Study of Lipoproteins in Patients with Brain Tumors

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ABSTRACT

For many years, a large number of evidences has been accumulated indicating a possible central role of endogenous cholesterol is played in the pathobiology of cancer.

This study examined the lipoprotein pattern in the plasma compartments in (60) patients with different types of brain tumors as well as in (30) healthy persons. The results indicated that total cholesterol, triacylglycerol, low density lipoprotein-cholesterol and very low density lipoprotein- cholesterol were significantly increased in sera of patients with brain tumors than that in control group ($p < 0.001$). While a significant decrease in high density lipoprotein-cholesterol was observed in sera of patients with brain tumors compared to control group ($p<0.01$).

Conclusion:-The results here with the other result obtained in our laboratory, confirm the hypothesis that oxidative stress and lipid peroxidation are a cause of cancer rather than one of its consequence.

Key words: Brain tumors, Cholesterol, HDL, LDL, &VLDL.

دراسة البروتينات الشحمية في مرضى أورام الدماغ

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الملخص

تجمع ولعدة سنوات العديد من البراهين التي تشير إلى الدور المركزي المحتمل للكوليسترول الداخلى في إمراضية السرطان.

قامت هذه الدراسه بفحص نمط البروتينا ت الشحميه فى بلازما (60) مريض باورام الدماغ المختلفه إضافة إلى بلازما (30) شخصاً سليماً. أشارت النتائج إلى أن مستوى الكولسترول الكلى وثلاثـى اسـيل الكليسرول وكولسترول الشحم البروتينى منخفض الكثافه وكولسترول البروتين الشحمى منخفض الكثافـة جداً قد ارتفعت ارتفاعاً ملموساً في مصول المرضى باورام الدماغ المختلفه عما هي عليه في مجموعـة الشاهد($p < 0.01$) . في حين أن انخفاض ملموس قد لوحظ في كولسترول البروتينات الشحمية عاليـة الكثافة عند مرضى أورام الدماغ مقارنه بمجموعة الشاهد ($p<0.01$).

الاستنتاج:-ان نتائج هذه الدراسه ودراسات اخرى اجريت فى مختبرنا تتوافق مع الفرضيه التى تذكر ان الضغط التأكسدى والاكسده الفوقيه للشحميات تسبب السرطان وليس ناتج عن وجود السرطان.

الكلمات المفتاحية: أورام الدماغ، الكوليسترول ,HDL,LDL,VLDL.

Introduction

For many years, a large number of evidences has been accumulated indicating that a possible central role of endogenous cholesterol is played in the pathobiology of cancer. Alteration in the synthesis [1-3], uptake [4-6]and membrane content of cholesterol have been observed in a variety of experimental tumor models as well as in human neoplesia[1-6]. It is known that cholesterol metabolism in the body is regulated through a complex series of transport and biosynthetic mechanisms, which rely on the continuous exchange between tissues and blood. Therefore any substantial alteration of cholesterol metabolism of the cellular level entails changes in the plasmatic pool of the cholesterol. Dessi *et al* reported that cholesterol content in tumor tissue inversely associated with LDL cholesterol in sera in patients with gastrointestinal cancer [7].

Cholesterol present in the plasma as VLDL, is produced in the liver and is subjected to lipase mediated digestion process that leads to intermediate density lipoprotein (IDL) production. This IDL will undergo an additional remodeling to produce LDL. HDL is synthesized in the liver and intestine, and also generated in part by lipolysis of chylomicorn and VLDL [8].

The sustained process of cellular growth presents an increase in cholesterol synthesis accompanied by an accumulation of cholesterol in growing tissues and a marked reduction of high density lipoprotein cholesterol (HDL) in the plasma compartment [7]. Oxidative stress can make some types of lipids more destructive to tissue. It appears that LDL-C is most harmful only after it is been modified in some way. When LDH is bombarded by oxygen radicals it is changed to oxidized LDL which is actually causes the toxicity to blood vessels wall and can degrade corrective tissues [9].

The process of lipid peroxidation is one of oxidative conversion of polyunsaturated fatty acids to products known as malondialdehyde (MDA), or lipid peroxides, which is the most studied, biologically relevant, free radical reaction[10]. MDA itself, owing to its high cytotoxicity and inhibitory action on protective enzymes, is suggested to act as a tumor promoter and a cocarcinogenic agent[11]. On the other hand, it was reported that lipid hydroperoxides decompose to yield reactive aldhydes, such as MDA and 4-hydroxynoneal. MDA is a well characterized mutagen that reacts with deoxyguanosine to form endogenous adduct found in the DNA of human liver [12]. Some of the effects of lipid peroxide and ROS include epithelial cell injury and

dysfunction alteration in membrane fluidity, altered membrane permeability to ions and proteins, enhanced adhesion and activation of neutrophils, increased LDL uptake in vessel wall, decreased protein synthesis, inactivation of enzymes, and increased production of toxic aldehydes [13].

