RESEARCH ARTICLE

Renal Cell Carcinoma is More Aggressive in Turkish Patients with the Metabolic Syndrome

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Abstract

Background: Metabolic syndrome (MetS) is a multifactorial disease characterized by impaired glucose tolerance/diabetes, obesity, high triglyceride levels, low HDL levels, and hypertension. In this study we evaluate the relationship between tumor size and grade, and presence of the metabolic syndrome in patients with renal cell carcinoma. Materials and Methods: Between 2007-2013, radical nephrectomy was performed for 310 patients with renal tumors in our clinic and those with pathology reported renal cell carcinoma were enrolled and divided into two groups, with and without metabolic syndrome diagnosed on the basis of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria. The relationship between tumor size and grade of the two groups (Fuhrman nuclear degree) was evaluated statistically. Results: The metabolic syndrome was found in 70 patients, with a mean age of 65.5 (40-87), as compared to 58.8 (31-84) years in the non-metabolic syndrome group. Tumor size over 7 cm was found in 54% and 33%, respectively, and tumor grade over Fuhrman 3 in 56% and 32% of patients. Patients with metabolic syndrome had significantly higher tumor size and grade ($p<0.05$). In the presence of hypertension, diabetes and high triglyceride levels, significant assocations were again observed ($p<0.05$). Tumor size and degree also increased with increasing body mass index but this was not statistically significant ($p>0.05$). Conclusions: Renal cancer is more aggressive in patients with metabolic syndrome. Lifestyle and risk factors were revealed to be significant influences in renal cancer patients.

Keywords: Metabolic syndrome - renal cell carcinoma - tumor size - Furhman grade

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Introduction

Renal cell carcinoma (RCC) is a relatively rare disease in human, accounting for about 2% of all cancers worldwide. Approximately 150 000 new cases and 78 000 deaths from the disease occur annually (Pantuck et al., 2001). It is a disease typically presenting in elderly patients with the mean age at diagnosis being around 60 years (Patard et al., 2004). RCC involving the renal parenchyma accounts for the majority of cases. The predominant subtype of RCC is clear cell type that represents 80% of RCC and is derived from the tubular epithelium. Other types of RCC are papillary (15%), chromophobe (5%), and collecting duct (Shanks, 1999; Rodriguez et al., 2005). 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 world-wide until recently (Chow et al., 2010; Weikert and Ljungberg, 2010; Choi et al., 2011). The increase can be partly explained with the widespread usages of ultrasound, abdominal computerized tomography (CT) and magnetic resonance imaging in recent years (Chow et al., 1999).

Several well-established life-style risk factors, such as BMI, hypertension, and smoking, have been identified as potentially predisposing to renal cell carcinoma development(Rini et al., 2009). Previous studies have reported that diabetes type 2 among women and high BMI and blood pressure among men are independent risk factors for RCC,however, those studies had no data of blood lipids (Chow et al., 2000; Joh et al., 2011). The Swedish AMORIS study reported that high levels of triglycerides were associated with risk of RCC. A study conducted in Austria found that patients who were being treated with statins for control of dyslipidemia appeared to have a significantly reduced risk of kidney cancer, while serum triglyceride concentrations showed positive association with renal cancer in men (Ulmer et al., 2009). However, relationships between dyslipidemia and renal cell carcinoma have not been established yet.

Metabolic syndrome (MetS) is an important public health problem worldwide, and its prevalence is increasing (Gorbachinsky et al., 2010). MetS characterized by

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impaired glucose tolerance/diabetes, obesity, high triglyceride levels, low HDL levels, and hypertension is a multifactorial chronic disease associated with high mortality (Eckel, 2007). Throughout the years, numerous definitions of MetS have been proposed by various organizations. Each of the definitions shares many similarities, including the presence of criteria relating to obesity, hyperglycemia, dyslipidemia, and hypertension. However, several differences among the classifications are noted. The National Cholesterol Education Program(NCEP) Adult Treatment Panel III (ATP III) definition is the one most used today because it incorporates the key concepts of MetS, relies on commonly used laboratory studies available to most physicians, and is less restrictive than the other classifications (Huang, 2009).

The aim of this study was to evaluate the relationship between tumor size and grade with Metabolic syndrome 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. Metabolic syndrome was defined according to the criteria established in 2005 by the NCEP/ATP III. For the criteria for metabolic syndrome, abdominal obesity was defined as waist circumference >102 cm in men and >88 cm in women, according to the NCEP/ATP III obesity criteria.Metabolic syndrome was diagnosed in those who satisfied at least 3 of the following 5 criteria: waist circumference >88 cm in women and >102 cm in men, triglyceride concentration >150 mg/dL or undergoing treatment for hypertriglyceridemia, HDL cholesterol concentration <40 mg/dL in men and <50 mg/dL in women or undergoing treatment for low HDL-C level, blood pressure >130/85 mm Hg or undergoing treatment for hypertension, and fasting plasma glucose level >100 mg/dL or undergoing treatment for hyperglycemia. We divided the patients into two groups whether they have metabolic syndrome or not. We analyzed the following clinicopathologic variables: age, gender, the presence of hypertension, diabetes, body mass index (BMI), tumor size, histologic subtype, Fuhrman nuclear grade, HDL and trigliseride levels. Plasma fasting glucose, high-density lipoprotein (HDL) cholesterol levels and triglycerides 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 betweentumor size and nuclear grade of the two groups were evaluated statisticaly.Local ethics committee approval had been obtained before the commence of the study.

