Abant Tıp Dergisi

Abant Medical Journal

Abant Med J 2025;14(1):19-27, doi:10.47493/abantmedj.1594807

Dynamic Thiol / Disulfide Homeostasis in Patients with Nasal Polyps and The Effects of Smoking on Homeostasis Parameters

Nazal Polipli Hastalarda Dinamik Tiyol / Disülfid Homeostazi Ve Sigaranin Homeostaz Parametreleri Üzerine Etkileri

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Geliş Tarihi (*Received*): 02.12.2024 **Kabul Tarihi (*Accepted*):** 13.04.2025 **Yayın Tarihi (*Published*):** 30.04.2025

Abstract

Objective: The aim of this study is to investigate dynamic thiol/disulfide homeostasis as an oxidative stress marker in nasal polyposis (NP) patients and the effects of smoking on homeostasis parameters in these patients.

Materials and Methods: A total of forty NP patients and 36 healthy volunteers participated in the current study. Participants were categorized into two groups: 20 smokers and 20 non-smokers. Erel and Neşelioğlu developed an automated method to analyze thiol-disulfide homeostasis parameters in samples of serum from the participants. Groups were compared. Each parameter related to thiol/disulfide homeostasis—native thiol (SH), total thiol (ToSH), disulfide (SS), SS/SH (%), SH/ToSH (%), and SS/ToSH (%)—was evaluated separately.

Results: There were notable differences across the groups relating markers associated with thiol-disulfide balance. Total Thiol (ToSH) µmol/L (p=0.005), Native Thiol (SH) µmol/L (p=0.001), and SH/ToSH (%) levels were lower in patients with nasal polyps than the control group, and disulfide (SS) (p=0.001), SS/NT (%) (p=0.001), and SS/ToSH (%) levels were statistically significantly higher than the control group (p=0.001). Total Thiol (ToSH) and Native Thiol (SH) µmol/L levels were lower in the smoker group, while SS/NT% levels were higher, but the differences were not statistically significant (p > 0.05).

Conclusion: In NP patients, thiol/disulfide homeostasis shifts towards disulfide formation because of native thiol oxidation. Also, parameters of Thiol/disulfide homeostasis can serve as new oxidative stress markers in nasal polyps.

Keywords: Nasal Polyp, Oxidative Stress, Smoking, Thiol/Disulfide Homeostasis.

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Öz

Amaç: Bu çalışmanın amacı, nazal polipozis (NP) hastalarında bir oksidatif stres belirteci olarak dinamik tiyol/disülfid homeostazını ve sigaranın bu hastalardaki homeostaz parametreleri üzerindeki etkilerini araştırmaktır.

Gereç ve Yöntemler: Çalışmamıza 40 NP hastası ve 36 sağlıklı gönüllü birey dahil edildi. Hasta grubu kendi içerisinde 20'si sigara içen ve 20'si sigara içmeyen hasta olarak 2 gruba ayrıldı. Tüm katılımcıların serum örneklerinde tiyol-disülfit homeostazisi parametreleri Erel ve Neşelioğlu tarafından geliştirilen yeni otomatik ölçme yöntemi ile analiz edildi ve guruplar arasında karşılaştırıldı.

Bulgular: Tiyol-disülfid dengesine bağlı belirteçler açısından gruplar arasında belirgin farklar gözlemlenmiştir. Total tiyol (ToSH) µmol/L (p=0,005), native tiyol (SH) µmol/L (p=0.001) ve SH/ToSH (%) düzeyleri, nazal polipli hastalarda kontrol grubuna göre daha düşük bulunmuş, disülfid (SS) (p=0,001), SS/NT (%) (p=0,001) ve SS/ToSH (%) düzeyleri ise kontrol grubuna kıyasla istatistiksel olarak anlamlı derecede yüksek bulunmuştur (p=0,001). Total Thiol (ToSH) ve Native Thiol (SH) µmol/L düzeyleri sigara içen grupta daha düşük, SS/NT% düzeyleri ise daha yüksek bulunmuş, ancak bu fark istatistiksel olarak anlamlı olmamıştır (p > 0,05).

