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Research Article

Role of intranasal Insulin in management of post COVID-19 olfactory dysfunction

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Abstract

Background: Olfactory dysfunction associated with COVID-19 is a significant issue that impairs quality of life. We address the potential of intranasal insulin as a therapeutic agent considering the limitation of viable medicines for this issue. **Aim of the study:** Assessment of intranasal insulin's therapeutic impact on post-COVID-19 Olfactory Dysfunction. **Methodology:** This study included 40 patients suffering from post-COVID-19 olfactory dysfunction at the ENT outpatient clinic of Minia University Hospital. They were divided into two groups: group 1 included 20 patients who received intranasal insulin fast-dissolving films while group 2 included 20 patients who received plain intranasal films (placebo). **Results:** The mean score of the Butanol threshold test for the intervention group was 3.4 while for the placebo group was 2.4 after the fourth session and the mean scores reached 5.7 for the intervention group and 2.6 for the placebo group after the eighth session reflecting a statistically significant improvement in olfactory function for the intervention group than the placebo group. **Conclusion:** Finally, our results showed that administering intranasal insulin to patients greatly shortened their anosmia duration. Notably, a highly statistically significant rise in Butanol Threshold test scores compared to pre-treatment scores highlights the potential advantages of intranasal insulin in treating olfactory impairment in patients who have recovered from COVID-19.

Keywords: Intranasal insulin, post-COVID-19, olfactory dysfunction, intranasal, fast-dissolving film

Introduction

Olfactory dysfunction, which includes partial or total loss of smell, is a prevalent disorder that can have a serious negative effect on a person's quality of life and is recently challenging to treat.

A person's ability to smell is influenced by a number of variables, including physical activity, heredity, diet, smoking, head trauma, medical interventions, and viral infection. [(1)]

Between 3% and 20% of people suffer from hyposmia or anosmia, which is an impairment of the sense of smell. Impaired olfaction has a substantial negative effect on quality of life, impairing social interactions, personal hygiene, and the enjoyment of food. It also increases the severity of depression symptoms and impairs general physical and mental health. [(2)].

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection that causes coronavirus disease 2019 (COVID-19) is a multiorgan manifestation that was initially identified in Wuhan, China, in 2019. While most SARS-CoV-2 infections result in a mild illness, about 5%

of cases go on to have multiorgan failure and disseminated viral pneumonia [3]
Numerous patients have developed anosmia during the COVID-19 pandemic. It is regarded as one of the distinctive signs of an infection with COVID-19[4]. Based on a meta-analysis, it has been approximated that 52.73% of COVID-19 patients have olfactory impairment. [5].

High concentrations of the angiotensin-converting enzyme 2 receptors are seen in nasal epithelial cells, which is necessary for SARS-CoV-2 entrance. Because of this property, coronaviruses can cause post-infectious olfactory impairment [6].

Numerous drugs have been suggested as possible anosmia therapies. Although olfactory impairment has historically been suggested to be treated safely and effectively with olfactory training, no drugs are currently approved to treat this condition. The effects of corticosteroids on COVID-19-related gustatory and olfactory dysfunctions have been thoroughly researched. However, using them could induce additional risks and could slow down the body's ability to get rid of the virus. [7]

Insulin was suggested as a local therapy for post-viral anosmia in recently revised publications. Rezaeian A suggested insulin as the treatment of concern in 2018. [8].

It has been discovered that growth factor hormone and insulin co-work directly to improve smell perception. Cyclic adenylate monophosphate (cAMP) and cyclic guanylate monophosphate (cGMP), two growth factors (GFs), are elevated because of insulin's actions on the nitric oxide cycle as a phosphodiesterase enzyme inhibitor. Growth factors (GFs) have been shown in numerous studies to stimulate the olfactory epithelium; as a result, a decrease in GF levels may cause olfactory sensory deprivation. [9]

The goal of the April 2021 study was to develop the only dosage form that could facilitate and modify doses for safe intranasal delivery of insulin using intranasal films. They are incredibly thin, readily positioned on the mucosal tissue, and adhere to the application site with the aid of rapid hydration. Once the film has dissolved, the medication substance is released for absorption into the targeted region. [10].

