Research Article / Araştırma Makalesi

Serum Levels of IL-21, IL-23 and 8-hydroxy-2'-deoxyguanosine in Pediatric Severe Pneumonia Cases

Pediatrik Şiddetli Pnömoni Vakalarında IL-21, IL-23 ve 8-hidroksi-2'-deoksiguanozin Serum Düzeyleri

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Abstract

Background: Pneumonia causes the majority of acute respiratory distress syndrome (ARDS) cases. The microbes that cause pneumonia are very diverse. In addition to DNA, RNA viruses, Gram-negative and Gram-positive bacteria cause two types of cytokine imbalances, anti-inflammatory and pro-inflammatory. It can also influence the prognosis of sepsis and other infectious diseases. This study aims to search for 8-hydroxy-2'-deoxyguanosine (8-OHdG), IL-21, IL-23, and c-reactive protein (CRP) and compare cytokine levels. It is also to determine if Pediatric pneumonia patients CRP and cytokine levels correlate with results.
Materials and Methods: In the study, blood was drawn from approximately 43 pediatric pneumonia patients and 43 healthy controls who came to the pediatric clinic to investigate serum IL-21, IL-23, 8-OHdG, and CRP levels. The levels of biomarkers were determined by ELISA method. Serum CRP levels were measured using the ATELLICA IM Analyzer.
Results: Serum CRP, 8-OHdG, IL-21 and IL-23 levels were significantly higher in the pediatric pneumonia patient group than in the control group.
Conclusions: Increased serum IL-21, IL-23, 8-OHdG and CRP expression in pediatric pneumonia patients is a potential determinant suggesting that IL-21, IL-23-related cytokines may play a role in endothelial cell activation reported in patients. Increased 8-OHdG oxidative stress is more pronounced in patients without pediatric pneumonia while pro inflammatory cytokines are higher in pediatric pneumonia patients. However, it is used as a possible therapeutic target to reduce inflammation. Further study on the impact of these findings on comorbidities with larger number test size is needed

Key Words: Pneumonia, IL-21, IL-23, 8-OHdG

Öz

Amaç: Pnömoni, akut solunum sıkıntısı sendromu (ARDS) vakalarının çoğuna neden olur. Zatürreye neden olan mikroplar çok çeşitlidir. Ayrıca RNA virüsleri, DNA virüsleri, zarflı virüsler, zarfsız virüsler, Gram pozitif ve negative bakteriler, proinflamatuar ve antiinflamatuar olmak üzere iki tip sitokindeki dengesizliği etkiler ve sepsis ve diğer enfeksiyöz ve inflamatuar hastalıkların prognozunu etkileyebilir. Çalışmanın amacı, IL-21, IL-23, 8-hidroksi-2'-deoksiguanozin (8-OHdG) ve c-reaktif protein (CRP) araştırılması gereken şiddetli pnömonili genç hastalarda klinik özellikleri ve sitokin düzeylerini karşılaştırmaktı (Pediyatrik pnömoni hastalarında CRP) seviyeleri, pediatrik şiddetli pnömoni vakalarında sitokin düzeylerinin sonuçla ilişkili olup olmadığı amaçlanmıştır.
Materyal ve Metod: Bu çalışmada pediatri polikliniğine gelen yaklaşık 43 pediatrik pnömoni hastası ve 43 sağlıklı kontrolden serum IL-21, IL-23, 8-OHdG ve CRP düzeylerini araştırmak için kan alındı. Test edilen biyobelirteçlerin seviyeleri Elisa yöntemi ile çalışıldı ve serumun CRP seviyeleri Atellica IM Analyzer kullanılarak ölçülmüştür.
Bulgular: Serum CRP, 8-OHdG, IL-21 ve IL-23 düzeyleri pediatrik pnömoni hasta grubunda kontrol grubuna göre anlamlı olarak yüksekti.
Sonuç: Pediatrik pnömoni hastalarında artmış serum IL-21, IL-23, 8-OHdG ve CRP ekspresyonunu gösteren sonuçlarımız, bunun potansiyel bir belirleyici olduğu sonucuna vararak, IL-21, IL-23 ile ilişkili sitokinlerin rol oynayabileceğini düşündürmektedir. Hastalarda bildirilen endotel hücre aktivasyonu. Artmış 8-OHdG oksidatif stres, pediatrik pnömonisi olmayan hastalarda proinflamatuar sitokinler pediatrik pnömoni hastalarına göre daha yüksektir. Bununla birlikte, enflamasyonu azaltmak için olası bir terapötik hedef olarak hizmet edebilir. Bu kavramları test etmek için ek preklinik deneyler ve daha büyük kohort boyutlarına sahip klinik deneyler gerekecektir.

