Association of potent inflammatory Cytokine and Oxidative DNA Damage Biomarkers in Stomach cancer patients

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Abstract:

The infection with H. Pylori stimulates a signaling cascade that causes the generation of Cytokines and provokes Oxidative stress that is involved in the chronic inflammatory response leads to Gastric cancers. Reactive oxygen species (ROS) produce 8-Hydroxydeoxyguanosine (8-OHdG), the persistent oxidative DNA damage product. The study objective was to assess if there was a link between inflammatory cytokine levels and the presence of Oxidative DNA damage in Gastric tumor patients. In addition, evaluation of the diagnostic and prognostic value of Oxidative DNA damage and inflammatory cytokine biomarkers for Stomach cancers is being conducted. The study was accomplished on medically diagnosed Stomach cancer patients before any form of treatment. A total of 33 patients with Gastric cancers were selected and divided into Stages I, II, and III according to clinical pathology, and 32 age-matched healthy subjects as a control group. The Serum 8-OHdG, IL-6, TNF-α, IFN-γ & CEA were evaluated. The results revealed a highly significant rise ($P<0.0001$) in blood levels of 8-OHdG, TNF-α, & IFN-γ, and a non-significant ($P=0.4747$) increasing in IL-6 in GC patients compared to Controls, with levels gradually increasing as disease stages progressed. Furthermore, in GC patients, there was an insignificant ($P=0.3472$) positive correlation (r=0.1292) among 8-OHdG, IL-6, and CEA levels, but a noteworthy ($P<0.0001$) positive correlation (r=0.7235) among 8-OHdG, TNF-α, and CEA levels. In GC patients, however, there was an insignificant ($P=0.6342$) negative correlation (r=-0.06559) among 8-OHdG, IFN-γ, and CEA levels. The results of the current study show a strong link between serum levels of the 8-OHdG as well as inflammatory cytokines in GC patients. The significant enhancement in oxidative DNA damage, as well as overexpression of inflammatory cytokine biomarkers and CEA in the blood suggests that Oxidative stress and chronic inflammation are included in GC carcinogenesis. These observations suggest that 8-OHdG, TNF-α, & IFN-γ are viable biomarkers for the Gastric tumor prediction.

Keywords: Gastric cancer, Inflammatory cytokines, Oxidative stress, Oxidative DNA damage.

Introduction:

Oxidative free radicals play a crucial role in the disablement of biological molecules. Nuclear DNA, Proteins, plus Lipids of living organisms are suggested to be mutilated by Oxygen radical species. The damage of a biological cell, which is the consequence of Reactive oxygen species (ROS) is named Oxidative stress (OS) [1]. The initiation as well as progression of human cancer-associated mutations attribute to damage of nuclear DNA by Reactive oxygen species (ROS) [2]. Oxygen radicals prompt DNA damage comprises altered nitrogen bases, breakage of strands, DNA-protein crosslinks (the single and double-strand), exchange of genes between two identical sister chromatids, the subsequent generation of clastogenic factors, and modifications in the nitrogenous base structures [3]. Oxidative damage to Pyrimidine & Purine bases attributes to the Oxidation of nuclear DNA. Guanine base incline is the more oxidized one among all the nitrogen bases. 8-Hydroxyguanine (8OHGua), 8-Hydroxy-2'-deoxyguanosine (8-OHdG), 5-Hydroxy-6-hydrothymine, 5-Hydroxymethyluracil, 5-Formyluracil, 8-Hydroxyadenine, 5-Hydroxy-5-methyl hydantoin

are among the many DNA damage products reported in preliminary investigations [4]. The most prevalent biological marker of the Oxidative stress was 8-oxo-2'-deoxyguanosine (8-oxodG), also known as 8-Hydroxydeoxyguanosine (8-OHdG). 8-OHdG levels in the blood could be evaluated at high sensitivity, also their levels are linked to cancer risk and Oxidative stress (OS) in target cells. As a result, 8-OHdG is a very useful biological marker in the oxidative damage research [5].

Stomach cancer (SC) is the third most major reason of mortality among all malignancies, making it a significant public health concern all over the globe [6]. The infection of gastric mucosa by H. Pylori is a key danger factor in approximately 65 percent of whole distal stomach cancer cases; also, the evidence implies that it may also play the role in proximal stomach cancer. The interaction of the H. Pylori via the gastric epithelium promotes the production of interleukins (IL-8 and IL-6). This cytokines function as a chemotactic substance for neutrophils as well as mononuclear cells, creating a multiplication response with widespread neutrophil and macrophage diffusion in the stomach mucosa, resulting in chronic active gastric inflammation [7]. Dendritic cells T & B cells besides H. Pylori also promote gastric mucosal infiltration and stimulate releasing of Cytokines such as Tumor necrosis factor-α (TNF-α), Interleukins (IL-10, IL-12), Transforming growth factor-beta (TGF-β), also Interferon-gamma (IFN-γ) [8]. The mediators of inflammation created by this decades-long gastritis might contribute to nuclear DNA damage, boost proliferation, so prevent apoptosis, between other negative impacts that predispose gastric mucosa cells to acquire genetic and epigenetic changes which may ultimately develop Gastric cancers [9]. The objective of this study was to assess the potent link between inflammatory cytokine levels and oxidative DNA damage in patients with gastric cancer. Furthermore, evaluation of the diagnostic and prognostic significance of oxidative DNA damage and inflammatory cytokine biomarkers for stomach malignancies.

Materials and Methods:

The study included 65 people, 32 healthy people their age and sex-matched and 33 of clinically and histologically diagnosed stomach cancer at various stages, the majority of which were stage III, IV, and V. Thirty-one of the 33 patients had gastric adenocarcinomas (GAC), one had Gastrointestinal stromal tumor (GIST), and the other had Neuroendocrine tumors (NETs) subtype. Besides, the CEA level of all patients had been recorded. Nanakaly Hospital for blood diseases and cancer and Rizgary Hospital (Oncology Unit) in Erbil City provided the samples. Patients were evaluated based on their complete medical history to rule out any existing systemic disease or drug use that could affect the parameters being studied. They were compared to a control group. Before being selected, all healthy persons are tested for Anti-H. Pylori IgG antibody, also those who test positive for H. Pylori were deselected and removed from the control group. The information of all patients as well as control subjects is summarized in Table 1.