Patients and methods

This study was conducted at the ENT department outpatient clinic, Minia University Hospital from June 2023 to December 2023 to investigate the role of intranasal insulin in the management of post-COVID-19 olfactory dysfunction

Sampling criteria:

In this study, 40 patients from ENT outpatient clinic at Minia University Hospital suffering from post-COVID-19 olfactory dysfunction were divided into two groups: group 1 of 20 patients (Intervention group) who received intranasal insulin fast-dissolving films and group 2 of 20 patients who received plane intranasal films (placebo). The 40 patients were examined and analyzed.

Participants

participants of this research were recruited from patients with olfactory dysfunction following COVID-19 infection at the ENT outpatient clinic, at Minia University Hospital.
Patients of both groups received fast-dissolving films two times per week for 4 weeks with a total number of 8 sessions.

Inclusion criteria:

Age: Adults 18 years or older patients.
Sex: both sexes were included randomly.
History of COVID-19 infection confirmed by PCR test or recovery confirmed also by negative PCR suffering from sudden onset olfactory dysfunction. Patients were randomly selected for the study.

Exclusion criteria:

1- patients with an acute attack of nasal allergy.
2- patients suffering from chronic rhinosinusitis.
3- patients with nasal polyposis.
4- History of nasal surgery, severe head trauma or any medical disorder altering smell sensation.

Methodology:

contributors in this study were assessed by:

1- Detailed history taking including age, sex and duration of anosmia.

2- General medical examination to exclude any general medical conditions that may alter the sense of smell as Parkinson's disease.

3- ENT local examination by nasal endoscope (4- mm, zero and thirty-degree nasal endoscope, KARL STORZ, Germany) to exclude local nasal pathologies that may affect the sense of smell as severe septal deviations or nasal polyps.

4- Butanol threshold test: This test is used to evaluate the baseline olfactory threshold before intervention and after every session to monitor the impact of the intervention on the olfactory outcome of the patient.

5- Butanol threshold test

This method was used to compute the olfactory threshold or the lowest odour concentration at which a person can consistently perceive an odour. The olfactory threshold was ascertained using bottles labelled 0 to 9 that contained different concentrations of butanol alcohol.

6- The highest concentration (4%) bottle (0) was diluted with deionized water at different ratios, starting with 1:1 and going up to 1:2, 1:3, and 1:4 to create the remaining butanol concentrations. Bottle 9 had the lowest concentration of butanol as a result. The lower the olfactory function, the higher the concentration at which the patient could smell**.** [10]

7- Olfactory discrimination test:

In the discriminatory test, nine triplets of typical odorants like vanilla, cinnamon and coffee and cumin with the same concentrations were used. Each triplet is made up of one vial containing a different odor and two vials containing the same odor. As the Patients were asked to distinguish one scent from the other two. regarding the nine triplets, the total number of correct answers was noted as the olfactory discrimination score [11]

Materials:

SEDICO (Cairo, Egypt) supplied Insulin H Mix® (100 I.U./ml); Research Lab Fine Chem Industries (Mumbai, India) supplied hydroxypropyl methyl cellulose (HPMC); and Fischer Scientific LTD (Loughborough, UK) provided polyvinyl alcohol (PVA, m. wt. about 25,000). The remaining substances and reagents were all analytical grades.

Methods:

1- Insulin fast dissolving intranasal film preparation:

Various insulin film formulations were made using various amounts of PVA and HPMC in addition to 100 IU of insulin. [10].

Figure (1) A digital camera photo showing the even surface of the prepared fast dissolving intranasal insulin film. [10].

