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Original article

Obesity as defined by waist circumference but not body mass index is associated with higher renal mass complexity

Laura A. Bertrand, M.D.[a], Lewis J. Thomas, M.D.[a], Peng Li, Ph.D.[b], Claire M. Buchta, Ph.D.[a], Shannon K. Boi, M.S.[c], Rachael M. Orlandella, B.S.[c], James A. Brown, M.D.[a,d], Kenneth G. Nepple, M.D.[a,d,1], Lyse A. Norian, Ph.D.[e,f,1,*]

[a] *Department of Urology, The University of Iowa Carver College of Medicine, Iowa City, IA*
[b] *Department of Biostatistics, School of Public Health, The University of Alabama at Birmingham, Birmingham, AL*
[c] *Graduate Biomedical Sciences, University of Alabama at Birmingham, Birmingham, AL*
[d] *Holden Comprehensive Cancer Center, The University of Iowa Carver College of Medicine, Iowa City, IA*
[e] *Department of Nutrition Sciences, The University of Alabama at Birmingham School of Health Professions, Birmingham, AL*
[f] *Comprehensive Cancer Center, The University of Alabama at Birmingham, Birmingham, AL*

Abstract

Objectives: Obesity, typically defined as a body mass index (BMI) $\geq$ 30 kg/m^2, is an established risk factor for renal cell carcinoma (RCC) but is paradoxically linked to less advanced disease at diagnosis and improved outcomes. However, BMI has inherent flaws, and alternate obesity-defining metrics that emphasize abdominal fat are available. We investigated 3 obesity-defining metrics, to better examine the associations of abdominal fat vs. generalized obesity with renal tumor stage, grade, or R.E.N.A.L. nephrometry score.

Methods and materials: In a prospective cohort of 99 subjects with renal masses undergoing resection and no evidence of metastatic disease, obesity was assessed using 3 metrics: body mass index (BMI), radiographic waist circumference (WC), and retrorenal fat (RRF) pad distance. R.E.N.A.L. nephrometry scores were calculated based on preoperative CT or MRI. Univariate and multivariate analyses were performed to identify associations between obesity metrics and nephrometry score, tumor grade, and tumor stage.

Results: In the 99 subjects, surgery was partial nephrectomy in 51 and radical nephrectomy in 48. Pathology showed benign masses in 11 and RCC in 88 (of which 20 had stage T3 disease). WC was positively correlated with nephrometry score, even after controlling for age, sex, race, and diabetes status ($P = 0.02$), whereas BMI and RRF were not ($P = 0.13$, and $P = 0.57$, respectively). WC in stage T2/T3 subjects was higher than in subjects with benign masses ($P = 0.03$). In contrast, subjects with Fuhrman grade 1 and 2 tumors had higher BMI ($P < 0.01$) and WC ($P = 0.04$) than subjects with grade 3 and 4 tumors.

Conclusions: Our data suggest that obesity measured by WC, but not BMI or RRF, is associated with increased renal mass complexity. Tumor Fuhrman grade exhibited a different trend, with both high WC and BMI associated with lower-grade tumors. Our findings indicate that WC and BMI are not interchangeable obesity metrics. Further evaluation of RCC-specific outcomes using WC vs. BMI is warranted to better understand the complex relationship between general vs. abdominal obesity and RCC characteristics. © 2017 Published by Elsevier Inc.

Keywords: Renal cell carcinoma; Obesity; Waist circumference; Body mass index; Nephrometry

1. Introduction

Obesity, defined as a body mass index (BMI) score of $\geq$30 kg/m^2, is an established risk factor for renal cell carcinoma (RCC) with multiple studies showing a positive association between obesity as determined by BMI and increased RCC risk [1,2]. Clear cell histology is the most common subtype of RCC and is most strongly associated with obesity [3]. Despite increasing RCC risk, prior studies

Current address: CM Buchta, The University of Virginia.

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[1]These authors contributed equally to this work.

* Correspondence to: Department of Nutrition Sciences, The University of Alabama at Birmingham School of Health Professions, 1824 6th Ave, Birmingham, AL 35242. Tel.: +1-319-335-3013.

E-mail address: lnorian@uab.edu (L.A. Norian).

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have found that obesity as measured by BMI is associated with better pathologic features [4] and improved survival [5] in patients with RCC with organ-confined tumors. These findings of increased survival in patients with RCC with high BMI has been called an "obesity paradox" [1].

