Determination of some biochemical parameters in erythrocytes and serum of patients with prostate cancer related to lipid peroxidation

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Abstract :-

The aim of this study is to assess some biochemical parameters related to oxidative stress in erythrocytes and serum of patients with prostate cancer. Glutathione - S – transferase (GST) , glutathione peroxidase (GPx) and Xanthine oxidase (XO) activities was measured in erythrocytes , malondialdehyde(MDA), High density lipoprotien cholesterol (HDLc) , Low density lipiprotiens (LDLc) and selenium (Se) levels was measured in serum . Patients divided into two groups of men suffering from prostate cancer:- group A included (25) men suffering from this disease a period (1-2) years. Group B consisted of 25 patients suffering from this disease a period (2-4) years. Patients groups were compared with (25) healthy individual as a control group. Results have suggested that (GST) , (GPx) and (XO) activities were elevated in group (A) when compared to normal control. [$P<0.001$ for (GST) , (GPx) and , (XO)] , but then were decreased for group B [$P<0.01$ for (GST) , (GPx) and , (XO)]. Malondialdehyde (MDA) level was increased in group A $P<0.01$ and this increasing was continued in group B $P<0.001$ .High density lipoprotiens (HDLc) level was decreased in group A $P<0.01$ and this decreasing was continued in group B $P<0.001$ while low density lipoprotiens (LDLc) level was increased in group (A) $P<0.01$ and this elevation was continued in group (B) $P<0.001$. Selenium (Se) was decreased in group (A) $P<0.01$ compared to healthy control, this decreasing was also continued in group (B) $P<0.001$.

Keywords :- prostate cancer . lipid profile . GPx . GST . malondialdehyde.

Introduction :-

Prostate cancer is the most prevalent cancer found in men above the age of fifty years. Although the specific etiological factors of cancer are not yet known , considerable evidence indicate that both genetic and environment play a role in the evolution of prostate cancer. Diet may not initiate prostate cancer but rather may promote its progression. Diets high in vegetables have been reported to

decrease the risk and high fat , saturated fat and animal fat to increase the risk. Fat consumption has long been suspected to be a risk factor for prostate cancer. As a result, prostate cancer is high probably among atherosclerosis patients. Prostate cancer which is the third most common cancer in men is associated with lipid peroxidation. [1,2,3,4]

Reactive oxygen species are known to be mutagenic and therefore playing an impotant role in cancer formation. The mutagenic capacity of free radicals is due to the direct interaction of hydroxyl radicals with DNA. Reactive oxygen species induce membrane damage by peroxidizing lipid moiety with a chain reaction known as lipid peroxidatuon. The initial reaction generates a second radical , which in turn can react with a second macromolecule to continue the chain reaction. Among the most susceptible targets are polyunsaturated fatty acids. A newly formed free radical reacts with next lipid molecule and destroying there by, propagation the lipid peroxidation.process with the continuous formation of new free radical. The process is also terminated by free radical scavengers such as enzymatic and non-enzymatic antioxidant systems.[5,6]

On the other hand , the chemotherapeutic agents such as phpsphocycloamide (cytoxan) and deoxorubicin (adriamycin) now commonly used for treatment of cancer, have all been shown to increase lipid peroxidation and generation of reactive oxygem species. [7]

Glutathione peroxidase (GPx) is an antioxidant enzyme. It has been reported as the first and best characterized mammalian selenoprotien , capable of reducing equivalents form glutathione to detoxify hydrogen and lipid peroxides.[8]

Glutathione - S – transferase (GST) , also antioxidant enzyme , plays a central role in the defense against free radicals , peroxides and a wide range of xenobiotics and carcinogens. [9]

In contrast , Xanthine oxidase (XO) promotes lipid peroxidations. It converts Xanthine and hypoxanthine to uric acid. The last reaction is associated with transferring electrons from xanthine and hypoxanthine to uric acid and in the same time oxygen molecule is reduced super oxide anions that initiate lipid peroxidation. [10]

Selenium (Se) is a very important component of antioxidant protect mechanism and anticancer properties. It has a protective effect against oxidative damage by decreasing the amount of free radicals and increasing the synthesis of glutathione peroxidase (GPx). [8,11]

Malodialdehyde(MDA) , the end product of lipid peroxidation owing to its high cytotoxicity has been suggested to act as tumor promoter and co-carcinogenic agents. Malodialdehyde(MDA) levels have been found to be useful as tumor marker for diseases related to lipid peroxidation. [12,13]

Lipids specially cholesterol are important constituents of the cell. They play key roles in many vital physiological functions. Cholesterol is vital in the maintains of the structure and functional integrity of all biological membranes . Lipids (except HDL) might be associated with cancers as they have an integral role in the maintenance of cell integrity. Despite raised lipids are strongly associated with pathogenesis of atherosclerosis, researchers have also reported an association between plasma / serum lipids and lipoproteins (except HDL)with different types of cancers. [14,15]