Anahtar Kelimeler: Pnömoni, IL-21, IL-23, 8-OHdG

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Introduction

Pneumonia is inflammation of the lung tissue. It occurs due to various microorganisms, especially bacteria. While microbial infection causes the disease, the pathogenesis of the disease is determined by the host response (1,2). Although the disease can be seen at any age, it is one of main causes of mortality in children less than 5 years old and particularly with a very weak immune system. (1). Although pneumonia is an acute condition, it results from pre-existing chronic conditions and has long-term consequences, particularly manifested by pulmonary and arterial hypoxemia. Therefore, pneumonia is a lower respiratory tract infection (3,4). The microbes that cause pneumonia are extraordinarily numerous and diverse.

Streptococcus pneumoniae is the most common cause of pneumonia other causes may be *Haemophilus influenzae, Chlamydia pneumoniae, Mycoplasma pneumoniae* and *Staphylococcus aureus.* When evaluated in terms of age, *S. pneumoniae* is the most common bacterial pathogen in children aged 3 to 4 years, while *M. pneumoniae* and *C. pneumoniae* are the most common bacterial pathogens in children aged 5 years and older. Viral pathogens may be common causes of lower respiratory tract infections in infants and young children less than five years old. Respiratory syncytial virus and human rhinovirus are the most frequently identified pathogens, especially in children younger than two years of age. It can also be caused by others, such as exposure to fungal agents and toxic substances (3). In healthy individuals, microorganisms cannot enter the alveoli due to the protective mechanisms of the alveoli. In patients with a weakened immune system, microorganisms enter the alveoli, and many cell cytokines are activated, initiating and maintaining the inflammatory response (5). IL-6 and other cytokines secreted from macrophages can be stimulate release of CRP and fibrinogen from liver. The balance between systemic inflammatory response and anti-inflammatory processes is important to maintain lung homeostasis in infectious diseases (6,7). The prognosis of sepsis and inflammatory diseases is an imbalance of two types of cytokines, pro inflammatory and anti-inflammatory (8). These cytokines that activate the immune system are primarily IL-1β, IL-6, IL-21, (TNF-α and IFN-γ). IL-23 and IL-1 receptor antagonists have an important role in regulating the activities of transforming growth factor (TGF) cells and other cytokines. In addition, macrophages in the lung secrete anti-inflammatory cytokines to reduce inflammation (9,10). It has been observed that T helper (Th) cells, which can further strengthen the inflammatory cascade with the secretion of pro inflammatory cytokines, support the transition to Th1 (11,12). Oxidative stress may be result of the imbalance between highly production of reactive oxygen species (ROS) and antioxidant substances.

Excess ROS production had negative consequences on cellular physiology (12,13) causing oxidative damage to proteins, lipids, and DNA. The resulting oxidized products can be seen in the urine. 8-hydroxy-2'-deoxyguanosine (8-OHdG) is main product of DNA oxidation (14,15). In this study, it was aimed to investigate the changes in serum 8-OHG, IL-21, IL-23, and CRP levels in patients with severe pneumonia and to investigate the relationships between these parameters.

Materials and Methods

Establishment of working groups

A total of 86 subjects, 43 (13 females, 30 males) pediatric patients with pneumonia, and 43 (16 females, 27 males) healthy children were included the study. The ages of subjects in the control and patient groups were under ten years. The patients were selected among those who applied to Harran University, Faculty of Medicine, Department of Pediatric Clinic, due to respiratory complaints. The blood of our healthy control group was selected from the blood coming to the Biochemistry laboratory, and those who did not have any chronic or metabolic diseases were selected. Informed consent forms were obtained from the parents of the children.

Preparation of samples

Blood samples were taken from individuals in the patient and control groups. Children's parents were asked to fast them for 12 hours, and blood samples (5 ml) were taken. Blood samples were centrifuged at 5000 rpm for 10 minutes and serum samples were collected. Samples were stored at -80°C until analysis. Serum IL-21, IL-23, and 8-OHdG were measured in all patients and healthy controls using the ELISA method according to the company's recommendations (Elabscience Biotechnology Co., Ltd, Wuhan, China). CRP levels of the serum were measured using Atellica IM Analyzer (Atellica IM Analytical Module, USA).