Disintegration time in vitro (hydration test)

A documented approach was used to determine the disintegration behavior of the produced films [12, 13]. For the investigation, simulated nasal fluid with a pH of 6.5, 7.45 mg/mL NaCl, 0.32 mg/mL $CaCl_2 \cdot 2H_2O$, and 1.29 mg/mL KCl was generated. A petri dish was filled with 10 ml of the simulated fluid, and the film was then added. The disintegration time was defined as the amount of time needed for the films to lose their solid-state affording gel characteristics [14]. It was found that the invitro disintegration time for insulin from the fast-dissolving film when placed in a simulated nasal fluid is about 6 to 7 minutes on average. [10]

Clinical assessment:

The study included forty post-COVID olfactory-deaf patients, ranging in age from 17 to 73. An ENT specialist performed an endoscopic examination of the nasal cavity on the patients to confirm the cause of their anosmia. The participants who took part in the study did not have any acute sinonasal illnesses or medications that are known to impair sensory perception. Individuals with polyposis nasi, acute allergic rhinitis, persistent sinusitis, or any other serious deviation of the nasal septum were not included in the study. Similarly, those with a history of serious head trauma, nasal surgery (such as septoplasty or polypectomy), diabetes, deep anesthesia, or any other illness that would impair smell were excluded.

Additionally excluded were patients with morphological abnormalities such adenoid hypertrophy, septal deviation, acute or chronic rhinosinusitis, or choanal atresia. The inclusion and exclusion criteria were followed in the process of enrolling patients. The study was conducted at Minia University Hospital's ENT department and outpatient clinic between June 2023 and December 2023. Prior to the commencement of the trial, each participant provided an informed consent.

The research employed a randomized parallel design that was single-blinded. Two groups were created at random from the patients. 20 patients, 9 males and 11 females, with an average age of 34 ± 13.5 years, made up Group 1, the intervention group. 100 units of insulin fast-dissolving film were administered to the patients in this group. Twenty patients, eight males and twelve females, averaging 29.7 ± 6.3 years old, made-up Group 2, the placebo group. The corresponding insulin-free fast-dissolving film was applied to this group. It is noteworthy to remark that participants who discontinued the study, required corticosteroids, skipped follow-up, or had serious side effects were excluded. Four patients who were in the placebo group did not receive follow-up care during the research. They were therefore omitted from the research.

An ENT specialist carried out the therapy procedures. A minimum of one hour before the intervention, the patients were instructed to have their last meal. Through a 30-degree nasal endoscopy, the fast-dissolving insulin films were placed into the olfactory cleft for patients in group 1. Group 2 patients received similar treatment, with fast-dissolving insulin-free films (plain). For eight weeks, the treatment was administered twice a week. According to Edwin Thanarajah et al., (2019) the patients were examined using two validated tests for evaluating smell disorders before and 30 minutes after the treatment. According to Veyseller et al., (2014), these tests consist of the olfactory discrimination test and Sniffin's or butanol threshold test. [11,15]

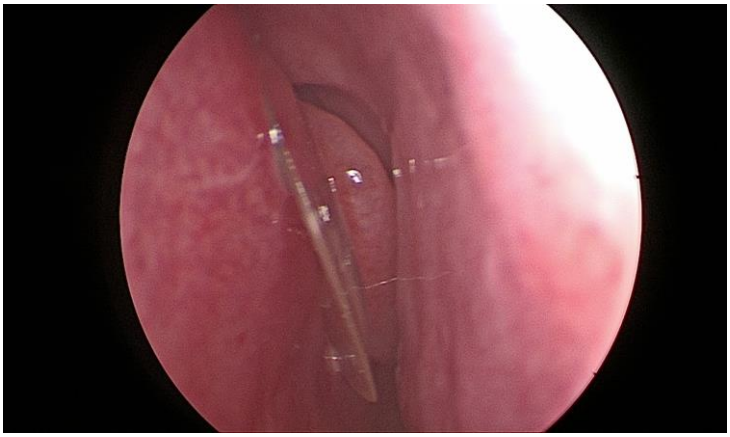

Figure (2): local application of the insulin fast dissolving film into the olfactory cleft.

Results

Table (1): Distribution of the studied cases according to age and sex

Butanol threshold test	intervention (N=20)	Control (N=20)	p value
Age	34.1 ± 13.5 (17 - 73)	29.7 ± 6.3 (19 – 40)	0.480
Sex N (%): • **Male** • **Female**	45 (45%) 55 (55%)	40(40%) 60 (60%)	0.749

Table 1 shows a comparison between both the study and the control groups as regards two demographic parameters: Age and sex.