Materials and Methods :-

Blood samples were collected from 50 men with cancer of the prostate. , with age range of 60-70 years. The work was divided into two groups :- group A included 25 men suffering from prostate cancer a period 1-2 years and group B consisted of 25 men suffering from the disease for 2-4 years. Two groups were selected to study the correlations between the determined parameters and period of time suffered from prostate cancer. Data resulting from group A and group B were compared to 25 healthy men with age 60 - 70 control group. Blood samples were collected from patients from (Al – benok) laboratory in Baghdad and the work was perfected by cooperation with the center of chemical researches in Ministry of science and technology. Patients were treated with chemotherapic drugs (cyclophosphamide and deoxorubicin). No treatment was given to control group patients. Seven parameters were measured in this study :- glutathione - S - transferase (GST) , glutathione peroxidase (GPx) , Xanthine oxidase (XO) malodialdehyde(MDA) , High density lipoprotien cholesterol (HDLc) , Low density lipoprotein cholesterol (LDLc) and selenium (Se) . All patients were suffering from atherosclerosis.

Methods of assay :-

Glutathione - S - transferase (GST) activity was determined in erythrocytes using using glutathione as a substrate , the absorption was recorded at (340 nm). Glutathione peroxidase (GPx) activity was measured in erythrocytes using glutathione and and hydrogen peroxide (H_2O_2), the detection was recorded at (340 nm). [18]

Xanthine oxidase (XO) activity was determined in erythrocytes depending on the enzymatic oxidation of xanthine to uric acid, the detection was recorded at (293 nm). [19]

Malodialdehyde(MDA) level was measured in serum on the basis of formation of colored complex upon the reaction with thiobarbutyric acid this complex was absorbed at (500 nm). [16]

High density lipoprotien cholesterol (HDLc) was determined in serum according to phosphotungestic acid in the presence of magnesium ions , the detection was recorded at (510 nm). Low density lipoprotien cholesterol (LDLc)

was also determined in serum depending on [17]
selenium (Se) level was determined by atomic absorption flameless. [20]

Statistical analysis :-

Students t.test was used as a statistical analysis. Results have been expressed in tables as Mean ± S.D .Values of ($p<0.01$) were considered to be high significant while values of ($p<0.001$) were considered to be very high significant

Results :-

Table (1):- Mean ± S.D values of serum GST activity in patients with prostate cancer compared to control group.

subject	number	GST activity (U/gm Hb)	t.test
control	25	1.95±0.40	
A	25	2.50±1.51	(P<0.001)
B	25	2.26±1.84	(P<0.01)

Table (2):- Mean ± S.D values of serum GPx activity in patients with prostate cancer compared to control group.

Subject	number	GPx activity (U/gm Hb)	t.test
control	25	27.2±4.6	
A	25	35.4±6.3	(P<0.001)
B	25	31.3±5.2	(P<0.01)

Table (3):- Mean ± S.D values of serum XO activity in patients with prostate cancer compared to control group.

Subject	number	XO activity (U/gm Hb)	t.test
control	25	0.025±0.01	
A	25	0.057±0.02	(P<0.001)
B	25	0.045±0.025	(P<0.01)

Table (4) :- Mean ±S.D malondialdehyde of value serum patients with prostate cancer compared with healthy control group.

Subject	Number	MDA nmole / mL ±S.D	t.test
control	25	3.5±0.15	
A	25	15.4±5.2	(P<0.01)
B	25	19.2±6.1	(P<0.001)

Table (5):- Mean ± S.D values of serum HDLc level in patients with prostate cancer control group.

Subject	number	HDLc (mg/dL)	t.test
control	25	46.2±5.3	

A	25	43.1±6.2	(p<0.01)
B	25	37.1±7.2	(P<0.001)

Table (6):-Mean ± S.D values of serum LDL level in patients with prostate cancer compared to control group.

Subject	number	LDLc (mg/dL)	t.test
control	25	114.5±12.5	
A	25	125.1±15.2	p<0.01
B	25	147.1±2.02	P<0.001

Table (7) :- Mean ± S.D values of serum Selenium (Se) level in prostate cancer patients compared to healthy control.

Subject	Number	(Se) level (µgm / dL)	t.test
control	25	14.5±1.22	
A	25	12.4±1.5	(P<0.01)
B	25	9.54±2.6	(P<0.001)

Discussion :-

1- Determination of GST activity.

