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Original Article

The Relationship between Obesity and Allergies with Olfactory Disorders in Covid-19 Patients

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Abstract

Background : The prevalence of olfactory disorders is around 68–85% which occurs in COVID-19 patients with obesity and allergies as risk factors. The abnormalities olfactory pathways can cause by inflammatory response in adipose tissue in obese patients and excessive inflammation due to hyperreactivity of the immune system to allergens in allergic patients. This study aims to analyze the relationship between obesity and allergies to the occurrence of olfactory disorders in COVID-19.
Methods : It was an observational study during pandemic. Subjects were adult COVID-19 patients in the dr. Kariadi Hospital from June to July 2021. Patient with complete medical record ask for olfactory and allergic questionnaire. Patient with nasal tumor were excluded.
Results : We found 100 subjects who meet the criteria. There was a significant difference in smell disturbances between obese and non-obese subjects. (p = 0.019, OR 4.99). There was a significant difference (p=0.001) in complaints of olfactory disorders between allergic and non-allergic subjects, whereas all allergic subjects experienced olfactory disorders.
Conclusion : Obesity and allergies are corelated with impaired smell in COVID-19 patients.

Keywords : COVID-19, olfactory disorders, obesity, allergies

INTRODUCTION

Coronavirus Disease (COVID-19) is a form of inflammation in upper respiratory mucosal.[1] It is known as severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) caused by a large single-stranded RNA virus.[2,3] Symptoms include fever, dyspnea, cough, headache, sore throat, stuffy nose, runny nose, weakness, and loss of smell.[4] Several studies have stated that patients who have certain co-morbidities can increase the severity of COVID-19. One of the most reported cases is the occurrence of olfactory disorders.[4,5] Olfactory disorders are defined as loss of smell such as anosmia (patient loss their ability to smell) and hyposmia (patient loss their ability to smell partially). Pathological processes along the olfactory pathway, such as inflammation, infectious, tumoral, or congenital processes, result in conductive or sensorineural disturbances.[6,7] Olfactory disturbance is one of the clinical manifestations and occurs in the beginning of COVID-19 disease.[7,8]

The actual risk for COVID-19 are obesity and allergies. In obesity activated dendritic cells in vitro express less CD83 (a marker of dendritic cell maturation) and also produce IL-10. IL-10 inhibits the ability of dendritic cells to stimulate CD4+ T cells and downregulates MHC-II, CD86 (co-stimulator signal protein), and antigen presentation to CD4+ T cells. High leptin concentrations in obesity, which are also known to trigger IL-6 and TNF-α production from adipose tissue and increase the risk of viral infections.[9] Hyperactivity of the inflammatory response can cause a cytokine storm that causes systemic inflammation throughout the body. This inflammation or inflammation can cause defects in the olfactory pathways that lead to disturbances in olfactory function. In addition, viral infection through the enzyme converting angiotensin 2 (ACE 2) can cause inflammation of the olfactory submucosa which disrupts olfactory integrity and function.

In allergies, there is type 2 inflammation, and the mediator is eosinophils. IgE-mediated hypersensitivity reactions explain the occurrence of allergic disease. An allergen is captured by an antigen-presenting cell (APC), which is then processed and presented to T-helper lymphocyte cells. This communication takes place due to the presence of specific human leukocyte antigen receptors present on both APCs and specific T-cell receptors. TH2 cells present the allergen or allergy epitope on B lymphocytes, which have B cell receptors for that antigen. All of these receptors must be present for an allergic response to occur. IL-4 and other allergic cytokines can trigger B cells to turn into IgE-producing plasma cells. The IgE travels through the circulatory system and binds to IgE receptors on basophils and mast cells. Re-exposure to specific allergens causes IgE-mediated degranulation of basophils and mast cells. This will release inflammatory mediators such as histamine. Histamine binds to histamine receptors on endothelial cells and vascular smooth muscle causing vasodilation and increasing permeability. So that the symptoms of rhinorrhea, sneezing and stuffy nose arise.[10] The olfactory sensory neuron will suffer if the olfactory mucosa is inflamed.[11] In COVID-19 patients there are also olfactory disturbances caused by excessive inflammation which results in damage to the olfactory neurons. Therefore, in COVID-19 patients who have accompanying allergies, the symptoms of olfactory disturbances can worsen.[5] The objective of this study is to assess the correlation between obesity and allergies with the occurrence of impaired sense of smell in COVID-19.

