RESEARCH ARTICLE

Diabetes Mellitus as a Risk Factor for High Grade Renal Cell Carcinoma

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Abstract

Background: Diabetes is a chronic disease characterized by impaired fasting blood glucose that leads to disturbances in various organs. In this study, we evaluated relationships between tumor size and grade in a population of diabetic and non-diabetic patients with renal cell carcinoma. Materials and Methods: Between 2007-2013, in our clinic radical nephrectomy performed to 310 patients for renal tumors and pathology reported renal cell carcinoma cases were enrolled in the study. Patients with and without a history of diabetes regarding fasting glucose and HgA1c levels were evaluated during surgery for tumor size and Fuhrman grade. Results: Diabetes was found in 95 patients. The mean age of the patients with and without diabetes mellitus was 64.3 (40-79) and 58.4 (31-87) years, respectively. In the diabetes group 51% of patients had a tumor size over 7 cm and 54% a tumor grade over Fuhrman 3. The respective figures in the non-diabetes group were 35% and 30% ($p<0.05$ in both cases). Conclusions: Renal cancer appears more aggressive in patients with diabetes. In this study lifestyle and risk factors with diabetes regulation were observed to be important for renal cancer patients. Multicenter studies are needed in larger series for more accurate results.

Keywords: Diabetes - renal cell carcinoma - tumor size - Furhman grade - HgA1c

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Introduction

Renal cell carcinoma (RCC) is the most common renal malignancy in adults and leads to mortality of over 100,000 per year worldwide. In the United States. renal cell carcinoma accounts for 2.3% of all cancer deaths (Jemal et al., 2007). RCC is more prevalent in men than in women and occurs most often at 50-70 years of age. Cancer involving the renal parenchyma accounts for the majority of cases, while the minority of cases is usually due to cancer of the renal pelvis (Rodriguez et al., 2005). The predominant subtype of RCC is clear cell type that represents 70-90% of RCC and is derived from the proximal tubular epithelium (Washio et al., 2013). The highest incidence of RCC is found in North America and Europe. The incidence and the incidental detection of RCC in asymptomatic patients have been increasing worldwide until recently (Chow et al., 2010; Weikert and Ljungberg, 2010; Choi et al., 2011). The increase can be partly explained by the widespread usage of ultrasound, abdominal computerized tomography (CT) and magnetic resonance imaging in recent years (Lee et al., 2012).

Diabetes mellitus (DM), a metabolic disease, is one of the major causes of morbidity and mortality worldwide (Anderson and Chu, 2007). The global prevalence of DM in 2010 was 284 million people worldwide, constituting around 6.4% of the world population, and is expected to continue to increase in the future (Farag and Gaballa, 2011). Epidemiologic studies have shown that patients with diabetes mellitus are at higher risk than the general population for developing certain malignancies including kidney, liver, biliary tract, pancreas and colon. The importance of diabetes as a potential risk factor for cancer has been shown in clinical and autopsy studies (Wideroff et al., 1997; Lindblad et al., 1999; Czyzyk and Szczepanik, 2000). In the retrospective International Cancer Study, a 5- to 10-year history of diabetes increased the relative risk of cancer by 40% in both men and women (Schlehofer, 1996). Several mechanisms caused in the development of renal cancer in diabetes have included increased growth factors and/or their receptors, hyperinsulinemia and glucose availability (Giovannucci, 2001; Ozbek et al., 2014).

Meanwhile, controversies continue with regard to the

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potential association between RCC and DM. Although DM has been associated with an increased risk of several cancers, its impact on the risk of RCC is still a subject of debate (Larsson and Wolk, 2011). The aim of this study was to evaluate the relationship between tumor size and grade commonly in the population of diabetes in patients with renal cell carcinoma.