Ethical approval

This study was approved by the Ethics in Research Committee at Harran University Faculty of Medicine (Reference number: HRU-21.06.29 dated 15.03.2021*).*

Statistical method

Mean standard deviations were represented by metadata, numbers, and percentages. Variables were compared using the chi-square test. In data comparison, the student's t-test, Mann-Whitney U and Kruskal-Wallis test was used. P value less than 0.05 value was considered significant.

Results

A total of 86 people, 43 patients in the patient group and 43 healthy people in the control group were included in the study: According to the gender of all participants: 29 (33.3%) were female and 57 (66.7%) were male. In addition, the mean age of the pneumonia patient group was 8.16 ± 6.23 and the mean age of the control group was 9.34 ± 6.09 years. There was no statistically significant difference between the groups in terms of age and gender (p=0.957).

The samples for the study were obtained from 86 individuals, 43 of whom were in the patient group and 43 of whom were in the control group, and the data were analyzed (Table 1, Figure 1). The serum values of IL-21 (ng/L), IL-23 (ng/L), 8-OHdG (ng/ml), and CRP (mg/dl) were analysed.

The results showed that IL-21, IL-23, 8-OHdG, and CRP levels were statistically significantly higher in the both pre-treatment pneumonia group and post-treatment pneumonia group, and pneumonia-free group. It showed that IL-21, IL-23, 8-OHdG, and CRP levels were positively correlated with the pre-treatment pneumonia patient group. IL-21, IL-23, 8-OHdG, and CRP levels showed a strong and positive correlation with the post treatment pneumonia patient associated control group (Table 2, Figure 2 and 3).

The Games-Howell post-hoc analysis results were presented in Table 2. The test yielded mean increases in 8-OHdG values from pneumonia before treatment, diagnosed pneumonia after and to other groups healthy control group those were statistically significant (p=0.00, p=0.00, and p=0.00), respectively. The test also provided mean decreases in terms of other two groups, pneumonia treated with and healthy control group those were statistically significant (p=0.00, and p=0.00), respectively. An analysis of the means in treated group and healthy control group were also significantly different as well (p=0.00).

Table 1. Comparison of serum levels of 8-OHdG, Il-21, IL-23, and CRP parameters in pneumonia patients and the control groups

Variables	Patient group							Control group			
	Pre-Treatment			Post-Treatment							
	Min	*Max*	$\bar{X} \pm SD$	*Min*	*Max*	$\bar{X} \pm SD$	*p*-value*	*Min*	*Max*	$\bar{X} \pm SD$	*p*-value¥
8-OHdG (ng/ml)	12.52	20.40	16.77±2.16	9.25	13.88	11.66±1.32	0.00	3.02	6.47	4.23±0.80	0.00
IL-21 (ng/L)	92.01	147.47	126.54±14.04	50.12	84.72	62.23±7.64	0.00	33.18	55.75	41.58±6.13	0.00
IL-23 (ng/L)	120.15	164.62	136,99±9.41	75.18	126.13	111.63±3.78	0.00	53.56	106.38	85.08±13.35	0.00
CRP (mg/dl)	1.49	7.51	4,59±1.45	0.35	1.60	0.89±0.45	0.00	0.23	0.45	0.31±0.07	0.00

**: significance between pre-treatment and post-treatment*

¥: pre-treatment and control P3, significance between refractory-control.

Table 2. Pearson's correlation matrix between variables

	IL-21	IL-23	CRP	Groups
8-OHdG	-0.163 (0.390)	-0.191 (0.312)	0.190 (0.314)	Pre-Treatment
	-0.055 (0.773)	0.274 (0.143)	-0.070 (0.715)	Post-Treatment
	-0.161 (0.397)	0.138 (0.468)	-0.020 (0.918)	Control
	IL-21	-0.054 (0.778)	0.169 (0.371)	Pre-Treatment
		-0.597 (0.000)	0.128 (0.501)	Post-Treatment
		-0.207 (0.273)	**-0.388 (0.034)**	Control
		IL-23	-0.012 (0.951)	Pre-Treatment
			0.192 (0.309)	Post-Treatment
			-0279 (0.136)	Control

