Urinary orosomucoid excretion in patients with diabetes

Results from cohort studies, pathophysiological investigations and assay validation

Merete Skovdal Christiansen

This PhD dissertation was accepted by the Faculty of Health Science of the University of Copenhagen, and defended on March 31, 2005.

Official opponents: Jannik Hilsted, Peter Rossing and Per Erik Jørgensen.

Tutors: Bo Feldt-Rasmussen, Eva Hommel and Erik Magid.

Correspondence: Merete Skovdal Christiansen, Eschrichtsvej 20, 2500 Valby, Denmark. E-mail: skovdal@dadlnet.dk

Dan Med Bull 2005;52:96.

ABSTRACT

The PhD dissertation is based on research carried out during employment at the Department of Clinical Biochemistry, Amager Hospital. The dissertation comprises five papers studying the value of orosomucoid excretion in urine as a putative risk marker of cardiovascular complications in patients with type 2 diabetes.

Orosomucoid is an acute phase reactant shown to exert a regulatory, dampening influence on the inflammatory cascade, thereby protecting against tissue damage from excessive inflammation. Orosomucoid is a prominent component of the temporary proteinuria which occurs in association with exercise, inflammation and acute coronary syndrome. Patients with type 2 diabetes have increased risk of cardiovascular mortality compared to the background population. In a 5-year follow-up study of 430 patients with type 2 diabetes we found that urinary orosomucoid excretion rate (UOER) predicted cardiovascular mortality independently of classic cardiovascular risk factors and urinary albumin level. Furthermore, we demonstrated that increased UOER was a powerful predictor of cardiovascular mortality even in the subgroup of patients with normal urinary albumin excretion rate.

We validated a particle-enhanced immunoassay for the quantitative determinations of low concentrations of orosomucoid in urine and achieved a 20-times lower detection limit than the conventional assay; using the optimised assay we established a set of reference values of orosomucoid in urine from healthy persons.

Important factors involved in the development of atherosclerosis and the increased morbidity and mortality of type 2 diabetes are chronic low-grade inflammation, endothelial dysfunction and left ventricular impairment. In a cross-sectional study of patients with type 2 diabetes and healthy control persons we found signs of chronic subclinical inflammation and endothelial dysfunction in patients with increased UOER. The increase in UOER in type 2 diabetes was not preceded by arterial dilatory dysfunction, left ventricular dysfunction or renal impairment. These results support our hypothesis that UOER is an early marker of cardiovascular risk not preceded by evident cardiovascular or renal dysfunction.

We conclude that UOER is an independent, powerful predictor of cardiovascular mortality in patients with type 2 diabetes at 5-year follow-up. Our results suggest that UOER may be a better marker of cardiovascular complications than microalbuminuria. The relation between increased UOER and cardiovascular mortality may be caused by chronic low-grade inflammation and early endothelial dysfunction. Further longitudinal investigations and intervention studies are needed to establish appropriate therapeutic consequences of increased UOER in patients with type 2 diabetes.