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Assessment of the Expression of GLUT1 in Renal Cell Carcinoma and its Various Subtypes

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Abstract

BACKGROUND: Renal cell carcinoma is one of the most common tumors of the kidney. Glucose transporters, transport glucose, and increased expression of these transporters have been reported in various tumor types. Glucose transporter 1 (GLUT1), the best-known glucose transporter, has an important role at several stages in cancer progression. The overexpression of GLUT1 in the tumor cells indicates an increased proliferation and invasive behavior of the tumor.

AIM: This study aims to investigate the expression of GLUT1 in renal cell carcinoma and its subtypes.

METHODS: This study is a descriptive cross-sectional study that was performed on patients with renal cell carcinoma. Seventy reports of formalin fixed; paraffin-embedded blocks of renal cell carcinoma were selected from pathology archives. The samples included: clear cell type renal cell carcinoma, RCC clear cell type with sarcomatoid feature, papillary renal cell carcinoma, and chromophobe renal cell carcinoma.

RESULTS: In this study, 50 male and 20 female samples (71.4% and 28.6%) with the mean age of 57.9 ± 13.1 years were studied. Forty-three samples (61.4%) were positive for GLUT1 and 27 (38.9%) were negative for it. For the GLUT1 expression being positive or negative between the two groups, was not significantly affected by the age, sex, and the grade of the tumor, </AQ17>while the difference between the two groups was statistically significant in terms of stage and type of tumor (p < 0/001, p = 0.039).

CONCLUSION: Renal cell carcinoma of ccRCC type is associated with increased GLUT1 expression. Therefore, the GLUT1 immunohistochemistry marker can be a useful marker for diagnosis of RCC, specifically ccRCC type.

Introduction

Renal cell carcinoma (RCC) is one of the most common tumors of the kidney [1]. The worldwide incidence of renal cell carcinoma has increased in the past three decades. It is estimated that 63,300 and 54,390 patients are diagnosed every year in the EU and US, respectively, of which 39,000 eventually succumb to the disease [2]. It has been known for 70 years that cancer cell growth is an energy related process supported by an increased glucose metabolism. This phenomenon suggests a need for a corresponding increased uptake of glucose across the plasma membrane through an enhancement in the glucose transporter proteins [3], [4], [5], [6], [7]. Intracellular glucose transport is necessary for survival, growth, proliferation, and function of cells [8], [9], [10]. However, tumor cells have a reduced ability to use oxidative metabolism and rely instead on an increased rate of glycolysis and glucose use. A more active glycolytic metabolism is reflected in an increased rate of glucose uptake [2], [4], [5], [6], [7], [11], [12], [13]. In comparison with normal cells, tumor cells can tolerate hypoxia by increasing glucose uptake [2]. Glucose transporters have a crucial role in the supply of glucose and other sugars to metabolically active cells. GLUT1, the best-known glucose transporter, has an important role at several stages in cancer progression [14], [15], [16]. A number of studies have demonstrated that the overexpression of glucose transport 1 (GLUT1) in tumor cells indicates increased proliferation and invasive tumor behavior [2]. This differential glucose uptake between normal and tumor cells is the basis for the diagnosis of various tumors by positron emission tomography using the glucose analogue fluorine-18-fluorodeoxyglucose [17]. Recently, an expanding family of transmembrane proteins has been identified that are responsible for the facilitative glucose transportation. Their distribution and affinity

for monosaccharides differ according to specific tissue requirements [3]. The glucose transporter (GLUT) protein family consists of 14 members grouped into three major classes based on sequence homology and substrate selectivity [17], [18]. GLUT proteins mediate the transport of glucose and other monosaccharides into and out of mammalian cells according to the concentration gradient [19]. The expression of five facilitative glucose transporter genes, GLUT1 (erythrocyte type), GLUT2 (liver type), GLUT3 (brain type), GLUT4 (muscle/fat type), and GLUT5 (small intestine type), is relatively tissue specific [20]. GLUT-1 is largely undetectable by immunohistochemistry on normal epithelial tissues and benign epithelial tumors but are expressed in a significant proportion of a variety of human cancers [3]. GLUT1 has been found to be overexpressed in breast, colorectal, lung, brain, skin, uterus, and ovarian cancers. It is also found to be associated with decreasing patients survival [2]. Reviewing the available resources show that there are very few studies investigating the expression of GLUT1 in distinguishing various types of renal cell carcinoma. Therefore, this study was aimed to investigate the expression of GLUT1 in renal cell carcinoma and its subtypes, in a selected Iranian population.

