LDLC: low density cholesterol; TG: triglyceride.

Effect modification of the association between FPG and DKD by hs-CRP

On the multivariable logistic regression model, we noted that both higher values of FPG and hs-CRP were significantly associated with a higher probability of DKD. The ORs (per 1 mmol/L FPG) and 95% CIs were 1.104 (1.038, 1.175) and 1.08 (1.026, 1.137), respectively. Moreover, the interactive terms of above two variables was statistically significant ($OR_{interaction}$ = 1.028; 95% CI: 1.006, 1.05; $P_{interaction}$ = 0.012), suggesting the association between FPG and DKD was significantly modified by hs-CRP.

Figure 1A shows the binning estimates of marginal effect, i.e. log (odds), of FPG across three hs-CRP groups, i.e. L: <1.7 mg/L, M:1.8–7.1 mg/L, H: >7.1 mg/L, on DKD. It appeared to be disagreement with the estimates from the linear interaction model, which indicated the LIE assumption was invalid (P_{wald} = 0.052). In Fig. 1B, a kernel smoothing estimation also reveals the marginal effects of FPG on DKD among two hs-CRP groups, i.e. lower and higher 3 mg/L, were different. For participants with hs-CRP lower than 3 mg/L, there no existed an interaction effect among FPG and hs-CRP for DKD ($P_{interaction}$ = 0.3) and the OR of FPG for DKD was 1.07 (95% CI: 0.99–1.16; P = 0.073). In contrast, a significant interaction effect among FPG and hs-CRP was noted when hs-CRP was higher than 3 mg/L ($P_{interaction}$ = 0.003). In this group, the OR of FPG for DKD was 1.18 (95% CI: 1.05–1.33; P = 0.006) and the marginal effect of FPG on DKD linearly rose with hs-CRP increasing.

Effect modification of the association between 2 h-PG and DKD by hs-CRP

Same as FPG, both higher values of 2 h-PG and hs-CRP were also significantly associated with a higher probability of DKD on the multivariable logistic regression model. The corresponding ORs (per 1 unit) and 95% CIs were 1.046 (1.006, 1.086) and 1.081(1.028, 1.138), respectively. The interactive terms of this two variables was also statistically significant ($OR_{interaction}$ = 1.014; 95% CI: 1.002, 1.026; $P_{interaction}$ = 0.018).

Different from FPG, the binning estimates of marginal effect of 2 h-PG across three hs-CRP groups, i.e. L: <1.7 mg/L, M:1.8–7.1 mg/L, H: >7.1 mg/L, on DKD were in agreement with the estimates from the linear interaction model ((P_{wald} = 0.816), suggesting the LIE assumption is valid (Fig. 2A). The kernel smoothing estimation also supported it with a linear relationship between hs-CRP and marginal effect of 2 h-PG on DKD (Fig. 2B). Johnson-Neyman plot (Fig. 2C) showed when hs-CRP was lower than 2.4 mg/L the marginal effect, i.e. log (odds), of 2 h-PG was nonsignificant (boundary of 95%CI included zero) and it became significant as hs-CRP higher than 2.4 mg/L (boundary of 95%CI excluded zero). The corresponding ORs of 2 h-PG in the above two hs-CRP groups, i.e. <2.4 mg/L and > = 2.4 mg/L, were 1.04 (95%CI: 0.99, 1.09, P = 0.153) and 1.07 (95%CI: 1.0, 1.14, P = 0.051), respectively. Based on the range of clinical normal value of hs-CRP (< 3 mg/L), we also divided the participants into two groups, i.e. <3 mg/L and ≥ 3 mg/L. Among these two groups, the ORs of 2 h-PG for DKD were 1.03 (95%CI: 0.98, 1.08, P = 0.282) and 1.10 (95%CI: 1.02, 1.19, P = 0.013), respectively (Fig. 2D).

