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Effect of Type 2 Diabetes Mellitus on Prognosis of Nonmetastatic Renal Cell Cancer

Evren Süer, Erdem Öztürk, Ömer Gülpınar, Aytaç Kayış, Sümer Baltacı

Department of Urology, Ankara University School of Medicine, Ankara, Turkey

Purpose: We evaluated the prognostic value of type 2 diabetes mellitus (DM) in patients treated surgically for localized renal cell carcinoma (RCC).

Materials and Methods: Between 1995 and 2011, 588 patients with renal tumor diagnoses were treated surgically and 492 patients with pathologically confirmed nonmetastatic RCC diagnoses were included in the study. The associations of clinical and pathologic parameters with a type 2 DM diagnosis were evaluated. Kaplan-Meier estimations for disease-specific survival (DSS) and overall survival (OS) were generated according to type 2 DM diagnosis, and the log-rank test was used to compare survival according to the variables.

Results: The mean age of the patients was 56.7±12 years (range, 15 to 84 years; median, 58 years) and the mean length of follow-up was 35.9±28 months (range, 1 to 145 months; median, 34.3 months). Of the 492 patients, 62 (12.6%) had a diagnosis of DM at the time of surgery (group I) and 430 did not have DM (group II). The mean age and the incidence of clear cell RCC histological subtype were significantly higher in group I than in group II ($p < 0.001$ and $p=0.036$, respectively). Although DSS and OS were lower in group I, this difference was not significant. Type 2 DM was not detected as an independent prognostic factor for DSS and OS.

Conclusions: This study investigated the role and effect of DM on the prognosis of localized RCC that was treated surgically. The present study did not detect DM as an independent prognostic factor for RCC.

Keywords: *Prognosis; Renal cell carcinoma; Type 2 diabetes mellitus*

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Corresponding Author:
Erdem Öztürk
Department of Urology, Ankara University School of Medicine, Adnan Saygun Caddesi, Altındağ, Ankara, Turkey
TEL: +90-3125082258
FAX: +90-3123112167
E-mail: drerdemoz@gmail.com

INTRODUCTION

Renal cell carcinoma (RCC) forms 2% to 3% of all cancers, with the highest incidence in Western Europe and the United States [1,2]. The incidence of RCC has steadily and gradually increased throughout the world, with some exceptions such as Scandinavian countries [3,4]. The established risk factors for RCC are smoking, obesity, and hypertension [5]. Hypertension and obesity in particular are increasing in the United States, and this increase may help to explain the rise in incidence of RCC [6,7]. Hypertension is an independent risk factor for the development of RCC [8]. The association of RCC with the duration of hypertension and the blood pressure level was also shown in previous studies [9,10]. Obesity is another important risk factor that may increase the relative risk for development of RCC to 2.76 in patients with a body mass index >40 kg/m^2 [11]. The main etiologic mechanism in these patients is hyperinsulinemia and increased insulin growth factor (IGF) secretion. The high prevalence of diabetes mellitus (DM) in patients with obesity and epidemiologic evidence for an association of DM with multiple cancers suggests a possible role of DM in the pathogenesis of RCC [12,13]. Additionally, hypertension and obesity are highly linked with type 2 DM and metabolic syndrome. Although DM is not accepted as a risk factor for RCC development, studies have shown a slightly or significantly increased risk of RCC in subjects with DM [14-16]. However, data concerning the

prognostic effect of DM on RCC are absent. In the present study, therefore, we aimed to investigate the effect of DM on the prognosis of localized RCC that was treated surgically.

MATERIALS AND METHODS

We retrospectively analyzed 586 consecutive patients who had been treated surgically (by either partial or radical nephrectomy) at our department for renal tumors between 1995 and 2011. Patients with nonmetastatic RCC were eligible for inclusion in the study. After excluding patients with histopathologically diagnosed benign tumors, those who had inadequate follow-up, and those who had lymph node involvement or distant-site metastasis, 492 of the 586 patients were enrolled in the study. All patients had preoperative laboratory tests. Preoperative characteristics including age, gender, history of type 2 DM, and medication for DM were recorded. The 2009 TNM classification was used for pathologic tumor staging. The Fuhrman grading system and Heidelberg histologic classification were used to define the tumor grade and histologic subtype, respectively.