Materials and Methods

Study design and setting

This study is a descriptive cross-sectional study with practical objectives that was performed on patients with renal cell carcinoma in the pathology department of Labbafinejad Hospital/Tehran/Iran from April 2011 to March 2017.

Participants

Seventy patients with a definitive diagnosis of renal cell carcinoma were selected based on histopathological findings. Inclusion criteria included definitive diagnosis of renal cell carcinoma based on histopathological findings, and the exclusion criteria included specimens with necrosis, hemorrhage and severe sclerosis, patients who had received or were currently on chemotherapy or radiotherapy, and samples lacking immunohistochemical staining for GLUT1 marker.

Data collection

Seventy formalin fixed; paraffin-embedded blocks of renal cell carcinoma were selected from archives of the pathology department of Labafinejad Hospital/Tehran/Iran from April 2011 to March 2017.

Tumor and tissue samples

The samples included: clear cell type renal cell carcinoma (ccRCC) (39 samples), RCC clear cell type with sarcomatoid feature (two samples), papillary renal cell carcinoma (pRCC) (seven samples), and chromophobe renal cell carcinoma (chRCC) (21 samples). All stained histology slides were evaluated by two separate pathologists in terms of variables. The variables of the study, including the immunoreactivity for GLUT1 marker, the expression rate of the GLUT1 marker (0: no staining, +1: <10%, +2: 10%-50%, +3: >50%), intensity of GLUT1 staining (From 0 up to 3+), the stage of renal cell carcinoma (based on TNM system), the grade of renal cell carcinoma (based on the WHO/International Society of Urologic Pathologists[ISUP] system), and age and gender were retrieved from pathology reports and were evaluated independently.

Statistical analysis

Data were collected by the simple sampling method**.** For data analysis, SPSS 26 software was used and descriptive statistical methods of mean and Chi-square tests were used for categorical variables, whereas independent t-test and Fisher's exact test were used for continuous variables. p-value less than 0.05 were considered to be statistically significant.

Ethical considerations

This study was approved by the Ethical Committee of Infectious Disease and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences/Tehran.

Results

In the studied sample, 50 patients out of 70 samples with renal cell carcinoma were male (71.4%) and 20 cases were female (28.6%) with a mean age(±st) 57.9 ± 13.1 years. The mean staining percentage of cells was 69.1 ± 19.6 (least 20% and a maximum of 100%). The difference between the two groups for being positive or negative for GLUT1 expression was not statistically significant in terms of age and sex (p= 0.57 and p = 0.1), respectively (Table 1).

Tumor and tissue samples analysis

Forty-three samples (61.4%) were positive for GLUT1 and 27 (38.9%) were negative. Of the 43 samples with GLUT1 positive, RCC clear cell type was the most frequent subtype. The difference of 43

Table 1: Demographic characteristics of patients with renal cell carcinoma

Variables	Frequency (%)		p
	GLUT1 (+)	GLUT1 (−)	
Sex			
Female	9 (20.9)	11 (40.7)	0.1
Male	34 (79.1)	16 (59.3)	
Intensity of GLUT1 staining			
1+	11 (15.7)	27 (38)	
2+	24 (34.3)	0	
3+	8 (11.4)	0	
Total	43 (100)	27 (100)	
Age (year)	60.1±2.9	54.1±12.7	0.57

GLUT1: Glucose transporter 1.

studied cases for being positive or negative for GLUT1 expression was not significant in terms of grade (p = 0.56). The difference between the two groups with and without GLUT1 was statistically significant in terms of the stage and tumor type (p = 0.039, p < 0.001, respectively) (Table 2).

