Acta Diabetologica (2019) 56:383–384
https://doi.org/10.1007/s00592-018-1251-7

LETTER TO THE EDITOR

Reply to comment: Serum bilirubin concentrations, type 2 diabetes, and incident coronary heart disease

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Received: 27 October 2018 / Accepted: 30 October 2018 / Published online: 22 November 2018

Keywords Bilirubin · Type 2 diabetes · Coronary heart disease · Renal function · Uric acid

We appreciate the comments by Dr. Kawada on our article [1], which recommended to conduct comprehensive analysis by including renal function and serum uric acid concentration in the multivariate model to assess the associations of serum bilirubin levels and coronary heart disease (CHD) risk among type 2 diabetes (T2D) cases [2]. As indicated in Table 1, further introduction of estimated glomerular filtration (eGFR) and serum uric acid into the multivariate model did not materially change the association of total bilirubin, direct bilirubin, and indirect bilirubin with CHD risk. The eGFR level was related to the incident CHD risk among T2D cases with marginally statistical significance (hazard ratio: 1.00; 95% confidence interval 0.99–1.00; $P=0.033$), while serum uric acid concentration was not (hazard ratio: 1.00; 95% confidence interval 0.92–1.08, $P=0.94$).

Dr. Kawada pointed out that serum bilirubin levels were protective factors in the development of chronic kidney disease. Our former study reported similar results among T2D cases that elevated serum bilirubin level was an independent protective factor for the development of diabetic kidney disease. In addition, our recent meta-analysis of prospective studies showed that serum uric acid levels were independently associated with increased risk of decreased eGFR among T2D cases [3]. However, whether higher serum uric acid level is an independent indicator for the risk of CHD still remains controversial [4]. A recent Mendelian randomization study suggested that there was no causal relationship between serum uric acid and CHD in the general population [5]. In the present multivariate model, adjustment for some common risk factors of hyperuricemia and CHD, such as obesity, lack of exercise, dyslipidemia, hypertension, and hyperglycemia might to some extent attenuate the effects of serum uric acid on CHD risk among T2D cases. In addition, it is observed that diabetic subjects with glycosuria had higher fractional excretion of uric acid and diabetes cases had reduced risk of hyperuricemia or gout, which might be due to the uricosuric effect of glycosuria. Therefore, the associations of uric acid with CHD risk among T2D cases might be different from the general population and still remained to be further investigated.

Bilirubin has been known as a potent endogenous antioxidant and could inhibit oxidation of LDL, suppress proinflammatory responses, and attenuate vascular endothelial activation. This might be the potential mechanism of the reverse associations of serum bilirubin levels and CHD risk among T2D cases.

Managed by Massimo Porta.

This reply refers to the comment available online at https://doi.org/10.1007/s00592-018-1250-8.

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Table 1 Baseline bilirubin levels and the risk of incident coronary heart disease in type 2 diabetes ($n = 2918$)

Characteristics	Total	Non-CHD	CHD	*HR* (95% CI)	*P*
N	2918	2478	440		
eGFR, mL min^{-1} 1.73 m^{-2}	87.4 (25.2)	88.4 (25.4)	82.0 (23.4)	1.00 (0.99-1.00)	0.033
Serum uric acid, mg/dL	5.04 (1.44)	4.98 (1.42)	5.33 (1.56)	1.00 (0.92–1.08)	0.94
Quartiles of total bilirubin					
Q1	729	600	129	1 [Ref]	
Q2	718	617	101	0.96 (0.73–1.26)	0.74
Q3	740	629	111	0.90 (0.69–1.18)	0.44
Q4	731	632	99	0.80 (0.60–1.07)	0.13
P for trend				0.12	
Quartiles of direct bilirubin					
Q1	693	564	129	1 [Ref]	
Q2	764	664	100	0.66 (0.50–0.86)	0.003
Q3	702	606	96	0.79 (0.60–1.04)	0.09
Q4	759	644	115	0.78 (0.59–1.04)	0.09
P for trend				0.30	
Quartiles of indirect bilirubin					
Q1	704	575	129	1 [Ref]	
Q2	755	651	104	0.79 (0.60–1.04)	0.09
Q3	727	619	108	0.85 (0.65–1.11)	0.24
Q4	732	633	99	0.75 (0.57-1.00)	0.05
P for trend				0.09	

Data in means ± SD for continuous variables and numbers for categorical variables

The analysis model adjusted for age, sex, central obesity, education level, smoking status, drinking status, physical activity, family history of coronary heart disease, systolic pressure, triglyceride, high-density lipoproteins, use of medications (hypotensor, lipid-lowering, aspirin), liver function (alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase), fasting plasma glucose, use of antidiabetic, duration of diabetes, eGFR, and serum uric acid levels

CHD coronary heart disease, *eGFR* estimated glomerular filtration rate, *HR* hazard ratio, *Q* quartile

Funding This work was funded by the grant from the National Natural Science Foundation (grant NSFC- 81872698, 81522040 and 81473051); the Program for HUST Academic Frontier Youth Team; National Key R&D Program of China (2017YFC0907501); the 111 Project (No. B12004); Innovative Research Team in University of Ministry of Education of China (No. IRT1246); China Medical Board (No. 12–113).The Natural Science Foundation of Hubei Province of China (2017CFC856) and Faculty Development Grant from Hubei University of Medicine (2016QDJZR12).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict.

Human and animals rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent Informed consent was obtained from all patients for being included in the study.

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