Table 1. The host information of the studied groups

Groups	No.	Gender		Age
		Male	Female	Mean ± SD
Controls	32	18	14	49.88±12.33
Patients	33	34	9	55.52±9.162
Stage III	2	1	1	41.00±5.657
Stage IV	15	10	5	54.13±8.814
Stage V	16	13	3	57.25±10.43
Total	65	42	32	52.74±11.12

Sample collection:

Each subject had 5 to 6 mL of blood drawn, collected in Gold-top serum separator tubes (Gold-Top SST), left to stand at ambient temperature for 10 minutes, and then centrifuged for 15 min at (3500 rpm). Serum samples were immediately transferred to pre-labeled and patient-coded Eppendorf tubes. Until the day of laboratory analysis, these samples were kept frozen at –20°C. Serum samples that had been hemolyzed were discarded.

Measurement of Biochemical parameters

The concentrations of 8-OHdG, IL-6, TNF-α, & IFN-γ in serum samples were measured by ELISA method utilizing the kits manufactured by BioVision. Moreover, the serum level of CEA in patient samples was measured by LIAISON® XL which is a fully automated chemiluminescence analyzer.

Statistical analysis

The statistical analyses were performed utilizing the SPSS version 21 and GraphPad prism 8 computer applications. The findings of Statistical tests and Bar graphs were expressed as means ±SD. The normality studies of Kolmogorov-Smirnov (K-S) & Shapiro-Wilk (S-W) was used to assess the normal distribution of study data. The studied parameter means were compared among the patient and control groups using a parametric independent t-test. To compare the studied parameter means among GC disease stages (III, IV, and V), a One-way ANOVA test was utilized. The parametric Pearson's correlation test (r) was performed to identify statistical correlations among 8-OHdG,

CEA and associated biochemical parameters in the patient group. Because the Confidence interval (CI) of choice was 95%, the *P*-value of ≤0.05 was judged significant.

Results and Discussion:

Serum levels of 8-OHdG

The results in Fig. 1 show that there is a remarkable elevation ($P<0.0001$) in serum 8-OhdG concentration in gastric cancer patients (268.2 ± 5.7) as compared to the control group (22.58 ± 1.5).
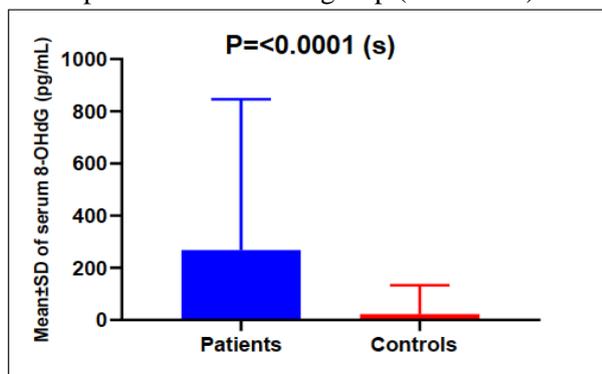

Figure 1. Mean value of 8-OHdG concentration in sera samples of control and patient groups

The 8-Hydroxy-2-deoxyguanosine level was determined to assess DNA damage due to the oxidative stress in the Gastric tumor. In the current research, the 8-OHdG concentration in sera samples of patient group was found notably elevated, while compared via that of the control group. This result is conformable with various studies that confirmed the presence of a remarkable increase in 8-OHdG level in patients with different types of cancer [10-15].

The elevation in the 8-OHdG level can be explained by a few approaches. Because the stomach is a delicate digesting organ, it is susceptible to and exposed to exogenous microorganisms from the diet. The stomach promotes oxidative stress in response to such infections that may be associated with the progression of stomach organic disorders like gastric cancer, gastritis, gastric ulcers, & functional diseases like functional dyspepsia. Helicobacter pylori, in particular, is important in triggering and encouraging oxidative stress in the stomach. The high concentration of oxidative stress is created while the generation of the free radicals exceeds the cell's capacity to remove them, causing the deregulation of Redox-sensitive signaling pathways, as well as in the chemical damage of most cellular biomolecules, comprising DNA [16, 17].

Reactive nitrogen species (RNS), as well as Reactive oxygen species (ROS), could damage DNA in two ways: (a) by generating single or double-strand breaks, and (b) by modifying nitrogenous bases and causing crosslinks. When cells are unable to repair these oxidative damages, necrosis, replication mistakes, or increased cell growth and division, angiogenesis, and a high frequency of mutations within the genome of a cellular lineage occur, ultimately leading to the incidence of cancer [16, 18]. Because 8-Hydroxy-2-deoxyguanosine (8-OHdG) was the most abundant by-product formed by these net outcomes, estimating its blood or urinary quantity may be useful in determining the load of the oxidative DNA damage in the cell. The concentration of 8-OHdG in the blood can be useful in determining the involvement of oxidative stress in stomach tumor growth and treatment. The substantial oxidative DNA damage is seen in gastric tumor, which could be due to antioxidant activity deficiencies, suggests oxygen free radicals play the important role in stomach carcinogenesis. As a result, blood levels of 8-OHdG could be used as a sensitive biomarker for gastric cancer patients. As an oxidative DNA damage biomarker, blood 8-Hydroxydeoxyguanosine (8-OHdG) levels increased dramatically in the current study. 8-OHdG levels in the blood provide a valuable biomarker and a repeatable method for assessing oxidative DNA damage in vivo. Many prior studies have documented increased oxidative DNA damage in patients with GC cancer, indicating a depleted antioxidant system and an enhance in the amounts of reactive oxygen species in gastric cancer patients [12, 19].