Table 2: The expression of glucose transporter 1 in renal cell carcinoma

Variables	Frequency (%)		p
	GLUT1 (+)	GLUT1 (−)	
Tumor type			
Clear cell	39 (90.7)	1 (3.7)	< 0.001
Papillary type I	0	3 (11.1)	
Papillary type I I	1 (2.3)	3 (11.1)	
Chromophobe	1 (2.3)	20 (74.1)	
Sarcomatoid clear cell	2 (4.7)	0	
Grade			
I	1 (2.4)	0	0.56
II	21 (51.2)	0	
III	13 (31.7)	1 (100)	
IV	6 (14.6)	0	
Total	43 (100)	1 (100)	
Stage			
Ia	5 (11.6)	2 (7.4)	0.039
Ib	7 (16.3)	12 (44.4)	
IIa	7 (16.3)	7 (25.9)	
IIb	1 (2.3)	1 (3.7)	
IIIa	17 (39.5)	4 (14.8)	
IIIb	5 (11.6)	0	
IIIc	1 (2.3)	0	
IV	0	1 (3.7)	

GLUT1: Glucose transporter 1.

Comparison of the incidence of renal cell carcinoma for being positive or negative for GLUT1 expression based on tumor stage is shown in (Figure 1) and tumor type in (Figure 2).

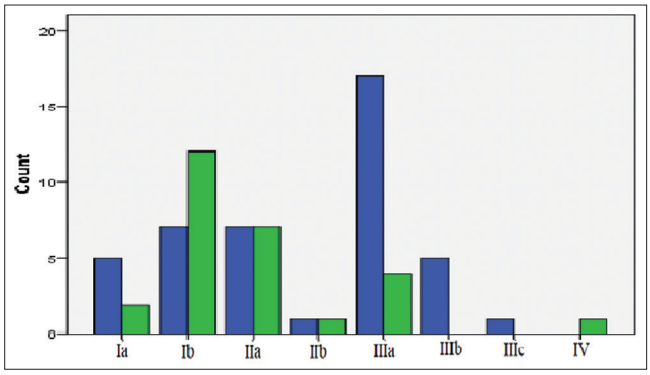

Figure 1: The freqency of renal cell carcinoma with GLUT1 expression by tumor stage

Discussion

The cancerous cells have high levels of anaerobic glycolysis to produce energy [21]. GLUT1 plays a role of transferring the glucose into cells to supply the energy source [22]. The GLUT1 overexpression in tumor cells causes tumor growth at the host tissues [23]. Increased GLUT1 expression has been shown in many cancers including the liver, pancreas, breast, esophagus, brain, kidneys, lungs, skin, colorectal, endometrium, ovary, and carcinoma of the cervix [2]. It has also been shown that increased GLUT1 expression is associated with poor prognosis of the tumor [24]. Based on the WHO 2016 classification of renal cell carcinoma, clear cell RCC is the most common adult RCC, representing 70% of all RCCs. Papillary RCC and chromophobe RCC account for 10% and 5% of RCCs, respectively. Other subtypes are considered <1%. Therefore, the GLUT1 expression was evaluated in most common subtypes of renal cell carcinoma [16]. The review of available resources presents little information about the expression of GLUT1 in various types of renal cell carcinoma [25].

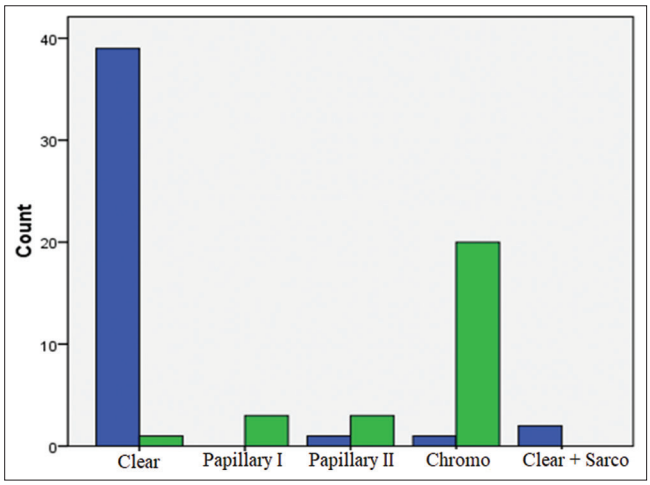

Figure 2: The frequency of renal cell carcinoma with GLUT1 expression by tumor type

