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ASSOCIATION BETWEEN GUSTATORY AND OLFACTORY DYSFUNCTIONS AND GHRELIN, IL-6, AND IL-10 LEVELS IN COVID-19 PATIENTS

COVID-19'LU HASTALARDA TAT VE KOKU ALMA BOZUKLUKLARI İLE GHRELİN, IL-6 VE IL-10 DÜZEYLERİ ARASINDAKİ İLİŞKİ

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ABSTRACT

Objective: The aim of this study was to examine the association between gustatory and olfactory dysfunctions and ghrelin, IL-6, and IL-10 levels in patients with COVID-19.

Materials and Methods: A total of 80 COVID-19 patients were enrolled in the study: 57 patients with gustatory and/or olfactory dysfunctions and 23 patients without gustatory or olfactory dysfunctions. The plasma ghrelin, IL-6, and IL-10 levels of all patients were determined using the ELISA method.

Results: COVID-19 patients with gustatory and/or olfactory dysfunctions had higher IL-6 and lower ghrelin and IL-10 levels compared with COVID-19 patients without gustatory or olfactory dysfunctions ($p<0.001$).

Conclusions: These results demonstrate that an inflammatory process mediated by ghrelin, IL-6, and IL-10 contributes to the development of gustatory and olfactory dysfunctions in COVID-19 patients.

Keywords: Ghrelin, IL-6, IL-10, COVID-19, Gustatory dysfunction, Olfactory dysfunction

ÖZ

Amaç: Bu çalışmanın amacı, COVID-19'lu hastalarda tat ve koku alma bozuklukları ile ghrelin, IL-6 ve IL-10 düzeyleri arasındaki ilişkiyi incelemekti.

Gereç ve Yöntemler: Çalışmaya tat ve/veya koku alma bozukluğu olan 57 hasta ve tat ve ya koku alma bozukluğu olmayan 23 hasta olmak üzere toplam 80 COVID-19 hasta dahil edildi. Tüm hastaların plazma ghrelin, IL-6 ve IL-10 düzeyleri ELISA yöntemi kullanılarak belirlendi.

Bulgular: Tat ve/veya koku alma bozukluğu olan COVID-19 hastaları, tat ve koku alma bozukluğu olmayan COVID-19 hastalarına kıyasla daha yüksek IL-6 ve daha düşük ghrelin ve IL-10 düzeylerine sahipti ($p<0.001$).

Sonuçlar: Bu sonuçlar, ghrelin, IL-6 ve IL-10'un aracılık ettiği inflamatuar bir sürecin, COVID-19 hastalarında tat ve koku alma bozukluklarının gelişimine katkıda bulunduğunu göstermektedir.

Anahtar Kelimeler: Ghrelin, IL-6, IL-10, COVID-19, tat alma bozukluğu, koku alma bozukluğu

INTRODUCTION

Coronavirus disease 2019 (COVID-19), a highly contagious disease caused by the spread of a coronavirus known as SARS-CoV-2, has primary clinical symptoms such as fever, dry cough, fatigue, headache, nasal congestion, and myalgia (1, 2). Besides these common symptoms, gustatory and olfactory dysfunctions have also been reported (3-5). A meta-analysis revealed that 47% of COVID-19 patients experienced gustatory and olfactory dysfunction, with the percentage rising to 67% in patients with mild to moderate symptoms (4).

The exact mechanisms underlying the impact of SARS-CoV-2 on gustatory and olfactory dysfunctions have not yet been clarified. However, it is considered that COVID-19 can lead to the dysfunction of these senses through various mechanisms, such as local inflammation. Infection with SARS-CoV-2 can trigger immune system dysfunction, leading to the overproduction of pro-inflammatory cytokines. This local excessive immune response and inflammation can further contribute to tissue damage and impair sensory functions (5, 6). Ghrelin is a hormone primarily recognised for its role in appetite regulation, food intake, and energy balance. Moreover, it has been demonstrated

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Table 1: Comparison of the demographic and biochemical data