Discussion

In this cross-sectional study, we noted that FPG, 2-h PG and hs-CRP were all independently associated with DKD in T2DM; Moreover, the associations of the 2-h PG as well as FPG with DKD were modified by hs-CRP; with hs-CRP increasing, the strengths of the association between blood glucose and DKD linearly rose, especially when hs-CRP values were higher than 3 mg/L. To the best of our knowledge, this is the first time the association between blood glucose and DKD was found to be modified by hs-CRP in T2DM.

Hyperglycemic burden has been recognized to be the most important risk factor for DKD in diabetes[5]. Of the other risk factors of DKD, hs-CRP, an inflammatory biomarkers, might be one of the correlators of DKD[18–20], though few studies do not approve of this view[21] [22]. In one recent cohort study, Lili Liu and his colleagues followed 3924 individuals with impaired fasting glucose or diabetes for 5 years and revealed reduction in hs-CRP levels was associated with the decreased risk of DKD in these participants[23]. A recent animal study also showed that hs-CRP could bind to FcγRII on apoptotic cells and exacerbate epithelialmesenchymal transition via the Wnt/β-catenin and ERK1/2 signal paths, which could promote the development of diabetic kidney disease[24]. This present study enriched the knowledge on their relationship.

Among their relationship, our current study presented one interesting and clinically valuable finding that the associations of both FPG and 2-h PG with DKD were modified by hs-CRP. In practice, only a subset of

patients with DM develops DKD even if they have higher level of blood glucose. Previous studies have demonstrated that there might be a strong effect of genetic susceptibility to influence development of DKD in both animal [25–27] and human beings [28, 29]. Gurley and his colleagues found a marked triggering of immune and inflammatory gene expression profiles in the mice with DM was associated with susceptibility to development of DKD[8]. Given the fact that hs-CRP is one of the inflammatory biomarkers, the aforementioned findings, at least partly, support our current results that hs-CRP modified the association of blood glucose and DKD.

Findings from this investigation might be of great clinical significance. ACCORD trial indicates intensive hypoglycemic therapy with lower A1C target (e.g., less than 6% vs. 7–8%) has been associated with a reduction in DKD but at the cost of more hypoglycemic events and an increase in total and cardiovascular disease-related mortality[30, 31]. Thus intensive hypoglycemic therapy should be avoided to prevent hypoglycemia in the process of hypoglycemic treatment. The findings from present study indicated the effect of hyperglycemia on DKD might be small in patients with DM and lower hs-CRP value, such as those with hs-CRP < 3 mg/L. Thus to avoid hypoglycemia, intensive hypoglycemic therapy might be unnecessary for these individuals from the perspective of prevention of DKD and the findings in ACCORD trial. These subjects, i.e. those with hs-CRP < 3 mg/L, account for a larger proportion in this study (68%).

For patients with higher hs-CRP, such as those with hs-CRP higher than 3 mg/L, on the basis of hypoglycemic therapy, anti-inflammatory therapy may be a wise choice in view of the fact that the effect of hyperglycemia on DKD was lower as hs-CRP value became low, i.e. lower intensity of inflammation. One animal experiment showed adding a statin to a background of ACE inhibition and angiotensin II receptor blockade therapy normalized proteinuria and provided better renoprotection than a dual RAS blockade in rats with overt diabetic nephropathy [32]. Apart from lipid-regulating effects, statins also interfere with prenylation of Ras and Rho family small GTP-binding proteins, leading to block of the activation of signaling pathways and transcription factors, which regulate inflammatory and fibrogenic genes related to renal disease progression[33]. Pentoxifylline is a possible nonselective inhibitor of inflammatory mediators. In a prospective, randomized, placebo controlled trial enrolled macroalbuminuric patients with type 2 diabetes, after 6 months, patients treated with pentoxifylline had a significant reduction in albuminuria compared with placebo[34]. Thus, based on these research results, our finding suggests on the top of hypoglycemic therapy anti-inflammation might provide a way to manage DKD for subjects with DM and a higher hs-CRP value, i.e. higher inflammatory response.

