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Increased urinary orosomucoid excretion is not related to impaired renal function in patients with type 2 diabetes

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Abstract

Objectives: Increased urinary orosomucoid excretion rate (UOER) independently predicted cardiovascular mortality in patients with type 2 diabetes at 5-years of follow-up. To further explore UOER in relation to local renal physiological phenomena, we studied renal glomerular and tubular functions in patients with type 2 diabetes and normal or increased UOER. **Methods:** We performed a cross-sectional study of 40 patients with type 2 diabetes (normal UOER, n=16; increased UOER, n=24) who displayed no signs of cardiovascular disease and 21 healthy control persons. The renal clearance values of [^{51}Cr]ethylenediaminetetraacetic acid ([^{51}Cr]EDTA), lithium, orosomucoid, albumin, and sodium were measured. **Results:** Patients with type 2 diabetes had normal glomerular filtration rate (GFR) measured by [^{51}Cr]EDTA clearance. The clearance value of orosomucoid was highly increased in patients with increased UOER. The clearance values of albumin were similar in patients with increased UOER and in healthy controls. Investigations of renal tubular function revealed normal and similar levels of lithium clearance and proximal and distal reabsorption of sodium and water. Serum values of orosomucoid were higher in patients with increased UOER than in healthy controls (P<.001), but were still within reference limits, suggesting chronic low-grade inflammation. UOER was associated with increasing values of orosomucoid clearance (P<.0001) independently of serum orosomucoid. **Conclusions:** Patients with type 2 diabetes and increased UOER had normal GFR and showed no signs of renal glomerular or tubular dysfunction. We therefore hypothesize that increased levels of UOER may be caused by local renal production of orosomucoid due to chronic low-grade inflammation.

Keywords: Lithium clearance; Renal tubular function; Type 2 diabetes; Urinary albumin excretion; Urinary orosomucoid excretion

1. Introduction

Patients with type 2 diabetes have an increased risk of cardiovascular and all-cause mortality compared to the background population (Gu, Cowie, & Harris, 1998; Morrish, Wang, Stevens, Fuller, & Keen, 2001; Roper, Bilous, Kelly, Unwin, & Connolly, 2002). In the presence of increased urinary albumin excretion (microalbuminuria), this risk is even higher; microalbuminuria has, for years, been recognized as a strong and independent predictor of the development of diabetic nephropathy and cardiovascular mortality in type 2 diabetes patients (Mogensen, 1984; Schmitz & Vaeth, 1988).

Previously, we have shown that an increased urinary excretion rate of another protein [i.e., urinary orosomucoid excretion rate (UOER)] is also an independent predictor of

Abbreviations: [^{51}Cr]EDTA, [^{51}Cr]ethylenediaminetetraacetic acid; HbA_1c, blood hemoglobin A_1c; UAER, urinary albumin excretion rate; UOER, urinary orosomucoid excretion rate.

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all-cause and cardiovascular mortality in patients with type 2 diabetes (Christiansen, Hommel, Magid, & Feldt-Rasmussen, 2002). Even in patients with normal urinary albumin excretion rate (UAER), increased UOER was a powerful predictor of cardiovascular mortality (Christiansen, Hommel, Magid, & Feldt-Rasmussen, 2005). The predictive value of UOER was independent of both classic cardiovascular risk factors and UAER level. It is therefore possible that UOER will turn out to be an even earlier predictor of cardiovascular mortality than microalbuminuria. The pathophysiological mechanisms underlying the relation between UOER and increased risk of cardiovascular mortality are, however, unknown.

Orosomucoid, a 41-kDa single-chain polypeptide with a high carbohydrate moiety (42%) and a strong negative charge (isoelectric point, 2.7), is mainly produced in the liver (Schmid, 1989). Orosomucoid is an acute-phase reactant and member of a subgroup of lipocalins recently labeled *immunocalins* (Logdberg & Wester, 2000). Immunocalins exert a regulatory dampening influence on 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 (Poortmans & Haralambie, 1979) and acute inflammation (Jensen & Henriksen, 1974; Pang, Ginanni, Dongre, Hefta, & Opitek, 2002). Proteinuria is regarded as the most commonly recognized sign of kidney disease, with its origin being prerenal, glomerular, tubular, or postrenal (Guder & Hofmann, 1992).

In order to explore the UOER in relation to local renal physiological phenomena, our aim was to study renal glomerular and tubular functions in patients with type 2 diabetes and normal or increased UOER.

