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ORIGINAL ARTICLE

Association of Leptin and Ghrelin Serum Levels with Anosmia and Ageusia in Iraqi COVID-19 Infected Patients

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ABSTRACT

Early indications of COVID-19 infection include anosmia (inability to smell) and ageusia (incapability to taste), which were recorded in up to 85–90% of patients. This investigation was aimed at determining the association of leptin and ghrelin serum levels with anosmia and ageusia in Iraqi COVID-19 infected patients. Three categories of participants were formed in this case-control study: thirty patients infected by COVID-19 at an active state with anosmia and ageusia (group 1), thirty patients infected by COVID-19 without anosmia and ageusia (group 2), and thirty healthy subjects as controls (group 3). The mean serum levels of leptin was significantly higher in group 1, as compared to group 2 and group 3where p-value was ($p<0.0001$), while the mean serum levels of ghrelin was significantly lower in group 1, as compared to group 2 and group 3wherep-value was ($p<0.0001$). Blood was obtained from the three groups and the amounts of total leptin and ghrelin in the blood were evaluated. The results showed that the average serum level of leptin was significantly ($p < 0.0001$) higher in groups 1 and 2 compared to group 3, while the mean serum level of ghrelin was significantly ($p < 0.0001$) reduced in groups 1 and 2, compared to group 3. It was observed that the occurrence of these changes at the start of the disease is significantly higher, and it is therefore recommended that assessments of smell and taste dysfunction be used as indicators of infection with COVID-19.

Keywords: Leptin and Ghrelin, serum level, Anosmia and Ageusia, COVID-19

INTRODUCTION

Coronavirus disease (COVID-19) is a global pandemic; its transmission is mainly through human-to-human salivary and respiratory droplets (1). It has resulted in millions of illnesses and over a hundred thousand fatalities around the world (2, 3). Anosmia (total loss of capacity to smell) or macrosomia/ hyposmia (decreased sense of smell) has been identified as a characteristic symptom of COVID-19 and is most likely the first sign of coronavirus infection (4, 5). Olfactory dysfunction was frequently linked to gustatory dysfunction, such as ageusia or hypogeusia, with a wide range of incidence rates, which depends on sex, nation, and techniques such as self-report or testing, etc. of 5-95% for olfactory dysfunction and 38-89% for gustatory dysfunction in coronavirus with female predominance (6, 7). Coronavirus entry into host cells is dependent on the availability of angiotensin-converting enzyme-2 (ACE2), a cell receptor, and the transmembrane protease serine-2 (TMPRSS2), both of which are absent in olfactory neurons (8, 9). However, non-neuronal cells, present in the olfactory epithelium (OE), especially supporting cells expressing both ACE2 and TMPRSS2 (and other supporting cells such as horizontal basal cells, Bowman glands, and microvilli cells) can be infected. It was discovered that there is a coronavirus that can cause the olfactory neurons to suffer collateral damage and die (9, 10). Additionally, ACE2 and TMPRSS-2, as well as neuropilin-1 (NRP1), a highly expressed transmembrane receptor in the sensory (and respiratory) epithelium, may promote the invasion of SARS-CoV-2, but its impact on nerve injury has not been determined (11).

Taste receptor cells, such as olfactory neurons lack ACE2, and therefore cannot be attacked by a coronavirus. They recognize substances within the saliva and send signals to the brain. However, other tongue support cells that contain the receptors can become infected, causing collateral harm to the taste receptor cells (10, 12, 13). Ageusia/hypogeusia can also be caused by cytokine-induced taste receptor cell injury (12, 14). Salivary hormones are also thought to play a role in the development of taste buds, as well as influencing taste perception. Glucagon, leptin, ghrelin, oxytocin, and insulin have all been linked to taste modalities in animal research (15, 16). A high level of leptin is directly linked to the development of obesity and/or sequelae of metabolic disease (17) and are all important risk factors linked to an increase in COVID-19 mortality (18,19). An elevated level of leptinemia is linked to patients with inflammatory diseases, like respiratory illnesses and sepsis (20, 21).

ACE2 enzyme hydrolyzes ghrelin, apelin-13, and other proteins in addition to angiotensin proteins. Angiotensin-converting enzyme (ACE2) may be increased by angiotensin receptor blockers (ARBs), which can promote infection and lower levels of apelin-13 and ghrelin (22).