The aim of the present study was to investigate the changes in serum total cholesterol and its different fractions in patients with brain tumors.

Samples

Case control study conducted in the period from October 2003 – April 2006.

Participants in this study included 30 patients with different benign brain tumors: (Astrocytoma I-II, Meningioma and Low grade glioma) and 30 with different malignant brain tumors (Astrocytoma III-IV, Meningioma, high grade glioma and Aden carcinoma) their ages ranged between 19-52 years, their BMI was16-18,& 50 percent of them were male, attending Al-Gomla Al-Asabea Hospital. The diagnoses of malignant and benign tumors were confirmed by histological and cytological examination for biopsy specimens, which were carried in the laboratories of the above mentioned hospital.

Blood samples were collected from these patients, and from healthy individuals with no significant signs or symptoms of any disease, these were used as a control group (n=30). Their ages ranged between 24 – 55 years.

Six milliliters of venous blood were collected in test tubes. The serum was separated immediately from the cells by centrifugation at 3000g for 10 minutes, stored frozen until use to estimate the different parameters. The sera which were obtained from blood samples should be unhemolyzed and non-jaundice, in order to avoid any interference with the obtained results.

Methods

During this work total cholesterol, triglycerides, HDL-C, LDL-C and VLDL-C were measured in the sera of control group, and of patients with benign and malignant brain tumors.

Total cholesterol was determined in the present study according to the enzymatic method[14-16] using bioMericex kit. Triglyceride was determined using Giesse kit, which is based on enzymatic method [17, 18].

HDL-C was measured by using bioMericex kit that is based on precipitation of VLDL-C and LDL-C then the HDL-C was determined by the enzymatic method[19].

VLDL-C and LDL-C were estimated by applying the following equation [8]:

$$\text{VLDL-C (mg/dl)} = \frac{\text{Triglyceride (mg/dl)}}{5}$$

$$\text{LDL-C (mg/dl)} = \text{Total cholesterol} - (\text{VLDL-C} + \text{HDL-C})$$

Results

When the total cholesterol, triglyceride, HDL-C, LDL-C and VLDL-C were measured in the sera of control and patients with benign and malignant brain tumors group as described in the method section, an elevation of cholesterol and triglyceride in the sera of patients with benign and malignant brain tumors was observed (Figure 1). This elevation was found to be significant when compared with that of the control group ($p<0.01$).

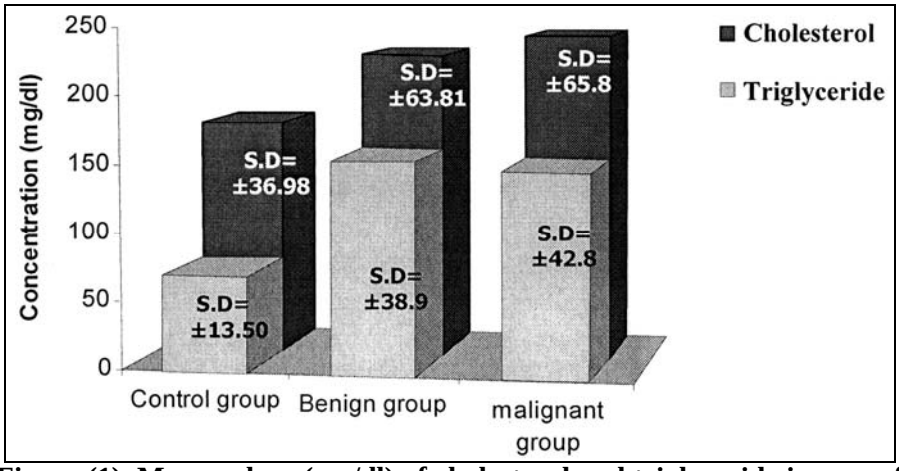

Figure (1). Mean values (mg/dl) of cholesterol and triglyceride in sera of control, benign and malignant groups.

Significant increase of LDL-C and VLDL-C was noticed in sera of patient groups when compared with that of the control group as shown in table (1) ($p<0.001$).

An increase of total cholesterol, triglyceride, VLDL-C and LDL-C concentrations was observed here, This agrees with the study conducted by Ray *et al.* [20] and Kokoglu *et al.* [21] on patients with breast cancer. An elevation in LDL-C was also noticed by Spiegel *et al.* [22] in sera of patients with acute leukemia.

The results in table (1) show that a decrease of HDL-C was detected in the sera of the patients with benign and malignant brain tumors, when compared with that of control group ($p<0.01$). However, no significant difference was observed in all the parameters in the sera of patients with malignant brain tumors in comparison with those of benign brain tumors.

Table (1). Mean values (mg/dl) of cholesterol, HDL-C, LDL-C and VLDL-C in the sera of control, benign and malignant groups.