Analyses were completed using Chi-square tests and Logistic regression analysis. 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 analyzis were demonstrated in table-1. Metabolic syndrome was found in 70 patients. The mean age of patients with the metabolic syndrome group was 65.5±12.34 and non-metabolic syndrome group was 58.8±11.84 years. Tumor size were determined over 7 cm in 54% of patients with metabolic syndrome and in 56% of patients tumor grade was over Fuhrman nuclear grade 3. In non- metabolic syndrome group 33% of patients were found to have tumor size over 7 cm and in 32% of patients tumor grade was over Fuhrman nuclear grade 3. Patients with metabolic syndrome were compared to patients without metabolic syndrome, tumor size and grade were detected significantly higher (p<0.05). These charasteristics were shown in table-2 and table-3. Table-4

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

Parameters	Patients with Metabolic Syndrome (N= 70)	Patients with Non-Metabolic Syndrome (N=240)	p value
Average age	66.5±12.34	58.8±11.84	0.25
Gender(noun and %)			
Male	39 (56)	137 (58)	0.71
Female	31 (44)	103 (42)	0.62
BMI			
<25	1	33	
25-30	31	174	
>30	38	35	
Hypertension (noun and%)	51 (72)	109 (45)	0.001
Diabetes (noun and%)	60 (85)	35 (14)	0.0001
Trigliserid level (mean±SD)	196.52±36.4	151.98±39.2	0.011
HDL level (mean±SD)	43.02±4.01	46.13±4.82	0.148
Hystological subtype (noun and%)			
Clear cell	65 (92)	207 (86)	
Papillary	2 (2)	19 (7)	
Chromophope	3 (6)	12 (5)	
Others	0 (0)	2 (2)	
Pathologic stage (n and%)			
T1A	15 (21)	78 (33)	0.002
T1B	13 (19)	66 (27)	0.013
T2A	20 (29)	50 (21)	0.011
T2B	1 (1)	8 (3)	0.125
T3	20 (29)	36 (15)	0.002
T4	1 (1)	2 (1)	1
Furhman grade (noun and%)			
GRADE 1	0	5 (2)	
GRADE 2	30 (43)	159 (66)	
GRADE 3	37 (53)	60 (25)	0.003
GRADE 4	3 (4)	16 (7)	

Table 2. Tumor Size and Nuclear Grade Distribution in two Groups.

Parameters	Patients with Metabolic Syndrome (N= 70)	Patients with Non-Metabolic Syndrome (N=240)	p value
Tumor size			
≥ 7 cm	38 (%54)	81 (%33)	0.002
< 7 cm	32 (%46)	159 (%67)	0.009
Furhman nuclear grade			
3 and 4	40 (%56)	76 (%32)	0.001
1 and 2	30 (%44)	164 (%68)	0.004

Table 3. Logistic Regression Analysis of the Relationship of Metabolic Syndrome and Demographic Characteristics to Tumor Size and Furhman Grade.

Covariates	Tumor Size		Fuhrman Grade	
	OR	p	OR	p
Gender	0.966	0.917	0.737	0.364
Age	1.067	0.001*	1.036	0.002*
History of cancer	0.141	0.452	0.271	0.052
Smoking	1.224	0.545	1.470	0.253
Alcohol consumption	0.592	0.256	0.635	0.346
Metabolic syndrome	0.312	0.001*	0.102	0.001*

*Statistically meaningful

Table 4. Logistic Regression Analysis of the Relationship of Metabolic Syndrome Parameters to Tumor size and Furhman Grade

Covariates	Tumor Size		Fuhrman Grade	
	OR	p	OR	p
Hypertension	5.527	0.001*	6.293	0.001*
Diabetes mellitus	1.906	0.035*	6.003	0.001*
BMI	1.084	0.116	0.965	0.512
Triglyceride level	1.011	0.011*	1.009	0.042*
HDL level	1.005	0.904	0.986	0.728

*Statistically meaningful, BMI: body mass index, HDL, high density lipoprotein.

