The Relation Between Oral Microbiome Dysbiosis and Covid-19

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INTRODUCTION

The human oral microbiome consists of groups of microorganisms that interacts in complex ways. When there is a disruption in the microbiome, dysbiosis can occur, causing an imbalance that has various effects in the health of an individual. Respiratory diseases like COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have various implications based on the role of the human oral microbiome. The focus on non-bacterial fungi and viruses' alteration of the microbiota causing dysbiosis and the onset of disease is yet to be fully comprehended. Thus, the mechanism of the oral microbes' interactions and regulations of the Covid-19 virus requires studying. Considering the oropharynx route of COVID-19, identifying the complex alterations in the oral microbiome is significant with the ongoing prevalence of the disease.

OBJECTIVE

The aim of the literature review is to determine how it can help treat COVID-19 patients from an early on phase of the disease encountered in the oral cavity. Bringing focus to the specific components of oral dysbiosis that occurs in COVID-19 patients can be used to develop other means of interventions and prevention of the disease. Studying the significant alterations to the oral microbiome can help the COVID-19 patients that may become severely symptomatic. Thus, this literature review will explore and identify the relation between oral microbiome dysbiosis and COVID-19, particularly in relation to virus and fungi of the oral cavity to develop various treatment options to halt the onset and progression of this disease.

METHODS

An extensive search was conducted using the search engine database PubMed. The search consists of a combination of key terms: "microbiome AND oral dysbiosis AND SARs-CoV-2." To narrow the search, full text studies published within five years were selected. This resulted in a total of thirty-three results. I excluded studies involving gut microbes by adding onto the search: "microbiome AND oral Dysbiosis AND SARS-CoV-2 NOT Gut microbes." Based on the keywords and the relevancy of the 29 research articles, one study was selected to identify the key relations between oral dysbiosis and Covid-19 that is specifically related to the non-bacterial microbes of the oral cavity.

RESULTS

To identify bacteria, fungi, and viruses in the oral cavity simultaneously, a total of seventy-five oral rinses were collected and analyzed by the Whole Genome Sequencing with thirty-nine from COVID-19 patients and thirty-six from the control group. In linking the Human Oral Microbiome profile with the replication of the virus in the oral cavity, the amount of SARS-CoV-2 was quantified by using the digital droplet PCR. With the assessment of the oral microbes, local inflammation and immune response were also assessed by measuring pro-inflammatory cytokines: L-6, IL-17, TNFa, GMCSF and secretory immunoglobulins A (sIgA). According to the findings, COVID-19 patients experienced oral dysbiosis when compared to the control group. In COVID-19 patients, the study found a significantly lower value of alpha-diversity and a decreased richness in species. The study found oral dysbiosis to be associated with symptom severity ($p = 0.006$), and local inflammation increase ($p < 0.01$). In patients that were severely symptomatic, the response of sIgA was decreased ($p = 0.02$). This finding indicates the local secretory immune response plays a critical role during the initial phase of the virus, and the Human Oral Microbiome profile is influenced by such a response.