However, additional evidence suggests that associations between obesity and RCC are complex and not fully explained by the obesity paradox paradigm. One prior study found that increased visceral adipose tissue was an independent predictor of higher Fuhrman grade in T1a RCC [6]. This is notable as abdominal and subcutaneous adipose tissue may differentially contribute to obesity-related pathologies [7,8], and abdominal obesity as measured by waist circumference (WC) has been associated with greater all-cause mortality in U.S. adults, independent of BMI [9]. Additionally, Gonzales et al. found that in breast and other cancer patients, the obesity paradox existed only when BMI was used to define obesity, but not the more definitive bioelectrical impedance analysis [10].

Given the growing discrepancies reported in biological and outcome data with respect to fat distribution and obesity characteristics, our goal was to examine potential associations between various metrics of obesity and indicators of renal tumor histology, stage, and complexity in 1 cohort of RCC subjects.

2. Materials and methods

2.1. Study subjects

Between October 2012 and May 2014, adult patients with no evidence of metastatic disease undergoing resection of renal masses suspicious for RCC at the University of Iowa Hospitals and Clinics were offered enrollment in an Institutional Review Board–approved study. Informed consent was obtained for 99 subjects. Exclusion criteria included the following: active secondary malignancy, immune-modulating medications, and metastatic disease. Demographic information, including age, race, BMI, and clinical data, including final pathology, was obtained from the electronic health record.

2.2. Evaluation of obesity

BMI was calculated from subject's height/weight information as documented in patient medical records. As per World Health Organization guidelines, BMI $\geq 30\ kg/m^2$ was used as the principal metric to define obesity. Subjects' preoperative computed tomography (CT) and/or MRI scans or both were reviewed to determine 2 metrics of abdominal fat accumulation: retrorenal fat (RRF) pad distance (i.e., distance from the posterior aspect of the kidney to the posterior abdominal wall), and waist circumference (WC), which encompasses subcutaneous, visceral, and RRF depots. RRF pad distance was measured on the contralateral kidney at the level of the renal vein, as described [11]. Radiographic WC was used to measure WC at 1 cm above the umbilicus [12].

2.3. Evaluation of renal mass complexity

Preoperative imaging was available for 97/99 patients. R.E.N.A.L. nephrometry scores were calculated for each subject. R.E.N.A.L. nephrometry scoring includes tumor radius, exophytic vs. endophytic characteristics, nearness to the collecting system, anterior/posterior location, and location to polar lines [13]. Maximum mass diameter was obtained from imaging (L.B.). Masses were categorized as hilar or nonhilar, as this has been shown to correlate with tumor grade [14]. Subjects who had undergone a previous radical or partial nephrectomy or those with polycystic kidney disease were excluded, given the effect their distorted anatomy might play in calculating both nephrometry score and RRF. A single investigator performed all RRF, WC, and nephrometry score calculations (L.B.) with randomly selected subjects' measurements confirmed by a separate investigator (K.N.). Prior studies showed high interobserver correlation and reproducibility when using nephrometry scores [15].

2.4. Statistical analyses

Patients' demographics and clinical characteristics were summarized as mean ± standard deviation (SD) for continuous variables and frequency (proportion) for categorical variables. The group comparison was conducted using a two-sample t test for continuous variables and chi-square test or Fisher's exact test for categorical variables. The obesity metrics among Fuhrman grade or tumor stage were evaluated using analysis of variance (ANOVA) and two-sample t test for group comparisons. Associations between obesity metrics and potential contributing factors were evaluated with univariate analyses. BMI and RRF were log-transformed to meet the normality assumption for hypothesis testing. The associations between R.E.N.A.L. score and obesity metrics were evaluated with univariate analyses, and multivariate analyses controlling for age, sex, race, and diabetes status, using general linear regression. The raw P values were presented, and $P < 0.05$ was considered as statistically significant. All analyses were conducted using SAS 9.4 (Cary, NC).

3. Results

3.1. Study subject characteristics

Tables 1 and 2 summarize the clinical characteristics of all consented study subjects ($n = 99$). The mean BMI of our overall cohort was $32.6\ kg/m^2$. Most tumors were the clear cell histologic subtype (76.8%), and 12.1% were either