	Group 1 (n=57)	Group 2 (n=23)	p
Age, years	49.81±17.36	48.09±15.86	0.682
Gender (F/M), n (%)	28 (49.1)/29 (50.9)	8 (34.8)/15 (65.12)	0.243
WBC (10^3/µL)	5.82 (4.99-8.57)	6.13 (4.18-8.22)	0.911
Neutrophil, (10^3/µL)	4.04 (2.95-6.39)	3.92 (2.97-5.75)	0.493
Lymphocyte (10^3/µL)	1.55 (1.07-2.10)	1.42 (0.79-1.87)	0.258
Platelet (10^3/µL)	250 (199-302)	218 (197-293)	0.361
CRP (mg/L)	11.74 (3.76-61.4)	4.78 (2.22-17.8)	0.214
Procalcitonin (ng/mL)	0.06 (0.02-0.12)	0.04 (0.02-0.16)	0.565
D-dimer (ng/mL)	400 (265-690)	500 (380-730)	0.066
LDH (U/L)	220 (180-302)	223 (184-271)	0.869
ALT (U/L)	21 (16.9-36.9)	22 (14.0-34.0)	0.562
AST (U/L)	22 (19.0-40.2)	21 (16.0-28.0)	0.253
BUN (mg/dL)	13.5 (10.0-18.2)	12.3 (9.20-16.8)	0.632
Creatinin (mg/dL)	0.89 (0.76-1.07)	0.77 (0.63-0.96)	0.042

ALT: Alanine transaminase, AST: Aspartate aminotransferase, BUN: Blood urea nitrogen, CRP: C-reactive protein, LDH: Lactate dehydrogenase, WBC: White blood cell

Table 2: Comparison of the plasma levels of ghrelin, IL-6, and IL-10

	Group 1 (n=57)	Group 2 (n=23)	p
Ghrelin (pg/mL)	165.00 (138.75-211.31)	206.70 (203.51-234.64)	<0.001
IL-6 (pg/mL)	15.09 (13.22-16.20)	11.78±1.05	<0.001
IL-10 (pg/mL)	73.77±28.27	110.03±25.64	<0.001

that this endogenous ligand possesses distinct properties, such as oxidative stress, inflammation, inhibition of cell proliferation, apoptosis, and involvement in metabolic processes. Ghrelin counteracts the effects of pro-inflammatory cytokines by acting as an anti-inflammatory mediator (7). Studies on COVID-19 have shown that ghrelin plays a crucial role in modulating the immune response and could be considered a potential treatment option to reduce complications associated with COVID-19 (7, 8). Interleukin-6 (IL-6), a potent pro-inflammatory cytokine, regulates a variety of physiological inflammatory and immunological processes (9). Increased IL-6 levels are related to complications, adverse outcomes, and disease severity in COVID-19 patients, according to current research. Furthermore, IL-6 has been considered a negative prognostic factor due to its involvement in the cytokine storm reported in severe COVID-19 patients (10-12). Interleukin-10 (IL-10), a pleiotropic cytokine, possesses immunosuppressive and anti-inflammatory properties (13). The role of this cytokine in COVID-19 is intricate and multifaceted, and it has been linked to the severity of the disease (14-16). Although the importance of these cytokines in the severity of COVID-19 disease has been reported, there are limited studies investigating their relationship with gustatory and/or olfactory dysfunctions. Therefore, in this study, we investigated the association between gustatory and olfactory dysfunctions and ghrelin, IL-6, and IL-10 levels in patients with COVID-19.

MATERIALS AND METHODS

Ethics and study design

Ethical approval was granted by the Non-Invasive Ethics Committee of Niğde Ömer Halisdemir University (Date: 08.04.2021, No: 2021/40) after obtaining approval for the study's scientific research from the Directorate General of Health Services of the Ministry of Health. All participants received written informed consent after being fully informed about the study.

This prospective study was conducted on 80 COVID-19 patients with RT-PCR-confirmed diagnosis admitted to the Department of Neurology, Faculty of Medicine, Niğde Ömer Halisdemir University between June 15 and December 15, 2021. The patients with COVID-19 were separated into two groups: those with gustatory and/or olfactory dysfunctions (Group 1) and those without gustatory or olfactory dysfunctions (Group 2). Blood samples from patients were collected within 24 h. World Health Organization (WHO) diagnostic criteria were used to classify the severity of COVID-19 (17). Because the patients had mild/moderate cases, they were conscious and able to communicate. Gustatory and/or olfactory dysfunctions were documented based on the patients' verbal statements. The demographic and biochemical data, including alanine transaminase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), C-reactive protein (CRP), D-dimer, lactate dehydrogenase (LDH),

lymphocyte, neutrophil, platelet, procalcitonin, and white blood cell (WBC), were retrieved from the medical records of the patients.

The study inclusion criteria for both groups were as follows: (1) a laboratory-confirmed diagnosis of COVID-19, (2) age≥ 18 years, (3) no history of nasal surgery, and (4) no pre-existing conditions that affect gustatory and olfactory functions. The exclusion criteria for both groups were as follows: (1) the presence of a chronic inflammatory disease, (2) a metabolic disease, (3) an active upper respiratory tract infection other than COVID-19, (4) pregnant or lactating women, and (5) diseases affecting carbohydrate and lipid metabolism.