The results revealed no statistically significant difference between both groups as regards age of the patients where P value was 0.4

Also, there was no statistically significant difference between both groups as regards sex where P value was 0.7

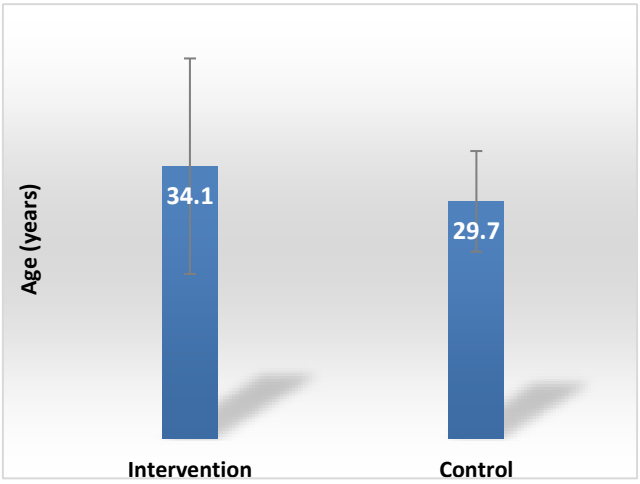

Figure (3): shows the mean age for both groups being 34.1 in the intervention group and 29.7 in the control group.

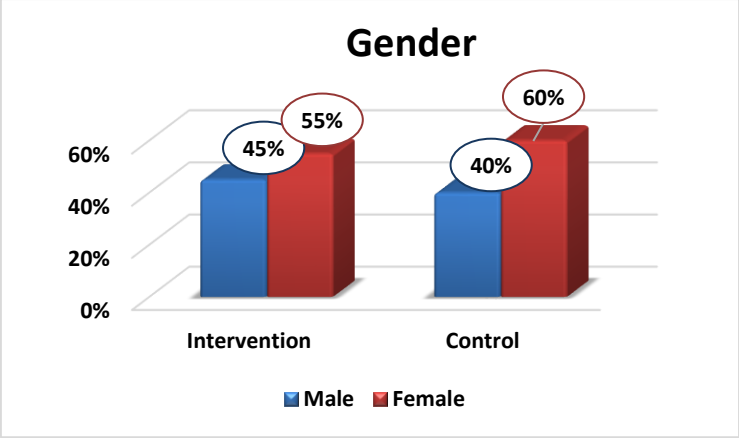

Figure (4): shows sex distribution between the two groups. In the intervention group males were 45% and females were 55% while in the control group males were 40% and females were 60%.

Table (2): Results of Butanol threshold test in both groups during the 8 sessions.

Butanol threshold test	intervention (N=20)	Control (N=20)	p value
butanol threshold test 1 (baseline)	0 (0 – 0)	0.1±0.2 (0-1)	0.234
butanol threshold test 2	2.2 ± 1.9# (0– 4)	1.25 ± 0.4# (1 – 2)	**0.034***
butanol threshold test 3	2.8 ± 0.5 (2 – 3)	2.2±1.9# (0-4)	**0.037***
butanol threshold test 4	3.45 ± 1.3 (2 – 5)	2.4±1.9# (0-4)	**0.048***
butanol threshold test 5	4.1 ± 1.6 (2 – 6)	2.8±2.3# (0-6)	**0.044***
butanol threshold test 6	4.85 ± 1.8 (2 – 7)	2.4±2.4# (0-6)	**<0.001***
butanol threshold test 7	5.5 ± 2.3 (3 – 8)	2.6±2.2# (0-6)	**<0.001***
butanol threshold test 8	5.7 ± 2.25 (3 – 8)	2.6±2.5# (0-6)	**<0.001***
p value (overtime)	**<0.001***	0.861	

The results of Butanol threshold test in both study and control groups showed no significant difference between both groups at the start of our intervention (P value = 0.2) but after serial sessions of our intervention the difference between both groups regarding the olfactory state of the patients measured by Butanol threshold test became significant and P value reached less than 0.001.

