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RESEARCH ARTICLE

LIPID PEROXIDATION AND ANTIOXIDANT STATUS IN BLADDER CANCER

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ABSTRACT

Bladder cancer (BC) is one of the most widespread cancers distressing men and women and thus has a philosophical impact on health care. Free radicals lead to lipid peroxidation which is destructive in nature and has been suggested to play a role in cancers.

Aims and Objectives: To determine the role oxidative stress and level of antioxidants in bladder cancer (BC) by estimation the expression of Hexanoyl-lysine (HEL) as lipid peroxidation marker in cancerous tissue of bladder and total antioxidants capacity (TAC) in serum of bladder cancer.

Material and Methods: In present study 50 patients with bladder cancer, 18 non-cancer subjects as control aged between (31-85) years were enrolled. The diagnosis of patients was confirmed by a pathologist in the hospital referred to above according to WHO/ISUP grading system (MacLennan *et al.*, 2007). Serum was analyzed for total antioxidants capacity (TAC) using ELISA, tissue was analyzed for expression of lipid peroxidation marker (HEL) using immunohistochemistry (IHC).

Results: Serum TAC levels were significantly lower ($P < 0.0001$) in bladder cancer patients as compared to control. The finding of IHC showed a highly significant difference ($p < 0.0001$) in the mean of immunoreactivity score of HEL when compared to that of controls.

Conclusion: Increased levels of lipid peroxidation product (HEL) and depletion of total antioxidants capacity in patients with bladder cancer may suggest that oxidative stress plays a key role in the genesis of bladder cancer.

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INTRODUCTION

Bladder cancer is the 10th most common cancer worldwide, with the highest rates reported in Europe, North America and Australia (Meliker and Nriagu 2007). Haematuria, frequent urination and pain during urination, are the most common symptoms of bladder cancer (Zeegers *et al.*, 2004; Shariat *et al.*, 2009). Antioxidants play an essential role in protection of the cells from oxidative damage. They include several agents such as enzymes (glutathione peroxidase, superoxide dismutase, catalase), large molecules (ferritin, albumin), and small molecules (uric acid, glutathione, bilirubin, ascorbic acid, α tocopherol, and vitamin E). Their defense mechanism in biological system involves chain breaking (superoxide dismutase) and preventive (Vitamin E) mechanism (Kwak and Yoom, 2007). Lipid peroxidation is an oxidative process which occurs at low levels in all cells and tissues. Under normal conditions variety of antioxidant mechanisms serve to control this peroxidative process (Patil *et al.*, 2007). Lipid peroxidation gives rise to the formation of highly reactive aldehydes which are extremely diffusible and attack or form covalent links with distant cellular components/targets (Matveychuk *et al.*, 2011).

Many studies reported an increase in lipid peroxidation and a decrease in antioxidants protection leading to oxidative stress on different pathologies (Giovanni *et al.*, 2014) For the aforesaid reasons, the present study was conducted to study the lipid peroxidation product, Hexanoyl-lysine (HEL) and total antioxidants capacity (TAC) in bladder cancer.

MATERIALS AND METHODS

The present study was carried out in the Ghazi AL-Hariri Hospital for Specialized Surgery/Baghdad Medical City /Iraq, from March 2013 to February 2014. The study was approved by Institutional Ethical Committee. A total of 68 study subjects ranging in age from 31-85 years, attending clinic of Urology Department were enrolled. Out of 68 subjects, 50 patients with bladder cancer and 18 control subjects were selected. On admission, 10ml venous blood sample was collected under aseptic conditions from each subject and separated serum was used for the estimation of total antioxidants capacity (TAC) using Fast Track kit (LDN, Germany) (Martinez *et al.*, 2001). Formalin-fixed paraffin-embedded blocks of each bladder biopsy were subjected to cut as serial thin sections of (4 μ m) thickness and were stuck on charged slides for immunohistochemistry (IHC) to detect Hexanoyl-lysine (HEL).

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A semiquantitative analysis for counting the expression of HEL if present was done using a modified immunoreactivity scoring system from that of German scoring system (Remmele and Schickelanz 1993). The demographic and laboratory obtained data were analyzed by the SPSS software (version 20). Descriptive results were reported as mean (standard deviation). Independent sample t-tests, and Chi-square were used to compare the results among groups. P value of <0.05 was considered as statistically significant.

RESULTS

Demographic characteristics of the studied subjects were presented in Table (1). The table showed no significant difference ($P > 0.05$) regarding the age group between patients and controls. The table also showed no significant difference ($P > 0.05$) between males and females. Moreover, there was a significant difference ($P = 0.0001$) regarding to smoking between patients and controls suggesting smoking as a risk factor for BC.

