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Clinical significance of DNA damage, lipid peroxidation and protein oxidation in Ovarian Cancer

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Background: several factors are implicated in the occurrence of cancer basing on the degree of DNA damage to which, in turn, is equivalent to the extent of reactive oxygen and nitrogen stresses, 8-Hydroxydeoxyguanosine (8- OHdG) is consider as a marker of oxidative stress in DNA molecule . **Objective:** This research was conducted to assess serum markers of protein oxidation, DNA damage, and lipid peroxidation levels in ovarian cancer. **Patients and methods**. The present study is composed of 85 women (mean age = 62.03±12.4 yrs) with clinically and pathologically confirmed ovarian cancer and 65 healthy women as a control group (mean age = 61±12.1 yrs). The measured biochemical parameters included: the level of serum protein oxidation, DNA damage, and lipid peroxidation **Results:** The results demonstrated significantly high values of 8-OHdG ($p<0.0001$) and significantly high ($p<0.001$, $p<0.002$)values in advanced oxidation protein products (AOPPs) & **3-**Nitrotyrosine (3-NT) in ovarian cancer in comparison with control group. There were also significantly high ($p<0.05$, $p<0.001$) values of sera, 4-hydroxynonenal 4-(HNE) and (8-isoprostaglandin F2alpha(8-PGF) in women ovarian cancer in comparison with control group. **Conclusion**: Assessment marker of, DNA damage, lipid peroxidation and protein oxidation May serve as prognostic tools in Ovarian carcinoma and the role of oxidative stress as a carcinogenic factor in ovarian cancer pathogenesis.

Key words: Ovarian cancer, DNA damage, lipid peroxidation, protein oxidation

Introduction

The evolution of cancer comprising several steps or stages that includes a complex sequence changes at cellular and molecular levels mediated by a variety, of internal and external and exogenous stimulant [1]. Chemically reactive chemical species containing oxygen. include peroxides, superoxide, hydroxyl radical, singlet are very unstable species and react quickly with various molecules. They have an ability to directly interact with DNA molecules and they cause Lipid peroxidation and protein oxidation producing intermediates that interact with DNA molecules. It has been reported that formation of reactive oxygen species from DNA damage and mitochondrial oxidative stress is exactly, associated with tumorigenesis [2]. Several forms of DNA damage have been identified such as oxidized purine and pyrimidine bases (which characterized by strand breaks of DNA molecules [3].
Among various types of DNA damage that take place as a result of reactive oxygen species generation that enhance risks of cancer, the most examined base damage is 8-oxoguanine (8-oxoG) [4]. Formation of (8-oxoGua) in DNA is a mutagenic species and possibly carcinogenic occurrence since the oxidized base has changed hydrogen bonding: that forms hydrogen bond with adenine instead of cytosine [5]. The altered base 8-oxo-guanine, its deoxy-nucleoside derivative 8-OH-dG (8-hydroxy- 2'-deoxyguanosine) and 8-oxo-adenine have been utilized as important indicators of DNA damage which is generated from oxidative stress [6].
Oxidized damaged DNA molecules has often been considered as a possible basis for such physiological alteration linked to cancer.[7]. 8-Oxo-7,8-dihydroguanine (8-oxoGua), one of the oxidatively altered DNA bases, is an important marker of oxidative stress and may play a key role in tumorigenesis. The existence of 8-oxoGua residues in DNA contribute in the point mutation in DNA in which purine (A or G) is changed for a (one ring) pyrimidine (T or C), unless DNA repair system precede to DNA replication.[8] Therefore, the existence of (8-hydroxy- 2'-deoxyguanosine) may contribute in mutagenesis and tumorigenesis in vivo.[9]

Proteins are liable to be influenced by oxidative injury, generating cross-linkage species and aggregation cpompounds that are withstand toward proteolytic pathways. Indicators of protein oxidation were described

by [10], and called as advanced oxidation protein products (AOPPs), since they collaborating various similarities with advanced glycation end products modified proteins (AGEs-modified proteins), biomarkers of oxidative stress process that consideras a protein glycooxidation. Circulating concentrations of dvanced oxidation protein products increase with development of chronic diseases [11], therefore, dvanced oxidation protein products have been regarded as disorder linked indicators for oxidative stress. AOPPs are considered as cross-linked protein products contain that dityrosine amino acids the existence of advanced oxidation protein products may be a more accurate indicators of oxidative stress than lipid peroxidation products [12]. **3-**Nitrotyrosine (NT) has been recognized as an indicator of overproduction of nitric oxide (·NO) by the action of reactive nitrogen species (RNS) formation. **3-**Nitrotyrosine is a stable final product of nitration process of tyrosine amino acid by the reactive nitrogen species such as nitrogen dioxide and peroxynitrite. The peroxynitrite is a strong oxidant and toxic because of its capacity to oxidize such molecules like enzymes, lipids, proteins and DNA [13-15].