Patients were divided according to their diabetic status. Group I consisted of patients with type 2 DM and group II consisted of nondiabetic patients. Diabetic patients were defined as having a diagnosis of type 2 DM at the time of surgery. The DM diagnosis was based on preoperative fasting glucose levels >126 mg/dL [17] and receiving current medical therapy for DM, such as oral antidiabetics or insulin. In group I, 41 and 21 patients were using oral antidiabetics and insulin, respectively. Owing to inadequate data for glycated hemoglobin (HbA_{1c}) levels, we did not include this parameter in the statistical analysis. The clinicopathologic parameters evaluated and compared were as follows: age, gender, tumor size, pathologic stage, tumor grade, histological subtype, and multifocality. Disease-specific survival (DSS) and overall survival (OS) were assessed to determine the status of the disease in these patients.

Patient follow-up was individualized for every patient. In general, the patients were assessed four times in the first year by physical examination and abdominal ultrasonography; abdominal computed tomography (CT) and chest X-ray or thoracic CT was performed 6 months postoperatively. Depending on the patient's risk status, follow-up in the second and third years was either twice or once per year. Patients were followed up yearly thereafter if there was no sign of recurrence.

The chi-square test was applied to evaluate the association between categorical variables. The Mann-Whitney test was used to compare all mean values of continuous variables. The Kaplan-Meier estimates for DSS and OS were obtained according to DM status, and the differences were examined by the log-rank test. To determine independent prognostic factors, multivariate survival analysis was performed by a Cox regression model with respect to potential influencing factors including DM, age, grade, stage, and histological subtype. Statistical significance in this study was defined as $p<0.05$. All statistical analyses were performed by using the SPSS ver. 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The mean age of the patients was 56.7±12 years (range, 15 to 84 years; median, 58 years) and the mean length of follow-up was 35.9±28 months (range, 1 to 145 months; median, 34.3 months). One hundred thirty-six patients had undergone partial nephrectomy and 356 had undergone radical nephrectomy. All patients who underwent nephron-sparing surgery had negative margins. Of the 492 patients, 62 (12.6%) had a diagnosis of DM at the time of surgery (group I) and 430 did not have DM (group II). The baseline characteristics of the patients are compared in Table 1. The mean age and the incidence of clear cell RCC histological subtype were significantly higher in group I than in group II ($p<0.001$ and $p=0.036$, respectively). Other clinicopathological parameters including gender, tumor size, tumor grade, pathologic stage, and multifocality were

TABLE 1. Clinicopathological parameters according to diabetic status of the patients

Parameter	DM (+) (group I, n=62)	DM (-) (group II, n=430)	p-value
Mean age	63.27	55.76	<0.001
Gender			0.476
Female	22 (35.5)	147 (34.1)	
Male	40 (64.5)	283 (65.9)	
Pathologic stage			0.550
T1a	17 (27.4)	121 (28.1)	
T1b	21 (33.9)	125 (29.1)	
T2a	6 (9.7)	59 (13.7)	
T2b	2 (3.2)	30 (7.0)	
T3a	14 (22.6)	71 (16.5)	
T3b–4	2 (3.2)	24 (5.6)	
Fuhrman grade			0.350
Low grade (1+2)	36 (58.1)	276 (64.2)	
High grade (3+4)	26 (41.9)	154 (35.8)	
Histologic subtype[a]			0.036
Clear cell	57 (91.9)	342 (79.5)	
Papillary	3 (4.8)	68 (15.8)	
Chromophobe	1 (1.6)	19 (4.4)	
Multifocality			0.392
Negative	3 (4.8)	34 (7.9)	
Positive	59 (95.2)	396 (92.1)	
Tumor size (cm)			0.255
≤7	46 (74.2)	288 (67.0)	
>7	16 (25.8)	142 (33.0)	

Values are presented as number (%).
DM, diabetes mellitus.
[a]:Two patients (one in each group) had collecting duct carcinoma and were not included in the statistical analysis.

