LETTER

Normoalbuminuric chronic kidney disease in type 1 diabetes: is it real and is it serious? Reply to Rigalleau V, Blanco L, Alexandre L et al [letter]

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Received: 23 June 2017 / Accepted: 28 June 2017 / Published online: 2 August 2017
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Keywords Albuminuria · Chronic kidney disease · CKD-EPI · Glomerular filtration rate · Type 1 diabetes mellitus

Abbreviations

Alb ⁺	Albuminuric (CKD phenotype)
Alb [−]	Non-albuminuric (CKD phenotype)
CKD	Chronic kidney disease
CKD-	Chronic Kidney Disease Epidemiology
EPI	Collaboration
EDIC	Epidemiology of Diabetes Interventions and Complications
eGFR	Estimated GFR
MDRD	Modification of Diet in Renal Disease
mGFR	Measured GFR
RIACE	Renal Insufficiency And Cardiovascular Events

To the Editor: We really appreciated the interest and comments by Rigalleau and colleagues on our recent article [1]. We agree that the proportion of individuals with the non-albuminuric (Alb[−]) phenotype with type 1 diabetes and chronic kidney disease (CKD) in our study was surprisingly

high (17 out of 29, 58.6%) [2]. This figure is higher than that reported by Thorn et al [3] in the FinnDiane Study (78 out of 502, 15.5%; $p < 0.0001$, χ^2 test) and, also, in the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) Study [4], in which 23.6% of individuals (21 out of 89; $p < 0.001$, χ^2 test) were reported as having normoalbuminuria (albumin excretion rate [AER] ≤ 30 mg/24 h) and estimated GFR (eGFR) < 60 ml min^{−1} [1.73 m]^{−2}. Nonetheless, our figure is similar to the one reported in the Renal Insufficiency And Cardiovascular Events (RIACE) Study [5], which enrolled a large cohort of Italian individuals with type 2 diabetes and found that 1673 out of 2959 (56.5%) individuals with eGFR < 60 ml min^{−1} [1.73 m]^{−2} had normoalbuminuria. The reasons for these discrepancies are not readily apparent. Whether local pathogenic background and clinical management could contribute to these differences is a hypothesis that needs to be verified.

Rigalleau et al claim that our results may be overestimated by the assessment of glomerular filtration rate by the Modification of Diet in Renal Disease (MDRD) Study equation. Though we are fully aware of the limitations of this equation, this is unlikely to account for the observed discrepancies as the same approach was used in the DCCT/EDIC survey [4]. Moreover, as reported in the supplementary material of our study (ESM Table 5 [2]), individuals with CKD and the Alb[−] phenotype had higher MDRD equation-eGFR vs those with the albuminuric (Alb⁺) phenotype (52 ± 7 vs 45 ± 11 ml min^{−1} [1.73 m]^{−2}; $p < 0.05$). This difference was probably even larger in the FinnDiane [3] study, in which participants with CKD and the Alb[−] phenotype had a median (interquartile range) eGFR, calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [6], of 55 (49–58), whilst those with the Alb⁺ phenotype had an eGFR of 37 (23–51) ml min^{−1} [1.73 m]^{−2}. Furthermore, a less

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advanced renal failure has been consistently reported in those with CKD and the Alb⁻ phenotype compared with the Alb⁺ phenotype in the RIACE Study [5].

It is well known that the MDRD equation can underestimate GFR, as compared with measured GFR (mGFR), particularly in the normal to high range [7]. The CKD-EPI equation also appears to underestimate normal to high GFR to a similar extent as the MDRD equation in people with diabetes [8]. Whether MDRD equation-eGFR underestimation also occurs in individuals with stage 3 CKD is a matter of debate [9]. MacIsaac et al [8] suggest that the precision of GFR estimates by the MDRD and CKD-EPI equations improves with lower GFR values; in their study, in 60 participants with mGFR < 60 ml min⁻¹ [1.73 m]⁻², neither equation was found to significantly underestimate GFR. This is in full agreement with data reported by Rigalleau et al showing that MDRD equation-eGFR was similar to GFR measured by ⁵¹Cr-EDTA in 40 individuals with type 1 diabetes, even in those with stage 3a CKD. In 288 individuals with diabetes (125 with type 1 diabetes), we have previously shown that MDRD equation-eGFR underestimates GFR measured by iothelone plasma clearance to a progressively larger extent in those with mGFR >75 ml min⁻¹ [1.73 m]⁻², but not in individuals with mGFR 45–<60 ml min⁻¹ [1.73 m]⁻² [10]. In our hands [10], the difference between MDRD equation-eGFR and mGFR was -1.8% in individuals with stage 3a CKD and +2.8% in individuals with mGFR 60–<75 ml min⁻¹ [1.73 m]⁻².

