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Intranasal insulin for COVID-19-related smell loss: a pilot study

Abstract

Anosmia is defined as the absence of olfactory function, hyposmia as the decrease in olfactory function and parosmia as the aberrant olfactory perception. These are relatively common consequences of COVID-19 infection even months after resolution of the disease. SARS-CoV-2 has tropism for angiotensin-converting enzyme 2 (ACE2) in the respiratory system, suggesting it is the mechanism of damage to the olfactory neuroepithelium and of involvement at the central nervous system. The olfactory bulb is the organ with the highest intranasal insulin utilization. Insulin has been related to the production of multiple Growth Factors (GF) involved in the restoration of olfactory functions therefore it could be a viable treatment for patients with chronic olfactory disturbances. The aim of this study was to quantify improvement in olfaction after four weeks of using intranasal insulin, with the help of the Threshold, Discrimination and Identification (TDI) score based on the Sniffin Sticks®. The results showed 93% of the sample having an improvement. The initial mean TDI score was 67% compared to the final mean of 83% (95% CI, $p<0.001$). This is the first study to use a three-point assessment of olfaction in post-COVID-19 patients, while using the Sniffin Sticks® TDI score adapted to latin spanish.

Keywords: COVID-19, olfaction disorders, smell, olfactory receptor neurons, olfactory mucosa

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Abbreviations: Threshold, Discrimination and Identification (TDI), Angiotensin-converting enzyme 2 (ACE2), cyclic guanylate monophosphate (cGMP), Cyclic adenylate monophosphate (cAMP), Growth Factors (GF)

Introduction

Anosmia is defined as the absence of olfactory function, which is perceived by the subject as a quantitative reduction in smell. When classifying anosmia according to its pathophysiology, it can be divided into three different categories: conductive (obstruction of the passage of odorants to the olfactory neuroepithelium), sensory (damage or loss of the neuroepithelium) and central dysfunction (damage to the participating pathways of the central nervous system).[1] Other olfactory abnormalities include hyposmia, which is understood as decreased olfactory function, and parosmia, which is characterized by aberrant olfactory perception. Olfactory evaluation can be difficult for health professionals since in some cases the patient is not aware of the olfactory dysfunction. A variety of tools, such as the Sniffin Sticks® scent identification test are available, although cultural and geographical differences between evaluated groups should be taken into account since they may alter the results obtained.

COVID-19 is a respiratory[2] disease caused by SARS-CoV-2. Typical clinical features include: cough, fever, myalgia, headache, dyspnea, diarrhea, nausea and vomiting, anosmia, hyposmia, parosmia, ageusia, dysgeusia and rhinorrhea. Severe complications include respiratory failure, thromboembolic and neurological events that lead to a high rate of mortality and morbidity.[3]

The mechanism of infection involves binding of the virus to angiotensin-converting enzyme 2 (ACE2) receptors. The olfactory tract is composed of sustentacular cells, microvilli cells, Bowman's gland cells, horizontal basal cells and pericytes of the olfactory bulb that express ACE2 receptors. The precise mechanisms by which olfactory loss is triggered have not been precisely identified. However, it has been related to direct damage to the olfactory neuroepithelium and involvement of the central nervous system; the latter is believed to be due to direct transmission of the pathogen into the brain. At histological level, loss and remodeling of the olfactory epithelium, as well as changes in cell morphology and distribution, have been reported.[4]

Although olfactory disturbances are reported in less than 10% of COVID-19 cases, the incidence is thought to be higher. Olfactory symptoms rarely last longer than one month.[5] Evidence shows that patients with olfactory disorders tend to have concomitant taste disorders, namely ageusia or dysgeusia.[6]

Besides COVID-19, upper respiratory infection and sinus disease are very common causes of anosmia. Nasal trauma can cause mechanical obstruction, compromising the entry of odorants into the olfactory tract. Obstruction is a typical finding in nasal bone and septum fractures, as well as direct neuroepithelial lesions. Direct lesions to the olfactory nerve tract after contusions, intraparenchymal hemorrhages, and gliosis can cause dysfunction of the central structures involved in olfaction.[1]