The present study showed that membrane immunoreaction of GLUT1 was noted in 61.3% of renal cell carcinoma in the spectral range (55−85%), which was reported in previous studies. In Naguse study of 75 renal cell carcinoma samples, 55 samples (73.3%) were membrane-positive for the GLUT1 marker [26], Ozcan, in his study, reported that such membranous pattern was seen in 86.2% of 145 clear cell renal cell carcinoma specimens [8], Miyakita's study showed that out of 19 renal cell carcinoma samples, 11 samples (55%) were membrane positive for GLUT1 marker and five samples (25%) were weakly positive [27]. Furthermore, Guillermo Cantuaria *et al*. showed that GLUT-1 expression was observed in 85.6% of malignant tumors [3].

Results of this study showed that expression of GLUT1 was significant in terms of tumor type, and the increase in GLUT1 expression in the ccRCC type renal cell carcinoma was more than that in other types of renal cell carcinoma, including pRCC and chRCC; therefore

it was concluded that there is a strong correlation between clear cell renal cell carcinoma and the GLUT1 immunoreactivity. Clear cell RCC has large amounts of glycogen in their cytoplasm compared with tumor cells of pRCC and chRCC, which may be the reason of the higher expression of GLUT1 in the ccRCC type than the other types of renal cell carcinoma[26]. This finding is supported by several studies.Suganuma showed by RT-PCR that the amount of GLUT1 mRNA increased in ccRCC but did not increase in pRCC and chRCC [28]. The Ozean study by immunohistochemistry found that the expression of GLUT1 increased in ccRCC tumor but did not increase in pRCC and chRCC [8]. Nugase study also showed an increase in GLUT1 expression in ccRCC tumor, but, in this study, the expression of GLUT1 in other types of pRCC and chRCC was not investigated [26]. Therefore, the results of this study on the increase of GLUT1 expression in ccRCC tumor and its lack of increase in pRCC and chRCC types are similar to similar studies.

In the present study, there was no significant correlation between the tumor grade and GLUT1 expression, and this finding was confirmed by other studies, such as Naguse, Ozean, and Miyakita [8], [26], [27]. In these studies, there was no significant correlation between ccRCC tumor grade and GLUT1 expression, consistent with our study. Although, it should be noted, that in the study by Ambrosetti *et a*l. [29], there was a significant correlation between the ccRCC tumor and GLUT1 expression. Therefore, it seems that further studies are needed to evaluate the correlation between the tumor grade and GLUT1 expression. We found a significant correlation between the GLUT1 expression and the tumor stage. The higher the stage of ccRCC tumor, the higher the probability of GLUT1 marker becoming positive. However, all previous studies including Miyakita *et al*. [27], Nagase *et al*. [26], and Ozean *et al*. [8], contrary to our study, showed no significant correlation between the tumor stage and the GLUT1 expression. Thus, the results of our study are considerable in this regard. This study examined the correlation between the GLUT1 expression in renal cell carcinoma and demographic factors, and we showed that there was no significant correlation between the GLUT1 expression and sex.

Conclusion

Results showed that renal cell carcinoma of ccRCC type is associated with increased GLUT1 expression. Furthermore, the GLUT1 expression was correlated with the stage of tumor. Therefore, the GLUT1 immunohistochemistry marker can be a useful marker for diagnosis of RCC, specifically ccRCC type.

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Data Availability Statement

All the data generated or analyzed during this study are included in this published article.

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