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Lipid peroxidation and upper gastrointestinal cancers

TÜRKDOĞAN M.K.[1], ŞEKEROĞLU R.[2], HEKİM H.[1], AVCI E.[2]
Department of Gastroenterology[1] and Biochemistry[2], School of Medicine, Yüzüncü Yıl University, Van

Objective We purposed to investigate the relationship between lipid peroxidation and upper gastrointestinal (GI) cancers which have a high prevalence rate in Van region.

Method Plasma malondialdehyde (MDA), end product of lipid peroxidation was determined in 11 patients with esophageal cancer, 16 patients with gastric cancer and 14 healthy controls by thiobarbituric acid reactivity.

Results Mean MDA values were 5.20 ± 0.68 nmol/ml., 6.96 ± 1.24 nmol/ml. and 2.33 ± 0.27 nmol/ml. in esophageal cancer, gastric cancer and control groups respectively. In both of cancer groups MDA values were significantly higher than control group ($p<0.01$, student's t test) but were not different from each other ($p>0.05$).

Conclusion These findings suggest the role of lipid peroxidation in the etiopathogenesis of upper G I cancers.

Key words Lipid peroxidation, upper gastrointestinal cancers.

Introduction

Nowadays lipid peroxidation (LP) is accepted widely responsible in the pathogenesis of many systemic disorders (1). Gastrointestinal (GI) cancers are worldwide fatal health problem. We observed that in Van region of Eastern Turkey , especially upper GI cancers (esophageal and gastric) are the leading causes of mortality among all cancer groups (2). Therefore, we investigated the relationship of LP with GI cancer in this study.

Material and Method

Serum samples of 11 esophageal cancer (7 females, 4 males), 16 gastric cancer (10 males, 6 females) patients hospitalized in surgical units and 14 healthy (7 males, 7 females) control subjects were collected for determination of malondialdehyde (MDA), an end- product of fatty acid peroxidation. Mean age of the patients and the controls were 54 (31-73) and 51 (29-67) respectively ($p>0.05$). The cancer patients had not received any antineoplastic agent and were not complicated with any other diseases. They had not any distant organ metastasis. Esophageal and gastric cancer diagnosis was established by histopathological examination of biopsy specimens taken at endoscopic examinations. LP was estimated by thiobarbituric acid (TBA) reactivity. MDA reacts with TBA to form a coloured complex that has maximum absorbance at 532 nm. For this purpose, 1 ml of serum was transferred to a tube. We added to this tube 0.075 ml 0.1 mol/L EDTA and 0.25 ml. 1% TBA prepared within 0.5 mol/L NaOH. Tubes were mixed and kept in a boiling water bath for 15 minutes. Butylated hydroxytoluene, an antioxidant, was added to stop further formation of MDA during the assay. The addition of butylated hydroxytoluene to standard MDA did not affect the colour development with TBA. MDA values (nmol) were calculated from the absorbance coefficient of MDA-TBA complex at 532 nm., (1.56×10^5 cm^{-1} mol^{-1}). Student's t test was used for statistical analysis.

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Results

MDA levels and mean values with standard errors of each group are presented in Table I. In esophageal and gastric cancer patients mean MDA levels were significantly higher than that of the control group ($p<0.01$) but were not significantly different from each other ($p>0.05$). The remarkable relation of LP with upper GI cancer is shown in Fig 1.

Discussion

LP is a biological pathway concerning peroxidation of cell membrane phospholipids and polyunsaturated fatty acids (PUFA) by reactive free oxygen radicals. Hence, lipid peroxyl and hidroperoxyl radicals are formed. Aldehydic products such as malondialdehyde and 4 hidroxynonenal are produced consequently (1). Free radicals (FR) cause oxidative damage to nuclear DNA and consequently somatic mutations such as base changes, deletions and chromosomal strand breaks are developed (3,4). F R also activate oncogens and inactivate tumour supressor genes such as p53 by mutational changes (5). Procarcinogens ingested by foods are activated by host enzymes most often in the liver to yield electrophilic carcinogens that may then bind covalently to DNA and lead to mutations (6). Also, antioxidant enzymes (superoxide dismutase, glutathione peroxidase and catalase) may be decreased in these conditions. Nitric oxide (NO) is an actual biological mediator and inorganic radical concerned in the pathogenesis of many systemic disorders such as inflammation, ischemia, portal hypertension, malignity etc. (7,8). NO oxidation products (nitrate and nitrite) are produced in human organism and are converted to carcinogen nitrosamines in hipoacidic milieu by bacterial overgrowth (6). Nowadays, Helicobacter pylori infection in gastric mucosa is alleged as carcinogenic risk factor (9,10). NO synthesis and its oxidation