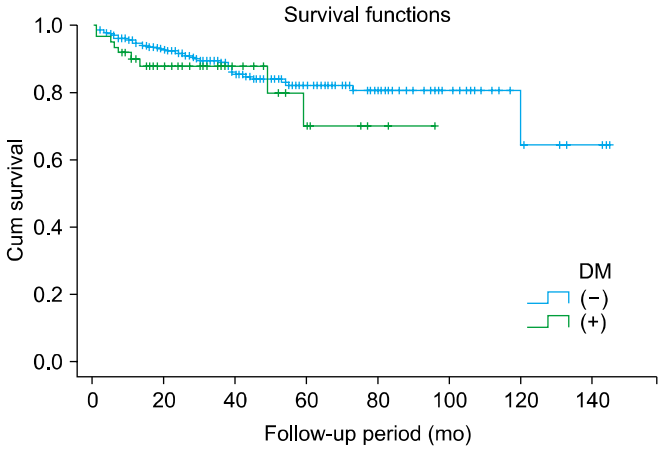

FIG. 1. Kaplan-Meier curve of the two groups for disease-specific survival. DM, diabetes mellitus.

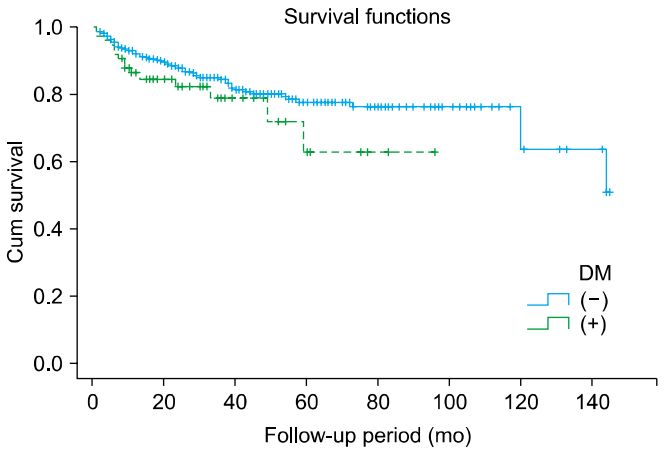

FIG. 2. Kaplan-Meier curve of the two groups for overall survival. DM, diabetes mellitus.

not significantly different between the two groups.

Kaplan-Meier analysis using a univariate log-rank test showed estimated 5-year OS as 62.9% and 77.7% for group I and group II, respectively (p=0.1). The 5-year DSS rate was 70% for group I and 82.2% for group II (p=0.3). The comparison of DSS and OS between these groups did not reveal any significant difference (Figs. 1, 2).

Cox proportional models were formed according to DSS and OS. Age, tumor size, pathologic stage, tumor grade, histological subtype, and multifocality were included in the multivariate analysis. Pathologic stage, tumor grade, tumor size, and multifocality were independent prognostic parameters for DSS (Table 2). The independent prognostic factors for OS were tumor grade, pathologic stage, and multifocality.

DISCUSSION

Similar to RCC, DM is also increasing worldwide. In the United States, the incidence of DM tripled from 1980 through 2007 [18]. The Western diet type and sedentary lifestyle are accepted as the major causes for the development of metabolic syndrome and type 2 DM. Meta-analyses performed for endometrial cancer, pancreatic cancer, and colorectal cancer have shown an increased incidence for these cancers in type 2 DM patients [19-21]. As mentioned before, established risk factors for RCC such as hypertension and obesity are highly linked with type 2 DM and metabolic syndrome. However, data concerning an association of RCC with DM are inadequate and conflicting [14,15]. In a large retrospective, population-based study, patients with DM were found to have an increased risk of RCC compared with the general population [22]. Distinctly, Joh et al. [14] demonstrated an independent association between type 2 DM and RCC in women. On the other hand, Zucchetto et al. [15] reported a nonsignificantly increased risk of RCC in subjects with DM. Although making a conclusive comment on the relationship between DM and RCC is not possible at the moment, this subject deserves further study.