The highly reactive molecule, formed by oxidative stress, can change the phospholipid bilayer and cause the oxidative degradation of lipids of polyunsaturated fatty acids leading to the production of Peroxyl radicals), which, in turn, reacts with a lipid to produce a lipid hydroperoxide and lipid radical. lipid hydroperoxide are unstable: they form new peroxyl and alkoxy radicals and decay the secondary products [16]. Some kinds free radicals that formed during oxidative degradation of lipids have some very internal influences, because of their short lifespan, but the products of lipid peroxidation breakdown may act as "oxidative stress second messengers," because of their prolonged half-life and their capacity to distribute from their site of production, compared to free radicals. [17].
4-hydroxynonenal is the very thoroughly, studied products of lipid peroxidation breakdown Among all products of lipid peroxidation, [18] 4-hydroxynonenal is a highly electron pair acceptor molecule that quickly bound with compounds with low-molecular-weight, like glutathione, with proteins and, and react with DNA at higher concentration, [19, 20]. 4-hydroxynonenal has ability to form covalent modifications on macromolecules (Carbohydrates, lipids, proteins, and nucleic acids) because of its chemical reactivity hence it exhibits some biological influences. Three chief functional groups that includes (aldehyde group, the C=C double bond, and the hydroxyl group contributes in The chemical reactivity of 4-hydroxynonenal, those functional groups have ability to react chemically solely or in sequence with other biomolecules.
Confirmations suppose that ovulation increases the circulating concentration of such inflammatory species, which can additionally cause mutations in DNA molecule [21–24]. Ovulation generates a void on the surface of ovarian, which leads to the replacement of damaged tissue by newly produced tissue, with elevated concentration of messenger that promote an inflammatory response and reactive chemical species It has been supposed that cancer cells from the fallopian tubes, the cervix lesions move to the ovaries and produce cancer cell near the corpus luteum [25].
The aim of this study is to evaluate protein oxidation, DNA damage, and lipid peroxidation in patients with ovarian cancer and to investigate the relationship between oxidative stress and ovarian cancer

Subjects
This study involved 85 females, aged 29–70 years, who were visited the Hiwa Hospital in Sulaymaniyah city. These women were diagnosed to have ovarian cancer. A total of 65 apparently healthy women from the outpatient department were involved in this study as a control group. Ethical approval and permission for the study was taken from the Ethical Committee of Sulaymaniyah University (Iraq). Informed consent was taken from all the study subjects purely for research purpose.

Samples
***1-Collection of the* Blood**
Blood was sampled before any treatment was given**.** Six milliliters of venous blood were taken without using tornique from each individual, collected in plane polyethylene tube, allowed to stand at room temperature for thirty minutes, then the sample was centrifuged at (2000xg) for 10 minutes, the obtained serum transferred immediately to another test tube. These samples were estimated directly for enzymes activities or frozen at – 20 C for subsequent analysis.

Determination of of Biochemical markers

The concentration of 8-hydroxydeoxyguanosine (8-OHdG), as a biomarker of DNA ,advanced oxidation protein products (AOPP), and 3-nitrotyrosine (3-NT) levels, as indicators of protein oxidation damage, and 4-hydroxynonenal (4-HNE), and 8-ISO-prostaglandin F2α (8-PGF) as a biomarker of lipid peroxidation in serum samples were determined by sandwich enzyme-linked immunosorbent assay (ELISA) technique using the kit manufactured by BioVision company.

