LETTER

Normoalbuminuric chronic kidney disease in type 1 diabetes: is it real and is it serious?

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Abbreviations

Alb ⁺	Albuminuric
Alb [−]	Non-albuminuric
CKD	Chronic kidney disease
eGFR	Estimated GFR
MDRD	Modification of Diet in Renal Disease
mGFR	Measured GFR

To the Editor: We were interested by the recent article by Penno et al, who reported that the majority (17/29) of their participants with stage ≥ 3 chronic kidney disease (CKD) and type 1 diabetes had the non-albuminuric phenotype (Alb[−]; albuminuria < 3.4 mg/mmol) [1]; this is an unexpectedly high proportion. As reported by the authors, these participants had higher Modification of Diet in Renal Disease (MDRD) Study equation-estimated GFR (eGFR) (52 ± 7 ml min^{−1} [1.73 m]^{−2}) vs those with the albuminuric phenotype (Alb⁺; albuminuria ≥ 3.4 mg/mmol), who had an eGFR of 45 ± 11 ml min^{−1} [1.73 m]^{−2} ($p < 0.05$); this was not commented on to a great extent in the article. Two hypotheses may explain this less advanced renal failure in the Alb[−] group.

First, participants with Alb[−] phenotype may not really have CKD. Although it works better than the old Cockcroft and Gault formula [2], the MDRD equation was built by multiple regression analysis from a population with renal insufficiency,

and it is well-known to underestimate normal and high GFR: according to the analysis from Froissard et al, 20.5% of MDRD equation-estimated stage 3 CKD was, in fact, stage 2 CKD based on ⁵¹Cr-EDTA analysis [3]. Penno et al recognised that estimation by the MDRD equation was a limitation of their study [1].

To investigate whether the higher MDRD equation-deduced eGFR in the Alb[−] group might have resulted from such underestimated eGFR, we compared the MDRD equation-eGFR to isotopically measured GFR (mGFR), analysed using ⁵¹Cr-EDTA, in 40 individuals with type 1 diabetes and MDRD equation-eGFR below 60 ml min^{−1} [1.73 m]^{−2}. Participants included 21 men (52.5%) aged 57 ± 13 years old, with a median albumin excretion rate (AER) of 189 mg/24 h (range 5–2500). Only three individuals had the Alb[−] phenotype. In our participants, the MDRD equation-eGFR was 41.7 ± 12.4 ml min^{−1} [1.73 m]^{−2}, which was similar to the mGFR (42.0 ± 21.9 ml min^{−1} [1.73 m]^{−2}). Regarding eGFR, individuals with stage 3a CKD in our study ($n = 22$) were similar to the individuals with stage 3 CKD in the study by Penno et al [1], and their MDRD equation-eGFR did not differ from mGFR (MDRD equation-eGFR: 51.1 ± 3.7 ml min^{−1} [1.73 m]^{−2}; mGFR: 50.7 ± 15.1 ml min^{−1} [1.73 m]^{−2}) (unpublished results, V. Rigalleau).

As demonstrated using data from the DCCT, in the 60–80 ml min^{−1} [1.73 m]^{−2} MDRD equation-eGFR range, ~80% of eGFR values may be underestimated by more than 20 ml min^{−1} [1.73 m]^{−2} as compared with the iothalamate clearance method [4]. This may explain the large number of individuals with MDRD equation-eGFR 60–74 ml min^{−1} [1.73 m]^{−2} in Penno et al's study who were categorised as Alb[−] ($n = 63$) vs Alb⁺ ($n = 8$). However, this does not seem to explain the high number of individuals with the Alb[−] phenotype with stage 3 CKD, who were probably highly renal insufficient.

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The second hypothesis is that the higher eGFR in individuals with the Alb⁻ phenotype with stage 3 CKD may, in fact, reflect less progressive renal failure, which seemed to be overlooked by Penno et al; although, in their conclusion, they did state that their findings ‘support the hypothesis of ‘two distinct pathways (Alb⁻ and Alb⁺) both potentially progressing to advanced kidney disease’, referring to the possibility of progressive renal decline with the Alb⁻ phenotype [5]. It should not be forgotten that progressive renal decline is three to five times more frequent in individuals with type 1 diabetes and albuminuria. Ten years ago, in individuals with type 2 diabetes (75%) and type 1 diabetes (25%), we reported that 17% with MDRD equation-eGFR below 60 ml min⁻¹ [1.73 m]⁻² were normoalbuminuric [6]. As with the participants in Penno et al’s study, the MDRD equation-eGFR was found to be 5 ml min⁻¹ [1.73 m]⁻² higher in individuals with normoalbuminuria vs those with albuminuria. By contrast with those with albuminuria, individuals with normoalbuminuria did not progress to dialysis or death during the 3 year follow-up [6]. Whether these individuals are more prone to cardiovascular events and mortality, as reported for type 2 diabetes [7, 8], is another important question. In another study (unpublished results, V. Rigalleau), of the 243 individuals with type 1 diabetes followed by our research team in Bordeaux, France, 35 had MDRD equation-eGFR below 60 ml min⁻¹ [1.73 m]⁻², and the history of cardiovascular events were similarly prevalent in the 19 individuals in the Alb⁺ group ($n = 5$, 26%) and the 16 individuals in the Alb⁻ group ($n = 4$, 25%). We speculate whether the 10 out of 29 participants with stage ≥ 3 CKD in Penno et al’s study who also had previous cardiovascular events (as reported in Table 1 in their article) were also similarly distributed between the Alb⁻ and Alb⁺ group. Further longitudinal studies will be required to determine whether Alb⁻ CKD seriously progresses to cardiovascular events, dialysis or death in type 1 diabetes.

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