The current study's findings are consistent with other studies of higher DNA damage in the patients with several malignancies. In the urine of the esophageal squamous cell cancer patient, Khadem-Ansari et al. discovered the rise in 8-OHdG levels [10]. Diakowska D et al. [20] and Kubo N et al. [21] also found that 8-OHdG levels were greater in human esophageal carcinoma. Similarly, M. Crohns et al. [22] and C. Cao et al. [23] found higher levels of the 8-OHdG in tissue extract and urine of lung cancer patients. Research performed by Wei et al. [24] also revealed greater levels in serum 8-OHdG in patients via Colon tumors than in healthy controls. Cobanoglu et al. [25] recorded the enhance in the blood concentration of 8-OHdG in patients via Lung tumor.

Serum levels of TNF-α

The results in Fig. 2 show a highly significant increase ($P<0.0001$) in TNF-α concentration in the gastric cancer group (100.9 ± 2.47) in comparison to that of the controls (18.42 ± 3.45).

Figure 2. Mean value of TNF-α concentration in sera samples of control and patient groups
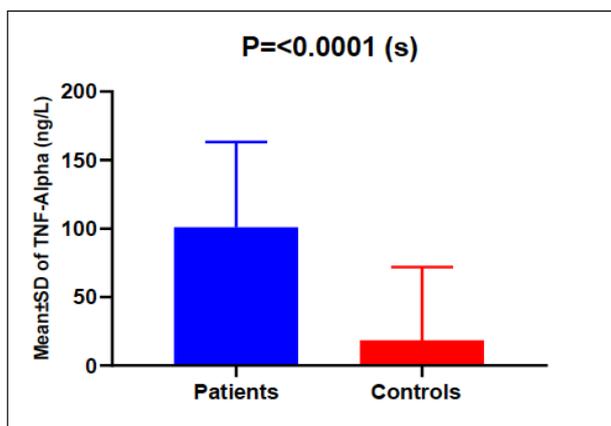

Figure 3. Mean value of IFN-γ concentration in sera samples of control and patient groups

The present study finding is in agreement with many previous studies [26-29]. Several studies tried to create a connection among carcinogenesis & inflammation, such as researches to consider the aptitude of pro-inflammatory cytokines like TNF-α, to induce tumors. TNF-α is the cytokine which is generated early in the inflammatory cascade as well as has been indicated to enhance oncogenesis in different kinds of human and animal tumors such as colonic tumors of Zucker obese (fa/fa) rats [30]. TNF-α was shown to promote carcinogenesis by up-regulating Nuclear Factor-kappa B (NF-κB) leading to up-regulation of further factors that contribute to cell morphogenesis causing cancer formation in the GIT [31].

TNF-α does not only act as a carcinogen but also has a remarkable role in cancer metastasis, Neovascularization, and Angiogenesis, cancer cell detachment from the primary site and increased tumor cell motility [32, 33]. TNF-α also increases invasion of the extracellular matrix [34]. TNF-α also facilitates the entry of tumor cells into vasculature and lymphatics and TNF-α may help in the proliferation of metastasized tumor cells [35, 36]. The significant rise in serum TNF-α concentration in H. Pylori positive gastric tumor patients seen in this study is consistent with previous reports, which showed that serum TNF-α levels were higher in patients with H. pylori infection and Stomach cancers [37-39].

Serum levels of IFN-γ

The mean values of IFN-γ concentration in samples of control and gastric cancer patient groups are presented in Fig. 3. The results show serum IFN-γ levels in gastric cancer patients (24.13±3.34) increased significantly (*P<0.0001*) in contrast to the healthy control group (8.133±1.19). The current study finding regarding IFN-γ is following many previous research studies [40-42].

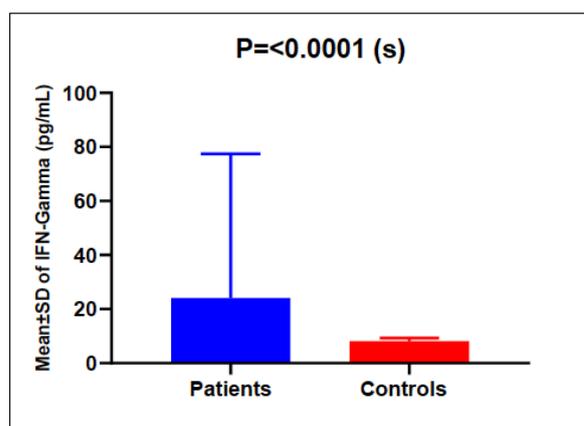The most prevalent factors that contribute to stomach inflammation are H. Pylori and Gastritis. Dendritic cells, B cells, and T cells are responsible for the effect of H. Pylori on stomach mucosal infiltration. Tumor necrosis factor-α (TNF-α), Macrophage chemotactic protein-1 (MCP)-1, IL-12, IL-10, Transforming growth factor-beta (TGF-β), as well as Interferon-gamma (IFN-γ) are all released in respond to H. Pylori infection. This long-term gastritis contributes to DNA damage, abnormal cell growth, and inhibits programmed cell death by producing inflammatory mediators [43, 44]. Even though the role of the IFN-γ in the initiation of a pro-inflammatory microenvironment in stomach tissue is still debated, increased concentrations of the IFN-γ in sera of stomach cancer patients in contrast to controls in this research can be representative of the role of IFN-γ in the initiation of a pro-inflammatory microenvironment in stomach tissue. Previous studies reported that after chronic H. Pylori infection, IFN-γ is augmented in the stomach mucosa [44]. Besides, IFN-γ plays a significant tumor suppressor role in addition to its role in bacterial infection responses [45]. Specific T-cell responses have been shown to play a key role in producing gastric mucosal inflammation, also IFN-γ may aggravate stomach inflammation & favor the growth of stomach cancer lesions [46, 47].

Serum levels of IL-6

The results presented in Fig. 4 show the mean values of serum IL-6 concentration in sera samples of gastric cancer patients in comparison with healthy individual controls.