The majority of evidence suggests that sustentacular cells are the main targets of SARS-CoV-2 in the olfactory epithelial layer. Most of the olfactory epithelium appears to be damaged by post-infection desquamation, as evidenced by the appearance of cell debris in the nasal cavity lumen. This desquamation will result in the extinction of some OSNs, but it may also result in the OSN dendrite layer loss, which is where olfactory transduction takes place (23).

Leptin is a peptide with one hundred and sixty-seven amino acids. It is mostly produced in adipose tissue, although it also occurs in other tissues like the ovaries, bone marrow, placenta, mammary epithelium, and lymphoid tissues (24). Growth hormone, prolactin, and interleukins are all members of type I helical family, which includes leptin (25). Increased leptin synthesis by adipose depots triggers a response that reduces eating and promotes energy expenditure (26–28). Equally, a drop in leptin levels, which is linked to a negative energy balance in the body, causes a strong desire to consume and save energy (28). Leptin release into the human circulatory system is pulsatile (29), peak levels occur between midnight and early morning, and reduced amounts occur between early morning and mid-afternoon (30). Obese and lean people had similar pulsatile secretion patterns (31) with larger pulse amplitudes in obese people (30). It operates on peripheral tissues and affects metabolic activity (32) by regulating dietary consumption, metabolic reaction, and energy output via its receptor in the hypothalamus (32, 33).

The activity of many hypothalamic neurons is then regulated, as well as the expression of some anorexia and appetite-suppressing neuropeptides, including galanin, galanin-like peptides, orexins, neuropeptide Y, melanin-aggregating hormones, and agouti-related proteins (34, 35).

Ghrelin is the first hunger hormone to circulate. Fat mass and food intake, an activity that occurs at the hypothalamic level is increased by ghrelin and synthetic ghrelin imitative growth hormone secretagogues (GHS). They stimulate the orexigenic neuropeptide Y (NPY) neurons, which are found in the arcuate nucleus. Both insulin and leptin affect the responsiveness of these nerve cells (36). Ghrelin activates the bonus mesolimbic cholinergic dopaminergic connections. This is a circuit that mediates the hedonic and enhancing properties of natural bonuses

for example food and addictive drugs such as ethanol (37). It's vital for taste, olfaction, and sniffing since it makes the olfactory system more sensitive to odors. Previous research has revealed that ghrelin receptors are found in the brain's sensory circuit, and that ghrelin promotes exploratory olfactory sensation, increasing olfactory sensitivity, thereby improving the ability to find, identify, and select meals (38). Its activity as a signal enhancer at the molecular interface between the environment and the neuroendocrine circuit that controls dietary stimuli and energy balance is consistent with this role (38).

Weight loss (linked to other dietary imbalances) would be the result of a reduction in energy intake. According to animal studies, SARS-CoV-2 causes a reduction in weight and an increase in inflammatory cytokines (39). COVID-19 induces anorexia, loss of weight, and low albumin levels in humans (40). Decreased energy intake results in weight loss (related to other nutritional imbalances). One animal study showed that SARS-CoV-2 is linked to loss of weight with an elevated inflammatory cytokine (39). COVID-19 causes weight loss, low albumin levels, and appetite loss in humans (40).

The current study sought to ascertain the association of leptin and ghrelin serum levels with anosmia and ageusia in Iraqi patients infected with COVID-19.

MATERIALS AND METHODS

Study group: The recruitment for this case-control study began in November 2021 and ended in January 2022 at Alatta Hospital for Communicable Diseases in Baghdad, Iraq, as well as a private clinic for outpatients. The 30 participants with COVID-19 infection with anosmia and ageusia (group 1), 30 subjects with COVID-19 infection without anosmia and ageusia (group 2), and 30 people who appeared to be healthy as controls (group 3) were separated into three groups.

Demographic of the study groups and ethical approval: Both groups 1 and 2 were 25-55 years old, while group 3 was 22-55 years old. Patients with cardiovascular illness, diabetes, hypertension, autoimmune disease, cancer, as well as alcoholics, obese patients, and antipsychiatric drug users, were excluded from the study. All subjects were given informed consent. The research was carried out following the Helsinki Declaration, verified by the College of Pharmacy's Ethics Committee at the University of Baghdad (41).