The cut-off point of hs-CRP, i.e. 3 mg/L, identified in present study is in line with the upper limit of normal value of hs-CRP used in our clinical practice. This adds the robustness of our findings. In terms of the effect modification of hs-CRP on relationship between 2 h-PG and DKD, a cut-off point of hs-CRP 2.4 mg/L was found, which is close to 3 mg/L, and a sampling error cannot be excluded. When we divided the participants into two groups based on the cut-off point 3.0 mg/L, there was no a significant association between 2 h-PG and DKD in those with hs-CRP value less than 3 mg/L, while there existed a significant relationship in the counterparts, i.e. those with hs-CRP value higher than 3 mg/L.

Several limitations should be considered in our study. First, the cross-sectional design prevents us from making causal inferences in this study. Therefore, prospective studies are warranted to confirm our findings. Second, blood glucose levels fluctuate over time and the single measure was used in this study. Nevertheless, not only the relationship between FPF and DKD was modified by hs-CRP, but the association of 2-h PG with DKD was also similarly influenced, which increases the robustness of our finding. Third, the LIE assumption regarding the effect modification of hs-CRP on the relationship between FPF and DKD appeared to be invalid, whereas it was valid in terms of association of 2-h PG with DKD. Whether such a discrepancy is attributed to sampling error is worth of verifying in future study. Finally, we adjusted many potential confounders in the multivariable model, however other residual confounders may still exist in this investigation.

Conclusion

In conclusion, our investigation indicated the strengths of the association between blood glucose, including FPG and 2 h-PG, and DKD were different across variant hs-CRP values in patients with T2DM. The higher the hs-CRP value, the stronger the strength of their associations. Such an effect modification of hs-CRP on the relationship between blood glucose and DKD appeared to be obvious as hs-CRP was greater than 3 mg/L.

Abbreviations

FPG: fasting plasma glucose; 2 h-PG:2-h plasma glucose; hs-CRP:hypersensitive C-reactive protein; DKD:diabetic kidney disease; T2DM:type 2 diabetes mellitus; DM:diabetes mellitus; BMI:body mass index; OGTT:oral glucose tolerance test; eGFR:estimated glomerular filtration rate; UAER:urinary albumin excretion rate; LIE:linear interaction effect; OR:odd ratio; CI:confidence interval.

Declarations

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study complied with the principles of the Declaration of Helsinki and was approved by the ethical review board of Chaoyang Hospital (Beijing, China). Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Kuibao Li and Zhi Yao designed the study, devised the project and collected, interpreted and analyzed the data. Chuang Li and Yuan Fu collected and performed the measurements and interpreted the data. All authors discussed the results and contributed to the final manuscript. All authors have read and approved the final manuscript.