The results reflected a non-significant increase (*P=0.4747*) of IL-6 in sera samples of the gastric cancer group (16.64±1.18) in comparison to that of the control (16.48±4.01). The present study outcomes are in perfect line with many previously published results [48-50].
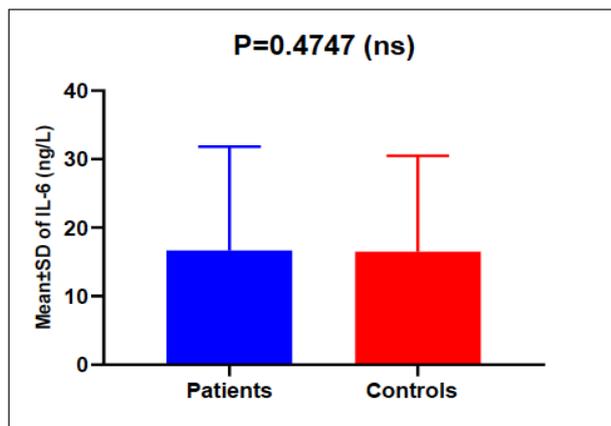
Figure 4. Mean value of IL-6 concentration in sera samples of control and patient groups

Chronic inflammation, such as that produced by H. Pylori infection and autoimmune gastritis, raises the risks of Stomach cancer. Adenocarcinomas that arise from epithelial cells in the chronically inflamed gastric mucosa, account for more than 90% of stomach malignancies. However, gastric cancer affects only a tiny percentage of chronic gastritis patients, showing both hereditary and environmental variables play a role in tumor developments. Several DNA polymorphisms tied to an enhanced risk of gastric tumor had been linked to Cytokine genes [51].

During chronic gastritis, many distinct cytokines are released by immune cells and epithelial cells. Many studies revealed a remarkable role of various Interleukins (ILs) in the progression of gastric cancer [52]. Interleukin-6 (IL-6) is an interleukin with two-edged actions like the pro-inflammatory & anti-inflammatory cytokine. Previous researches have shown that IL-6 had the role in the development as well as progression of gastric cancer by promoting neo-angiogenesis and the adhesion of cancer cells to the vascular endothelium, allowing gastric cancer to spread throughout the body. Furthermore, IL-6 promotes cancer cell survival in both a paracrine and autocrine manner [50, 53, 54]. In conjunction with IL-1 and TNF-α, IL-6 is one of the most substantial cytokines involved in inducing acute-phase inflammatory responses. IL-6 also promotes the chronic phase of inflammation that supporting an ideal environment for gastric tumor growth [55].

Serum levels of 8-OHdG among different stages of GC

The results presented in Fig. 5 show the mean concentration of the 8-OHdG in sera of GC patients via different disease stages in comparison with healthy controls.

The disease stage comparison reveals that serum 8-OHdG levels were gradually increasing

from stage III (32.10±3.465), IV (114.5±6.1) to V (504.9±8.4) of gastric tumor patients when in contrast to controls (22.58±1.5) and the difference was statistically remarkable ($P<0.0001$). On the whole, the serum 8-OHdG in different gastric cancer stages was notably higher contrasted to that of the Control group.
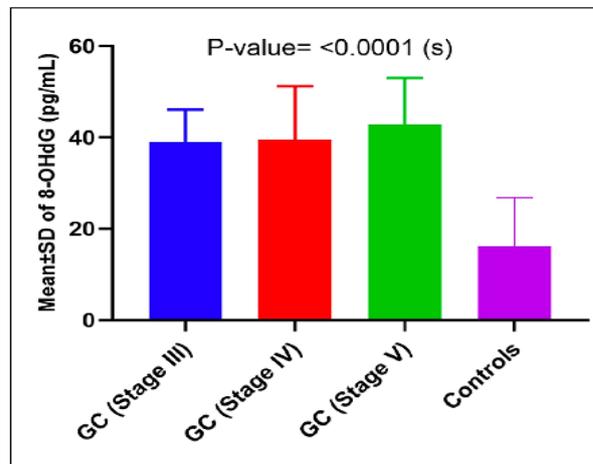

Figure 5. 8-OHdG serum levels in relation to GC stages

Oxygen radicals (OR) participate in all stages of Cancer development which include; initiation, promotion, and progression. In the initial stage, Reactive oxygen species (ROS) with high concentration can instigate structural damage to DNA which includes breaks in DNA strand, Point mutation, Proto-oncogenes, and Tumor suppressor genes mutation. The oxidation of nuclear DNA, as well as nitration and halogenations of DNA, takes place when products of DNA oxidation and nitration are directly bonded with DNA/RNA. Nuclear DNA damage is primarily caused by the synthesis of mutated DNA bases (hydroxylated form). The synthesis of 8-Hydroxy-2'deoxyguanosine (8-OHdG) is caused by the binding of a hydroxyl free radical to the deoxy guanosine residue's C-8 position. This oxidized adduct has been utilized as the biomarker for oxidative DNA damage for research purpose assays [56, 57].

A prominent biochemical marker of Oxidative stress is 8-Hydroxydeoxyguanosine (8-OHdG), a mutagenic DNA damage product. Reactive oxygen species (ROS) hinder cell-cell communication and change second messengers during the promotion stage of cancer. As a result, cell numbers increasing and apoptosis is reduced. In the progression stage, ROS-induced oxidized DNA adducts further add to DNA conversion to the proliferated cells. Reactive oxygen species are responsible for the activation of several signaling pathways resulting in the tumor progression which includes a variety of

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transcription factors such as NF-κB, AP-1(activator protein-1), MAPK [Mitogen-activated protein (MAP) kinase], p53, Sp-1(Specificity Protein-1), etc. The activation of these signaling pathways causes cell proliferation, angiogenesis, and metastasis [58, 59]. Enhanced oxidative stress has been observed during the advancement of gastric cancer, as evidenced by the decrease in antioxidant Vitamins and also an augment in lipid peroxidation [60].

The current study looked at the concentrations of serum 8-OHdG in patients via GC at various cancer stages to see if there was the link among oxidative DNA damage & gastric cancer growth. Stage III tumors are restricted to the stomach mucosa, stage IV tumors have localized lymph node metastasis, so stage V tumors have distant liver and lung metastases. The concentrations of blood 8-OHdG grew progressively from stage III to V, as presented in Fig. 5. This suggests that as GC progresses, oxidative damage gets more severe. Furthermore, for patients in the stage V via cancer regions also distant metastasis, the level of serum 8-Hydroxydeoxyguanosine (8-OHdG) is remarkably greater than that of patients in the stage IV & III lacking cancer metastasis (P<0.0001).