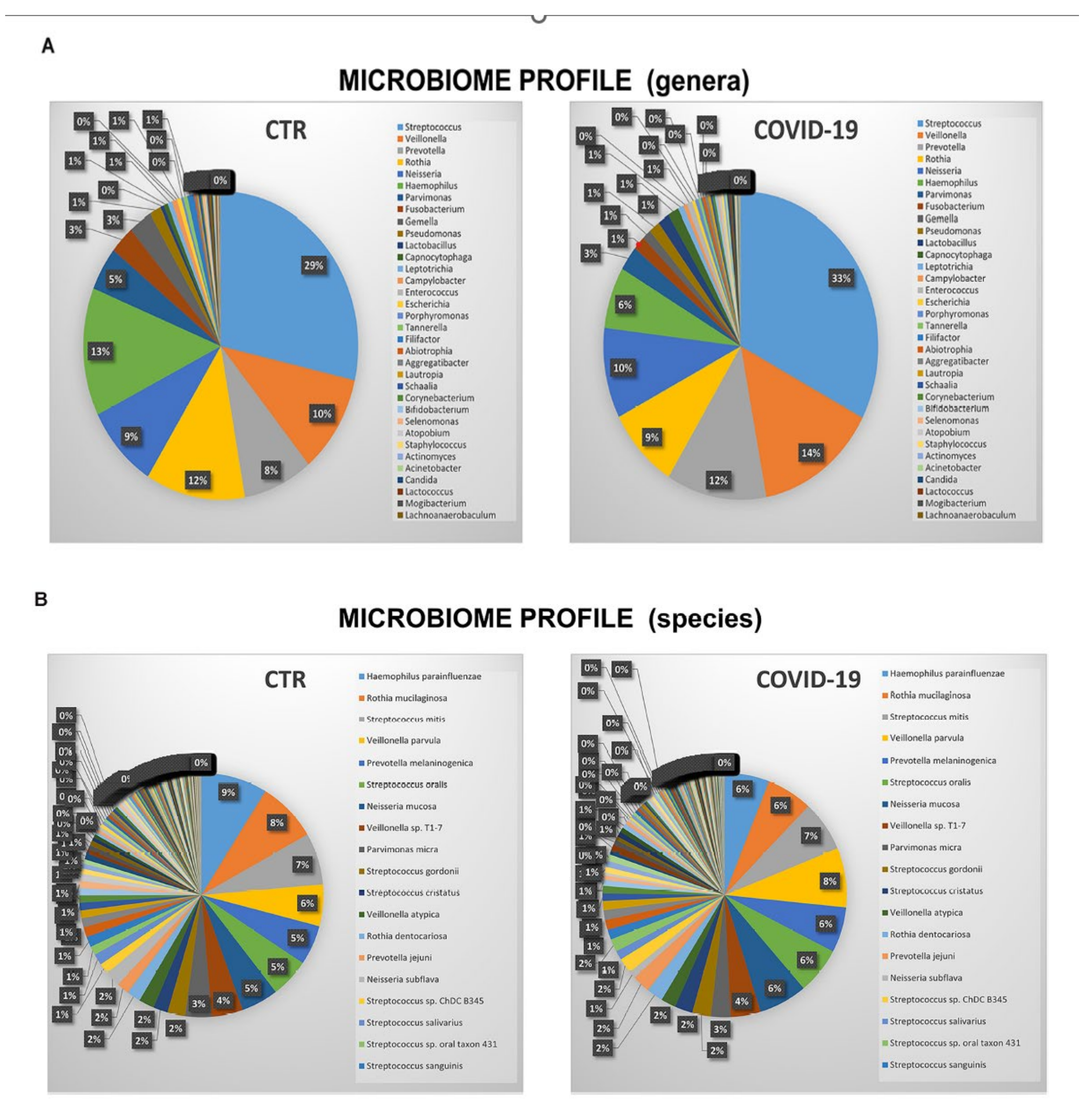

FIGURE 3 | Relative abundance and distribution of microorganisms in the oral cavity of control (CTR) and COVID-19 subjects. **(A)** Percentage distribution of most detected microbial genera. **(B)** Percentage distribution of most detected microbial species.

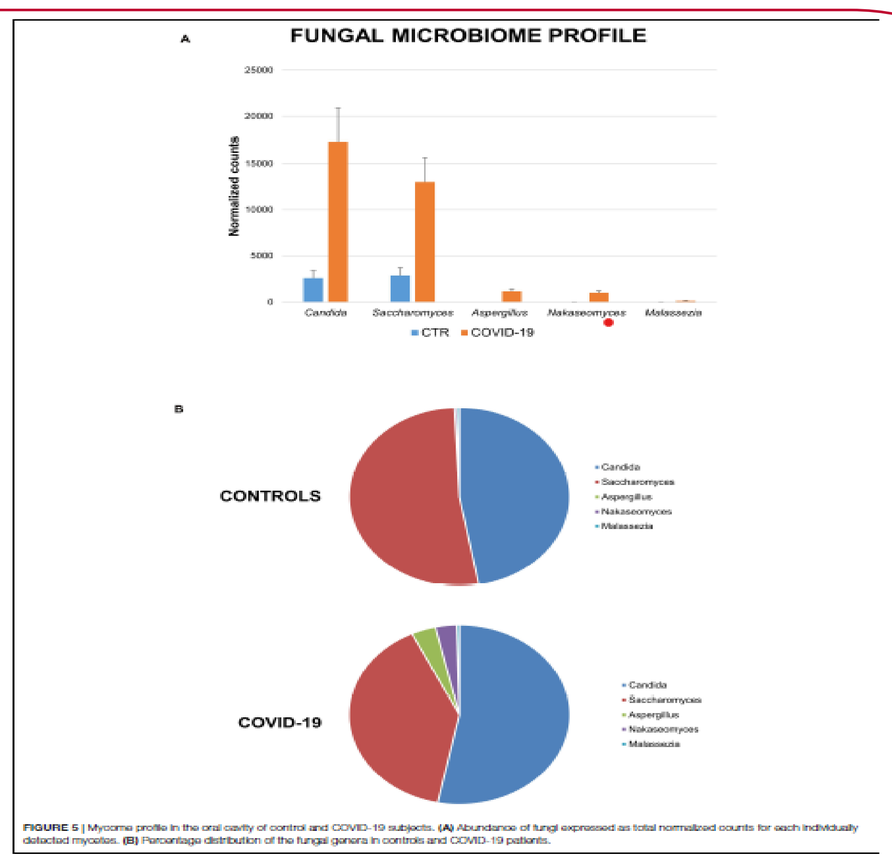

FIGURE 5 | Mycome profile in the oral cavity of control and COVID-19 subjects. **(A)** Abundance of fungi expressed as total normalized counts for each individually detected mycotes. **(B)** Percentage distribution of the fungal genera in controls and COVID-19 patients.