Sonuç: NP hastalarında, tiyol/disülfid homeostazı, native tiyol oksidasyonu nedeniyle disülfid oluşumuna doğru kaymaktadır. Ayrıca, tiyol/disülfid homeostaz parametreleri, nazal poliplerde yeni oksidatif stres göstergeleri olarak kullanılabilir.

Anahtar Kelimeler: Nazal Polip, Oksidatif Stres, Sigara Içme, Tiyol/Disülfid Homeostazı

Atıf/Cite as: Bayatkara Yilmaz T, Karalı E, Yis ÖM, Güneş A. Dynamic Thiol / Disulfide Homeostasis In Patients With Nasal Polyps And The Effects Of Smoking On Homeostasis Parameters. Abant Med J. 14(1):19-27.

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Introduction

Nasal polyp (NP) is a chronic condition associated with inflammation of the nasal or paranasal sinus mucosa. The source of this condition is still unclear and is the most common cause of nasal mass. The prevalence in the community varies between 2-4% (1). Chronic rhinosinusitis (CRS) is linked to disorders, such as cystic fibrosis (CF), allergic rhinitis (AR), bronchial asthma, and primary ciliary dyskinesia. NPs, which are edematous soft tissue masses that develop due to the nasal or paranasal sinus mucosa as a result of susceptibility to infection and vascular reorganization caused by mucosal inflammation, can expand and overflow into the nasal passage, producing symptoms like post-nasal drip, nasal congestion, headache, and runny nose. They also lead to secondary complaints such as decreased quality of life, snoring, CRS, and olfactory dysfunction

Extensive research has been conducted on the potential causes of NP, a condition with an unknown origin. Furthermore, histologic and pathophysiologic studies indicate that the process is multifactorial. Inflammation is thought to be a major factor. Therefore, free oxygen radicals and oxidative stress are some of the etiologic causes investigated (2,3).

The oxidative balance is the balance between reactive oxygen species (ROS generated in cells during normal physiological processes, and antioxidants, which eliminate them. Oxidative stress is an imbalance favoring ROS, characterized by insufficient endogenous defense systems in the cell and the accumulation of free oxygen radicals (4).

There are several parameters, some oxidants and some antioxidants, used to indicate oxidative stress in the body (5). Thiols, one of the antioxidant parameters, are organic compounds made up of sulfur and hydrogen atoms with a sulfhydryl (-SH) group attached to the carbon atom, also called mercaptan. Organic compounds containing thiol groups are important for defending against oxidative stress because of their reducing abilities. There are many thiol molecules in plasma (6).

Thiols interact with free radicals to inhibit ROS-induced harm to cells and tissues. FRs cause the oxidation of amino acid thiol groups containing sulfur and disulfide bonds through the above reaction. Disulfide bonds can be transformed into thiols through reduction. This is how the balance between thiol and disulfide compounds is preserved in cells and tissues. This helps regulate the antioxidant defense system, enzyme activities, detoxification, apoptosis, and intracellular signal transduction mechanisms. Decreased thiols and increased disulfide content result in decreased clearance of ROS products. Increased disulfide levels adversely affect protection against oxidation and redox products, leading to functional and structural abnormalities in various organs and systems. This increases the frequency of cellular damage and apoptosis (7).

Cigarette smoke contains more than 4000 chemicals, including tobacco-specific N-nitrosamines, polynuclear aromatic hydrocarbons, and aromatic amines. These chemicals are highly carcinogenic and can also cause oxidative stress by inducing the formation of free radicals. This redox imbalance can cause toxic effects that damage all elements of cells, especially proteins, lipids, and nucleic acids. Oxidative stress is considered to be significant in the advancement of various diseases. Previous research suggests that the acute and chronic effects of smoking may weaken antioxidant defense systems, which may ultimately lead to long-term pathologies. (8,9)

No existing study has evaluated the impact of TDH and smoking on homeostasis parameters in NP patients. The current study was conducted with the aim of exploring the impact of TDH as oxidative stress marker in the pathophysiology of NP as well as the impacts of smoking on parameters of homeostasis.