METHODS

This is an observational study with a cross-sectional design. It was conducted at Dr. Kariadi hospital in Semarang, Indonesia. Subjects are COVID-19 patients who were recorded in medical records from June to July 2021. The sampling method used was consecutive sampling. Adult patients (age 18–60 years) with complete medical record were included. We exclude patient with nasal tumor. The outcome are olfactory disorder, obesity and allergies. The *American Academy of Otolaryngology Head and Neck Surgery* (AAOHNS) questionnaire was use to assess the olfactory disorder in Covid-19. It consists of 17 question about anosmia and dysgeusia. Body mass index from WHO was use to asses obesity, BMI >25 were count as obesity. Patient with history of asthma, food allergy and others allergy or patient who had 2 or more allergic rhinitis symptoms was define as positive allergy. The blood sugar test was collect to determine patient with diabetic and non-diabetic using Indonesian Society of Endocrinology criteria.

Data was analyzed with Fischer's exact test. This research has received permission from the Health Research Ethics Commission, Faculty of Medicine, Diponegoro University/Dr. Kariadi Semarang and the Medical Council of RSUP Dr. Kariadi Semarang No.1038/EC/KEPK-RSDK/2022

RESULTS

COVID-19 patients in June – July 2021 at Dr. Kariadi hospital found as many as 3565 patients. The characteristics of the study from 100 subjects who met the criteria shows in Table 1. The subjects aged were 21–60 years with the median was 36 years. Female patients were more than male (60%: 40%). This study found that patients with olfactory disorders is 89%, obesity is 61%, and allergies is 61%. Most patients didn't have hypertension (92%) and diabetic (88%).

In subjects with obesity, 95.1% of subjects experienced olfactory disorders. There was a significant

TABLE 1
Characteristics of research subjects

Variable		Olfactory disorder	
		Yes	No
Obesity	Yes	58 (95.1)	3 (4.9)
	No	31 (79.5)	8 (20.5)
Allergies	Yes	61 (100)	0 (0)
	No	28 (71.8)	11 (28.2)
Diabetes	Yes	8 (100)	0 (0)
	No	81 (88)	11 (12)
Hypertension	Yes	12 (100)	0 (0)
	No	77 (87.5)	11 (12.5)

TABLE 2
Characteristics of research subjects

Variable		Olfactory disorder		p	r
		Yes	No		
Obesity	Yes	58 (95.1)	3 (4.9)	0.019*	0.236
	No	31 (79.5)	8 (20.5)		
Allergies	Yes	61 (100)	0 (0)	<0.001*	0.402
	No	28 (71.8)	11 (28.2)		

Fisher exact test, * Significant (p < 0.05)

difference (p=0.019) OR 4.99 CI (1.23–20.17) in complaints of smell disorders between obese and non-obese subjects. The obese patients have a risk 4.99 times greater for experiencing olfactory disorders than subjects who are not obese. In the obesity contingency coefficient test on olfactory disorders, it has a weak positive correlation r 0.236 (Table 2).

In subjects with allergies, all subjects experienced olfactory disturbances. There was a significant difference (p=0.001) in complaints of smell disturbances between allergic and non-allergic subjects. In the obesity contingency coefficient test on olfactory disorders, it has a moderate positive correlation r 0.402 (Table 2).

All subjects with diabetes experienced olfactory disturbances. There was no difference (p=0.380) in olfactory complaints between diabetic and non-diabetic subjects. All hypertensive subjects experienced olfactory disorders. There was no difference (p=0.226) in olfactory complaints between hypertensive and non-hypertensive subjects.