Several mechanisms are proposed for the association between cancers and type 2 DM. One of these mechanisms is the stimulation of cell proliferation by hyperinsulinemia and the secretion of IGF-1. Insulin and IGF-1 generate their effects through insulin receptors and IGF-1 receptors, respectively, to promote cellular proliferation and inhibit apoptosis in many tissue types. These effects might contribute to the formation of cancer. Additionally, the can-

TABLE 2. Multivariate analysis of predictors for disease-specific survival in patients with localized renal cell carcinoma

Variable	Hazard ratio	95% CI	p-value
Age (y)			
<60	1.000		
≥60	1.425	0.581–2.678	0.365
Tumor size (cm)			
≤7	1.000		
>7	2.657	1.037–6.809	0.052
Pathologic stage			
T1a	1.000		
T1b	0.572	0.139–2.349	0.488
T2a	0.437	0.074–2.591	0.313
T2b	0.309	0.280–3.357	0.395
T3a	2.102	0.543–6.129	0.322
T3b–4	6.340	1.592–25.239	0.005
Histologic subtype			
Clear cell	1.000		
Papillary	1.598	0.575–4315	0.407
Chromophobe	0.876	0.234–2.156	0.918
Multifocality			
Negative	1.000		
Positive	2.590	1.172–5.724	0.025
Tumor grade			
Low (1+2)	1.000		
High (3+4)	3.270	1.481–7.223	0.004

CI, confidence interval.

cer cells may demonstrate an overexpression of insulin receptors, and activation of these receptors may favor cancer progression and facilitate the growth of tumors [23]. The other possible mechanisms are hyperglycemia, inflammatory cytokines, and reactive oxygen products [24]. These causes may also affect the clinical course of RCC and enhance the aggressiveness of the cancer. Thus, it is reasonable to question whether the prognosis of RCC is different in patients with type 2 DM than in nondiabetic patients. Regarding this issue, Washio et al. [25] using the database of the Japan Collaborative Cohort Study for Evaluation of Cancer Risk showed that DM increased the risk of kidney cancer death in a Japanese population. However, DM failed to remain as a significant risk factor for death in RCC patients after other factors were controlled for.

The present study focused on the prognostic effects of type 2 DM and its impact on OS and DSS in patients with clinically localized, surgically treated RCC. The comparison of DSS and OS between patients with and without type 2 DM did not reveal any significant difference, and type 2 DM was not detected as an independent prognostic factor in the multivariate analysis. Antonelli et al. [26] evaluated the role of preexisting type 2 DM in the prognosis of RCC. Similar to our study, they did not find DM as an adverse factor for RCC and non-RCC-related mortality. Habib et al. [27] analyzed a total of 473 cases of RCC and reported that 25.4% of RCC cases were associated with DM. The prevalence of DM in our study group was 12.6%, which agrees with the reported prevalence of type 2 DM in Turkey [28]. Antonelli et al. [26] reported a prevalence of type 2 DM of 8.9% in their cohort. In our study, the mean age of the patients with DM was significantly higher than the mean age of the nondiabetics. This finding can be explained by the increasing incidence of type 2 DM in elderly patients. In this study, the only pathologic prognostic factor that exhibited a significant difference was histological subtype and clear cell subtype, which were significantly higher in type 2 DM patients than in nondiabetic patients. In their recent study, Habib et al. [27] also reported that clear cell histology was the most common histology (92%) in diabetic RCC cases. Additionally, they found a predominance of small, localized RCC in diabetic patients. The cumulative findings of our study and Habib et al's study may suggest an increased risk of development of the clear cell histological cell type in diabetic RCC patients.

This study had some limitations. The retrospective nature of this study was a limiting factor. Although inclusion of HbA_{1c} levels may have allowed us to predict previous blood glucose status, this test only covers the previous 3-month period, which seems to be inadequate to demonstrate the effects of blood glucose levels on the development and character of RCC. Only serial pre-RCC era HbA_{1c} measurements may meet the expectations of clinicians. The duration of DM, medication type, and medication time are also important aspects for evaluating the effects of type 2 DM on RCC development and characteristics. One other limitation is the evaluation of the prognostic role of type 2 DM without the inclusion of metabolic syndrome components in the evaluation. Obesity and hypertension, which are established risk factors for RCC, may also affect the prognosis in these patients. Currently, however, there are no studies investigating the prognostic effects of these diseases on RCC.

