Intraabdominal fat and elevated urine albumin excretion in men with type 1 diabetes

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INTRODUCTION

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 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 1441 subjects with type 1 diabetes randomized to intensive or conventional diabetes treatment, followed for 6.5 years on average. Details of and resources utilized for the DCCT and 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 current standard of diabetes care for patients with type 1 diabetes. However, these subjects, like the general population, are becoming heavier and more at risk for obesity-related complications (19). In our cross-sectional analysis four years after the end of the DCCT, waist-hip 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 intraabdominal fat (IAF) in particular relates more strongly to elevated albumin excretion than abdominal subcutaneous fat (SQF).

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 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). The study was restricted to men because only one woman had elevated albumin-creatinine ratio (ACR). Written informed consent was obtained; the study was approved by respective Institutional Review Boards.

Single-slice umbilical abdominal computed tomography (CT) scans for IAF and SQF were read by one trained technician at each center, each blinded to case/control status of study participants, utilizing well-validated software and analysis techniques (22-24). Urine was collected from second morning voids (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 University of Minnesota, the Core DCCT/EDIC Laboratory (15). Elevated urine albumin-creatinine ratio
(ACR) was defined as ≥ 30 mg/g creatinine. Hemoglobin A1c (HbA1c), 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-SE version 8.1 software was utilized for statistical analyses (27).

RESULTS

Nine of 64 men had elevated urine ACR (≥30mg/g) (six had microalbuminuria (ACR 30-300mg/g), three had clinical albuminuria). Compared to men with normal ACR, men with ACR ≥30mg/g were more likely to have received conventional insulin therapy during the DCCT, smoke, use ACE inhibitors; and have greater blood pressures, greater HbA1c, and dyslipidemia (higher low-density lipoprotein cholesterol [p=0.001] and triglyceride [p=0.002]).

IAF was greater in men with elevated ACR compared to men 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, 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 (β = 0.98 versus β = 0.99) and retained statistical significance (p=0.035), SQF was not associated with elevated ACR (β = 0.02, p=0.965). After adjustment for age, HbA1c, and smoking status, magnitudes of association with elevated ACR were similar for IAF, BMI, waist circumference, and WHR, with the association for BMI strongest (β = 1.28). Diabetes duration and treatment group 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 (data not shown).

CONCLUSION

In this study, we find urine ACR more strongly associated with IAF than with SQF in middle-aged males with type 1 diabetes, suggesting 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 the association between central obesity and elevated albumin excretion is at least as strong in women as in men. Given gender-related anthropometric measurement differences, specific strengths of associations between particular obesity measures and ACR may differ somewhat in women though.

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 is 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.
REFERENCES

27. Stata Corp.: Stata. 8.1 ed. College Station, TX, 2003
Table 1. T-test comparisons and regression analyses of obesity measures in relation to urine albumin-creatinine ratio (ACR).

<table>
<thead>
<tr>
<th>Obesity Measure</th>
<th>t-test comparisons</th>
<th></th>
<th>Regressions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACR&lt;30</td>
<td>ACR≥30</td>
<td>p</td>
<td>Scale**</td>
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<tr>
<td>Intraabdominal fat</td>
<td>82±44</td>
<td>136±69</td>
<td>.048</td>
<td>52 cm²</td>
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<tr>
<td>Subcutaneous fat</td>
<td>212±100</td>
<td>277±134</td>
<td>.199</td>
<td>106 cm²</td>
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<tr>
<td>Body mass index</td>
<td>26.6±2.8</td>
<td>29.5±4.3</td>
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<tr>
<td>Waist circumference</td>
<td>93±8</td>
<td>102±11</td>
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<tr>
<td>Waist-hip ratio</td>
<td>0.90±0.06</td>
<td>0.95±0.04</td>
<td>.006</td>
<td></td>
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</tbody>
</table>

* Each logistic regression model adjusted for age, smoking status, and HbA1c
** Each independent variable scaled to its standard deviation to facilitate comparisons