products were increased in Helicobacter gastritis (11,12). Also, NO and peroxynitrite radicals generated in Helicobacter inflammation lead to DNA fragmentation, apoptosis and cancer promotion (13,14). In Van region, we also observed that upper G I cancer patients had significantly elevated plasma NO products correlated with increased Helicobacter infection prevalence (15). Some researchers detected that LP products (malondialdehyde and 4 hidroxynonenal) in tumour tissues and body fluid samples (serum, urine, bile etc.) of cancer patients were increased (16-19). Nair J et al. reported that L P products derived from diet rich in PUFA form promutagenic exocyclic DNA adducts in human cells and contribute to cancer development (20). Ornithine decarboxylase activity which is a sensible marker of malign epithelial proliferation is increased in animals fed with diet rich in PUFA and L P products (21). Similarly, Poirier et al. reported that diet rich in chemical carcinogens (polycyclic aromatic hidrocancerrbons, MDA etc.) related to charbroiled meat leads to DNA adducts formation (22). Erhardt et al. also observed that hydroxyl radical production was 13 times greater in feces of subjects who consumed diet rich in fat and poor in fiber (23).

Table 1. Serum MDA levels (nmol /ml) of upper gastrointestinal cancers and controls

Patient no	Gastric Cancer	Esophageal Cancer	Control
1	21.372	10.945	1.619
2	9.779	4.987	1.036
3	4.598	5.375	1.425
4	6.023	6.023	1.554
5	8.095	5.569	3.044
6	6.994	6.412	1.101
7	4.533	3.044	2.332
8	3.756	3.951	2.461
9	5.052	2.202	1.360
10	4.728	4.728	3.756
11	2.267	4.015	3.303
12	4.793	-----	2.526
13	15.738	-----	2.785
14	3.303	-----	4.404
15	5.505	-----	-----
16	4.857	-----	-----
	n=16	n=11	n=14
Mean value±SE	6.962 ± 1.245	5.205 ± 0.689	2.336 ± 0.278
p:	<0.01	<0.01	

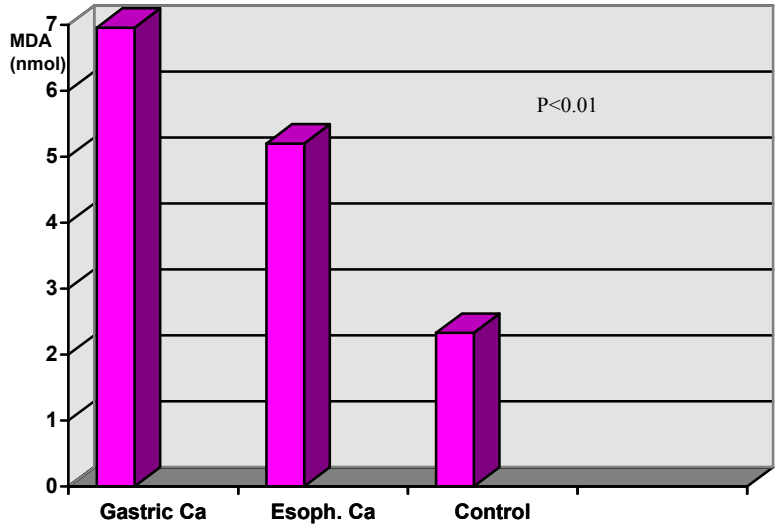

Fig 1. Mean MDA levels in upper GI cancers and the controls.

Takahashi et al. also reported that diet rich in sodium chloride promote carcinogenesis by enhanced lipid peroxidation (18). In Van region, upper GI cancer patients consume generally hot, salty, fatty, smoked and fried meat with inadequate intake of fresh fruits and vegetables (2). These dietary habits suggest that diet related to L P is an important cancer promoter in this region. Heavy metals and radioactivity may be responsible in the development of LP related cancers (3,24). Radiation and transition metals, particularly iron, copper, nickel are considered as cancer promoters. Irradiation of water produces hydroxyl radicals which react with DNA and lead to mutations (3,5). In Northern Mexico where GI cancer are endemic, radioactive elements (uranium, radon) and heavy metals (cadmium, lead) have been reported in high concentrations in the soil (25). In Chile, GI cancer incidence has been observed high in the regions with volcancernic soil properties where selenium , an antioxidant mineral, level was low (26). Similarly, Van region has also volcanic soil properties with high uranium and low selenium levels. Moreover, the analysis of the water of lake Van and mineral waters around the lake disclosed high radioactivity in some parts of the region (27, 28).

In our study we detected that serum MDA levels were significantly elevated both in gastric and esophageal cancer patients. These results suggested the important role of lipid peroxidation in the etiopathogenesis of upper GI cancers. Several environmental , especially dietary carcinogens are matter of question in Van region and we are convinced that all risk factors may contribute to cancer development by lipid peroxidation pathway.

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Yüzüncü Yıl Üniversitesi
Tıp Fakültesi Hastanesi
Gastroenteroloji BD, 65200 Van TÜRKİYE

Correspondence to:
Yrd. Doç. Dr. Kürşad TÜRKDOĞAN