CONCLUSIONS

This study investigated the role and effect of DM on the prognosis of localized RCC that was treated surgically. The present study did not detect DM as an independent prognostic factor for RCC.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

REFERENCES

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin 2007;57:43-66.
2. European Network of Cancer Registries. Eurocim version 4.0. European incidence database V2.3, 730 entity dictionary (2001). Lyon; European Network of Cancer Registries; 2001.
3. Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK. Rising incidence of small renal masses: a need to reassess treatment effect. J Natl Cancer Inst 2006;98:1331-4.
4. Lindblad P. Epidemiology of renal cell carcinoma. Scand J Surg 2004;93:88-96.
5. Ljungberg B, Cowan NC, Hanbury DC, Hora M, Kuczyk MA, Merseburger AS, et al. EAU guidelines on renal cell carcinoma: the 2010 update. Eur Urol 2010;58:398-406.
6. Hajjar I, Kotchen JM, Kotchen TA. Hypertension: trends in prevalence, incidence, and control. Annu Rev Public Health 2006;27:465-90.
7. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. JAMA 2006;295:1549-55.
8. Chow WH, Gridley G, Fraumeni JF Jr, Jarvholm B. Obesity, hypertension, and the risk of kidney cancer in men. N Engl J Med 2000;343:1305-11.
9. Grove JS, Nomura A, Severson RK, Stemmermann GN. The association of blood pressure with cancer incidence in a prospective study. Am J Epidemiol 1991;134:942-7.
10. Fraser GE, Phillips RL, Beeson WL. Hypertension, antihypertensive medication and risk of renal carcinoma in California Seventh-Day Adventists. Int J Epidemiol 1990;19:832-8.
11. Bjorge T, Tretli S, Engeland A. Relation of height and body mass index to renal cell carcinoma in two million Norwegian men and women. Am J Epidemiol 2004;160:1168-76.
12. Nicolucci A. Epidemiological aspects of neoplasms in diabetes. Acta Diabetol 2010;47:87-95.
13. Tsugane S, Inoue M. Insulin resistance and cancer: epidemiological evidence. Cancer Sci 2010;101:1073-9.
14. Joh HK, Willett WC, Cho E. Type 2 diabetes and the risk of renal cell cancer in women. Diabetes Care 2011;34:1552-6.
15. Zucchetto A, Dal Maso L, Tavani A, Montella M, Ramazzotti V, Talamini R, et al. History of treated hypertension and diabetes mellitus and risk of renal cell cancer. Ann Oncol 2007;18:596-600.
16. Lindblad P, Chow WH, Chan J, Bergstrom A, Wolk A, Gridley G, et al. The role of diabetes mellitus in the aetiology of renal cell

cancer. Diabetologia 1999;42:107-12.
17. American Diabetes Association. Standards of medical care in diabetes: 2012. Diabetes Care 2012;35 Suppl 1:S11-63.
18. Centers for Disease Control and Prevention. National Diabetes Surveillance System: prevalence of diabetes [Internet]. Atlanta: Centers for Disease Control and Prevention; [cited 2010 Apr 17]. Available from: http://www.cdc.gov/diabetes/statistics/prev/national/figpersons.htm.
19. Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia 2007;50:1365-74.
20. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer 2005;92:2076-83.
21. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst 2005;97:1679-87.
22. Wideroff L, Gridley G, Mellemkjaer L, Chow WH, Linet M, Keehn S, et al. Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. J Natl Cancer Inst 1997;89:1360-5.
23. Papa V, Pezzino V, Costantino A, Belfiore A, Giuffrida D, Frittitta L, et al. Elevated insulin receptor content in human breast cancer. J Clin Invest 1990;86:1503-10.
24. Suh S, Kim KW. Diabetes and cancer: is diabetes causally related to cancer? Diabetes Metab J 2011;35:193-8.
25. Washio M, Mori M, Khan M, Sakauchi F, Watanabe Y, Ozasa K, et al. Diabetes mellitus and kidney cancer risk: the results of Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study). Int J Urol 2007;14:393-7.
26. Antonelli A, Arrighi N, Corti S, Zanotelli T, Cozzoli A, Cosciani Cunico S, et al. Pre-existing type-2 diabetes is not an adverse prognostic factor in patients with renal cell carcinoma: A single-center retrospective study. Urol Oncol 2012 Jan 24 [Epub]. http://dx.doi.org/10.1016/j.urolonc.2011.12.013.
27. Habib SL, Prihoda TJ, Luna M, Werner SA. Diabetes and risk of renal cell carcinoma. J Cancer 2012;3:42-8.
28. Satman I, Yilmaz T, Sengul A, Salman S, Salman F, Uygur S, et al. Population-based study of diabetes and risk characteristics in Turkey: results of the turkish diabetes epidemiology study (TURDEP). Diabetes Care 2002;25:1551-6.