These findings suggest that the serum 8-Hydroxydeoxyguanosine (8-OHdG) level can be used to not only confirm the existence of GC, but also to determine whether the cancer has spread to lymph nodes or distant organs like the liver & lung. Similarly, the current study findings suggest that oxidative DNA damage biomarkers are a crucial component in the complex pathophysiology of gastric cancers, and that they are linked to disease progression. This is because elevated levels of 8-Hydroxydeoxyguanosine (8-OHdG) in stomach tumor patients are linked via disease progression as well as progression to higher greater stages of oncogenesis.

Serum levels of inflammatory cytokines among different stages of GC

The results presented in Fig. 6 show the mean concentration of the IL-6 in the sera of GC patients via different disease stages in comparison with healthy controls.

The disease stage comparison shows that serum IL-6 levels for patients at stage III (13.18±1.563) and IV (14.34±3.208) are relatively alike, but its level is peaked for stage V (21.67±2.32) patients. However, this difference was statistically non-significant and as a whole (P=0.7330), serum IL-6 levels are not gradually (steadily) increased from Stage III to V.
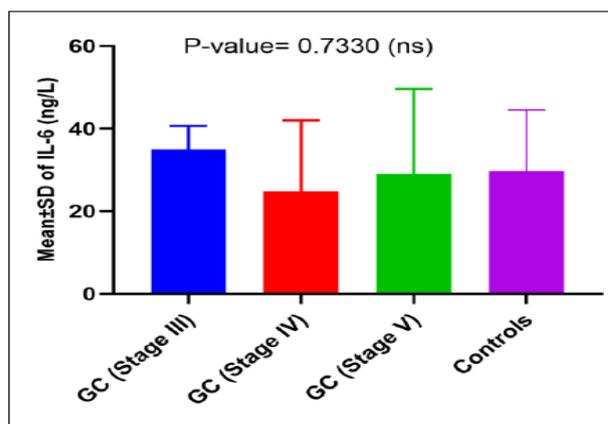

Figure 6. IL-6 serum levels in relation to GC stages

IL-6 is a pleiotropic cytokine generated by different cells, so it plays critical roles both in controlling the innate immune response and in stimulating the B-cell differentiation to antibody-producing plasma cells. IL-6 mRNA was found in a variety of stomach cancer cell lines, and it is claimed that IL-6 might increase stomach tumor cell proliferation when anti-IL-6 antibodies prevented this growth [61]. The Janus kinase (JNK)/signal transducer and activator of transcription-3 pathways direct IL-6 and IL-6 receptors to cancer cells. It binds to IL-6 receptors found on the surface of tumor cells after it is released by cancer cells. The mechanism of action IL-6 on tumor cells through hepatocyte growth factor (HGF) also accelerating invasion beside lymph node and/or hepatic metastasis. Increased serum IL-6 concentrations have been linked to tumor stage, liver metastasis, tumor depth, lymph node metastasis, lymphatic invasion, venous invasion, plus adverse consequences in patients via stomach tumor, according to several studies [61, 62].

The results presented in Fig. 7 show the mean concentration of TNF-α in sera of GC patients with different disease stages in comparison with healthy controls. The comparison of disease stages shows a reasonably gradual increase of sera TNF-α levels in stage III (1.180±0.1838) through stage IV (4.605±4.317) to stage V (38.74±1.03) of the disease. The mean TNF-α sera levels in stage V were considerably higher than in stage IV. However, the increased values were statistically non-significant (P=0.4462).

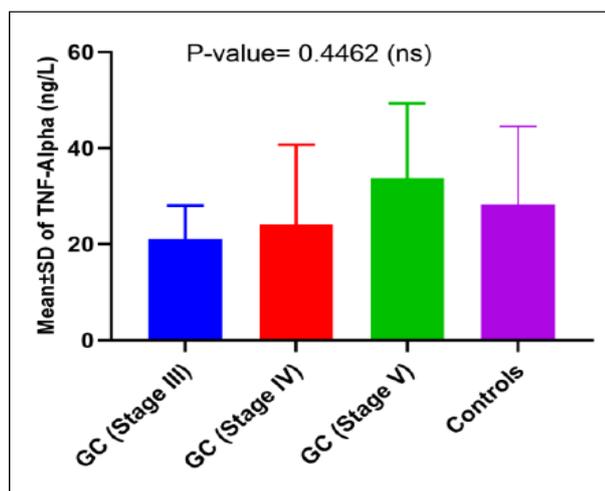Open Access
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Figure 7. TNF-α serum levels in relation to GC stages

The present study is in line with studies which also revealed the increasing in the TNF-α level in the advanced stage of GC and Colorectal adenocarcinoma [26, 63, 64]. This finding suggests that different cytokines might have a role in carcinogenesis as well as tumor development in Stomach cancer. Various potential pathways of cytokines contributing to cancer progression, both directly and indirectly include cytokines that directly stimulate oncogenesis & proliferation of cancer cells, as well as cytokines that suppress host antitumor immunity locally and/or systemically, thus indirectly contributing to cancer progression. TNF-α is released by cancer cells, leukocytes, and pro inflammatory cells in cancer microenvironments and operates largely through TNF receptor 1 in the autocrine as well as paracrine fashion. TNF-α has been linked to cancer growth by causing the breakdown of tumor vascular, which can promote angiogenesis. Thus, TNF-α might have a role in the developments of the tissue architecture required for tumor growth and cancer cell dissemination by boosting other pro inflammatory cytokines to contribute oxidative DNA damage [63, 64].

The results presented in Fig. 8 show the mean concentration of IFN-γ in the sera of stomach cancer patients among different disease stages in comparison with healthy controls.