Moreover, estimation of GFR by the CKD-EPI equation instead of the MDRD equation did not change the conclusions and the overall results presented in our paper [2]. In more detail, CKD-EPI equation-derived eGFR was 55.6 ± 8.1 ml min⁻¹ [1.73 m]⁻² and 48.2 ± 11.9 ml min⁻¹ [1.73 m]⁻² in those with CKD and the Alb⁻ and Alb⁺ phenotype, respectively (*p* = 0.056); only two out of the 17 individuals with the Alb⁻ phenotype and stage ≥3 CKD were reclassified as having stage 2 CKD because of a CKD-EPI formula-measured eGFR >60 ml min⁻¹ [1.73 m]⁻² (63.3 and 63.9 ml min⁻¹ [1.73 m]⁻²). Finally, out of 63 individuals with the Alb⁻ phenotype and eight individuals with the Alb⁺ phenotype, all with MDRD equation-eGFR 60–74 ml min⁻¹ [1.73 m]⁻², 16 and 2 were reclassified as having a higher eGFR using the CKD-EPI equation, respectively. However, even taking this into account did not affect results and conclusions of our analysis.

We agree with Rigalleau et al that relatively higher eGFR in individuals with the Alb⁻ phenotype and stage ≥3 CKD may reflect a slower rate of deterioration of renal function with reduced progression to end-stage renal disease (ESRD). Since we did not measure this outcome, data from our study cannot prove or disprove this theory. However, the hypothesis is supported by data reported by Rigalleau et al in a 3 year follow-up of their study [11] and by the FinnDiane's longer 13 year follow-up [3]. In the second Joslin Kidney Study, the prevalence of 'decliners' (those with renal decline ≥3.3% per year) was 10% in

individuals with the Alb⁻ phenotype, vs 32% with the Alb⁺ phenotype [12]. Of interest, the prevalence of decliners increased (Alb⁻ to 21% and Alb⁺ to 48%) among those with eGFR < 60 ml min⁻¹ [1.73 m]⁻², suggesting that individuals with CKD and the Alb⁻ phenotype can progress to advanced kidney disease.

The final question raised by Rigalleau and colleagues is also of importance: whether individuals with albuminuria are more prone to cardiovascular events and mortality. We have already speculated whether the distinct sets of factors associated with the Alb⁻ and Alb⁺ phenotype could confer a differential cardiovascular risk. This is actually supported by the results of the FinnDiane [3], which show an increased cardiovascular risk, even in individuals with the Alb⁻ phenotype with CKD (HR 2.0 [95% CI 1.4, 3.5]) vs individuals with the Alb⁻ without CKD (reference cohort). As far as our cohort is concerned, the distribution of individuals with CKD and a positive history of previous cardiovascular events did not differ between the Alb⁻ group (7 out of 17, 41.2%) and the Alb⁺ group (3 out of 12, 25.0%; *p* = 0.449).

In summary, given the many limitations of estimating vs measuring GFR, we believe our data are consistent with a growing literature showing a progressive increase of the prevalence of the non-albuminuric CKD phenotype. Since equations are commonly used in the clinical setting, it is important for physicians to appreciate the existence of such a phenotype and its implications in stratifying renal and cardiovascular risk.

Acknowledgements We are indebted to the Clinical Laboratory and the Medical Records Unit of the Department of Clinical and Experimental Medicine (both at the University of Pisa, Pisa, Italy).

Funding Work in the authors' laboratories is supported by a grant from Regione Toscana, Italy, Resolution 1157 (19 December 2011), ID number D55E11002680005. The funding body had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement All authors were responsible for drafting the article and revising it critically for important intellectual content. All the authors approved the version to be published.

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