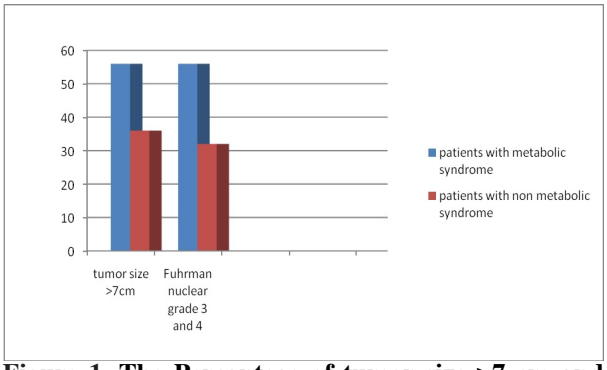

Figure 1. The Percantege of tumor size >7 cm and Nuclear Grade in two Groups in Chart

shows logistic regression analysis of the relationship of metabolic syndrome parameters to tumor size and furhman grade. The presence of hypertension, diabetes and high triglyceride levels; tumor size over 7 cm and tumor grade over fuhrman 3 is observed significantly higher ($p<0.05$).

Discussion

In our study we investigated the correlation between tumor size and grade with metabolic syndrome in renal cell carcinoma. Altough hypertension and obesity are the components of MetS and well known risk factors resulting in RCC, their connection with tumor size and nuclear grade are not researched in literature.

We have grouped the patients according to BMI and patients with >30 were assessed as obese. Especially viseral abdominal obesity may have impact on tumor biyogenesis since many tumoregenic factors are released from adipose tissue. Furthermore, obesity causes the changes in lipid regulation and results in insulin resistance that may foster cancer development (Ibrahim, 2010). Epidemiological studies performed to date have consistently shown an increased relative risk of RCC with increases in BMI (Bergstrom et al., 2001). In our study we observed ın obese patients tumor grade and size are higher but not statistically significant. Conversely, Parker et al found that patients with an increased BMI were more likely to present with a less aggressive form of RCC (Parker et al., 2006).

In epidemiological and autopsy studies, elevated fasting serum glucose and diabetes were risk factors for the development of cancer in several organs including kidney (Giovannucci, 2001). The predominant subtype of RCC is clear cell type that represents 80% of RCC and is derived from the tubular epithelium and diabetes facilitates this type tumor development in several pathways (Shanks, 1999). 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 tu-mor-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 pro-insulin products with some homol-ogy to IGF-1, raised growth factors and growth factor receptors (Lindblad et al., 1999). In our study % 85 of patients in metabolic syndrome group have diabetes mellitus and we observed higher for tumor grade and size in diabetic patients. Conversely, ın a study by Habib et al. (2012), diabetic RCC patients have been found to have a predominance of the clear cell type RCC, nuclear grade II, tumor size 1-5 cm.

Hypertension which is a common risk factor of RCC is an important component of metabolic syndrome. The relation between hypertension and RCC might be mediated by other risk factors, such as obesity, often in copresence with hypertension (Flaherty et al., 2005). Being associated with metabolic or functional changes, hypertension may induce renal injury or may predispose kidney to carcinogenesis (McLaughlin JK et al., 1995; Chow et al., 2000). The pathogenetic relationship between renal cell carcinoma and hypertension has been shown in clinical and experimental trials, where renin-producing renal cell carcinomas as well as endothelin-1 and urotensin-II-producing renal cell carcinomas were the cause of renal hypertension (Takahashi et al., 2001; Pflug et al., 2007). In our study, 72% of the patients in metabolic syndrome group were found to have hypertension and tumor size, grade were considerabely higher than non metabolic syndrome group.

Dyslipidemia (high triglyceride levels and low HDL levels) is an another major component of metabolic syndrome. There is controversy in literature how trigliserid levels affect cancer prognosis and incidence. Several studies have reported that cancer incidence and cancer mortality were lower in men with high baseline levels of TC (Eichholzer et al., 2000; Bowers et al., 2006). While this inverse association was seen in the majority of previous studies, others found cancer risk showed no relation at all (Stolzenberg-Solomon et al., 2002). Biological mechanisms that might link low

serum levels of HDLcholesterol with cancer are not well established (Fiorenza et al., 2000). The function of HDL-cholesterol in reverse cholesterol transport is important in development of atherosclerosis; however, it is not obvious how this function of HDL-cholesterol could influence carcinogenesis (Tall, 1998). We assessed trigliserid and HDL levels in patients in both metabolic syndrome and non metabolic syndrome groups. In our study, while trigliseride levels were significantly higher in metabolic syndrome patients, HDL levels were not found significantly different between two groups.

In conclusion, metabolic syndrome is a multifactorial originated disease which contains impaired glucose tolerance/diabetes, obesity, high triglyceride levels, low HDL levels, and hypertension. All these components may have effect on tumor carcinogenesis in similar pathways. In our study patients with metabolic syndrome were found to have statistically significant higher nuclear grade and tumor size. Further studies with more patients are needed to confirm our study.

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