Materials and Methods

We retrospectively reviewed the records of 310 consecutive patients with RCC who underwent radical nephrectomy at our institution between January 2007 and May 2013. We divided the patients into two groups whether they had DM or not. We analyzed the following clinicopathologic variables: age, gender, the presence of hypertension, body mass index (BMI), tumor size, histologic subtype, Fuhrman nuclear grade, fasting blood glucose and HgA1C levels.Diabetic laboratory parameters including fasting blood glucose and HgA1C levels were measured using enzymatic methods with an autoanalyzer. Pathologic staging was performed using the 7th edition of the American Joint Committee on Cancer (AJCC). Histologic subtype was determined according to the 1997 World Health Organization Heidelberg classification and tumor nuclear grading was performed according to the Fuhrman nuclear grading system. The relationship between diabetic laboratory parameters,tumor size and nuclear grade of the two groups were evaluated statisticaly. Local ethics committee approval had beenobtained before the commence of the study.

Analyses were completed using Student t-test and Chi-square tests. All statistical tests were two-tailed, and statistical significance was defined as $p<0.05$. All analysis were conducted using SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Among the 310 total patients analyzed in our study, there were 176 males (56.8%) and 134 females (43.2%). Demographic analyses are demonstrated in Table 1. Diabetes mellitus was found in 95 patients.The mean age of patients with the DM group was 66.3±9.65 and non-DM group was 58.7±13.03 years.In the diabetes group, 51% of patients had a tumor size over 7 cm and 54% of patients tumor grade over fuhrman 3. In non-diabetes group, 35% of patients had a tumor size over 7 cm and 30% of patients tumor grade over fuhrman 3. Patients with diabetes compared to patients without diabetes,tumor size and grade were detected significantly higher ($p<0.05$). These charasteristics are shown in Table 2. In patients with diabetes, HgA1C and fasting blood glucose levels were found significantly higher ($p<0.05$) compared to patients without diabetes. These charasteristics are shown in Table 2.

Discussion

In our study, we investigated the correlation between diabetic laboratory parameters, tumor size and grade with DM in renal cell carcinoma. Altough DM is a well known risk factor resulting in RCC, its connection with tumor size and nuclear grade are not researched enough in literature.

Our findings indicate that a high proportion of RCC cases are associated with diabetes, suggesting that diabetes is one of the factors for the development of RCC. At our institution, when RCC subjects were screened for a history of diabetes, we observed a higher incidence of diabetes in male RCC subjects compared to female subjects. Habib et al. (2012) and Gupta et al. (2012) observed a higher incidence of diabetes in female RCC subjects compared to male subjects. In addition, diabetic RCC patients had a predominance of nuclear grade III, tumor size >7 cm and the average HgA1C level had no significant difference

Table 1. Demographic Parameters and Clinical Features of the Patients in Two Groups

Parameters		Patients with DM (N=95)	Patients with Non-DM (N=215)	p value
Average age		66.3±9.65	58.7±13.03	0.250
Gender (No, %)	Male	51 (53)	125 (59)	0.620
	Female	44 (47)	90 (41)	0.710
BMI	<25	2	30	
	25-30	46	151	
	>30	47	34	
Hypertension (No, %)		54 (56)	104 (48)	0.001
HgA1C (mean±SD)		6.03±0.61	4.94±0.65	0.011
Fasting blood glucose (mean±SD)		158.02±21.01	90.21±12.82	0.028
Hystological subtype	Clear cell	88 (92)	184 (86)	
(No, %)	Papillary	4 (4)	17 (8)	
	Chromophope	3 (4)	12 (5)	
	Others	0 (0)	2 (1)	
Pathologic stage	T1A	19 (21)	74 (34)	0.004
(No, %)	T1B	21 (19)	58 (27)	0.016
	T2A	28 (29)	42 (21)	0.014
	T2B	2 (1)	7 (3)	0.135
	T3	24 (29)	32 (15)	0.004
	T4	1 (1)	2 (1)	1
Furhman grade	1	0	5 (2)	
(No, %)	2	44 (46)	145 (68)	
	3	45 (47)	52 (24)	0.001
	4	6 (7)	13 (6)	

Table 2.