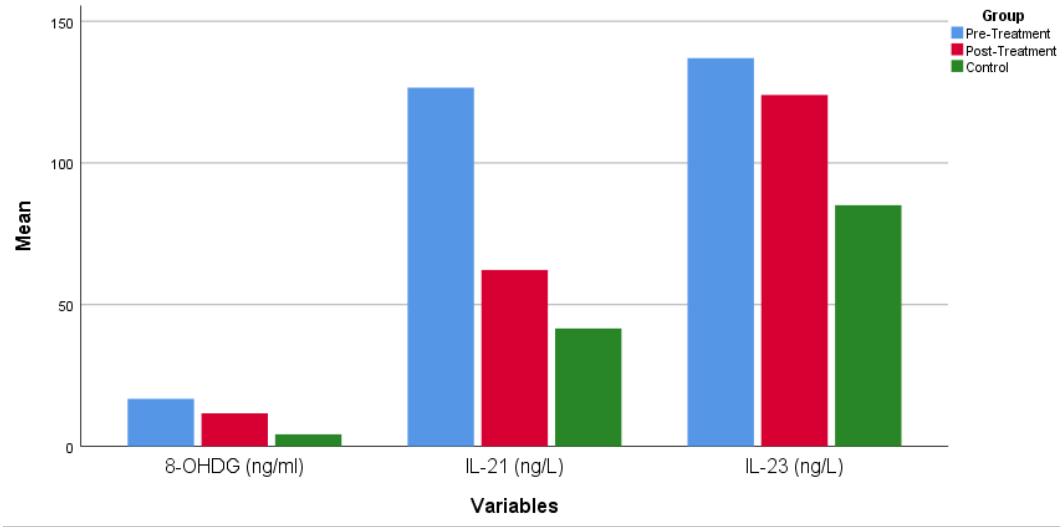

Figure 1. Mean serum IL-21, IL-23, 8-OHdG levels in the pneumonia patients and control group