Materials and Methods

Selection of Study Groups and Study Design

Patients diagnosed with nasal polyposis and a control group suitable for the demographic characteristics of the patients were included in the study. The study was prospectively conducted. All patients and the healthy control group provided verbal and written signed informed consent forms after being fully informed. The approval of the Bolu Abant İzzet Baysal University Ethics Committee, dated 13/07/2021 and numbered 2021/175, were obtained for the study.

Inclusion Criteria

The current study included 40 patients in total aged between 18 and 65, without systemic disease but with complaints of nasal congestion and were diagnosed with nasal polyposis. Patients were categorized into two groups: 20 individuals who smoke and 20 individuals who do not smoke. Thirty-six healthy volunteers, matched in age and sex, and without any complaints, were included in the control group all of whom were non-smokers.

Exclusion Criteria

Patients below 18 and over 65 years, those with additional systemic diseases (except asthma) such as hypertension, diabetes mellitus, thyroid hormone disorder, hyperlipidemia, active upper respiratory tract infection, chronic liver and kidney disease, those who are pregnant or breastfeeding, those who have used systemic steroids, antihistamines, and leukotriene receptor antagonists for any reason in the last three months, those with asthma in exacerbation, and those receiving antioxidant replacement.

The Lund Kennedy scoring system, determined endoscopically, was used to assess the severity of nasal polyp disease. A 4 mm rigid 0-degree endoscope (Karl-StorzVR GmBH & Co., Tuttlingen, Germany) was used for endoscopic examination.

Biochemical Examination

Blood samples were obtained from participants after an 8-hour fasting, between 08:00 and 10:00 AM. Patient and healthy control group samples were collected in a yellow-capped gel tube (biochemistry tube) and then transported to the laboratory. Following clotting, blood samples were centrifuged at 1500g for fifteen minutes to isolate the serum. The serum was moved to an Eppendorf tube and placed in a cooler at -80 °C for storage, following the appropriate storage conditions, until the analysis day. Serum samples were thawed on the study day, and thiol-disulfide homeostasis parameters were analyzed. This method consists of two steps: the first step involves determining the levels of native thiol (NT) using DTNB [5,5'-dithiobis-(2-nitrobenzoic) acid]. The second step, on the other hand, involves dynamic and reducible disulfide bonds (-S-S) being reduced to free functional (reactive) thiol groups (-SH) with sodium borohydride (NaBH4). Excess NaBH4 is disposed of by reacting it with formaldehyde. The total thiol (TT) groups, which include both NaBH4-reduced and native thiols, are measured by reacting them with DTNB [5,5'-dithiobis-(2- nitrobenzoic) acid]. The dynamic disulfide (SS) amount can be calculated by taking fifty percent of the concentrations of native thiol and total thiol differences. For measuring the native thiol (SH), total thiol (ToSH), and disulfide (SS) values, and other relevant parameters, determined by calculating the redox potential (Thiol Oxidation-Reduction Ratio, SS/SH%), oxidized thiol ratio (SS/ToSH%), and reduced thiol ratio (SH/ToSH%), this new method can be applied.

Parameters of tynamic thiol/disulfide homeostasis, an oxidative stress indicator, and their ratios, were compared between patients with nasal polyps and healthy volunteers.

The effect of smoking on these parameters was also evaluated.

Statistical Analysis

SPSS 22.0 for Windows packaged program was utilized for the statistical analysis. Furthermore, descriptive statistical methods were utilized. Kruskall Wallis Test was employed for comparisons involving three or more groups, while the Independent Sample T test was used to compare the groups. For analyzing the qualitative data, the Pearson Chi-Square test was utilized. The Pearson Correlation test was utilized for assessing the correlation of the measurements. Significance was assessed at p-values of less than 0.01 and 0.05.