Principle:

This ELISA kit uses Sandwich-ELISA type as the method. The Microelisa stripplate provided in this kit has been pre-coated with an antibody specific to each biochemical marker. Standards or Samples are added to the appropriate Microelisa stripplate wells and combined to the specific antibody. Then a Horseradish Peroxidase (HRP)-conjugated antibody specific for each biochemical marker is added to each Microelisa stripplate well and incubated. Free components (unbound conjugated antibodies) are washed away. The 3,3',5,5'-tetramethylbenzidine (TMB) substrate solution is added to each well. Only those wells that contain biochemical marker and HRP-conjugated biochemical marker antibody will appear blue in color and then turn yellow after the addition of the stop solution (0.16M H_2SO_4). The optical density (OD) is measured spectrophotometrically at a wavelength of 450 nm. The OD value is directly proportional to the concentration of each biochemical marker in standards and samples.

***Results&* Discussion**

Serum levels of 8-hydroxydeoxyguanosine (8-OHdG), a biomarker of DNAdamage

The results in Figure (1) showed that there was a significant increase ($p < 0.0001$) in serum 8-hydroxy-2-deoxy-Guanosine (8-OHdG) concentration in ovarian cancer group as compared to the control group

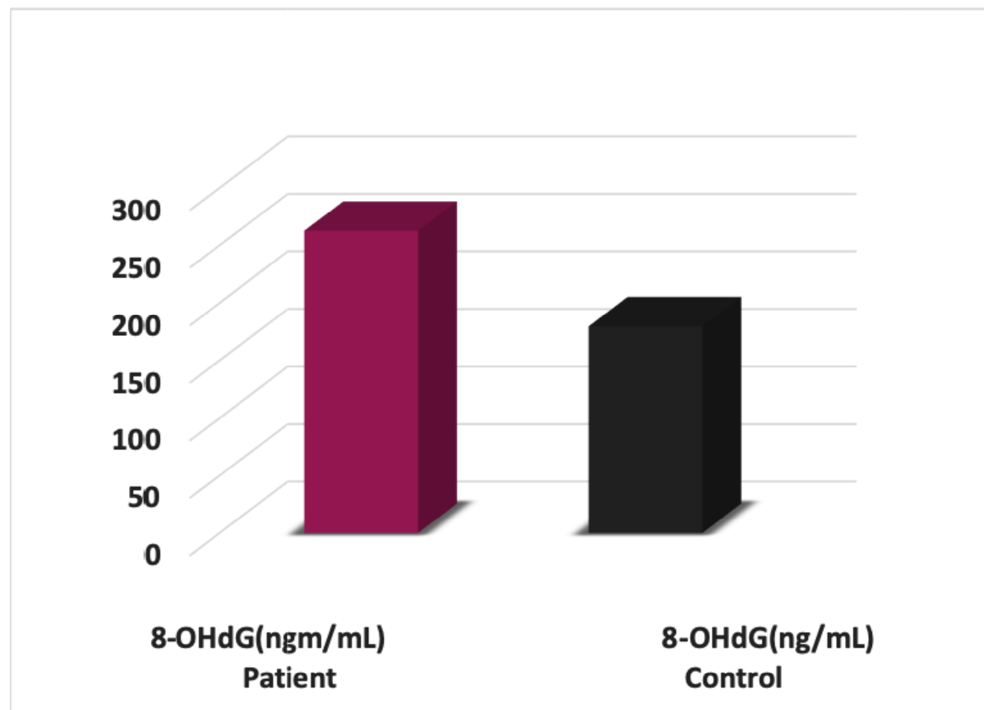

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Figure (1) Mean value of 8-OHdG concentration in sera samples of control and patient groups

8-hydroxy-2-deoxy-Guanosine level was measured to assess DNA damage due to the oxidative stress in ovarian cancer. In the current study, the 8-OHdG concentration in sera samples of patient group was found markedly increased, when compared with that of the control group. This result is in conformable with several studies referred to the presence of significant increase in 8-OHdG concentration in patients with different types of cancer [26-28, 29,30].

