

# Response by Sorensen et al to Letters Regarding Article, "Prediabetes and Type 2 Diabetes Are Associated With Generalized Microvascular Dysfunction"

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# Response by Sørensen et al to Letters Regarding Article, “Prediabetes and Type 2 Diabetes Are Associated With Generalized Microvascular Dysfunction: The Maastricht Study”

## *In Response:*

We appreciate Dr Tsuda and Brzezinski et al for their interest in our study,<sup>1</sup> in which we found retinal arteriolar and skin microvascular dysfunction in prediabetes and type 2 diabetes mellitus independent of major cardiovascular risk factors. These findings support the concept that generalized microvascular dysfunction precedes the clinical diagnosis of type 2 diabetes mellitus and may contribute to the development of microvascular complications in (pre)diabetes.

Resting albuminuria has long been favored as clinical biomarker for renal disease and is strongly associated with cardiovascular disease risk.<sup>2</sup> An explanation is that albuminuria may reflect generalized (microvascular and macrovascular) endothelial dysfunction.<sup>3</sup> Data on the association between direct measures of microvascular dysfunction and albuminuria are, however, scarce. Recently, we have shown an association between capillary rarefaction and 24-hour average albuminuria, irrespective of type 2 diabetes mellitus.<sup>3</sup> In addition, the results of a yet unpublished study of our group hint toward an association of retinal arteriolar and skin microvascular endothelial dysfunction with 24-hour average albuminuria. Both studies support the hypothesis that 24-hour average albuminuria is a biomarker of microvascular dysfunction.

The association of exercise-induced albuminuria with features of the metabolic syndrome highlights exercise-induced albuminuria as a possible tool in the early assessment of cardiovascular risk among dysmetabolic individuals.<sup>4</sup> Because of logistical reasons, we did not include urinary albumin excretion measurements after exercise in our study. Whether exercise-induced albuminuria is associated with microvascular dysfunction in (pre)diabetes can therefore not be answered from our data. However, because resting albuminuria may reflect generalized endothelial dysfunction,<sup>3</sup> and prediabetes has been associated with generalized endothelial dysfunction (ie, in the retinal and skin microvasculature<sup>1</sup>), it may be speculated that exercise-induced albuminuria is linked to retinal and skin microvascular endothelial dysfunction in prediabetes, although this inference should be formally tested.

Taken together, we believe that resting urinary albumin excretion, because of its common use, easy applicability, and its strong association with increased cardiovascular risk, is currently favored over exercise-induced urinary albumin excretion. However, research on earlier markers of renal damage, such as exercise-induced albuminuria, can be useful to improve prevention of renal and cardiovascular disease.

Dr Tsuda suggests that erythrocyte biomechanical properties, which depend on deformability, may be related to retinal and skin microvascular dysfunction. Decreased erythrocyte deformability may affect erythrocyte rheology, which could thereby lead to circulatory disorders. Unfortunately, data on erythrocyte deformability are not available, and we therefore cannot directly answer the question based on our own data. Although erythrocyte deformability may conceivably cause microvascular dysfunction, it is important to stress that any such association may also be explained

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by impaired nitric oxide availability in both endothelial cells and erythrocytes<sup>5</sup> caused by a common underlying cause, such as inflammatory activity and high levels of free fatty acids.<sup>6</sup> Alternatively, hyperglycemia itself may impair both erythrocyte deformability<sup>7</sup> and microvascular function.

Decreased deformability of erythrocytes hampers normal passage through capillaries, which may lead to mechanical damage of the endothelium, increased platelet activation, and thrombus formation, all of which increase shear stress. Retinal arteriolar %dilation, in our study, was measured in relatively large (>70  $\mu\text{m}$ ) vessels in comparison with the diameter of an erythrocyte (6–8  $\mu\text{m}$ ). Skin microcirculation comprised smaller arterioles and venules than retinal arterioles, with diameters as small as 10  $\mu\text{m}$ , but probably larger in the heat-induced dilated state. Therefore, whether passage of erythrocytes through retinal and skin microcirculation as measured in our study is truly abnormal remains to be shown.

We agree that future studies should investigate the association between erythrocyte rheological abnormalities and microvascular endothelial dysfunction, which may open new insights to the development of circulatory disorders in (pre)diabetes.

## DISCLOSURES

None.

## AFFILIATIONS

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