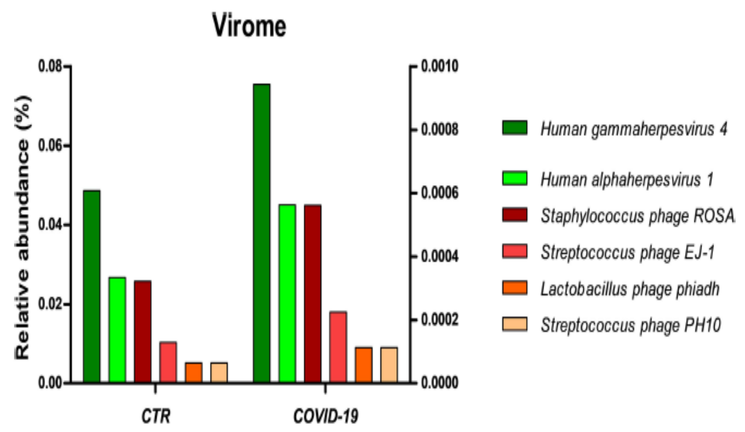

FIGURE 6 | Virome profile in the oral cavity of control (CTR) and COVID-19 subjects. The results are expressed as relative abundance (%). Left *y* axis refers to Human gammaherpesvirus 4 and Human alphaherpesvirus 1 (green bars), whereas right *y* axis refers to the amount of the four detected bacteriophage (orange-red bars).

DISCUSSION

When comparing the COVID-19 patients to the control, the fungal aspect of the oral microbiome was increased by the quantity and species richness. However, species richness in the oral bacteria decreased for COVID-19 patients. The control group for oral mycobiome consisted of the more common fungi genera, 47% of Candida and 52% of Saccharomyces spp. In contrast, the COVID-19 patients consisted of a larger variation of the oral mycobiome with 4% *Aspergillus*, 3% *Nakaseomyces*, and <1% of *Malassezia spp*. The increase in oral fungi may be due to the bacterial alterations triggered by COVID-19, causing more inflammation from the enzymatic and catabolic/ toxic reactions of the fungi. The viral component in COVID-19 patients also increased when compared to the control group. From the total oral microbes identified, the control group consisted of 0.07% viruses while the COVID-19 patients had a greater amount of 1.12% viruses. Identified in both groups were *Lymphocryptovirus* and *Simplexvirus* genera of the Herpesviridae family. However, in COVID-19 patients, 11/39 was reactivated with Epstein Barr Virus (EBV) while the control group consisted of 2/36. When compared to the control group, the COVID-19 patients had an increase in Herpes simplex virus type 1 (HSV-1) and four types of bacteriophages (Staphylococcus phage ROSA, Streptococcus phage EJ-1, Streptococcus phage PH10, Lactobacillus phage phiadh). Increase in the activation/ reactivation of the viruses in COVID-19 patients may be caused by the occurrence of oral dysbiosis. The ongoing cycle of action of the viruses may weaken COVID-19 patient's immune response. Other studies have found activation of EBV in COVID-19 patients' to have worsen symptoms and fatal results with greater amount of IL-6.

CONCLUSION

This cross-sectional study evaluated oral microbiome dysbiosis in COVID-19 patients and found correlations with symptom severity and local immune and inflammatory response. This study provides a comprehensive study of the oral microbiome, by exploring the alterations in the fungi and viruses of the oral cavity between COVID-19 patients and a control group. The findings can be useful to predict patients that may be more symptomatic from COVID-19. New effective treatments can focus on reversing the oral microbiome dysbiosis and inflammation to reduce symptoms and fatal outcomes. However, more research is indicated to understand if the change in the human oral microbiome is the cause or effect of SARS-CoV-2, since the disease may be the cause of oral microbiome dysbiosis. Other Studies found the viral load of COVID-19 to be reduced using chlorhexidine mouthwashes. Other means such as IL-6 inhibitors may decrease fatalities from COVID-19 and taking specific probiotics may possibly address the microbiome dysbiosis. Overall, a larger study with more participants is required for further data.

REFERENCES

Gupta, A., Bhanushali, S., Sanap, A., Shekatkar, M., Kharat, A., Raut, C., Bhonde, R., Shouche, Y., Kheur, S., & Sharma, A. (2022). Oral dysbiosis and its linkage with SARS-CoV-2 infection. *Microbiological Research*, *261*, 127055. https://doi.org/10.1016/j.micres.2022.127055

Miller, E. H., Annavajhala, M. K., Chong, A. M., Park, H., Nobel, Y. R., Soroush, A., Blackett, J. W., Krigel, A., Phipps, M. M., Freedberg, D. E., Zucker, J., Sano, E. D., Uhlemann, A. C., & Abrams, J. A. (2021). Oral Microbiome Alterations and SARS-CoV-2 Saliva Viral Load in Patients with COVID-19. *Microbiology Spectrum*, *9*(2). https://doi.org/10.1128/spectrum.00055-21

Soffritti, I., D'Accolti, M., Fabbri, C., Passaro, A., Manfredini, R., Zuliani, G., Libanore, M., Franchi, M., Contini, C., & Caselli, E. (2021). Oral Microbiome Dysbiosis Is Associated With Symptoms Severity and Local Immune/Inflammatory Response in COVID-19 Patients: A Cross-Sectional Study. *Frontiers in Microbiology*, *12*. https://doi.org/10.3389/fmicb.2021.687513

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