Several species like Reactive oxygen species and reactive nitrogen species are implicated in the damage of DNA molecules. Those reactive chemical species can DNA damage by the different ways(i)they can create single -strand break or double- strand break, and (ii) they can alter nitrogenous bases and make cross links Reactive oxygen species (ROS) and reactive nitrogen species (RNS) can damage DNA in many ways: (a) they can form a single or double-strand break, and (b) they can modify nitrogenous bases and induce cross links. When these damages are not repaired cells show replication errors, or progress elevated cell growth, undergo mortification, angiogenesis, and genetic instability, which finally results in the beginning of Cancer cell [31]. The most huge by-product formed by these consequences is 8-hydroxy-2-deoxyguanosine; therefore, determination of its concentration may be used to assess the load of oxidative DNA damage in the cell. This value could be important in understanding the role of oxidative stress in ovarian cancer progression. The higher oxidative DNA damage in the ovarian cancer, as a possible result of diminished activity of antioxidant species, indicates an important effect for reactive oxygen species in ovarian tumorigenesis. Therefore, the contents of 8-OHdG in serum could behave as a sensitive biomarker for ovarian cancer patients. The current study revealed remarkable increase in serum 8-hydroxy-deoxyguanosine (8-OHdG) levels as an oxidative DNA damage biomarker. An 8-OHdG supplied a useful indicator for the measurement of oxidative DNA damage in vivo. Increased oxidative DNA damage in patients with ovarian cancer may be linked with previous studies, which have suggested the diminish in antioxidant system as well as increase in reactive metabolites in ovarian cancer patients [32]. The disparity between oxidative stress/antioxidant system was considered as chief cause for the elevation and excessive formation of DNA damage compounds in ovarian cancer patients. The findings of the current study are in line with earlier study of increased DNA damage in patients with various cancers. Khadem-Ansari et al. Obtained an increase in 8-OHdG levels in the urine of esophageal squamous cell carcinoma [33]. Similarly, [34] recorded that 8-OHdG were higher in human oesophageal cancer. Crohns et al, likewise, recorded the increased concentrations of 8-OHdG in the urine of patients with lung cancer [35]. A study performed by Wei et al. demonstrated the higher concentration in serum 8-OHdG values in patients with colorectal cancer than in healthy controls [36]. Cobanoglu et al. reported an increase in the levels of 8-OHdG in patients with lung cancer [37]

Females with a high genetic risk of ovarian carcinoma have been shown to be distinctly possible to express multiple inclusion cysts in their ovaries [38] As a an indicator of oxidative stress, 8-OHdG levels have been described to be increased in ovarian surface cells in postovulatory follicles of humans and sheep .High 8-OHdG concentrations have also been found in the epithelia of pre- and postovulatory follicles in egg-laying hens [39].

Serum levels of Advanced oxidant protein products (AOPP)

The results presented in Figure (2) reveal the presence of a highly significant increase ($P<0.001$) in serum Advanced oxidant protein products (AOPP) levels in ovarian cancer group in comparison to that of healthy individuals.

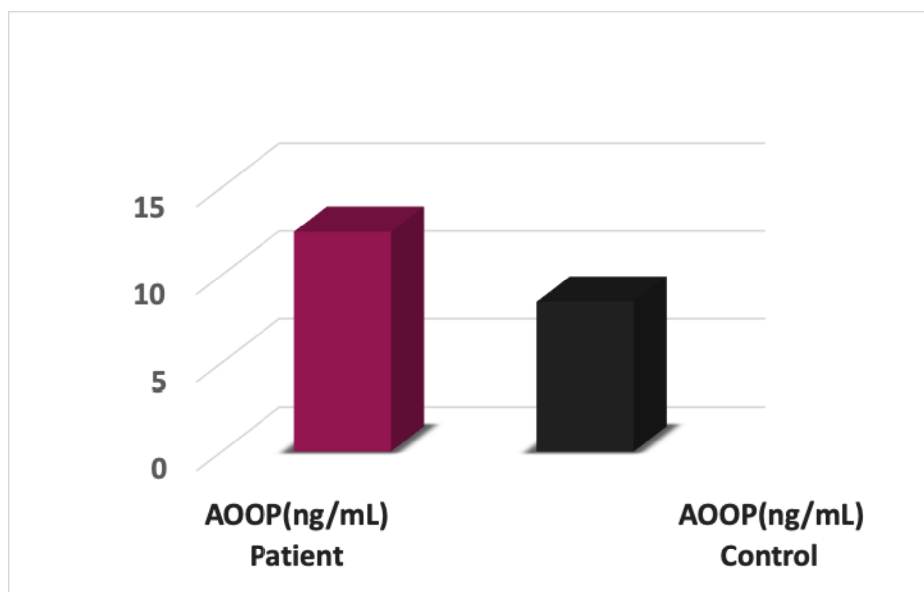

Figure (2) Mean value of (AOPP) concentration in sera samples of control and patient groups

Advanced oxidation protein products produced by various oxidation patterns that contribute in the generation of nitric oxide or hydrogen peroxide which propose their role in the production of various kinds of reactive oxygen species that set a tandem reaction with possibility to damage cellular micro-molecules, that causes cancers. [40]

Exhibition of proteins to reactive chemical species (reactive oxygen or nitrogen species) contribute in alteration of amino acid residues, altering the protein construction and biological function [41]. Indicators of protein oxidation are often associated with markers of oxidative stress status is being studied. Proteins are a chief goal for oxidative damage and nitrative damage in vivo, it is extensively. recognized that oxidation of proteins plays a key role in the biological mechanism of cancers [42].