DISCUSSION

Prevalence and characteristics of COVID-19 patients in previous studies conducted in several regions obtained almost the same results where COVID-19 patients were dominated by subjects aged 19–40 years who were dominated by women.[12,13,14] This condition indicates that the population detected by COVID-19 is concentrated in the productive age group. Recent studies have shown that the molecular and immune systems in male patient are fundamentally different with female when exposed to COVID-19. Several studies have described the role of ACE2, TMPRSS2, and the immune system in COVID-19 sex dimorphism. ACE2 is an X-linked gene located in the Xp22.22 region with a length of 41.04 kb. ACE2 is one of the X chromosome genes that 'escapes' the X chromosome inactivation mechanism, so the expression level of ACE2 is found higher in female than in male.[15,16,17]

The were 19.4% to 85.6% COVID-19 patients associated with olfactory dysfunction.[20,21] The prevalence

of olfactory dysfunction as the early symptom of COVID-19 are 11.8% to 27%.[21] Based on the initial results of the AAO-HNS "Anosmia COVID-19 Reporting Tool", reporting that nearly 75% suffer from anosmia noted that the event started before the diagnosis of COVID-19. Analysis showed that ability to smell worsened significantly from initial to two weeks after diagnosis but normalized within a month after confirming COVID-19.[22, 23]

The is unclear pathogenesis of the impairment of smell and taste related with COVID-19, the possibility is that the effect of the virus in the nasal epithelium and the central nervous system.[24] SARS-CoV-2 invaded the olfactory epithelium and infect the human central nervous system.[25] This virus enters the central nervous system through the peripheral olfactory or trigeminal nerves. Because of damage of the trigeminal and olfactory nerve can cause smell and taste disturbances. Another pathogenesis because of decreasing reflex sensitivity of sensory neurons cause by SARS-CoV-2 infection.[26]

In patients with obesity, the volume of the olfactory bulb is significantly lower than normal weight. Decreased olfactory bulb volume may be a consequence of obesity caused by metabolic and endocrine disturbances. Olfactory dysfunction is more prominent in severely obese patients than overweight or moderately obese patients. The elevation of leptin in obesity can inhibit olfactory function.[27] The HOMA-IR score asses the effect of insulin resistance on the relationship between BMI and olfactory function. The lower olfactory function associate with high BMI through insulin resistance. The early changes of olfactory function in obesity signing with decreased olfactory bulb volume.[28, 29, 30]

In a previous study, olfactory dysfunction in allergic rhinitis patients found that 50% of allergic rhinitis patients experienced hyposmia. In some cases, allergic rhinitis is related with an elevation of the olfactory threshold.[31] Although it has long been thought that the main cause of olfactory dysfunction in rhinitis is secondary caused by mucosal inflammation or nasal polyps that obstruct airflow across the olfactory epithelium. Other mechanisms include changes in the composition of nasal secretions, recurrent acute viral infection, or direct damage to the olfactory epithelium by an allergic inflammatory infiltrate.[32] Rhinitis has the potential to impair olfactory abilities in several ways. Airway constriction caused by inflammation can alter or block airflow through the nasal cavities, reducing the access of volatile compounds to sensory receptor cells, which are in relatively protected areas of the nasal passages.[33] Alterations in the composition and transport of the aqueous slime layer through which odorants must pass can interfere with access to or removal from receptor sites.[34]

Based on previous research there are other comorbid such as diabetes and hypertension. It showed that the odor recognition score was lower in diabetic patients (68 subjects), either type 1 and type 2 diabetes mellitus compared to 30 controls.[35] Similar results in a epidemiological study among 1900 adults in Sweden, the result showed even though diabetes was not associated with olfactory dysfunction in 1387 adults, it was considered as a risk factor for anosmia with odds ratio (OR) 2.6 and interval 95% confidence (CI) 1.3–5.5.[36] In a longitudinal cohort study of changes in smell and taste perceptions, it was found that individuals with changes in taste and smell perceptions had greater increases in systolic blood pressure and mean arterial pressure compared to individuals without taste and smell perceptions changes.[37] In this study we found there only few patient with diabetic and hypertension

The limitation of this study is that allergies were only evaluated based on the history of the patient's history, and no previous allergy diagnostic tests were carried out. In olfactory disorders only using a questionnaire does not use objective examination. Suggestions for further research are to carry out allergy diagnostic tests, specific Ig E or skin prick test, and examination of the sniffing stick test for olfactory disorders to get accurate results.

CONCLUSION

A relationship was found between obesity and allergies to olfactory disease in COVID-19 patients. Subjects with obesity are at risk of 4.99 times greater for experiencing olfactory disorders than subjects who are not obese.

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