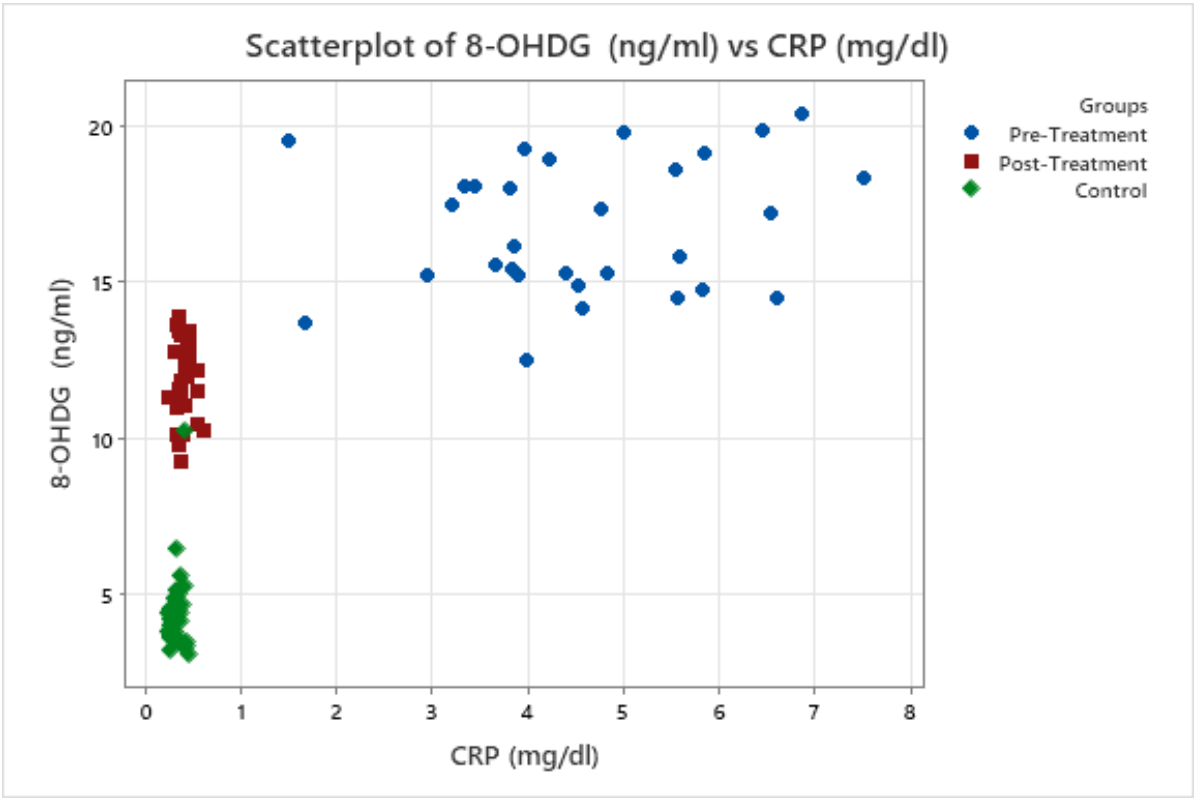

Figure 2. A scatterplot showing the relationship between a pair of variables 8-OHdG and CRP in a coordinate plane based on groups

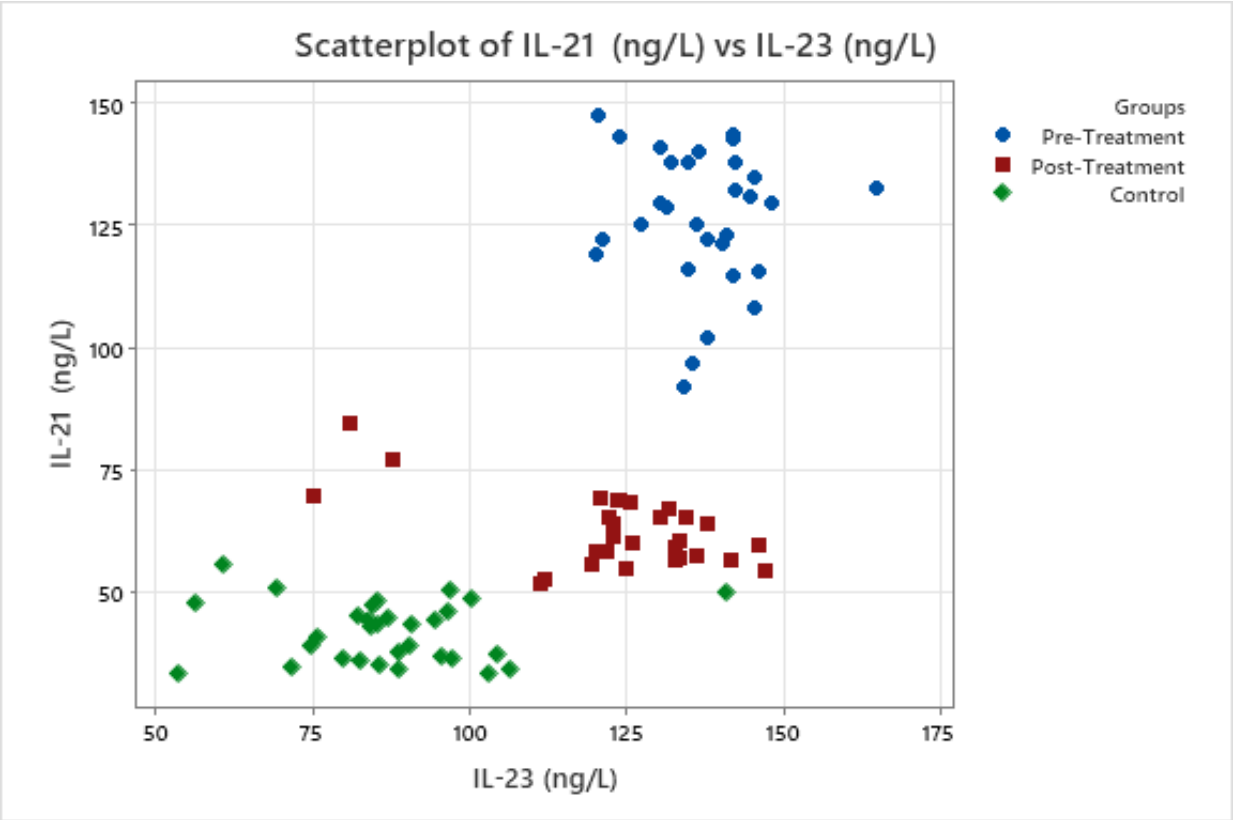

Figure 3. The relationship between IL-21and IL-23 variables for each group

Discussion

Pneumonia is a unilateral or bilateral infection of the lung tissue caused by factors such as viruses and bacteria. The infection usually starts and progresses like a simple cold, upper respiratory tract infection. In healthy individuals, microorganisms cannot invade the alveoli through the protective mechanisms of the alveoli. However, in patients with weakened immunity, microorganisms enter the alveoli and inflammation occurs. Many cytokines and various small soluble proteins are secreted in these patients, which have profound paracrine or autocrine effects on the development and function of hematopoietic and non-hematopoietic cells (16).

