## Post-COVID-19 olfactory training: How to improve results?

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**Objective**: To evaluate the response to olfactory training (OT) in patients with persistent olfactory dysfunction (OD) post-COVID-19, in addition to clarifying whether periodic change or increase in the number of essences in OT is capable of increasing therapeutic success in these patients.

**Method**: Multicenter randomized randomized trial, including individuals with post-COVID-19 OD who remained with olfactory complaints after 4 weeks of infection. The patients were randomized into 3 groups for OT: the first group received 1 kit with classical olfactory training (OCD) with 4 essences, the second received modified TO (TOM) (3 different kits with 4 essences in each, with monthly toggle of the kits) and the third received advanced TO (TOA) (3 kits with 8 essences each, with monthly alternation of the kits). All patients underwent a complete ENT physical examination, followed by subjective measurement of smell and taste through the Visual Analog Scale (VAS), in addition to psychophysical evaluation through the Smell Identification Test of the University of Pennsylvania (UPSIT). The evaluation was repeated after 12 weeks of follow-up.

**Results**: Of the 340 patients initially selected, 77 patients between 18 and 60 years of age were followed, with the following distribution: 25 patients in the OCD group, 23 in TOM and 29 in TOA. The groups had homogeneous distribution regarding age, gender, history of smoking, magnitude of the complaint in the infection and interval between infection and initiation of treatment. In all groups, there was a statistically significant improvement after 12 weeks in both UPSIT ($p < 0.0001$) and VAS ($p$ 0.001). The mean increase in UPSIT was 2.8 points and subjective improvement occurred in 74% of patients. In the comparison between the groups, there was no statistically significant difference between OCD, TOM and TOA both in the psychophysical test and in the subjective evaluation of smell and taste. Among the factors related to the therapeutic response, a negative correlation was found between the COVID-19 interval and the beginning of treatment and the increase in the UPSIT score with treatment ($p$ 0.032), but with a weak correlation (Spearman's correlation coefficient 0.24). In patients who reported olfactory fluctuation (periods of improvement and worsening) at the first visit, the UPSIT score was significantly higher both in the first evaluation ($p < 0.001$) and after 12 weeks ($p$ 0.001).

**Discussion**: Several studies continue to reinforce the central role of OD in the treatment of persistent OD1, but little is known about post-COVID-19 OD and it is very interesting to know how to optimize its results. In the present study, in 12 weeks of OT there was an improvement in both the UPSIT score ($p < 0.0001$) and the VAS ($p$ 0.001). This was the first study to compare the response to OCD and the variations performed, however, we did not obtain statistically significant differences between the OT groups. Rezaeyan et al. compared periodic alternation of odors with OCD and also found no difference. However, when studying post-infectious OD, Altundag et al., OT with alternating essences was higher than OCD at 36 weeks, but this difference was more significant only after 12 weeks. In the evaluation of the general group, patients who started OT early obtained significantly higher scores in the UPSIT, reinforcing the importance of not delayed the beginning of treatment. Olfactory fluctuation at the onset of OT was associated with better prognosis which may suggest that this symptom is related to neuroepithelium regeneration.

**Conclusion**: The data indicate that the early precocity of OT in patients with persistent OD post-COVID-19 is associated with better response, whereas periodic change or increase in the number of essences for 12 weeks is not superior to the classical method. In addition, a fluctuating olfactory ability at the beginning of treatment seems to be related to a better UPSIT score.

**Keywords**: Olfaction; COVID-19; Rehabilitation.

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## Correlation between acute inflammatory markers and late evaluation of post-COVID olfactory function

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**Objectives**: To evaluate the relationship between late olfactory function in post-COVID-19 patients and serological inflammatory markers in the acute phase.

**Methods**: Cross-sectional, analytical and observational study. A number of 123 patients with a history of hospitalization by COVID-19 were recruited. Olfactory dysfunction (OC) was evaluated using the Connecticut Chemosensory Clinical Research Center (CCCRC) test, and data from the medical records were reviewed regarding serological markers of acute systemic inflammation – lymphocytes, lactate dehydrogenase (LDH), ferritin, C-reactive protein (PCR) and D-dimmer.

**Results**: The mean interval between onset of COVID symptoms and the CCCRC test was 172 days. There was a significant association between age over 60 years and CCCRC ($p = 0.03$). It was verified the presence of a relationship with statistical significance between increased LDH values and worse score in the CCCRC ($p = 0.049$). However, the correlation found was weak ($r = 0.19$). The other markers evaluated did not present statistical significance when crossed with CRF. The result was similar in the cross between serum inflammatory markers and degree of severity of OD.

**Discussion**: In the presence of the pandemic by COVID-19, OD has become a complaint of high prevalence, leading to an important loss of quality of life for patients. According to Cazzola et al., the cells that express the angiotensin-