Blood sample collection: A venous blood specimen (5ml) was aspirated from each subject in the disease study group and the healthy control group. The blood sample was transferred into a sterile gel tube and then left for 15 minutes at room temperature to allow them to clot. Then, the sample was centrifuged for 15 minutes at 3000 rpm to obtain the serum, which was frozen at -20 ° C until it was used in an analysis for the studied parameters.

Laboratory analysis: All of the samples were defrosted once. The levels of total leptin and ghrelin in the blood were determined using a commercially available Human ELISA Kit (BT LAB, Bioassay Technology Laboratory).

Statistical analysis : The Statistical Package for Social Sciences (SPSS; version 25) was employed for the statistical analysis. Simple measures of frequency, percentage, mean, slandered error (SE), and range (minimum and maximum) were used to present the data. Statistical significance of categorical variables was determined by the Chi-square test, while the independent t-test was used to determine the degree of significance between two groups. In addition, one-way ANOVA was employed to evaluate if the difference was significant between the three groups. Statistical significance was considered when the p-value was less than or equal to 0.05.

RESULTS

The average age of group 1 patients was 39.12±2.92, with an age range of 25-55; 38.00±6.44 for group 2, with an age range of 25-55; and 36.55±3.99 for group 3, with an age range of 22-55, indicating that no significant difference existed in the average age between COVID-19 patients in both groups 1 and 2 and the control group, with a p-value = 0.551 (Table 1).

Table 1: Demographic characteristics of patients with infection covid-19

Groups	group 1 n=30	group 2 n=30	Control group 3 n=30	p-value
Age (years)				
Mean ±SD	39.12±2.92 a	38.0±6.44 a	36.55±3.99 b	0.551
Range	25-55	25-55	22-55	
BMI (kg/m2)				
Mean ± SD	23.46±0.18 a	23.36±0.17 a	22.70±0.23 b	0.0161**
Range	22-25	22-25	20-25	

(*) Refers to significant difference, (**) refers to highly significat difference and superscripts (a, b, c) among different groups indicate level of significance so that similar letters indicate no significant difference; whereas, different letters indicate significant difference and letter (a) takes the highest value followed by letter(b) and then by letter (c), Means having with the different letters in same column differed significantly. * (P≤0.05), ** (P≤0.01), O: one way anova.

While mean of BMI for group 1 patients was 23.46±0.18, 23.36±0.17 for group 2patientswhile group 3 patients was 22.70±0.23 , so there was significantly difference in mean BMI between covid-19 patients in both groups (1&2) and healthy control group 3 where p-value = 0.0161 as shown in table-1.

The mean serum leptin levels of group 1 were highest than group 2&healthy control group 3, it was significantly different in comparison with group 2 and healthy control group 3 where p-value < 0.0001, while there was no significant difference between group 2 & healthy control group 3, as shown in table-2, figure-1.

The mean serum ghrelin levels of group 1 were lowest than group 2&healthy control group 3, it was significantly different in comparison with group 2 and healthy control group 3 where p-value < 0.0001, while there was no significant difference between group 2 & healthy control group 3, as shown in table-2, figure-2.

As shown in Table 2 and Figure 1, the mean blood leptin levels of groups 1 and 2 patients were significantly ($p < 0.05$) different from healthy control group 3. As demonstrated in Table 2 and Figure 2, the mean blood ghrelin levels of groups 1 and 2 patients differ significantly ($p < 0.05$) from healthy control group 3.

Table 2: Serum levels of the studied parameters among the different groups

Variables	Group 1 (n=30)	Group 2 (n=30)	Group 3 (Control) (n=30)	p-value
Leptin				
Mean ±SD	4.128±0.15 a	2.584±0.12 b	2.533±0.11 b	0.0001**
Range	2.75-5.85	1.10-3.95	1.53-3.82	---
Ghrelin				
Mean ± SD	1.244±0.11 b	2.427±0.15 a	2.439±0.14 a	0.0001**
Range	0.525-3.92	1.44-5.34	1.44-5.34	---