Table (1) illustrated that GST activity in group A was increased (P<0.001) compared to control group. This increasing may be explained by that GST which is a group of multifunctional protein, plays a central role in the detoxification of electrophilic chemicals and hepatic removal of potential harmful hydrophobic compounds resulted from chemotherapy drugs. But with the progression of disease (group B) , GST activity was decreased (P<0.001). After a long time suffering from prostate cancer, toxic compounds resulted from chemotherapy treatment play an important role in decreasing of antioxidant enzymatic system. [1,2]

Chemotherapeutic drugs are hydrophilic and can not pentrate into the inner membranes of cells where they would be reduced by NADH located on the inner membrane surface. Chemotherapy drugs used in treatment of prostate cancer are able to enter the outer mitochondrial membrane and enter the cytosol. Intracellular rearrangements result in formation of a lipophilic dehydrogenase that can penetrate the inner membrane of the mitochondria.

These doxorubicin competes with the coenzyme Q10 as an electron acceptor and diverts electrons to molecular oxygen resulting in formation of superoxide radicals. Doxorubicin intercalates DNA coils and interferes with normal cellular metabolism through a diverse set of biochemical mechanisms that may explain its toxicity. It causes an increase in peroxidation of unsaturated

fatty acids of membrane phospholipids which leads to a decrease in the level of antioxidant enzymes like (GST) and generates a high level of oxidative stress.[1,2]

In other words, the low activity of GST might be due to depletion of antioxidant defense system. [1,2]

2- Determination of GPx activity.

Data in table (6) and figure(6) have shown that GPx activity was elevated in group A ($P<0.001$) compared to control group. Under conditions of chemotherapeutic treatment, lipid peroxidatuion level is generally increased , increasing of reactive oxygen species concentration may cause damage to many biomolecules like lipids , proteins and carbohydrates. GPx , which is an antioxidant, selenium dependent enzymem catalysis the reaction between glutathione and H_2O_2 that is confirmed a highly toxic oxygen species. GPx was increased in group A because it is one of the reactive antioxidant enzymes responsible for detoxification by transforming of H_2O_2 to water. [1]

Oppossitively, data have proved that GPx activity was declined for group B ($P<0.01$). This decreasing due toincreasing the level of lipid peroxidation in blood resulting from a long period of time after treatment with chemotherapy. [3,4]

A study have demonstrated that oxidative stress plays an important role for the intiation of DNA damage and decreasing activity of antioxidant system. [4]

Another study have investigated that the low activity of antioxidant enzymes (like GPx) might be due to depletion of antioxidant defense system. [20]

3- Determination of Xanthine oxidase (XO) activity.

Xanthine oxidase activity was significant increased in group A ($P<0.001$) compared in comparison with control group. Xanthine oxidase (XO) has been considered to play a crucial role in the pathogeneseis of lipid peroxidation in prostate cancer and atherosclerosis patients because the enzyme reaction that transfers electrons from hypoxanthine to uric acid is coupled with the reduction of molecular oxygen into super oxide anions. [19]

Reversely in group B, Xanthine oxidase (XO) activity was declined ($P<0.01$). This decreasing due to elevation of Allupurinol concentration in blood after a long time of giving chemotherapy drugs. Allupurinol is orally taken by cancer patients about (24-28) hours before treatment with chemotherapy drugs. Allupurinol which is an inhibitor of xanthine oxidase is given with some cancer chemotherapy treatment to prevent damage to the kidneysm the result is low activity of Xanthine oxidase (XO). [21,22]

4- Determination of malodialdehyde(MDA) level:-

Data in table (4) demonstrated that malondialdehyde(MDA) level in group Awas elevated ($P<0.01$) compared to healthy control. This elevation was

continued for group B (P<0.001) .In other words, there is a positive relationship between malodialdehyde(MDA) level and the progression of prostate cancer. This elevation in MDA level could be explained by generation by of free radicals and reactive oxygen species (ROS) that related to chemotherapy drugs. [12,13]

The prime targets of free radicals reactions are unsaturated bonds in membrane phospholipids.[21]

The consequence of these reactions termed , lipid peroxidation is the loss of membrane fluidity, receptor alignment and potential cellular lysis. Also free radical damage to sulfur containing enzyme and other proteins result in inactivation , cross linking and denaturation. Furthermore , nucleic acids can be attacked and subsequent to DNA can cause mutation that may be carcinogenic. [23,24]

Damage of cells resulted from LPO produces secondary products. The most important products indicates LPO is malondialdehyde(MDA), therefore MDA level was increased with the progression of any disease related to lipid peroxidation. [25,26]

5- Determination of HDLc level.