Diagnosis and management of newly formed pulmonary infiltrates in patients with immunocompromised pneumonia are often challenging and have diverse and often permanent deleterious consequences for multiple physiological systems (17).

In this study, we found that IL-23 concentrations in patients with pneumonia before treatment were higher in patients with pneumonia after treatment and in the healthy control group, suggesting that patients with pneumonia may respond rapidly to disease progression (18,19). Many studies have indicated role of IL-23 in the initiating and activation of many inflammatory reactions. Therefore, it plays an important role in the progress and development of chronic inflammation (20,21). Inhibition of IL-23 production is helpful in reduction of inflammatory pathways of pneumonia and mediates recovery processes (22,23). In our study, we found high levels of IL-21 and IL-23 in patients with pneumonia (R = 0.778). The correlation was stronger in patients with post-treatment pneumonia (R = -0.597), while it was significantly weaker in the healthy control group (R = -0.207) and pre-treatment pneumonia patients (R = -0.054) (Table 2).

Previous studies (23-25) have shown that cytokines interact with each other through dynamic pathways involving cytokine receptors and signaling pathways. In addition, in an inflammatory environment, antigens and inflammatory factors such as CRP can stimulate the production of T cells, macrophages, fibroblasts, and endothelial cells. Thus, In the study, we observed that the correlation between IL-21 and IL-23 was related to the degree of inflammation. IL-21 and IL-23 can be listed among major pro inflammatory cytokines, and positive correlations between disease severity have been demonstrated in cases of community-acquired pneumonia and can be used as diagnostic criteria. In progressive pneumonia and sepsis, anti-inflammatory cytokines such as IL-21 and IL-23 are produced to control excessive inflammation (26). Overall, the IL-23/IL-21 axis plays an important role in host defense against bacterial infections, causing a reduction in both IL-23 and IL-21 synthesis in the early stages of post-treatment infection, where it contributes to modulate innate immunity in response to lung infection. Nevertheless, certain pro inflammatory cytokines levels are increased in pneumonia but decreased after corticosteroid treatment. Microbial etiology, corticosteroids therapy, and degree of lung infection may affect their levels (27).

CRP is synthesized by the liver in response to factors released by macrophages and fat cells (adipocytes). CRP binds to phosphocholine expressed on the surface of bacterial cells such as pneumococcal bacteria. This activates the complement system, promoting phagocytosis by macrophages that scavenge necrotic and apoptotic cells and bacteria (28). In this study, we found that patients with pneumonia had significantly higher CRP levels than the healthy control group.

In light of the results of the studies, lung diseases have been associated with exaggerated 8-OHdG concentrations (29). In addition, 8-OHdG levels were changed by physical, chemical and biological factors (30,31). Urinary 8-OHdG levels increased after exposure to xenobiotic and were associated to increased oxidative stress and decreased lung function (32). Thus, it is difficult to define the exact background for cut-off values of 8-OHdG in such individuals

Conclusion

It can be underlined important role of IL-21 and IL-23 in pathogenesis of pneumonia. There was a significant increase in IL-21 and IL-23 levels in patients with pre-treatment pneumonia compared to post-treatment. In addition, our data suggest that elevated 8-OHdG is associated with increased pneumonia and higher CRP levels. Other prospective studies looking for biomarkers of pneumonia suggest that 8-OHdG may be directly associated with the detection of oxidative damage and adverse changes in endothelial function, rather than other indirect measures. These results may form a basis for future biochemical research to explore whether transient factors from 8-OHdG mediate the disease.

Ethical Approval: *This study was approved by the Ethics in Research Committee at Harran University Faculty of Medicine (Reference number: HRU-21.06.29 dated 15.03.2021).*

Author Contributions:
Concept: N.B., A.G.
Literature Review: N.B., A.Ö.
Design : N.B., A.G., M.B.
Data acquisition: N.B., M.B., A.Ö.
Analysis and interpretation: N.B., A.G., H.E.
Writing manuscript: N.B., M.B., .A,Ö.
Critical revision of manuscript: N.B., A.Ö.

Conflict of Interest: *All the authors declare that they have no conflict of interest in this work*

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