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Figures

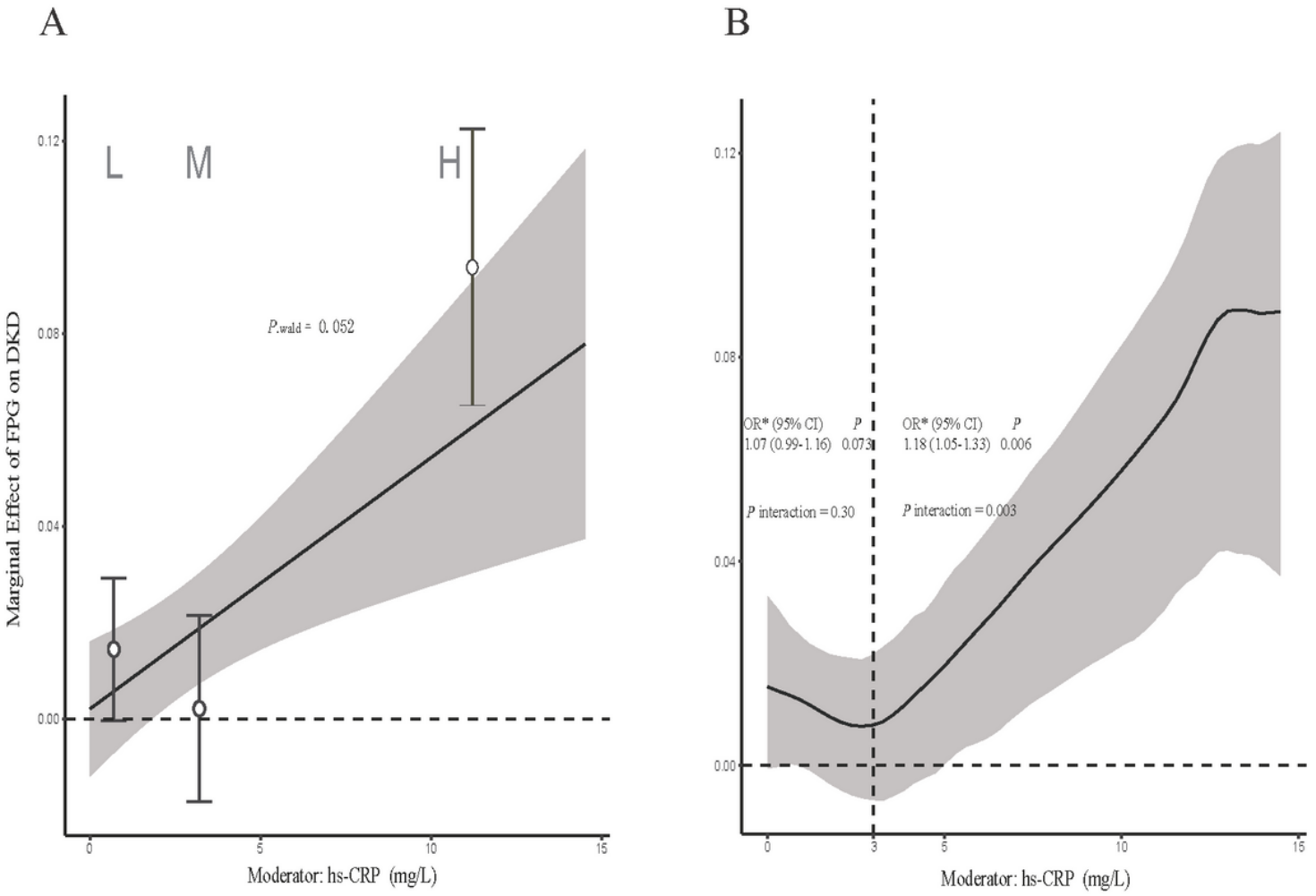

Figure 1

Association of fast plasma glucose (FPG) with diabetic kidney disease (DKD) across different hs-CRP levels. Figure 1A: Binning estimates of marginal effect, i.e. log (odds), of FPG across three hs-CRP groups, i.e. L: <1.7 mg/L, M: 1.8-7.1 mg/L, H: >7.1 mg/L, on DKD; Oblique solid line represents the linear relationship between hs-CRP and marginal effect of FPG on DKD; Figure 1B: a kernel smoothing estimation of the marginal effects of FPG on DKD. Shadows indicates 95% confidence interval (CI).