Results

While 52.6% (n = 40) of participants were in patient group, 47.4% (n = 36) were in the control group. Within the patient group, 50.0% (n = 20) did smoke, and the remaining 50.0% (n = 20) were non-smokers. In the patient group, 67.5% (n = 27) were male and 32.5% (n = 13) were female. In the control group, 63.9% (n = 23) were male and 36.1% (n = 13) were female. The average age of the patient group was 46.60±10.55 years, and the mean age

of control group was 44.14±10.84 years. There was no significant difference between the groups in terms of age and gender (p > 0.05).

Total Thiol (ToSH), µmol/L measurement (p = 0.005; p<0.01), and there were differences between groups in terms of Native Thiol (SH), µmol/L measurements (p = 0.001; p<0.01). The values in the control group increased.

Disulfide (SS), µmol/L measurement (p=0.001; p<0.01) and SS/NT% measurement (p=0.001; p<0.01) of patient and control groups were statistically significantly different. (p=0,001; p<0,01). The values in the patient group increased (Table 1).

Table 1.

Evaluation of Laboratory Measurements According to Patient Group and Control Group

	Patient Group (n=20)		*Control Group (n=36)*		
	Mean±Sd	**Min-Max (Median)**	**Mean±Sd**	**Min-Max (Median)**	**[a]p**
Total Tiyol (ToSH), µmol/L	446.36±82.51	146.98-567.88 (460.53)	497.22±68.6	327.3-600.82 (514.59)	***0.005****
Nativ Tiyol (SH), µmol/L	383.14±78.16	106.93-508 (399.33)	442.94±69.23	280.45-588.91 (456.71)	***0.001****
Disülfit (SS), µmol/L	31.61±5.17	20.03-44.31 (31.3)	27.14±5.48	5.96-36.34 (27.37)	***0.001****
SS/SH, %	8.63±2.37	5.75-18.73 (7.87)	6.31±1.65	1.01-10.36 (6.23)	***0.001****
SH/ToSH,%	0.85±0.03	0.73-0.9 (0.86)	0.89±0.03	0.83-0.98 (0.89)	***0.001****
SS/ToSH,%	0.07±0.02	0.05-0.14 (0.07)	0.06±0.01	0.01-0.09 (0.06)	***0.001****

Sd: Standard deviation, [a]Independent Sample T Test, **p<0.01.

The comparison of the patient and the control groups revealed that the SH/ToSH% measurements were statistically significantly different (p = 0.001; p<0.01). The values in the control group increased (Table 1).

The comparison between groups revealed that SS/ToSH% measurement were statistically significantly different (p=0.001; p<0.01). The values in the patient group increased (Table 1).

Evaluation of Laboratory Measurements Based on Patient Groups: Smokers and Non-Smokers is given in the Table 2.

The comparison of all groups revealed that Total Thiol (ToSH), µmol/L measurement had statistically significant difference (p=0.005; p<0.01). The level was elevated in the control group than both the smoking and non-smoking patient groups (Table 3).

According to the comparison of all groups, Native Thiol (SH) µmol/L measurement had a statistically significant difference (p = 0.001; p<0.01). The levels elevated in the control group than both groups of smokers and non-smokers (Table 3).

According to the comparison of all groups, disulfide (SS) µmol/L measurement was statistically significantly different (p = 0.001; p<0.01). The levels elevated in non-smokers than both the control and the smoking patient groups (Table 3).

According to the comparison of all groups, the SS/NT% measurement was statistically significantly different (p = 0.001; p<0.01). The levels elevated in smokers than both the control group and the non-smokers (Table 3).

Table 2.

