Relationship Between Abdominal Fatness and Onset and Progression of Albuminuria in Type 1 Diabetes

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Our previous studies on type 1 diabetes showed that abdominal fatness is strongly associated with nonalcoholic fatty liver (1), diabetic severe eye disease (2), and hospitalization and death due to heart failure (3). Additionally, visceral fat was higher in individuals with type 1 diabetes and albuminuria compared with those without albuminuria, and waist-to-height ratio (WHtR) best estimated the visceral fat (4).

This longitudinal study relates abdominal fatness, estimated by WHtR and general fatness estimated by BMI, to the onset and progression of albuminuria in a large cohort of adults with type 1 diabetes from the Finnish Diabetic Nephropathy (FinnDiane) Study.

We used three separate cohorts based on the participants' baseline albuminuria stage: normal (A1), moderate (A2), and severe (A3); the latter two were previously named microalbuminuria and macroalbuminuria (3). All cohorts were followed until progression to the next worse albuminuria stage or the end of 2017 and analyzed by linear and nonlinear Cox regressions adjusted for sex, age of diabetes onset, and diabetes duration only (model 1) or additionally adjusted for smoking, total cholesterol, triglycerides, glycated hemoglobin (HbA_{1c}), systolic blood pressure (SBP), estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration), and the use of renin-angiotensin-aldosterone system inhibitors (model 2). The common WHtR threshold of $\geq$0.5 defined central obesity. Kaplan-Meier survival curves estimated the influence of central obesity on albuminuria onset (progression from A1 to A2).

A total of 3,358 adults with type 1 diabetes (51.7% men) had a mean (±SD) age of 38.0 (11.9) years, 21.6 (12.0) years of diabetes duration, SBP of 134 (18) mmHg, and BMI of 25.2 (3.6) kg/m^2. From 2,274 individuals with A1, 250 experienced albuminuria onset (mean follow-up of 8.1 years), 100 out of 463 progressed from A2 to A3 (7.4 years), and 325 out of 621 progressed from A3 to kidney replacement therapy (KRT) (7.7 years). In all three cohorts, progressors had higher HbA_{1c} (A1/A2, 9.3 vs. 8.1%; A2/A3, 9.5 vs. 8.6%; A3/KRT, 9.3 vs. 8.7%; $P < 0.001$), triglycerides (A1/A2, 1.1 vs. 0.9 mmol/L; A2/A3, 1.5 vs. 1.0 mmol/L; A3/KRT, 1.6 vs. 1.2 mmol/L; $P < 0.001$), and total cholesterol (A1/A2, 5.0 vs. 4.8 mmol/L; A2/A3, 5.4 vs. 4.9 mmol/L; A3/KRT, 5.4 vs. 5.2 mmol/L; $P < 0.05$) than nonprogressors, whereas no differences in age, diabetes duration, age of diabetes onset, and BMI were observed. The WHtR was higher in those with albuminuria onset (0.50 vs. 0.49, $P = 0.002$) and in progressors from A2 to A3 (0.53 vs. 0.51, $P = 0.03$). Central obesity was more likely in individuals with albuminuria onset than in nonprogressors (49% vs. 39%, $P = 0.002$).

WHtR was linearly associated with an increased risk of albuminuria onset in model 1 (hazard ratio [HR] [95% CI] 1.58 [1.26, 1.98] per 0.1 increase) and model 2 (1.40 [1.08, 1.81]) and with the progression risk from A2 to A3 in model 1 (1.56 [1.13, 2.16]) but not in model 2 (1.40 [0.95, 2.07]). The WHtR-mediated progression risk from A3 to KRT was nonlinear. Importantly, individuals without baseline central obesity were less likely to develop albuminuria (Fig. 1). All BMI-mediated risks were nonlinear and nonsignificant (model 2).

In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study, waist circumference was associated with albuminuria onset (5). In the current study, an increase in WHtR increased the albuminuria onset risk in a larger cohort with a longer follow-up after full adjustment. Despite estimating abdominal fatness differently, central obesity was associated with albuminuria onset in both studies.

Novel study findings are that WHtR linearly increased the HR for albuminuria onset (40% per each 0.1 increase in the WHtR) and that individuals without central obesity were less likely to develop albuminuria. Another novelty is that an increase in WHtR linearly increases the

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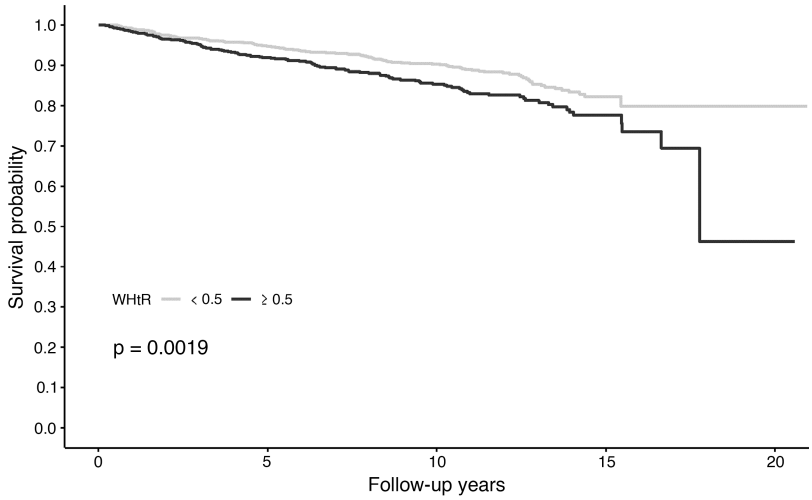

Figure 1—Kaplan-Meier plot for albuminuria onset according to baseline WHtR threshold of 0.5 in individuals with a normal albumin excretion rate at baseline.

progression risk from A2 to A3, regardless of unmodifiable risk factors. Although this association did not persist after all adjustments, a trend remained.

This study has limitations. Our results do not necessarily extend beyond a Caucasian-Finnish population. Abdominal fatness was estimated, but its estimator, the WHtR, best approximated visceral fat previously (4). In observational studies like ours, causality cannot be inferred. The strengths of the study are the large cohort, a long-term follow-up, and well-characterized participants.

In conclusion, abdominal fatness increases the risk of albuminuria onset and progression from moderate to severe albuminuria. Importantly, the HR of WHtR but not BMI was linear for albuminuria onset on top of traditional risk factors. Therefore, attention should be paid to the WHtR in individuals with type 1 diabetes. Interventional drug studies are needed to show whether treating abdominal fatness will improve kidney health in type 1 diabetes.

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