Studies have associated the use of intranasal insulin after olfactory bulb damage with the improvement of olfactory function. Interestingly, the olfactory bulb is the organ with the highest insulin utilization in the central nervous system. The most plausible relationship between intranasal insulin and the restoration of olfactory functions has been linked to the production of multiple insulin-induced Growth Factors (GF). Various diseases associated with insulin resistance and reduced GF levels are associated with hyposmia and anosmia, so increasing these GFs may be considered as a viable therapy. Insulin itself, as an inhibitor of the enzyme phosphodiesterase, participates in the nitric oxide cycle and increases cyclic guanylate monophosphate (cGMP) and cyclic adenylate monophosphate (cAMP), which are involved in inter and intracellular signaling.[7]

Intranasal insulin is a viable treatment opportunity and could be employed to improve the quality of life of patients who persist with chronic olfactory disturbances. The hypothesis supported in this work

is that insulin, in addition to its anabolic and hypoglycemic function, plays a role as a GF inducer. This particularity of the hormone could reverse or reduce the damage to the olfactory epithelium resulting from SARS CoV 2 infection and the immune response against this agent.

Materials and methods

The sample size was calculated according to the success rate demonstrated in previous publications and using "Satulator", patient recruitment was performed through a Google Forms questionnaire. The study population consisted of patients who had contracted COVID-19 in the last 3 to 18 months and who persisted with anosmia, hyposmia or other type of olfactory[8] dysfunction, chronically and without improvement (so that improvement was attributable to the intervention).

Characteristics considered exclusion criteria are the following: age under 18 years and over 59 years, diagnosis of pathological conditions that could cause olfactory alterations, such as: nasal tumors, chronic sinusitis, drug-induced sinusitis, nasal polyposis, neurodegenerative disease, smoking, pregnancy, etc. Patients with a tendency to suffer from hypoglycemia and/ or a previous diagnosis of diabetes mellitus or anatomical malformations such as septal deviation, rhinosinusitis or choanal atresia were also excluded. For each selected participant (n=27), a baseline olfactory measurement was obtained with Sniffin Sticks® (12 items) and a capillary glucose measurement was obtained with Dextrostix® NF before and after the intervention, in order to guarantee patient safety and reduce the risk of hypoglycemia.

The initial and final measurements were divided into three subsections with a different number of correct answers for each section. The following are listed below:

1. **Threshold (T):** the participant must distinguish the smell of Sniffin Sticks® from 2 butanol solutions at different concentrations. This test has eight possible hits, so the formula for calculating the overall TDI is weighted for this number of items.
2. **Discrimination (D):** in this section the patient smells three Sniffin Sticks®. Two are identical and one is different. The participant must recognize the different one for it to be considered a correct answer. This procedure is repeated 12 times.
3. **Identification (I):** the patient smells each of the twelve Sniffin Sticks® and is also provided with twelve cards with four different odor options (A, B, C, D). The objective that the patient selects the option that corresponds to the odor. In case that the patient is not able to distinguish the scent or cannot choose only one option, the answer will be marked as incorrect. This test has 12 possible points.

In the threshold (T) and discrimination (D) measurements, participants performed the tests blindfolded.

Subsequently, Gelfoam® cottonoids soaked in 40 IU of NPH insulin were placed on the nasal roof (between the nasal septum and the middle meatus) of each nostril. These remained in place for 15 minutes and were later removed. This procedure was performed in three visits one week apart. During the fourth and last visit, olfaction was reevaluated using the methods previously described.

Results

The recruited population consisted of 18 women and 9 men, 66% and 33% respectively, and the average time to intervention was 9.4 months (95% CI 7.923-10.877). Since a previous diagnosis of COVID-19 disease was part of the inclusion criteria, either a positive SARS-CoV-2 antigen test or a positive RT-PCR were required before the first intervention, ten subjects or 37% of the population had a positive RT-PCR, ten subjects had a positive antigen test, and the remaining 7 (25.9%) had both. Sample characteristics are summarized in Table 1.