Evaluation of Laboratory Measurements According to Smoking and Non-Smoking Patient Groups

	Smoking Patient Group (n=20)		*Non-Smoking Patient Group (n=20)*		[a]p
	Mean±Sd	**Min-Max (Medyan)**	**Mean±Sd**	**Min-Max (Medyan)**	
Total Tiyol(ToSH), µmol/L	437.87±95.16	146.98-559.86 (455.29)	454.85±69.03	281.98-567.88 (469.6)	***0.522***
Nativ Tiyol (SH), µmol/L	376.03±88.88	106.93-494.58 (394.77)	390.25±67.33	237.6-508 (401.54)	***0.572***
Disülfit (SS), µmol/L	30.92±5.37	20.03-44.31 (30.73)	32.3±5.01	22.19-41.4 (31.96)	***0.406***
SS/SH,%	8.78±2.87	6.55-18.73 (7.83)	8.49±1.79	5.75-12.16 (8.45)	***0.701***
SH/ToSH,%	0.85±0.04	0.73-0.88 (0.86)	0.86±0.03	0.8-0.9 (0.86)	***0.750***
SS/ToSH,%	0.07±0.02	0.06-0.14 (0.07)	0.07±0.01	0.05-0.1 (0.07)	***0.741***

Sd: Standard deviation, [a]Independent Sample T Test.

According to the comparison of all groups, the SH/ToSH;% measurement was statistically significantly different (p = 0.001; p<0.01). These values elevated in the control group (Table 3).

According to the comparison of all groups, the SS/ToSH;% measurement was statistically significantly different (p = 0.001; p<0.01). These values decreased in the control group (Table 3).

Table 3.

Evaluation of Laboratory Measurements by Groups

	Smoking Patient Group (n=20)		*Non-Smoking Patient Group (n=20)*		*Control Group (n=36)*		[a]p
	Mean±Sd	**Min-Max (Medyan)**	**Mean±Sd**	**Min-Max (Medyan)**	**Mean±Sd**	**Min-Max (Medyan)**	
Total Tiyol(ToSH), µmol/L	437.87±95.16	146.98-559.86 (455.29)	454.85±69.03	281.98-567.88 (469.6)	497.22±68.6	327.3-600.82 (514.59)	***0.009****
Nativ Tiyol (SH), µmol/L	376.03±88.88	106.93-494.58 (394.77)	390.25±67.33	237.6-508 (401.54)	442.94±69.23	280.45-588.91 (456.71)	***0.002****
Disülfit (SS), µmol/L	30.92±5.37	20.03-44.31 (30.73)	32.3±5.01	22.19-41.4 (31.96)	27.14±5.48	5.96-36.34 (27.37)	***0.001****
SS/SH, %	8.78±2.87	6.55-18.73 (7.83)	8.49±1.79	5.75-12.16 (8.45)	6.31±1.65	1.01-10.36 (6.23)	***0.001****
SH/ToSH,%	0.85±0.04	0.73-0.88 (0.86)	0.86±0.03	0.8-0.9 (0.86)	0.89±0.03	0.83-0.98 (0.89)	***0.001****
SS/ToSH,%	0.07±0.02	0.06-0.14 (0.07)	0.07±0.01	0.05-0.1 (0.07)	0.06±0.01	0.01-0.09 (0.06)	***0.001****

Sd: Standard deviation, [a]Kruskall Wallis Testi, *p<0.01.

A substantial negative connection was found between the Lund Kennedy score and Disulfide (SS) µmol/L measurement at 32.3% level (r = -0.232; p = 0.042; p<0.05). This relationship between Lund Kennedy Scoring and Laboratory Measurements is given in Figure 1 and Table 4.