The comparison of disease stages shows a relatively normal serum IFN-γ level in stage III (9.560±2.723) patients, while there is a sharp spike in IFN-γ serum levels in patients with advanced stages; IV (15.39±3.354) and V (33.88±5.33), and generally, the IFN-γ serum levels are significantly increased ($P<0.0001$) as the stages go up from III, IV, to V. As a whole, sera IFN-γ levels are significantly higher in stage III, IV, and V gastric

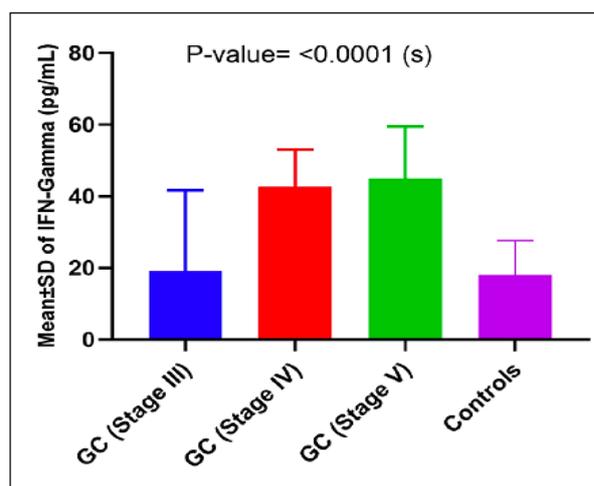cancer patients in comparison to that of the controlled subject group (8.133±1.19).

Figure 8. IFN-γ serum levels in relation to GC stages

The current study validated the findings of most authors, who found that IFN-γ blood levels in gastric tumor patients are greater than in controls, and that IFN-γ levels rise as disease stages progress [44, 65]. In the present research, the greater concentration of IFN-γ in sera of stomach tumor patients contrasted to healthy individuals could indicate that IFN-γ plays a role in producing the pro inflammatory milieu in a gastric tissue.

Many cytokines produced during chronic inflammation, such as IFN-γ, are thought to promote cancer growth also progression toward a highly malignant state through a variety of pathways, like induction of the DNA damage responses, angiogenesis, along with phosphorylation of signaling mechanisms that promote tumor cell multiplication[67]. IFN-γ can promote gastric tumor cell proliferation and metastasis in part by boosting the response of integrin 3-mediated NF-B signaling cascade, according to Yuan-Hua Xu et al., and inhibiting IFN-γ and integrin β3 could be a major role in stomach cancer therapy [66, 67].

Statistical Correlation among serum level of 8-OHdG, CEA and Inflammatory cytokines in GC patients

A statistical correlation test was performed between the serum levels of the oxidative DNA damage biomarker (8-OHdG) and the inflammatory cytokines investigated in this work. Moreover, each studied biochemical parameter also correlated with serum levels of Carcinoembryonic antigen (CEA) in GC patients.

The oncofetal glycoprotein Carcinoembryonic antigen (CEA) is generally expressed by mucosal

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cells. It is overexpressed in a number of Adenocarcinomas. Although it is most usually linked to Colon cancer, it's blood level can also be increased in Stomach cancers [68].

The scatterplot graph in Fig. 9 shows a correlation between serum 8-OHdG & IL-6 concentrations in patients with Gastric cancer. Besides, the scatterplot graph in Fig. 10 shows a correlation between serum 8-OHdG & CEA concentrations in patients with Gastric cancer. The serum levels of 8-OHdG and IL-6 were positively (r=0.1292) and non-significantly (P=0.3472) correlated. Likewise, the serum levels of 8-OHdG and CEA were positively (r=0.2866) and non-significantly (P=0.0824) correlated. Similarly, the serum levels of IL-6 and CEA were positively (r=0.1847) and non-significantly (P=0.1885) correlated. These results show that blood levels of 8-OHdG rises in tandem with the level of IL-6 and CEA. According to the correlation graphs, IL-6, a pro inflammatory mediator secreted in the tumor microenvironment by macrophages and epithelial cells along with other pro inflammatory cytokines, increases oxidative stress also play a foremost role in stimulating nuclear oxidative DNA damage.
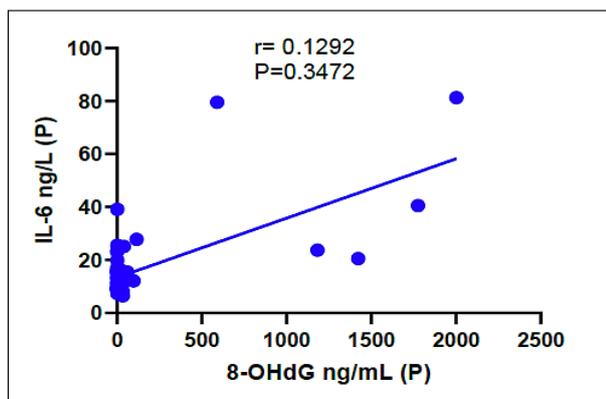

Figure 9. Correlation graph among serum 8-OHdG and IL-6 levels in GC patients
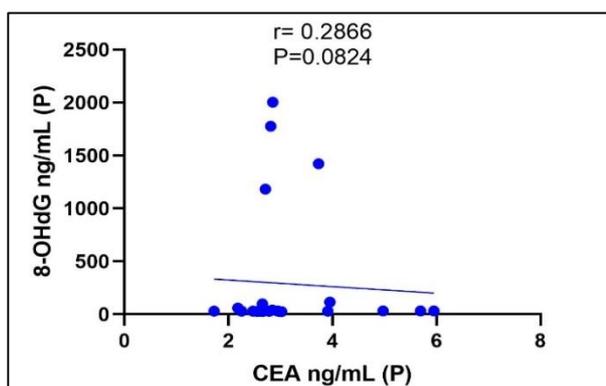