Advanced oxidation protein products, which is products of the effect of reactive species on proteins, were delineated by Witko-Sarsat et al. [43] for the first time. Advanced oxidation protein products is characterized by dityrosine containing cross-linked protein products and are considered to be dependable indicators to determine the grade of protein oxidation [44]. They are increased in patients with kidney insufficiency and they reach the highest concentrations in patients after kidney replacement treatment [45]. Elevated concentrations were also observed in cancer patients where they linked with indicators of oxidative stress [46, 47]. In the present study we found that the concentration of Advanced oxidation protein products was remarkably higher in ovarian cancer patients. In agreement with our results, Noyan et al. [48] revealed that Advanced oxidation protein products concentration was significantly higher in the serum sample from gastric cancer than those from the normal control. Advanced oxidation protein products are described as a marker of oxidative stress as well as indicators of neutrophil activation in chronic disease [49]. It has thus been demonstrating that chlorinated oxidants of neutrophil origin may cause oxidative stress, particularly protein oxidation.

Serum levels of 3-Nitrotyrosine. (3-NT)

The results presented in Figure (3) reveal the presence of a highly significant decrease ($P<0.002$) in serum *3-Nitrotyrosine. (3-NT) levels* in ovarian cancer group in comparison to that of healthy individuals.

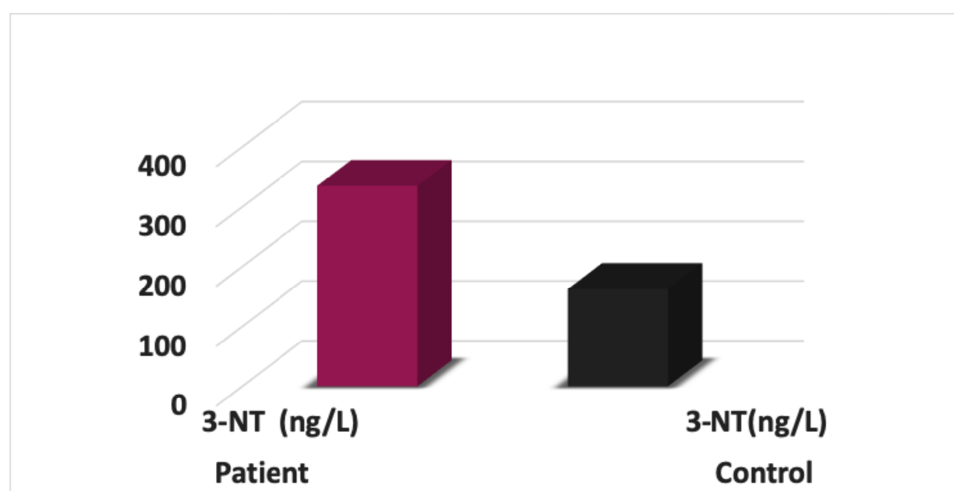

Figure (3) Mean value of (3-NT) concentration in sera samples of control and patient groups

Oxidized amino acids and changed amino acid side chains that containing reactive carbonyls are generated When proteins undergo Oxidation [50]. 3-nitrotyrosine is formed as a result of addition of a nitro group to the ortho position of tyrosine residues by the major product of peroxynitrite which attack on proteins. The major product of peroxynitrite attack on proteins is an addition of a nitro group to the ortho position of tyrosine residues to produce nitrotyrosine. 3-nitrotyrosine (3-NT) has been utilized as an indicator of nitrative damage in vivo [51, 52]. The existence of 3-nitrotyrosine (3-NT) in some carcinomas was previously recorded [53]. In this study, serum 3-NT level was remarkably y higher in the ovarian cancer patients. This finding is in line with other investigators' findings. Goto et al. [54] and Bancel et al. [55] found that 3-NT levels are increased in gastric cancer patients.

