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Intra-Abdominal Fat and Elevated Urine Albumin Excretion in Men With Type 1 Diabetes

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Earlier studies documented associations between central obesity and elevated albumin excretion rate or other renal injury indicators in nondiabetic subjects (1–11). A retrospective study conducted in a Kaiser Permanente mixed diabetic-nondiabetic cohort suggested that obesity increased risk for progression to end-stage renal disease (12). Studies also identified obesity as a risk factor for renal disease in type 1 diabetes (13,14). We previously examined obesity-related factors and albumin excretion within the total Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort. Conducted between 1982 and 1993, the DCCT included 1,441 subjects with type 1 diabetes randomized to intensive or conventional diabetes treatment and followed for 6.5 years on average. Details of resources utilized for the DCCT/EDIC (observational follow-up) study designs were previously published (15–18). These studies demonstrate the powerful effect of intensive insulin therapy on preventing and slowing progression of micro-and macrovascular complications and established intensive therapy as the current standard of diabetes care for patients with type 1 diabetes. However, type 1 diabetic subjects, like the general population, are becoming heavier and more at risk for obesity-related complications (19). In our cross-sectional analysis 4 years after the end of the DCCT, waist-tohip ratio (WHR), a visceral fat surrogate, was associated with elevated albumin excretion (20). In our longitudinal analysis, waist circumference was associated with subsequent development of persistent microalbuminuria (21). For this current analysis, we hypothesized that intra-abdominal fat (IAF) in particular relates more strongly to elevated albumin excretion than abdominal subcutaneous fat (SQF).

RESEARCH DESIGN AND METHODS

We analyzed IAF and other obesity measures in relation to urine albumin excretion in a group of men with type 1 diabetes. This study included DCCT/EDIC study participants (n = 64 men) at four participating DCCT/EDIC sites. Subjects were studied at the University of Washington (n = 32) between November 1997 and November 1999 and at the University of Minnesota (n = 32) between November 2001 and November 2003. Subjects studied at the University of Minnesota were recruited from three Minnesota DCCT/EDIC sites: the University of Minnesota (n = 20), International Diabetes Center (n = 11), and Mayo Clinic (n =1). This analysis was restricted to men because only one woman had an elevated albumin-to-creatinine

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

ratio (ACR). Written informed consent was obtained; the study was approved by the respective institutional review boards.

Single-slice umbilical abdominal computed tomography scans for IAF and SQF were read by one trained technician at each center, each blinded to the case/control status of study participants, utilizing well-validated software and analysis techniques (22–24). Urine was collected from second-morning voids (the mean of two different-day samples when possible). Participants with symptoms and urinary findings consistent with urinary tract infection were excluded. Urinary creatinine and microalbumin were measured at the Core DCCT/EDIC Laboratory, University of Minnesota (15). Elevated urine ACR was defined as ≥ 30 mg/g creatinine. A1C, history, and anthropometric measurements were assessed annually at DCCT/EDIC visits with standardized forms (25,26). Measures of obesity were compared using a two-sample *t* test, assuming unequal variance. Logistic regression was used to estimate the associations of obesity measurements with ACR status, with and without adjustment for potential confounders. STATA software (version 8.1; Stata, College Station, TX) was utilized for statistical analyses (27).

RESULTS

Of 64 men, 9 had elevated urine ACR ≥30 mg/g (6 had microalbuminuria [ACR 30–300 mg/g], and 3 had clinical albuminuria). Compared with men with normal ACR, men with ACR ≥30 mg/g were more likely to have received conventional insulin therapy during the DCCT, smoke, use ACE inhibitors, and have greater blood pressures, greater A1C, and dyslipidemia (higher LDL cholesterol [$P = 0.001$] and triglyceride [$P = 0.002$]).

IAF was greater in men with elevated ACR compared with men with normal ACR ($P = 0.048$); SQF was not (Table 1). Waist circumference ($P = 0.048$) and WHR ($P = 0.006$) were greater in men with elevated ACR, and BMI showed a similar trend ($P = 0.077$).

In logistic regression, elevated ACR was associated ($P < 0.05$) with greater levels of each obesity measure, except SQF (Table 1). When IAF and SQF were included as dependent variables simultaneously, magnitude of association for IAF did not change ($\beta = 0.98$ vs. $\beta = 0.99$) and retained statistical significance ($P = 0.035$), and SQF was not associated with elevated ACR ($\beta = 0.02$, $P = 0.965$). After adjustment for age, A1C, and smoking status, magnitudes of association with elevated ACR were similar for IAF, BMI, waist circumference, and WHR, with the association for BMI strongest ($\beta = 1.28$). Diabetes duration and DCCT treatment group status were not related to obesity measures or ACR status and did not lead to meaningful changes in the associations of obesity measures with ACR status in the full models (data not shown).

CONCLUSIONS

In this study, we find urine ACR more strongly associated with IAF than with SQF in middle-aged males with type 1 diabetes, suggesting that metabolic factors associated with visceral rather than subcutaneous adiposity may contribute to renal injury in this population.

There are some limitations to this cross-sectional study, conducted in a small group of people. On its own, it cannot demonstrate causality. However, our prior study in this population suggested causality by demonstrating temporality between obesity and abnormal albumin excretion. Only men were analyzed; we cannot necessarily generalize these findings to women. However, our prior studies (20,21) in this population suggest that the association between central obesity and elevated albumin excretion is at least as strong in women as in men. Given sex-related anthropometric measurement differences, however, specific strengths of associations between particular obesity measures and ACR may differ somewhat in women.

In summary, this study utilizes accurate assessments of adipose distribution in a small group of individuals, more firmly substantiating the conclusion from our earlier larger cross-sectional and longitudinal epidemiologic studies (20,21) that IAF is a more important contributor to renal injury than SQF in men with type 1 diabetes. Additionally, we find that the easiest measurements to obtain in clinical settings, BMI and waist circumference, are each strong predictors of elevated ACR in these subjects. Future studies are needed to elucidate mechanisms underlying the IAF–albumin excretion link.

Abbreviations

ACR, albumin-to-creatinine ratio; IAF, intra-abdominal fat; SQF, abdominal subcutaneous fat; WHR, waist-to-hip ratio.

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Table 1

Comparison (*t* test) and regression analyses of obesity measures in relation to urine ACR

	Comparisons				Regressions					
					Unadjusted			Adjusted†		
Obesity measure	**ACR < 30**	**ACR ≥ 30**	**p**	**Scale***	**β**	***r*²**	***P***	**β**	***r*²**	***P***
IAF	82 ± 44	136 ± 69	0.048	52 cm^2	0.99	0.151	0.012	0.95	0.262	0.020
SQF	212 ± 100	277 ± 134	0.199	106 cm^2	0.62	0.055	0.100	0.66	0.197	0.096
BMI	26.6 ± 2.8	29.5 ± 4.3	0.077	3.2 kg/m^2	0.92	0.126	0.017	1.28	0.330	0.006
Waist circumference	93 ± 8	102 ± 11	0.048	9.0 cm	1.05	0.138	0.016	1.18	0.286	0.014
WHR	0.90 ± 0.06	0.95 ± 0.04	0.006	0.06	0.99	0.118	0.013	0.88	0.209	0.072

Data are means ± SD unless otherwise indicated.

*Each independent variable scaled to its SD to facilitate comparisons.

†Each logistic regression model adjusted for age, smoking status, and A1C.