Figure 10. Correlation graph among serum 8-OHdG and CEA levels in GC patients
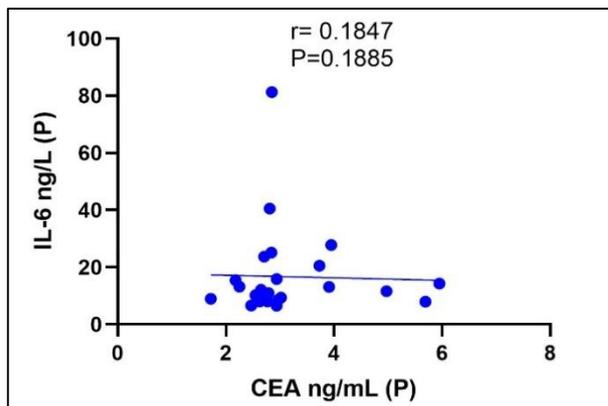

Figure 11. Correlation graph among serum IL-6 and CEA levels in GC patients

The scatterplot graph in Fig. 12 shows a correlation amid serum 8-OHdG & TNF-α levels in patients via Gastric cancer. Also, the scatterplot graph in Fig. 13 shows a correlation between serum TNF-α & CEA concentrations in patients with Gastric cancer. The blood levels of 8-OHdG and TNF-α were positively (r=0.7235) and significantly (P<0.0001) correlated. Furthermore, the blood levels of TNF-α and CEA were also positively (r=0.4812) and significantly (P=0.0074) correlated. The rise in TNF-α levels coincided with a rise in 8-OHdG and CEA levels. TNF-α is one of the strongest inflammatory cytokines generated by activated macrophages in the tumor microenvironment, largely as an immunological response to H. Pylori infection, according to the correlation graph. TNF-α might therefore cause a significant oxidative damage to gastric mucosa tissues by inducing long-term oxidative stress, which could result in elevated 8-OHdG blood levels. Augmented Oxidative stress and Oxidative DNA damages in patients can be evidenced by increased blood 8-OHdG levels while the development of Gastric adenocarcinomas can also be evidenced by increased serum CEA levels alongside 8-OHdG levels.
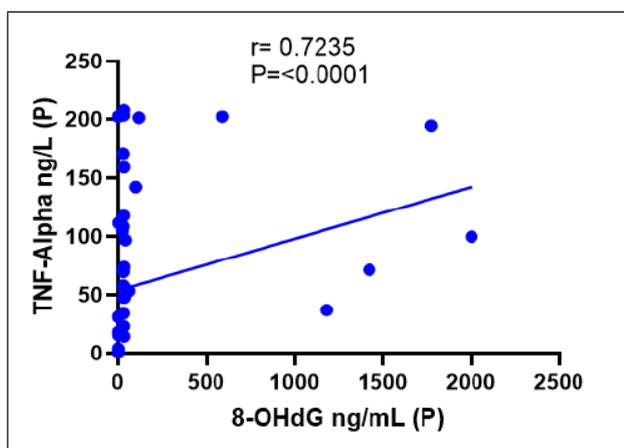
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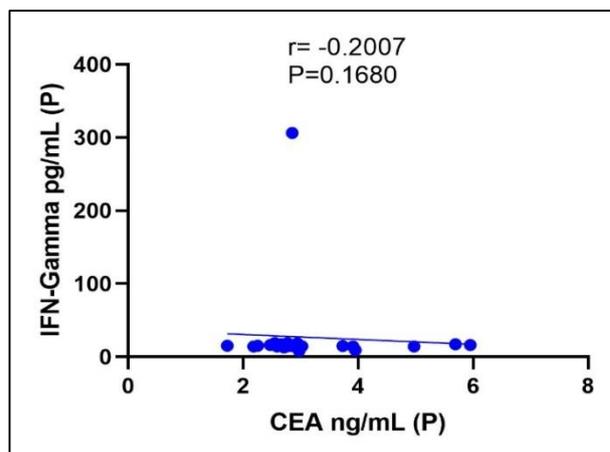**Figure 12. Correlation graph among serum 8-OHdG and TNF-α levels in GC patients**

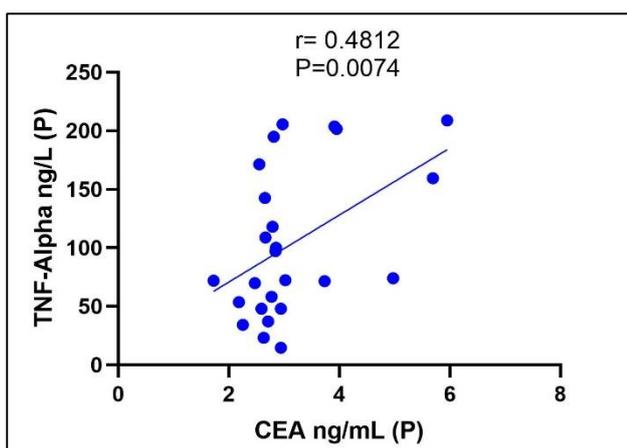**Figure 15. Correlation graph among serum IFN-γ and CEA levels in GC patients**

Figure 13. Correlation graph among serum TNF-α and CEA levels in GC patients
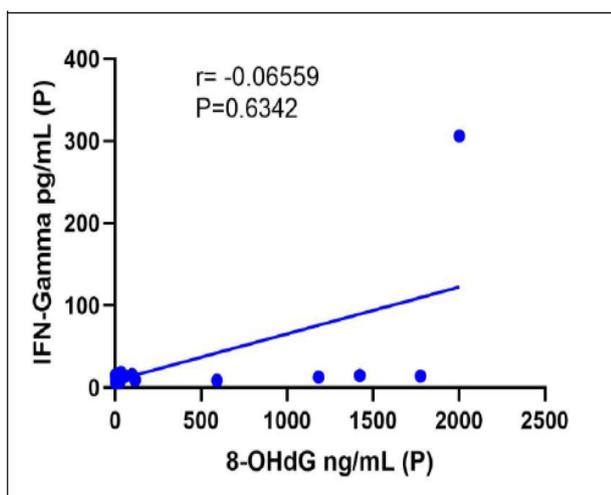

Figure 14. Correlation graph among serum 8-OHdG and IFN-γ levels in GC patients

The scatterplot graph in Fig. 14 shows an association between serum 8-OHdG & IFN-γ levels in patients via Gastric cancer. Additionally, the scatterplot graph in Fig. 15 shows a correlation between serum IFN-γ & CEA concentrations in patients with Gastric cancer. The blood levels of 8-OHdG and IFN-γ were negatively ($r=-0.06559$) and non-significantly ($P=0.6342$) correlated. Similarly, the blood levels of IFN-γ and CEA were also negatively ($r=-0.2007$) and non-significantly ($P=0.1680$) correlated. These results show serum levels of 8-OHdG increase as IFN-γ levels fall coupled with increased serum CEA levels. Owing to their negative correlation, the association of IFN-γ with 8-OHdG was not similar to other studied inflammatory cytokines. But, it's still in accordance with inclined CEA levels. These correlation results may infer that IFN-γ, a pro-tumorigenic pro inflammatory cytokine generated by infiltrating activated T-cells & Natural killer cells (NK) in the cancer microenvironment, may has minor impacts on promoting oxidative stress and DNA damage in mucosa glandular epithelial cells.