Table 1 Sample's characteristics

	Gender	Age	Test	Months until intervention	T1	D1	I1	TDI 1	T4	D4	I4	TDI 4
1	F	19	Both	6.3	8	7	3	0,61	8	11	4	0,75
2	F	20	PCR	7.7	8	7	8	0,75	8	11	10	0,92
3	M	21	PCR	13.6	8	12	7	0,86	8	12	9	0,92
4	M	22	PCR	3.9	8	9	10	0,86	8	10	11	0,92
5	M	22	Antigen	18.5	6	6	6	0,58	5	7	9	0,65
6	F	22	Antigen	9.3	7	10	2	0,63	7	11	4	0,71
7	M	23	Both	14.2	7	8	10	0,79	7	11	11	0,90
8	M	24	Both	9.9	6	10	7	0,72	8	12	9	0,92
9	F	25	Antigen	7.6	8	12	3	0,75	6	11	7	0,75
10	F	26	Antigen	3.3	7	8	8	0,74	8	10	10	0,89
11	M	27	Both	8.8	5	6	5	0,51	7	11	6	0,76
12	M	27	Antigen	6.5	6	8	4	0,58	8	11	5	0,78
13	F	32	Both	6.3	7	6	6	0,63	8	9	9	0,83
14	F	34	Antigen	6.4	8	11	9	0,89	7	11	10	0,88
15	F	35	Antigen	7.3	6	6	5	0,56	8	11	5	0,78
16	F	35	Both	2.9	6	8	7	0,67	8	11	7	0,83
17	F	36	Antigen	13.6	7	5	4	0,54	6	9	9	0,75
18	F	38	PCR	7.3	6	7	7	0,64	8	10	9	0,86
19	F	38	Antigen	7	3	8	6	0,51	8	12	10	0,94
20	F	43	PCR	9.7	5	10	8	0,71	8	11	10	0,92
21	F	46	Antigen	12.3	7	9	9	0,79	8	10	10	0,89

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Table Continued.....

	Gender	Age	Test	Months until intervention	T I	D I	I I	TDI I	T4	D4	I4	TDI 4
22	F	46	PCR	7.3	4	6	3	0,42	6	10	8	0,75
23	F	48	PCR	15.1	6	9	5	0,64	8	11	6	0,81
24	M	49	PCR	15	3	8	9	0,60	7	10	9	0,82
25	F	50	PCR	10.7	5	8	5	0,57	7	6	8	0,68
26	M	52	Both	10.8	7	8	7	0,71	8	12	10	0,94
27	F	60	PCR	12.5	6	8	9	0,72	7	8	9	0,76
Avg		34.1		9.4	6,30	8,15	6,37	0,67	7,41	10,33	8,3	0,83

After data collection and compilation, confidence intervals and student's paired t test were calculated. The analysis demonstrated that a high proportion of the participants (93% of the sample, 25/27 participants) showed an improvement, as measured by the TDI score. Regarding the overall assessment of the TDI score, the initial mean was 67% (95% CI 63-71), while the mean after the interventions increased to a value of 83% (95% CI 80-86, p<0.001) (Figure 1). The individual analysis of each item showed that each sub-division exhibited improvement, as demonstrated by the following findings: the initial mean of the threshold (T) was 6.3 (95% CI 5.77-7.02) and the final one was 7.4 (95% CI 7.04-7.75, p<0.05), recalling that the maximum score is 8. This is equivalent to an improvement from 80% to 92%. The initial mean for discrimination (D) was 8.1 (95% CI 7.46-8.84) and the final one was 10.3 (95% CI 9.76-11.03, p<0.005), which translates into an improvement from 68% to 86%. Finally, the identification test (I), had an initial mean of 6.3 (95% CI 5.506-7.234) and a final mean of 8.3 (95% CI 7.519-9.081, p<0.001), equivalent to a 54% to 70% change. The previous information is synthesized in Table 2.

Table 2 Overall and individual item analysis of the TDI score before and after the intervention

Initial T	**Final T**
6.30 (CI 95% 5.757,6.843)	7.41 (CI 95% 7.093,7.727) p <0.001
80% (CI 95% 72-85%)	92% (CI 95% 88-96%) p<0.001
Initial D	**Final D**
8.15 (CI 95% 7.46,8.84)	10.33 (CI 95% 9.776, 10.884) p<0.001
68% (CI 95% 62-73%)	86% (CI 95% 81-90%) p<0.001
Initial I	**Final I**
6.37 (CI 95% 5.506,7.234)	8.3 (CI 95% 7.519, 9.081) p<0.001
54% (CI 95% 45-60%)	70% (CI 95% 63-75%) p<0.001
Initial TDI	**Final TDI**
67% (CI 95% 63%-71%)	83% (CI 95% 80%-86%) p<0.001
Pre- intervention glucose(mg/dL)	**Post- intervention glucose (mg/dL)**
100.67	100.33

