studies in patients with known kidney disease) will at best delay the progression to start of renal replacement therapy a few years. There are arguments that the earlier start (at the time of a Stage 1 or 2 CKD) will offer more benefit in the long run. For example in the IRMA trial in diabetes, it has been shown that early ARB treatment will prevent the progression of Stage 1 or 2 to Stage 3 CKD [4], an approach that in the long run will be more cost saving [5].

We therefore suggest that we, in our activities to prevent end-stage renal and cardiovascular disease, should more clearly emphasize the impact of screening for albuminuria (as a manifestation of vascular and/or renal damage) instead of primarily emphasizing the impact of the level of eGFR as an indicator of (still) functioning renal mass.

Conflict of interest statement. None declared.

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doi: 10.1093/ndt/gfn335

Advance Access publication 10 April 2008

Increased serum advanced glycation end products are associated with impairment in HDL antioxidative capacity in diabetic nephropathy

Sir,

I read with interest the paper by Zhou et al. [1] in which an inverse relationship between organophosphatase activity and concentration of advanced glycation end products was reported. The organophosphatase assay used in that study is the commercially available EnzChek® Paraoxonase Assay Kit from Invitrogen™. The samples used for the assay were the supernatant from serum after precipitation of the non-high-density lipoproteins using dextran sulfate magnesium. Somewhat surprisingly, there was no citation for the use of this novel combination of reagent and sample for measuring human serum paraoxonase-1 activity. I have been unable to find any published reports validating this assay for the measurement of human serum paraoxonase-1 activity. This contrasts with other published works with novel paraoxonase-1 substrates, such as that by Gaidukov and Tawfik [2]. The EnzChek® assay has been used in one other study, where the results were corroborated by measurement of enzyme mass, but not by serum arylesterase activity [3]. Soukharev and Hammond report the development of a fluorogenic organophosphatase substrate [4] that is hydrolysed by purified human paraoxonase 1. However, no data have been published validating the substrate used in that paper, 7-diethylphospho-6,8-difluor-4-methylumbelliferyl (DEPFMU), in the context of a human serum matrix or the serum matrix remaining after divalent cation/polyvalent anion precipitations.

I would propose that the results of this type of assay be referred to as organophosphatase activity in the same way as results for phenyl acetate hydrolysis are referred to as arylesterase activity. Referring to this activity as paraoxonase activity would require rigorous validation and comparison with serum hydrolysis of paraoxon. I would also make an appeal that the introduction of novel assays be accompanied by the validation data with conditions described in sufficient detail to allow replication in subsequent studies.

Conflict of interest statement. None declared.


doi: 10.1093/ndt/gfn202

Advance Access publication 10 April 2008

Reply

Sir,

We thank Dr Philip W. Connelly for his interest in our paper, and for raising valuable comments on our methodology of measuring paraoxonase activity in HDL-containing supernatant from serum after the precipitation of apolipoprotein B-containing lipoproteins using the dextran-sulfate method. Paraoxonase 1 is an important HDL-associated antioxidative enzyme and there are data showing that paraoxonase 1 is active in the HDL-containing supernatant after dextran-sulfate precipitation. Navab et al. have reported that adding purified human paraoxonase 1 to HDL-containing supernatant after dextran-sulfate precipitation of plasma from patients with coronary heart disease can restore the antioxidative function of HDL [1].

Paraoxonase has multiple activities including organophosphatase, phosphotriesterase, arylesterase and thiolactonase [2]. The EnzChek® Paraoxonase Assay from Invitrogen® used in our study is a homogeneous fluorometric assay for the organophosphatase activity of paraoxonase. The substrate is a fluorogenic organophosphate analogue as indicated in the protocol provided by the manufacturer. As pointed out by Dr Connelly, the EnzChek® Paraoxonase Assay has also been used by Rector et al. for the measurement of paraoxonase-1 activity in serum and in HDL [3], and the results are corroborated by the measurement of enzyme mass but not by serum arylesterase activity. We welcome Dr Connelly’s suggestion that arylesterase activity should also be measured. We have shown that the organophosphatase activity in HDL was significantly reduced in diabetic subjects with microalbuminuria or proteinuria. Since we compared diabetic subjects with healthy controls in our study, and serum, plasma and HDL samples from diabetic subjects and healthy controls were all handled in the same manner, any methodological problem would apply to both groups and therefore unlikely to bias our results.

Conflict of interest statement. None declared.