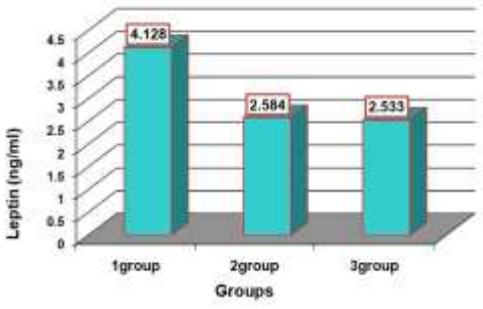

Figure 1: Comparison between different groups in leptin concentration

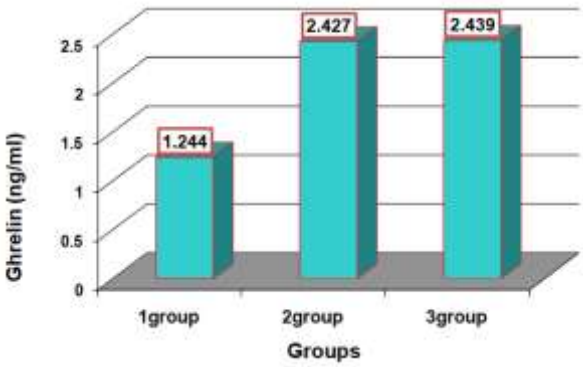

Figure-2: Comparison between different groups in ghrelin concentration

DISCUSSION

Anosmia is thought to affect 3–20% of the population. Chronic sinus disorders, severe head injuries, upper respiratory tract infections, and neuropathy increase the risk of olfactory dysfunction with age (42, 43). Because smell and taste examinations are not part of the usual medical tests, physicians always rely on patients' self-reports. Ageusia or taste impairment can present alone or in combination with anosmia. As a result, statistics on these symptoms are likely to be undervalued (42, 43). Hypogeusia (5.6%) and hyposmia (5.1%) were the most common complaints in Mao et al. investigation of patients with symptoms of the peripheral nervous system linked to COVID-19 infection (44). As olfactory symptoms became more well-known, recent research may have specifically screened patients for these symptoms, leading to an increased incidence of olfactory symptoms. Furthermore, only a few research used proven instruments to objectively assess "loss of scent" (45).

In the current investigation, mean blood leptin levels in group 1 were significantly higher than in patients group 2 and healthy control group 3, where the two groups differ significantly. Hematopoiesis, angiogenesis, and innate and adaptive immunity are all regulated by leptin (46). Its receptors can be found in pulmonary alveoli and bronchi, among other places. Increased inflammatory response to hyperoxia and ARDS (acute respiratory distress syndrome) are linked to high leptin levels, as well as impaired alveolar fluid clearance (47). Notably, leptin may be involved in the pathogenesis of many systemic and non-systemic symptoms observed in SARS-CoV-2-positive patients who are critically ill (48). Because high amounts of leptin affect the olfactory epithelium, the observed anosmia in SARS-CoV-2 disease could be explained in part by leptin (49).

In this study, mean blood ghrelin levels differ significantly by a reduction and lower in group 1 than in patients in group 2 and healthy control group 3, while there was no significant difference between groups 2 and 3. Ghrelin is important in appetite regulation and obesity development. It has been discovered that it has a receptor in the olfactory mucosa and that it is regulated by hunger (50). Ghrelin receptors can also be found in the olfactory bulb's glomerular, mitral, and granular cell layers, as well as the pyriform cortex. These findings imply that changed serum ghrelin and leptin levels may influence olfactory and taste processes, hence regulating food intake (51). Apelin-13, ghrelin, and other proteins are hydrolyzed by ACE 2 enzymes in addition to angiotensin proteins. ACEI and angiotensin-receptor blockers (ARBs) may enhance the ACE2 enzyme, which may promote infection and decrease apelin-13 and ghrelin levels (51). These medicines may raise the likelihood of having a stroke and other neurological problems in COVID-19 patients. The virus-induced acute lung damage may be exacerbated by a decrease in ghrelin levels. As a result, a drop in ghrelin levels may be responsible for various COVID-19 problems (52).

CONCLUSION

This study discovered that leptin serum levels were higher in group 1 than in group 2 patients, and in healthy control group 3, whereas ghrelin serum levels were lower. As a result, the incidence of these changes at the onset of the disease is significantly higher. Assessments of smell and taste dysfunction are recommended as indicators of COVID-19 infection.

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