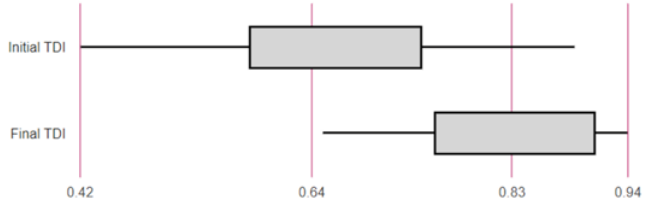

Figure 1 Mean after the interventions increased to a value of 83%.

Pre and post-intervention glucose measurements reported similar values. The mean pre-intervention glucose was 100.67mg/dL, and post-intervention 100.33mg/dL, and it is important to emphasize that no adverse events of any kind occurred.

Discussion

Multiple therapeutic options for anosmia have emerged throughout the pandemic, but the efficacy and safety of those treatments are not well established. For example, the usage of oral and intranasal corticosteroids has been proposed for treating the theoretical inflammatory component of postinfection anosmia. Nonetheless, glucocorticoids have not shown to be superior to other treatment modalities and are therefore not recommended as treatment. (Abdelrahman Ahmed Abdelalim, Rasheed Ali Rashid). Smell training performed with either specialized "kits" or essential oils, have shown to improve sensorial hyposmia and anosmia not only subjectively, but also demonstrated as an increased volume in the limbic system and thalamus in the brain. Eucalyptus, lemon, rose, and cloves are the most commonly used odors in smell training, the implementation of more scents has not shown to offer an advantage (Yu Zhang, Sachiko Koyama).

Regarding intranasal insulin, a similar methodology was used in Rezaeian's work, but some methodological and demographic differences are found. For instance, the population in our study persisted with smell alterations for a mean of nine months, in contrast to six months in Rezaeian's study. Furthermore, said study was conducted before the COVID-19 pandemic. The aforementioned study used the Connecticut Chemosensory Clinical Research Center score (which subdivides patients according to their level of olfactory dysfunction, with a maximum score of 7) and the butanol dilution olfactory threshold. The experimental group went from an initial mean score of 3.90 to a final 5.01, showing an improvement of 16%. Our study showed an improvement equivalent to 12%.

Mohamad explored the viability of different polymers that could dissolve and deliver insulin into the nasal cavity, and evaluated different odors before and after the use of the intranasal insulin. They reported an improvement in olfaction with a mean of 83% in the experimental group vs a 35% in the control. Our results showed a 92% improvement in threshold and 86% in discrimination. There are no reports on improvement of odor identification after intranasal insulin administration.

Typically, olfactory deficits are temporary, lasting from an average of seven to ten days to weeks or even months. The duration of the sensory defects is thought to be determined by the extent of affected epithelium (Rafal Butowt). The inclusion criteria for the study were based on this knowledge, selected patients presented with persistent olfactory dysfunction without improvement in order to ascertain the chronicity of the symptoms and the efficacy of the interventions; since the natural history of post-infectious smell disorders is prone to be self-limited and short-lived.

The present study has certain limitations. For instance, the high prevalence of COVID-19 cases at the time in which the study was performed made it impossible to include a control group. Because of the lack of a placebo group, this work ought to be considered a

"pilot study", and further experimental studies without this limitation could properly demonstrate the efficacy of intranasal insulin as a specific treatment for post COVID-19 olfactory dysfunction. On the other hand, not every patient had a prior nasal endoscopy performed, so the adequate colocation of the insulin soaked Gelfoam® was not completely guaranteed.

The systematic measurement of olfactory dysfunction, the implementation of evidence-based treatments and notifying the patients of the possible risks of olfactory alterations have been proposed strategies to take care of anosmic and hyposmic patients (Sanne Boesveldt). The TDI score intends to assess olfaction as a whole, achieving more accurate results in the initial assessment and a more precise quantification of improvement on follow-up visits.

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Conflict of interest

There aren't any conflict of interests.

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