2. Patients and methods

2.1. Subjects

All diabetic patients attending the outpatient clinic at Amager Hospital (Copenhagen, Denmark) were routinely screened by urinary analysis for orosomucoid and albumin. The patient files of 344 Caucasian diabetic patients aged <70 years were screened; they showed dipstick-negative urine results for nitrite, leucocytes, and hemoglobin, and UAER of less than 200 μg/min on initial urinary screening. Inclusion of patients was performed from May 2002 to June 2003. The exclusion and inclusion criteria of patients are shown in Fig. 1. Patients with Minnesota code 1.1–3, 4.1–4, 5.1–3, or 7.1 on resting electrocardiography records (Blackburn, Keys, Simonson, Rautaharju, & Punsar, 1960) were excluded from the study.

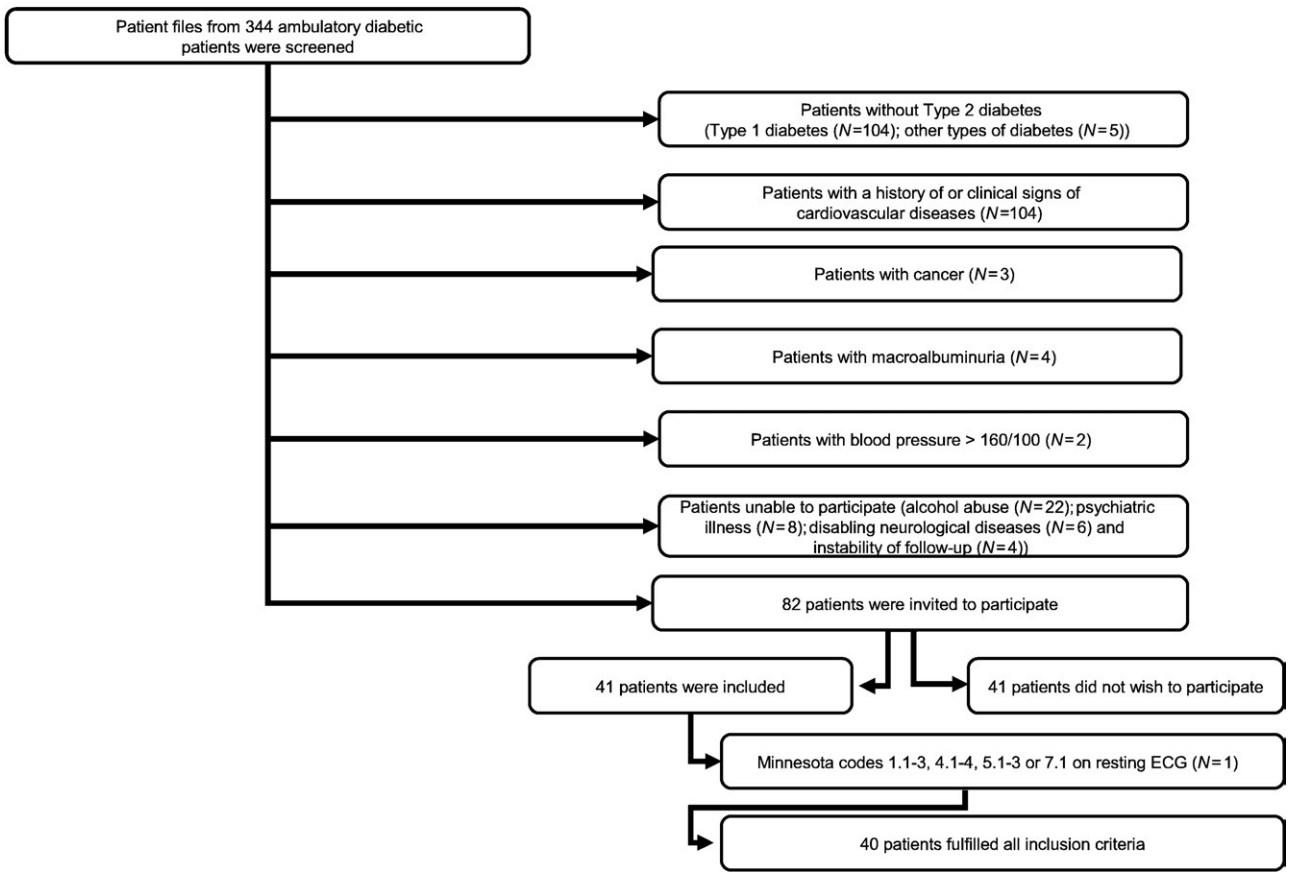

Fig. 1. Diagram of the exclusion and inclusion criteria for patients in this study.