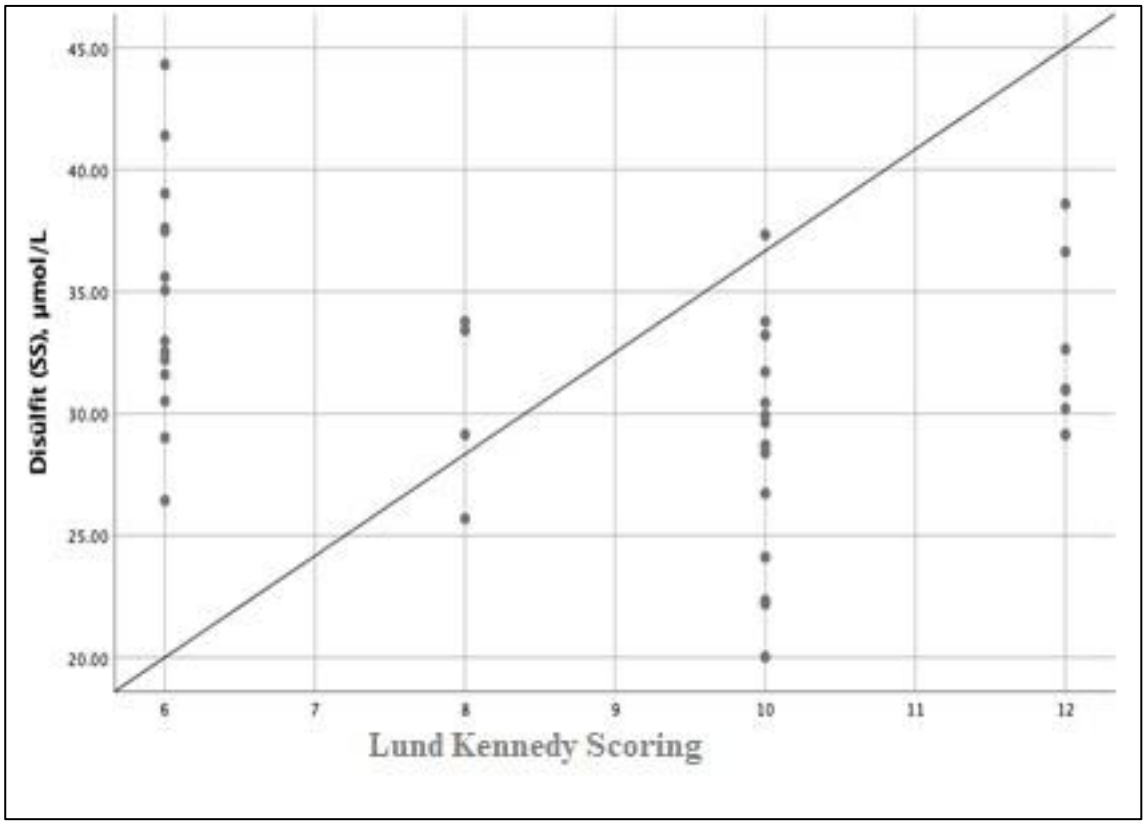

Figure 1. Relationship Between Lund Kennedy Scoring and Disulfide (SS), µmol/L Measurement

Table 4.
Relationship between Lund Kennedy Scoring and Laboratory Measurements

		Lund Kennedy Scoring
Total tiyol(ToSH), µmol/L	***r***	-0.170
	p	**0.293**
Nativ tiyol (SH), µmol/L	***r***	-0.137
	p	**0.399**
Disülfit (SS), µmol/L	***r***	-0.323
	p	**0.042***
SS/SH, %	***r***	-0.010
	p	**0.951**
SH/ToSH, %	***r***	0.022
	p	**0.895**
SS/ToSH, %	***r***	-0.022
	p	**0.895**

r=Pearson Correlation, *p<0.05.