Concentration of 3-nitrotyrosine has previously been examined in tissue sections of breast and ovarian tumors [56, 57]. Expression of nitrotyrosine could already be estimate in benign and borderline ovarian tumors and high levels of nitrotyrosine in ovarian tumors linked with poor survival. Our results reveal a similar result, tumors with high nitrotyrosine expression had a remarkably bad survival in ovarian cancer. It has been reported that the expression of nitrotyrosine was, higher in ovarian carcinomas, showing an over 80 % expression [58]. Studies demonstrate that nitrotyrosine and 8OHdG that reflecting nitric oxide and hydroxyl mediated carcinogenesis play a key role in the carcinogenesis of bladder cancer[58]

Serum levels of 8-isoprostaglandin F2alpha

The results presented in Figure (4) reveal the presence of a highly significant decrease (P<0.001) in serum ***8-isoprostaglandin F2alpha*** *levels* in ovarian cancer group in comparison to that of healthy individuals.

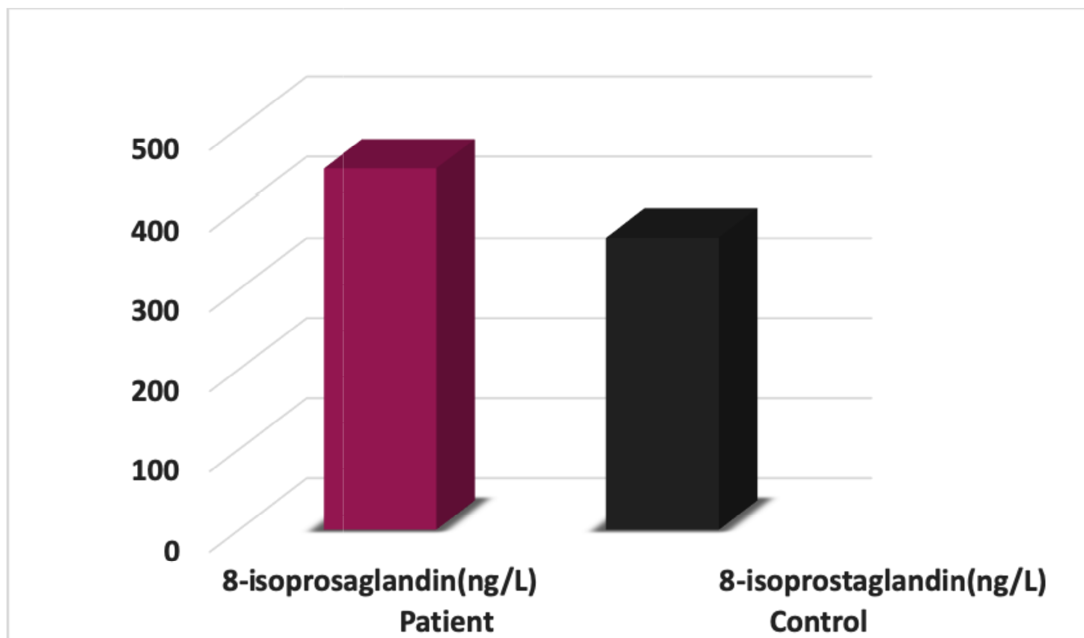

Figure (4) Mean value of (8-isoprostaglandin) concentration in sera samples of control and patient groups

The end products of oxidative degradation of lipids have an essential role in activating oncogenes through its effect disrupting the balance between the antioxidant/oxidative stress system and via expression of some genes that contribute to initiation of cancer and its development. Isoprostane (8-isoprostaglandin F2alpha is a compound generated from oxidative degradation of lipids and is an important indicator for oxidative stress evaluation. The 8-isoprostane is oxidative degradation of lipids during oxidative stress by a non-enzymatic method from lipid content of cell membranous which includes:phospholipids, glycolipids, and arachidonic acid.[59] In animal model studies, elevated levels oxidative degradation of lipid are closely associated to tumorigenesis . It has been reported that estimation of F2-isoprostanes provides a valuable approach for evaluating oxidative stress in vivo. Determinant of F2-isoprostanes has strongly confirmed the incident of oxidative stress in a wide ranges of disease states. In the present study, there was an increase in serum 8-isoprostane level in ovarian cancer patients compared with controls. These results concur with a previous study by [60]Khadem-Ansari et al., who also obtained an increase in esophageal squamous cell carcinoma patients. The study results are concordant with the study of [61]Dalaveris et al., who also obtained increased serum 8-isoprostane concentration in exhaled breath condensate and serum of patients with lung cancer.