Table (3): Results of Discrimination (Identification) test in both groups during the 8 sessions

Identification test	Intervention (N=20)	Control (N=20)	p value (between groups)
Identification test 1 (baseline)	0 (0 – 0)	0.1±0.3 (0-1)	0.144
Identification test 2	0.75 ± 0.4 (0 – 2)	0.5±0.5# (0-1)	0.088
Identification test 3	1.1 ± 0.7 (0 – 2)	0.7±0.5# (0-1)	**0.044***
Identification test 4	1.85 ± 0.8 (1 – 3)	0.7±0.4# (0-1)	**<0.001***
Identification test 5	2.1 ± 0.8 (1 – 3)	1.1±0.7# (0-2)	**<0.001***
Identification test 6	2.15 ± 0.8 (1 – 3)	1.1±0.6# (0-2)	**<0.001***
Identification test 7	2.25 ± 0.9 (1 – 3)	0.8±0.9# (0-2)	**<0.001***
Identification test 8	2.3 ± 0.8 (1 – 3)	0.7±0.8# (0-2)	**<0.001***
p-value (overtime)	**<0.001***	**<0.001***	

The results of the discrimination test in both study and control groups showed no significant difference between both groups at the start of our intervention (P value = 0.1) but after serial sessions of our intervention the difference between both groups regarding the olfactory state of the patients measured by discrimination test became significant and P value reached less than 0.001.

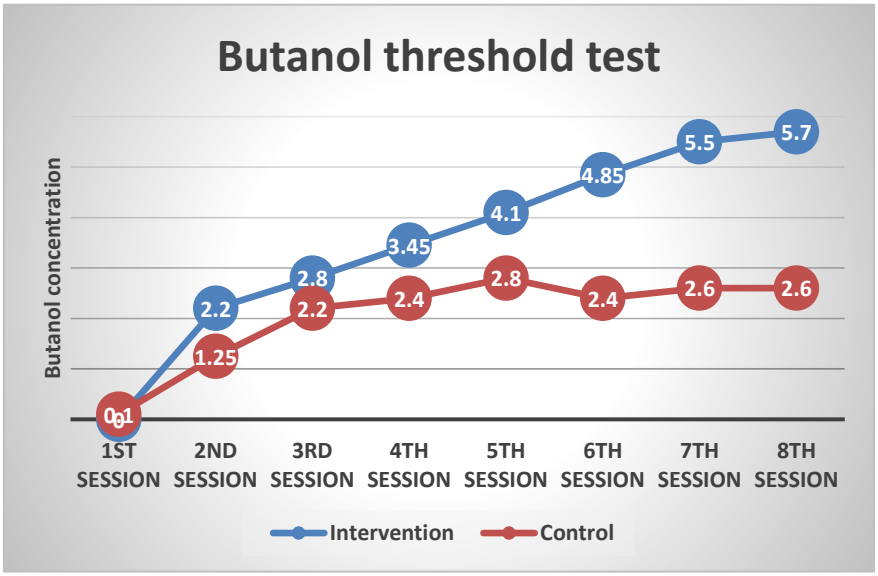

Figure (5) shows mean scores of butanol threshold test for both the intervention and control groups.