Discussion

Nasal polyps are a complex pathological condition, particularly associated with the effects of oxidative stress, which may play a significant role in the development and severity of the disease. The levels of alpha-tocopherol, ascorbic acid, retinol, reduced glutathione, beta-carotene, glutathione peroxidase, superoxide dismutase (SOD), and the combination of malondialdehyde and thio-barbituric acid as peroxidation products were measured in plasma in Dagli et al.'s study comparing 31 patients with NP with 19 control patients with turbinate hypertrophy and septal deviation. A comparison with the control group, blood antioxidant levels decreased, and oxidant levels of malondialdehyde thio-barbituric were significantly increased in the patient group with NP (10). Bozkuş et al. conducted a study comparing 38 patients with NP to 35 controls with septal deviation and middle turbinate hypertrophy. The researchers evaluated the TAS (total antioxidant capacity), TOS (total oxidative burden), and OSI (oxidative stress index) in samples of serum and tissues. Levels of TAS in serum and tissue samples were notably reduced, whereas OSI and TOS levels increased in NP patients in comparison to the control group (11). The studies offer compelling evidence that oxidative stress affects the development of NP and suggest that antioxidants may mitigate tissue damage induced by SR in NP.

There are many antioxidant and oxidant parameters used to study oxidative stress in the body 7). Recent studies suggest that measurement of thiol levels in serum may indirectly reflect antioxidant defense. It has been found that under oxidative stress, thiol levels should decrease, and disulfide levels should increase. Bozdemir et al. showed the involvement of oxidative stress in the development of mucosal inflammation in CRS patients without polyps by analyzing TDH parameters, which serve as an indicator for oxidative stress. CRS patients had significantly lower total thiol μmol/L levels and native thiol μmol/L than the control group ($p<.001$). The results of disulfide (SS) and SS/NT measurements in the groups showed no statistical difference. These results suggest that there is a thiol depletion in CRS, thus altering homeostasis in the direction of oxidation, possibly as a consequence of the inflammatory process of the disease (12).

According to the study conducted by Sevil et al., there was no statistically significant difference in the levels of total thiol of patients with CRS with NP and patients with CRS without NP ($p > 0.05$). There was a significant difference between CRS with NP and CRS without NP in %SH/TT, %SS/TT, %SS/SH, SS, and SH ($p<0.05$). Comparing the patient groups within themselves, it was observed that the SH level was higher in CRS without NP, whereas the SS level was higher in CRS with NP. While no significant difference was detected between CRS patients without NP and the control group in terms of %SS/TT, %SS/SH, %SH/TT, SS, and SH ($p>0.05$), there was a statistically significant difference ($p<0.05$) in CRS patients with NP and the control group in terms of %SS/TT, %SS/SH, %SH/TT, SS, and SH. The CRS group with NP had lower levels of TT and SH compared to the control group ($p<0.05$). According to these results, dynamic SH/SS homeostasis is changed towards SS creation as a consequence of SH oxidation in CRS patients (13).

Our initial hypothesis in this study was that dynamic TDH parameters would vary between the NP group and the control group, as we intended to evaluate the effect of oxidative stress on the NP and dynamic TDH parameters development. Each parameter related to TDH, native thiol (SH), total thiol (ToSH), disulfide (SS), SS/SH (%), SH/ToSH (%), and SS/ToSH (%) were evaluated separately. According to the results of our hypothesis analysis, there is a significant difference between the groups in parameters related to thiol-disulfide balance. Total Thiol (ToSH) μmol/L measurement ($p=0.005$; $p<0.01$), Native Thiol (SH) μmol/L measurement ($p=0.001$; $p<0.01$), and SH/ToSH% measurement show statistically significant differences, and these values in the NP group were lower compared to the control group. Disulfide (SS) μmol/L ($p = 0.001$; $p<0.01$), SS/NT% ($p = 0.001$; $p<0.01$), and SS/ToSH% ($p = 0.001$; $p<0.01$) showed statistically significant differences, and these values in the NP group evaluated compared to the control group.

Görgülü et al. aimed to examine the impact of smoking on the formation of NP. In the study, the serum cotinine levels, serum total IgE levels, and absorption levels were compared between 60 patients who underwent ESC (18 non-smokers and 42 smokers) and a control group of 50 individuals (both smokers and non-smokers). The results of this study revealed that smoking cessation, as one of the environmental factors influencing the etiopathogenesis in NP patients, and the prevention of exposure to cigarette smoke are important protective factors in preventing NP formation and protecting against recurrence (14)

In a research conducted by Solak et al., the native thiol, disulfide, and total thiol serum levels, and a comparison was made between the ratios of disulfide/total thiol, disulfide/native thiol, and native/total thiol

in 84 smoker patients and 86 non-smokers healthy volunteers. Smokers had decreased levels of total, native, and native/total thiols compared to control group, but increased levels of disulfide, disulfide/total thiol, and disulfide/native thiol. The results suggested that smoking may lead to oxidative stress and disrupt the balance of thiol/disulfide levels towards the disulfide side in comparison to the healthy group (15).