Table 1. Demographic characteristics of patients & controls

Characters		BC		Controls		P value
		No	%	No	%	
Age (years)	<60	13	26.0	5	27.8	0.144
	60--69	16	32.0	10	55.6	
	=>70	21	42.0	3	16.7	
Gender	Males	40	80.0	15	83.3	0.758
	Females	10	20.0	3	16.7	
Smoking	Smokers	37	74.0	3	16.7	0.0001*
	Non-smokers	13	26.0	15	83.3	

Serum total antioxidants capacity (TAC) were significantly decreased ($P < 0.0001$) in BC patients than controls as showed in Figure (1).

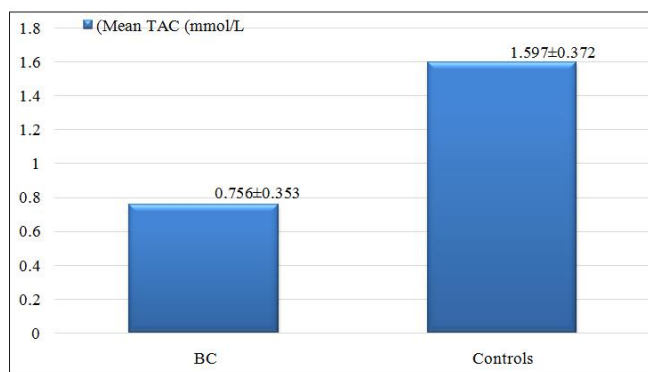


Figure 1. Mean distribution of TAC in serum of studied groups

Table 2. Distribution of oxidative stress markers in BC & controls expressed as Mean±SD

Tissue markers	TBC	Tissue Controls	P-value
	Mean±SD	Mean±SD	
	No=50	No=18	
IRS of Score HEL	7.160±3.909	1.444±0.616	0.0001*

The results demonstrated in Table (2) and Figure (2) show that there was a highly significant difference ($p < 0.0001$) in the mean of immunore activity score (IRS) of HEL (7.160±3.909) when compared to that of controls (1.444±0.616).

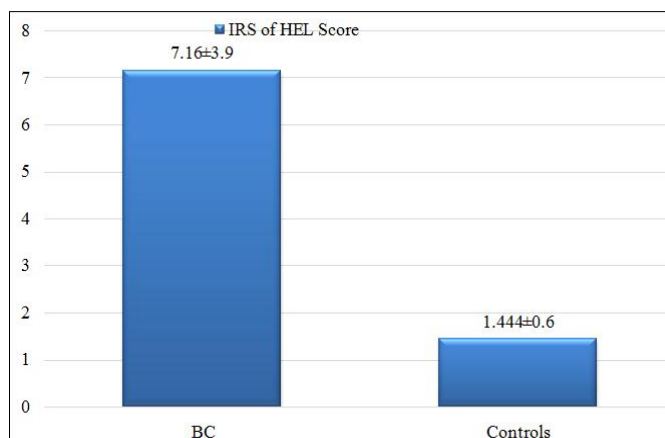


Figure 2. Mean distribution of IRS of Hexanoyl-lysine (HEL) in bladder tissue of studied groups

DISCUSSION

Free radicals by their unstable and transient nature are difficult to measure directly, hence their tendency to cause lipid peroxidation has been used as an indirect measure (Anjum and Alka, 2013). One of the important consequences of free radical formation is lipid peroxidation which is reaction of oxidative deterioration of polyunsaturated fatty acids involving direct reaction of oxygen and lipid to form lipid peroxides. Lipid peroxidation is particularly damaging because it proceeds as self-perpetuating chain reaction (Phalak *et al.*, 2013). Our results revealed significant decreased levels of TAC in bladder cancer patients compared to healthy ones ($p = 0.0001$). These results came in accordance with previous study done by (IlhanGecit *et al.*, 2012) which demonstrated a significantly decreased serum TAC levels in bladder cancer patients than in control subjects. Antioxidant depletion in the circulation may be due to the scavenging of lipid peroxides as well as sequestration by tumor cells (Sharma *et al.*, 2007). However, if these systems are insufficient, severe metabolic malfunctions and oxidative damage to DNA may result, which, experimental studies in animals and in vitro have suggested, to be an important factor in carcinogenesis (Marnett, 2000).

In the present study, we have observed that tissue expression of HEL have been significantly increased ($p < 0.0001$) in bladder cancer patients as compared to controls. Lipid peroxidation gives rise to the formation of highly reactive aldehydes which are extremely diffusible and attack or form covalent links with distant cellular components/targets (Matveychuk *et al.*, 2011). Once induced, lipid peroxidation is capable of self-propagating and initiating chain reactions (Catalá, 2010). In most cases, the reactions continue except they are terminated (e.g., by intervention with antioxidants such as vitamin E) or there is complete substrate utilization. Thus, estimation of TAC levels, Lipid peroxidation marker (HEL) may have a predictive role in the assessment of the extent of oxidative damage in bladder cancer.

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