The current study results found a significant positive association between serum 8-OHdG concentration and inflammatory cytokine biomarkers accompanied by increased CEA levels, indicating that oxidative stress and chronic inflammation are closely linked processes during Stomach carcinogenesis. These findings proved that combining estimates of multiple inflammatory biomarkers can aid in the understanding and treatment of the GC patients. Therefore, the present study results indicate that 8-OHdG and inflammatory cytokines (TNF-α, IL-6, IFN-γ) could be used as a diagnostic biomarker as well as a guide for choosing the best treatment options.

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Conclusions:

The current original study findings suggest a substantial link between 8-OHdG concentrations and inflammatory cytokines. According to current research, 8-OHdG plays a critical role in stomach carcinogenesis after an increasing in Oxidative stress. The current findings show that a prolonged inflammatory microenvironment in the gastric mucosa leads to increase in the oxidative stress, tumor growth, faster tumor development in consort with escalated blood CEA levels. Furthermore, the current data show that irregular oxidative damage plays an essential role in the onset as well as progression of Stomach tumor, and that the antioxidant-oxidant state plays a significant role in modulating gastric carcinogenesis process. According to the findings of the study, the blood levels of 8-OHdG and inflammatory cytokines (TNF-α, IL-6, IFN-γ) in conjunction with CEA could be possible new tumor biomarker for diagnosis and prognosis of Stomach cancer and other gastrointestinal adenocarcinomas.

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Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are mine ours. Besides, the Figures and images, which are not mine ours, have been given the permission for re-publication attached with the manuscript.
- Authors sign on ethical consideration's approval
- Ethical Clearance: The project was approved by the local ethical committee in Soran University.

Authors' contributions statement:

A. J. M. had performed the conception, design, acquisition of data, statistical analysis, drafting of the manuscript. While P. A. I. had performed interpretation of study results, revision, paraphrasing and proofreading of the manuscript.

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إرتباط محركات الخلية الالتهابية القوية بالمؤشرات الحيوية لتلف الحمض النووي المؤكسد في مرضى سرطان المعدة

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الخلاصة:

تحفز الإصابة بالبكتيريا الحلزونية سلسلة إشارات تؤدي إلى إنتاج السيتوكينات وتسبب الإجهاد التأكسدي، الذي يشارك في الاستجابة الالتهابية المزمنة التي تؤدي إلى الإصابة بسرطان المعدة. تنتج أنواع الأكسجين التفاعلية (ROS).(8- 8-Hydroxydeoxyguanosine (8-OHdG) منتج متلف الحمض النووي المؤكسد المستمر. الغرض من الدراسة هو تقييم الارتباط بين مستويات السيتوكينات الالتهابية ووجود تلف الحمض النووي المؤكسد في مرضى المصابين بسرطان المعدة. بالإضافة إلى ذلك، تم إجراء تقييم للقيمة التشخيصية والإنذارية لتلف الحمض النووي المؤكسد والمؤشرات الحيوية السيتوكينية الالتهابية لسرطان المعدة. أجريت الدراسة على مرضى سرطان المعدة الذين تم تشخيصهم طبيا قبل اخذ العلاج. حيث تم اختيار 33 مريضا من المصابين بسرطان المعدة وتقسيمهم إلى المراحل الأولى والثانية والثالثة وفقا لعلم الأمراض السريرية، و32 فردا من الأشخاص الأصحاء المتطابقين مع العمر كمجموعة ضابطة. تم قياس مستوى كل من (8-OHdG)، السيتوكينات (IL-6، TNF-α،CEA ،IFN-γ). أظهرت النتائج ارتفاعاً بشكل ملحوظ (P<0.0001) في مستويات الدم كل من 8-OHdG و TNF-α و IFN-γ ارتفاعاً بشكل غير ملحوظ (P=0.4747) (IL-6) في مرضى GC بالمقارنة بالمجموعة ضابطة، مع زيادة المستويات تدريجياً مع تقدم مراحل المرض. علاوة على ذلك، كان هناك ارتباط إيجابي ضئيل (r=0.12) (P=0.3472) بين مستويات 8-OHdG وIL-6، وارتباط إيجابي ملحوظ (r=0.7235) (P<0.0001) بين مستويات 8-OHdG, CEA, TNF-α. في مرضى سرطان المعدة ومع ذلك، كان هناك ارتباط سلبي ضئيل (r=-0.06559) (P= 0.6342) بين مستويات 8-OHdG وIFN-γ. تظهر نتائج الدراسة الحالية وجود صلة قوية بين مستويات مصل 8-OHdG والسيتوكينات الالتهابية في مرضى GC. تشير الزيادة المعنوية في تلف الحمض النووي المؤكسد والمؤشرات الحيوية للسيتوكينات الالتهابي وCEA في الدم إلى أن الإجهاد التأكسدي والالتهاب المزمن متضمنان في تسرطن المعدة. تهدف هذه الملاحظات إلى أن 8-OHdG وTNF-α وIFN-γ هي مؤشرات حيوية قابلة للتطبيق لتشخيص ورم المعدة.

الكلمات المفتاحية: سرطان المعدة، السيتوكينات الالتهابية، الإجهاد التأكسدي، تلف الحمض النووي التأكسدي