Blood sample collection and determination of ghrelin, IL-6, and IL-10 plasma levels

Blood samples of 5 mL were obtained from each patient and placed into tubes containing EDTA. The samples were centrifuged at 1500 x g at 4°C for 15 min and stored in aliquots at -80°C until enzyme-linked immunosorbent assay (ELISA) testing was conducted using a BioTek ELx800 absorbance microplate reader. Plasma levels of ghrelin, IL-6, and IL-10 were measured using commercial ELISA kits (USCN, Wuhan USCN Business Co., Ltd., China, Product No: CEA991Hu (Version: 13.0); SEA079Hu (Version: 13.0); SEA056Hu (Version: 13.0), respectively) according to the manufacturer's instructions.

Statistical analysis

The data analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM Corp, Armonk, NY, USA). The Shapiro-Wilk test was performed to assess the normality of the data. Mean±standard deviation (SD) and/or median [interquartile ranges (IQR; 25%-75%)] were used to analyse both normally and non-normally distributed data. For comparisons between groups, the Student's t-test was used for normally distributed data, and the Mann−Whitney U test was used for non-normally distributed data. Statistical significance was defined as a p-value <0.05.

RESULTS

In this study, 80 COVID-19 patients were enrolled. Group 1 included 57 patients with gustatory and/or olfactory dysfunctions; of these, 28 were male (49.1%) and 29 were female (50.9%), with a mean age of 49.81±17.36 years. Group 2 included 23 patients without gustatory or olfactory dysfunctions; of these, 8 were male (34.8%) and 15 were female (65.1%), with a mean age was 48.09±15.86 years. There were no significant differences between the groups in terms of age, gender, and laboratory parameters except for creatinine. Group 2 had significantly lower creatinine levels than Group 1 (Table 1).

In Group 1, the plasma ghrelin, IL-6, and IL-10 levels were 165.00 (138.75-211.31) pg/mL, 15.09 (13.22-16.20) pg/mL, and 73.77±28.27 pg/mL, respectively. In Group 2, ghrelin, IL-6, and IL-10 levels were 206.70 (203.51-234.64) pg/mL, 11.78±1.05 pg/mL, and 110.03±25.64 pg/mL, respectively. Data analysis showed that the IL-6 level was significantly higher in Group 1 than in Group 2 ($p<0.001$). Conversely, the levels of IL-10 and ghrelin were significantly lower in Group 1 than in Group 2 ($p<0.001$) (Table 2).

DISCUSSION

Gustatory and olfactory dysfunctions have been recognised as prevalent symptoms of COVID-19; however, the underlying pathological mechanisms remain unclear. A severe cytokine storm mediated by pro-inflammatory cytokines is thought to cause damage in cases of gustatory and olfactory dysfunctions resulting from COVID-19 infection (5, 6). Ghrelin, a ligand for the growth hormone secretagogue receptor 1A (GHSR1A), is predominantly produced by the P/D1-like cells in the human stomach (8, 18). Ghrelin and GHSR1A are also expressed in lymphoid tissues, immune cells, natural killer cells, and monocytes. Some studies show that ghrelin prevents the synthesis of pro-inflammatory cytokines. Furthermore, it increases the levels of the anti-inflammatory cytokine IL-10 and exhibits protective properties in various models of inflammatory diseases (7, 8, 19). Azizzadeh et al. demonstrated that in a rat model of inflammatory pain, ghrelin exerted analgesic effects by modulating the levels of IL-10 and TGF-β (19). In this regard, ghrelin is acknowledged as a hormone with anti-inflammatory and immunomodulatory properties. Because of these effects, ghrelin has recently become an attractive agent to mitigate the complications related to SARS-CoV-2. Additionally, by downregulating NF-κB expression and upregulating PPARγ, ghrelin is capable of reducing the uncontrolled production of cytokines that lead to acute lung injury (7). An in silico study by Russo et al. found that ghrelin exerts an immunomodulatory function during the progression of SARS-CoV-2 (8). There are only a few studies on the levels of ghrelin in COVID-19 patients. Kuliczkowska-Płaksej et al. demonstrated that ghrelin levels were notably elevated six months after a mild SARS-CoV-2 infection (20). In contrast, Hakami et al. found no significant changes in ghrelin levels in the blood samples of COVID-19 patients. Nonetheless, they speculate that ghrelin might exhibit potential changes in saliva rather than its effects in the blood (21). Ghrelin also influences sensory function and plays a notable role in taste sensation, sniffing, and olfaction (18). Ghrelin receptors have also been detected in the granule cell layers of the olfactory bulb, glomerular and mitral cells, and the piriform cortex (22). Recent research has indicated that ghrelin cells are chemosensory and possess taste receptors (23). In our study, we found that COVID-19 patients with gustatory and/or olfactory dysfunctions had lower levels of ghrelin compared with patients without gustatory or olfactory dysfunctions. There is only one study in COVID-19 patients on the relationship between ghrelin and these dysfunctions. Shanyoor et al. demonstrated that the ghrelin levels in COVID-19 patients with anosmia and ageusia were considerably lower than those without these symptoms (24). These findings consistent with our results.