Data in table (5) have shown that HDLc level was elevated positively with the progression of prostate cancer. HDLc is able to counter balance and prevent LPO. It has been suggested that HDL-cholesteol prevents both enzymatic and non-enzymatic generation of reactive oxygen species like H_2O_2 and thus acts as an anticarcinogen and powerfull antioxidant. [25,26]

Since precuser particles of HDLc are thought to drive from lipolysis of TG , and the lipoprotein lipase (LPL) activity which responsible for TG lipolysis is decreased in cancer and atherosclerosis patients, increased TG may be an important factor that results in lower HDLc concentration. [26]

6- Determination of LDLc level.

Table (6) represented that LDLc level was increased with the propagation of disease. (P<0.01) for group A and (P<0.001) for group B LDL-cholesterol is more susceptible to oxidation in various pathological conditions , which result in higher lipid peroxidation associated with prostate cancer and atherosclerosis. [14]

Many studies have supported a relationship between cholesterol in prostate tissues or secretions and benign or malignant prostate growth. [25,27]

7- Determination of selenium (Se) level.

Data in table (7) have demonstrated that Se level was positively declined in prostate cancer patients compared to control group. (P<0.01) for group A and (P<0.001) for group B. Selenium is a trace element that is known to be essential for the activation of GPx, which is a key enzyme in the defense against

oxidative stress. for this reason, Se supplementation alone and in combination with other micronutrients has been extensively studied. [29]

A study has shown that dietary constituents have been reported to play vital roles in the development or prevention of cancer. Selenium, an essential trace nutrient , has been reported to improve immune function in animals, enhance neuropsychological function in humen and ameliorate specific disease conditions in humen and animals. Selenium deficiency has been associated with initiation of events leading to the development of tumors. Low levels of selenium have been associated with a higher risk of athrosclerosis and cancer in humen. [30,31]

The ability of selenium compounds to inhibit growth and induce tumor cell apoptosis has been suggested to be a potential mechanism for cancer chemoprevention. [32]

Conclusions :-

1. MDA and LDLc levels were increased positively with the progression of prostate cancer.
2. HDL level was decreased positively with the progression of prostate cancer.
3. GST, GPx and XO activities were increased in prostate cancer patients in its first two years but in the third and fourth years , they decreased relatively.
4. Se level was decreased positively with the progression of prostate cancer.

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تقدير بعض البارامترات (الأنزيمية و غير الأنزيمية) المرتبطة بالأكسدة الفوقية للدهون لرجال مصابين بسرطان البروستات.

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الخلاصة:-

إن الغرض من هذه الدراسة هو تقدير بعض المتغيرات المرتبطة بشدة الأكسدة في كريات الدم الحمراء و مصل الدم في المرضى المصابين بسرطان البروستات عن طريق قياسها و مقارنتها مع مجموعة السيطرة. تم قياس فعاليات أنزيمات الكلوتاثايون – أس – ترانسفيريز و الكلوتاثايون بيروكسيديز و الزانثين أوكسيديز في كريات الدم الحمراء وكذلك تم قياس مستويات المالونداي ألديهايد والبروتينات الدهنية عالية الكثافة والبروتينات الدهنية قليلة الكثافة والسلينيوم في مصل الدم في مجموعتين من المرضى المصابين بسرطان البروستات.

تتضمن 25 من الرجال المصابين بسرطان البروستات ولمدة تتراوح مابين سنة إلى سنتين. Aالمجموعة أيضا تتضمن (25) من الرجال المصابين بنفس المرض ولمدة تتراوح ما بين سنتين إلى أربع سنوات. Bوالمجموعة إن مجاميع المرضى تمت مقارنتهم ب (25) من الرجال الأصحاء كمجموعة سيطرة .

أثبتت النتائج فعاليات الكلوتاثايون–أس–ترانسفيريز والكلوتاثايون بيروكسيديز والزانثين أوكسيديز إرتفعت في بمقارنتها مع مجموعة السيطرة (A) المجموعة

ولكنها إنخفضت في المجموعة ($p<0.001$) وبمستوى إحتمالية قدره (B)

. إن مستوى المالونداي ألديهايد إرتفع لدى المجموعة كما أن هذا الإرتفاع سيستمر (A)

. إن مستوى البروتينات الدهنية عالية الكثافة إنخفضت في المجموعة(B)لدى المجموعة (A)

مقارنة بقيم السيطرة كما أن هذا الإنخفاض سيستمر لدى أفراد المجموعة إرتفع في الحالة المرضية بالمقارنة مع قيم . وعلى العكس فإن مستوى البروتينات الدهنية قليلة الكثافة (B)

السيطرة. إن عنصر السلينيوم إنخفض مستواه في الحالة المرضية مقارنة مع مجموعة السيطرة كما أن هذا الإنخفاض يتناسب طرديا مع الفترة الزمنية للإصابة بالمرض.

مجلـــــــ