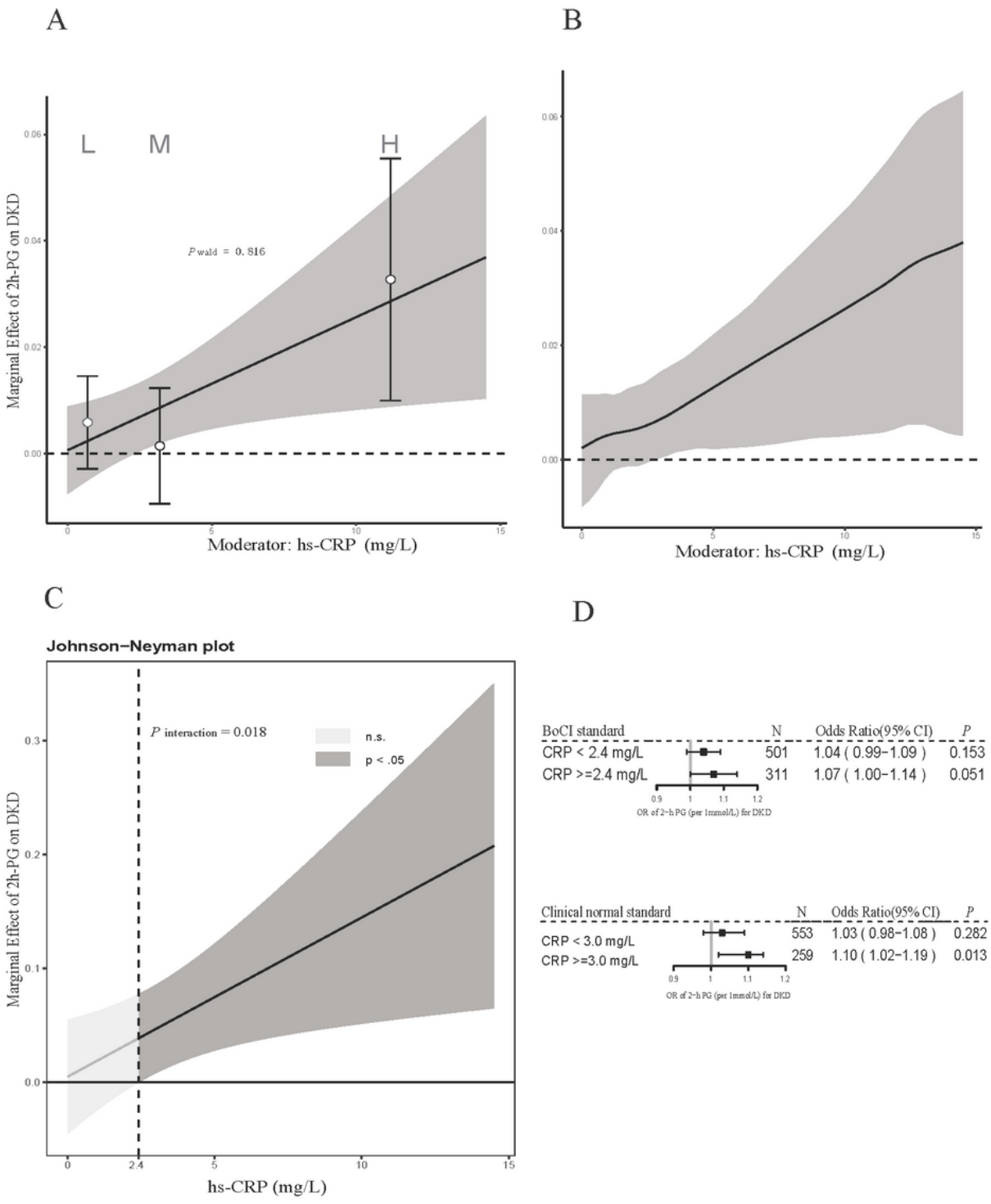

Figure 2

Association of 2 hours plasma glucose (2h-PG) of OGTT with diabetic kidney disease (DKD) across different hs-CRP levels. Figure 2A: Binning estimates of marginal effect of 2h-PG across three hs-CRP groups, i.e. L: <1.7 mg/L, M:1.8-7.1 mg/L, H: >7.1 mg/L, on DKD. Oblique solid line represents the linear relationship between hs-CRP and marginal effect of 2h-PG on DKD; Figure 2B: Kernel smoothing estimation of the marginal effects of 2h-PG on DKD. Figure 2C: The association of hs-CRP with marginal

effect of 2h-PG on DKD in Johnson-Neyman plot. Figure 2D: The ORs with 95% confidence intervals (CIs) of 2h-PG (per 1mmol/L) for DKD in different hs-CRP groups, which were based on boundary of 95%CI in Johnson-Neyman plot (the top forest graph) and range of clinical normal value of hs-CRP (the bottom forest graph), respectively. Shadows indicates 95% confidence interval (CI).