		Cholesterol	HDL-C	LDL-C	VLDL-C
Control group	**Mean (mg/dl)**	174.3	63.45	89.39	14.10
	± S.D	36.98	14.64	40.213	2.70
	Range	97.6-203.8	27.9-86.4	27.8-211	6.1-19.7
Benign group	**Mean (mg/dl)**	226.18	48.01	152.9	37.8
	± S.D	63.81	18.52	48.2	10.14
	Range	108-330	19.5-92.1	15.7-214	13.1-68.1
Malignant group	**Mean (mg/dl)**	241.1	44.05	169.0	30.06
	± S.D	65.8	17.65	59.4	8.57
	Range	110-382	16.9-87.5	17.4-278	11.4-63.9

The decrease of HDL-cholesterol concentration in this study agrees with the result reported by Baccino *et al.* [7], where a decrease in HDL-cholesterol was observed in the sera of patients with gastrointestinal cancer, and also agrees with Ray *et al.* [20] and Kokoglu *et al.* [21] who pointed that HDL-cholesterol concentration is significantly decreased in the sera of women with breast cancer.

Discussion

Several sustained processes of cellular growth are characterized by alteration of cholesterol metabolism not only in the proliferating tissues but also in the plasma compartment[7]. A major function attributed to HDL is to maintain normal cell cholesterol homeostasis by removing excess cholesterol from intracellular pools. Because the use and storage of cholesterol are increased within the tumor tissue during growth[7], it is possible to hypothesize that the low HDL-C levels observed in this study were associated with increased

cholesterol metabolism in proliferating tissues. It is also worth mentioning that some nutritional studies pointed to the presence of a relationship between tissue cholesterol levels and metastasis in human [23].

Sarrel revealed that androgens are key modulators of serum lipid levels and in particular of serum HDL-C levels [24]. Meanwhile Furberg *et al* suggested that low HDL-C is related to increased levels of several cancer promoting hormones (e.g. androgens, estrogens, insulin and IGF-1)[25]. Furthermore it is known that Lipoprotein receptors play a central role in lipid metabolism. Lipoproteins are taken up by their receptors and both cholesterol and TG are delivered into the cells .LDL receptors and VLDL receptors seemed to be controlled under different mechanisms in the regulation of their expression, VLDL receptors expression is not down regulated by lipoprotein concentration[26], whereas LDL receptors expression does, in order to prevent an excess energy source from entering cells[27]. It has been shown that some cancer cells including prostate cancer lack feedback regulation of LDL receptors, this provides an extra energy source to promote uncontrolled growth of these cells [28].

Ramachandrian has shown that lowered membrane cholesterol lead to increased cell adhesion, probably as a result of increased membrane fluidity[29]. Higher levels of total cholesterol and triglyceride may play an important role in carcinogenesis. Furthermore the elevated plasma LDL-C concentration, which is more susceptible to oxidation, may result in higher lipid peroxidation.

The mechanism of the increase in LDL is not yet known. They are permeable to the basal membrane and cause activation of a certain receptor. They are easily oxidizable as well. Normally, these LDLs are protected from circulating antioxidants in subendothelial space, but when oxidized they form oxidized LDL. These in turn, being highly reactive, alter the membrane proteins and phosphoproteins, which increase the expression of signaling molecules. The process of oxidation is fought in the body by more and more utilization of antioxidation enzymes. However, the decreased concentration of HDL-C reported in this study, and many antioxidants are not likely to be sufficient enough to counter higher reactive oxygen metabolites production reported in patients with brain tumors[30]. This may cause oxidative stress leading to cellular and molecular damages there by resulting in cell proliferation and malignant conversions[20]. On the other hand Oram *et al.,*[31] demonstrated that HDL binds to cell surface receptors and promotes selective removal of excess cholesterol

from the intracellular pool. The activities of these receptors are regulated by both the availability of exogenous cholesterol and growth state of the cells. The alteration of cholesterol during tumoral growth is not related to the cancer itself, but rather to cell proliferation *per se*. Because in the body the endogenous and exogenous pools of cholesterol are directed according to the functional demands of the cells. It is possible that alterations in sera lipoprotein profile are least partially dependent on the altered cholesterol metabolism occurring in proliferating tissues[32]. Generally under physiological condition several mechanisms protect LDL against oxidation, but under some pathological conditions some of these protective mechanisms are less effective, and may be expected to lead to increase serum LDL oxidation.[33] The results here with the other result obtained in our laboratory, confirm the hypothesis that oxidative stress and lipid peroxidation is a cause of cancer rather than one of its consequences. In order to support this, further investigation is required where patients with different stages of the disease should be studied and more sample size is required. At the same time further study is needed to investigate the relationship between lipoprotein induced cell proliferation and lipoprotein receptor expression in patients at different stages of brain tumors. Such study will contribute a new understanding on pathophysology of brain tumors.

Note: This work was carried out at the Chemistry Department/ College of Science/Baghdad University.

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