Parameters		Tumor size and nuclear grade distribution in two groups			Comparison of HgA1C in different sizes and grades of Renal Cell Carcinoma			Comparison of fasting blood glucose in different sizes and grades of Renal Cell Carcinoma		
		Patients with DM (N=95)	Patients with Non-DM (N=215)	p value	Patients with DM (N=95)	Patients with Non-DM (N=215)	p value	Patients with DM (N=95)	Patients with Non-DM (N=215)	p value
Tumor size	≥ 7 cm	49 (51%)	75 (35%)	0.003	6.03±0.52	4.98±0.53	<0.01	165.1±13.02	90.4±7.2	0.003
	7 cm	46 (49%)	140 (65%)		6.00±0.73	4.94±0.49		161.1±12.7	89.9±6.9	
Furhman nuclear grade	3 and 4	51 (54%)	65 (30%)	0.002	6.15±0.82	5.04±0.65	0.025	163.2±17.81	92.88±8.42	0.003
	1 and 2	44 (46%)	150 (70%)		5.99±0.63	4.88±0.61		158.2±16.48	89.23±7.95	

in diabetic patients with tumors size >7 cm compared to <7 cm in our study. Habib et al. (2012) observed diabetic RCC patients had a predominance of nuclear grade II, tumor size <5 cm and the average HgA1C level was significantly higher in patients with tumors size <5 cm compared to >5 cm.

RCC is the most common renal malignancy in adults, with a greater incidence in males than females and average age at diagnosis in the early 60s (Jee et al., 2005). Similarly, the incidence of RCC was predominated in males with the dominant age range at presentation being 60-70 years in our study. Habib et al. (2012) observed the incidence of RCC was predominated in males with a dominant age range at presentation being 50-59 years. Females dominant ages were consistent with other series ın both studies. This is slightly younger than the mean age of presentation reported by most case series and may be due to early detection .

In epidemiological and autopsy studies, IGF-1, elevated fasting serum glucose and diabetes were risk factors for the development and mortality of cancer in several organs including kidney (Giovannucci, 2001; Ozbek et al., 2014). The predominant subtype of RCC is clear cell type that represents 70-90% of RCC and is derived from the proximal tubular epithelium and diabetes facilitates this type tumor development by several pathways (Washio et al., 2013). In 98% of these tumors, whether familial, sporadic or associated with Von Hippel-Lindau (VHL) syndrome, they typically result from a somatic mutation within the VHL tumor-suppressor gene found on the short arm of chromosome 3 3p25 (Bruce et al., 2000; Giovannucci, 2001; Lowrance et al., 2009). Mutation of VHL activates hypoxia-inducible factor-1 (HIF-1), leading to increased transcription of pro-angiogenic factors including PDGF and VEGF that play a key role in renal cell tumorigenesis. In diabetic patients, other pathogenetic mechanisms previously described may also contribute to clear cell RCC including: prolonged exposure to proinsulin products with some homology to IGF-1, raised growth factors and growth factor receptors, increased endogenous estrogen levels, end-stage renal disease due to diabetic nephropathy and hypertension (Sonksen et al., 1993; Lindblad et al., 1999; Miyajima et al., 2003; Parker et al., 2004).

The incidence of all stages of kidney cancer is increasing worldwide, particularly T1 disease and primarily reflects small tumors discovered incidentally on abdominal imaging (Wallen et al., 2007). In our study, RCC cases with DM showed a predominance of tumor size >7 cm and hıgh nuclear grade disease. Conversely,diabetic RCC cases had a predominance of tumor size <5 cm and low nuclear grade disease. Tumor staging in adult RCC is a strong prognostic indicator and the presence of lower-stage tumors in DM patients suggests a favorable response to therapy and survival.

In conclusion, patients with DM were found to have statistically significantly higher nuclear grade and tumor size in our study.Renal cancer remains more aggressive in patients with diabetes. Lifestyle and risk factors with diabetes regulation are important for renal cancer patients. Multicenter studies are needed to further evaluate the importance of glycemic control and effective reduction of glucose levels on the outcome of RCC.

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