We compared the smoking group with NP with the group of non-smoking in our study. The results of laboratory measurements were as follows: Total Thiol (ToSH) and Native Thiol (SH) μmol/L measurements were numerically lower in the smoker group, while SS/NT% measurements were numerically higher; however, they were not statistically significantly different ($p > 0.05$). The absence of statistical significance in our findings may be due to the small sample size.

The Lund Kennedy scoring system is a widely used method for assessing the severity of nasal polyposis (NP). It evaluates the extent of nasal polyp involvement based on the findings from endoscopic examination, considering factors such as the location, size, and number of polyps present in the nasal cavity and paranasal sinuses. In our study, attempting to assess the relationship between the disease severity and oxidative stress, we found a significant negative relationship between the Lund Kennedy score used in the evaluation of NP disease severity and Disulfide (SS), μmol/L measurement at 32.3% level ($r = -0.232$; $p = 0.042$; $p<0.05$). Typically, an increase in oxidative stress is expected to correlate with a rise in disease severity, and therefore, a positive correlation is anticipated. However, the sample size in our study may have contributed to the emergence of this inverse correlation.

As far as we know, no study has assessed the impact of dynamic TDH and smoking on the parameters related to the homeostasis of NP patients. The current study investigated the effect of dynamic TDH as an indicator for oxidative stress in the pathophysiology of NP as well as the effects of smoking on parameters related to homeostasis.

It was limited by the small number of cases. Our study may have been inadequate in representing larger groups due to the fact that patients were selected according to certain exclusion criteria and 40 patients in total were assessed, potentially impacting the results.

In conclusion, each parameter related to thiol/disulfide homeostasis—native thiol (SH), total thiol (ToSH), disulfide (SS), SS/SH%, SH/ToSH%, and SS/ToSH%—was evaluated separately in our study, aiming to explore the effect of dynamic TDH as an indicator of oxidative stress in the pathophysiology of NP and the impact of smoking on hemostasis parameters. We found significant differences between the groups in our hypothesis analysis regarding indicators associated with thiol-disulfide balance. These results suggest that TDH is shifted towards SS formation caused by SH oxidation in NP patients. These results suggest that oxidative stress may be important for NP.

Ethics Committee Approval: The study was approved by the Bolu Abant İzzet Baysal University Ethics Committee (date: 13.07.2021 and decision number: 2021/175).

Informed Consent: Written consent was obtained from the participants.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support.

Acknowledgment: This study is derived from the medical specialty thesis titled 'Dynamic Thiol/Disulfide Homeostasis in Patients with Nasal Polyps and the Effects of Smoking on Homeostasis Parameters,' which was completed in 2022 at the Faculty of Medicine, Abant Izzet Baysal University.

Author Contributions: Idea/Concept: T.B.Y., E.K., O.M.Y.,A.G.; Design: T.B.Y., E.K., O.M.Y Supervision: T.B.Y., E.K., O.M.Y.; Funding: T.B.Y., E.K., O.M.Y; Materials: T.B.Y., E.K., O.M.Y; Data Collection/Processing: T.B.Y., E.K., O.M.Y.; Analysis/Interpretation: T.B.Y., E.K., O.M.Y.,A.G; Literature Review: T.B.Y., E.K., O.M.Y.,A.G.; Drafting/Writing: T.B.Y., E.K., O.M.Y.,A.G; Critical Review: T.B.Y., E.K., O.M.Y.,A.G. The authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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