IL-6 is a crucial cytokine involved in the immune response to infections. Numerous studies have shown that increased IL-6 levels are linked to the disease severity and adverse outcomes

in COVID-19 patients. Hence, increased IL-6 levels are considered a negative prognostic factor for COVID-19 (10-12). Research examining the relationship between this cytokine and gustatory and/or olfactory dysfunctions is relatively limited. Some studies have found a link between them, while others have not established a relationship (25-29). Henkin et al. showed that there were increased IL-6 levels in the saliva, plasma, and nasal mucus of patients with hyposmia and that these alterations can be attributed to systemic or local inflammatory processes, which may underlie or result in hyposmia pathology (25). Cazzolla et al. found a significant association between lower IL-6 levels and the improvement of olfactory and gustatory dysfunctions (26). Likewise, Liang et al. observed a significant relationship between increased IL-6 levels and an increased risk of olfactory dysfunction in patients infected with the Omicron variant. They also noted that groups with olfactory dysfunction displayed higher levels of IL-6 compared with the control group and proposed a hypothesis suggesting that elevated IL-6 levels might be considered a possible causal factor for initiating olfactory dysfunction following local or systemic infection, owing to immunological and inflammatory alterations (27). Chang et al. also showed that IL-6 levels were increased in nasal swab samples from COVID-19 patients with olfactory dysfunctions (29). A recent study conducted by De Melo et al. revealed that in patients with olfactory dysfunction, this infection was found to be connected to inflammation of the olfactory mucosa. Notably, the researchers observed pronounced pro-inflammatory conditions in both the nasal turbinates and olfactory bulb, with up-regulation of IL-6 (30). In line with previous studies, our study indicated that COVID-19 patients with gustatory and/or olfactory dysfunctions had higher IL-6 levels than those without. In line with previous studies, our study indicated that COVID-19 patients with gustatory and/or olfactory dysfunctions had higher IL-6 levels than those without. The findings of the current study were consistent with the literature data indicating a significant relationship between the increased IL-6 levels and gustatory and/or olfactory dysfunctions in COVID-19 patients.

IL-10 is primarily recognised for its anti-inflammatory and immunosuppressive properties (13). However, in the context of COVID-19, the role of IL-10 is intricate and multifaceted. Various studies have indicated that elevated levels of IL-10 are linked to severe cases of COVID-19 compared to mild or moderate cases, implying its potential pro-inflammatory effects (14-16). However, adequate research on the relationship between gustatory and/or olfactory dysfunctions and IL-10 levels has not been conducted, and only one study has been undertaken on this topic to date. In our study, we observed that COVID-19 patients with gustatory and/or olfactory dysfunctions had reduced IL-10 levels compared with patients without gustatory or olfactory dysfunctions. Similar to our findings, Locatello et al. showed that the recovery of gustatory dysfunction was linked to elevated IL-10 levels. Furthermore, they proposed that immunological parameters may be valuable in monitoring the progression of chemosensory impairments in patients with COVID-19, and the elevated IL-10 levels should be regarded as a marker of recovery (31).

The relatively small sample size was a limitation of this study. The results of our study demonstrate that ghrelin, IL-6, and IL-10 might play a significant role in the development of these dysfunctions in COVID-19 patients, indicating their involvement in an inflammatory process. Further research is needed to understand the association between ghrelin, IL-6, and IL-10 levels and gustatory and olfactory dysfunctions in patients with COVID-19.

Ethics Committee Approval: This study was approved by Non-Invasive Ethics Committee of Niğde Ömer Halisdemir University (Date: 08.04.2021, No: 2021/40).

Informed Consent: All participants received written informed consent after being fully informed about the study.

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