***Serum levels of* 4-hydroxynonenal (HNE)**

4-hydroxynonenal (HNE) concentration in sera samples of control and ovarian cancer patient groups was measured .The results in (Fig. 5)showed that serum HNE levels of ovarian cancer increased significantly ($P < 0.05$) comparing with the healthy control group.

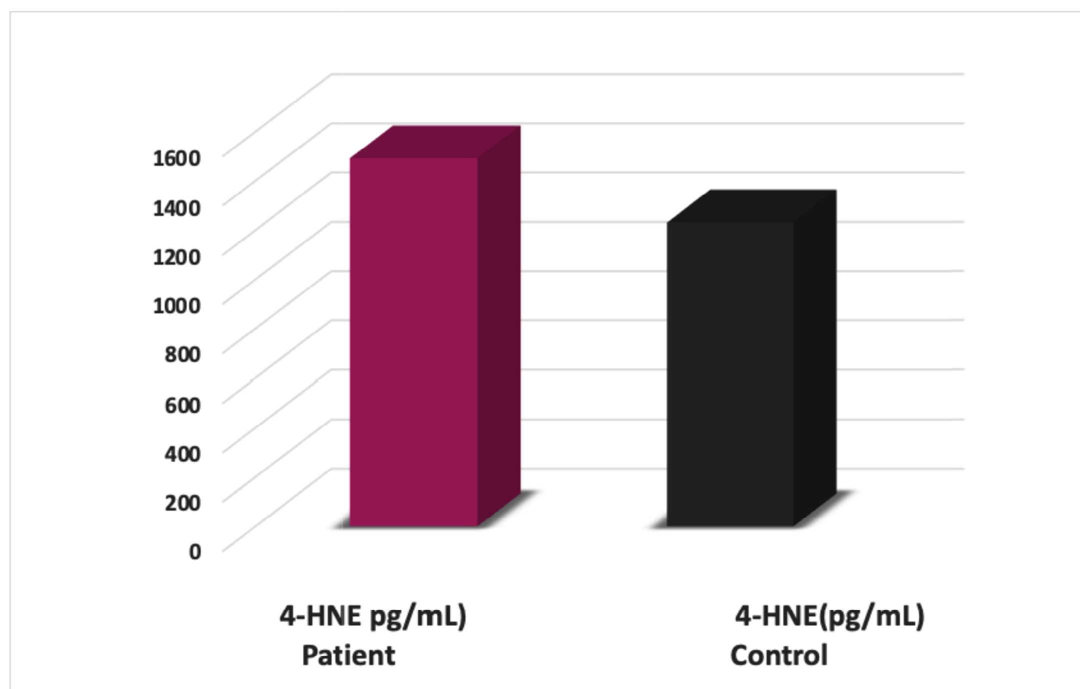

Figure (5) Mean value of (4-HNE) concentration in sera samples of control and patient groups

4-hydroxynonenal is considered to involved to the mutagenic effects and carcinogenic effects correlated with oxidative stress- caused oxidative degradation of lipids [62–65]. 4-hydroxynonenal and or its related bioactive metabolites can damage DNA, contribute in the formation of pro-mutagenic lesions in inflammation-driven cancers [66]. Various studies have demonstrate that production of protein -4-hydroxynonenal adducts in kidney and colon cancer cells and tissues are correlated to growth and development of renal and colon cancers [69–70]. Elevated 4-hydroxynonenal or protein-4-hydroxynonenal concentrations were found in renal proximal tubules in a rat model of renal adenocarcinoma [71]. Further, elevated 4-hydroxynonenal has been shown to be related to hepatocarcinogenesis initiation in rats model and these studies revealed that protein alteration by 4-hydroxynonenal could be a possible mechanism of cellular disturbances causing cancer initiation [72, 73].

Conclusions

These findings suggest that there was severe DNA damage (8-OHdG), and lipid peroxidation damage, protein oxidation in ovarian carcinoma patients. An increased serum DNA damage (8-OHdG), protein oxidation, and lipid peroxidation level are highly remarkable prognosticator of poor prognosis and their estimation could be helpful as an important diagnostic adjunct in the early diagnosis of ovarian carcinoma.

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