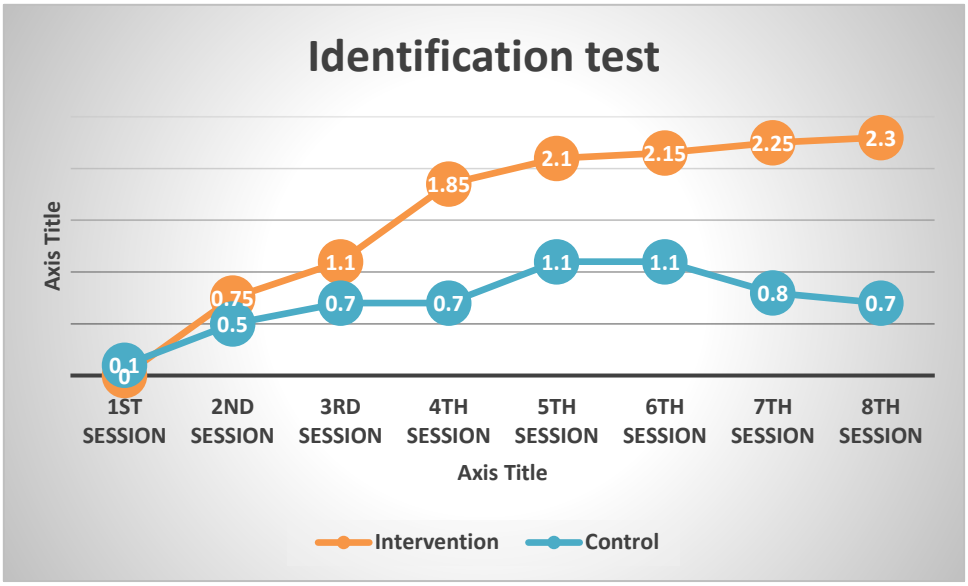

Figure (6) shows the mean scores of the identification test for both the intervention and control groups.

Discussion

According to research on the frequency of olfactory loss in populations, 22% of the population between the ages of 25 and 75 are affected according to Vennemann et al., (2008). 19% of individuals are over 20 and 24% of adults are over 53 years old, according to Brämerson et al., (2004) and Murphy et al., (2002). The majority of males who suffer from this illness are older. Upper respiratory tract infections, which are frequently brought on by inflammatory disorders of the nose or paranasal sinuses (53%), respiratory dysfunction (19%), or postviral illnesses (11%), are the most common causes of smell loss or dysfunction.[16,17,18,19]

The coronavirus disease 2019 (COVID-19), an emerging viral disease, is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). fever or chills, coughing, shortness of breath or breathing difficulties, tiredness, headaches, body pains, sudden loss of taste or smell, unpleasant taste or smell, diarrhea, nausea, vomiting, runny nose, and sore throat are some of the symptoms of the condition [20]

Globally, as of July 2, 2021, there have been over 182 million COVID-19 cases and over 3.95 million deaths documented [20].

Although the exact pathophysiology of post-infectious anosmia is unknown, approximately 62% of patients who tested positive for COVID-19 also had anosmia.[21].

95% of patients experience spontaneous remission of post-COVID olfactory dysfunction (PCOD) within two weeks, with a mean recovery period of nine days. [22]. On the other hand, in 75% of individuals with persistent COVID-19 symptoms, persistent PCOD is a common symptom. Longer duration of COVID-19 disease, diabetes mellitus, and advanced age are risk factors for chronic PCOD [23]

Several studies have suggested that a decrease in growth factor (GF) release could be the cause of hyposmia since GFs activate the olfactory epithelium. In a recent study, the conditions that can cause GF-level drops together with hyposmia were described in detail. These illnesses include, but are not limited to, deficits in trace elements and vitamins, liver problems, diabetes mellitus, metabolic syndrome, and otolaryngologic and neurodegenerative issues. Thus, one potential treatment for hyposmia could be to increase GF secretion. Furthermore,

some research has indicated that insulin increases GF levels. [8].

Numerous studies have shown that insulin acts as a PDE enzyme inhibitor thus it affects the nitric oxide cycle, which in turn can raise levels of growth factors including cyclic guanylate monophosphate (cGMP) and cyclic adenylate monophosphate (cAMP).[24].

This provides strong evidence in favor of the notion that anosmic patients' better olfactory abilities may be facilitated by improved CNS insulin signalling with intranasal insulin [25].

Schöpf et al., (2015) looked at the effects of administering a single intranasal insulin dose to anosmic patients in a clinical pilot research. Each participant participated in four testing sessions that formed the study.

Following an ENT endoscopic examination and the exclusion of individuals with nasal polyps, severe septal deviations, allergic rhinitis, chronic sinusitis, and a history of head trauma, 10 anosmic patients were added to the study. [25]

To calculate the threshold, discrimination, and identification (TDI) scores, the first session comprised ENT screening and the first olfactory performance session using the Sniffin' Sticks test.

During the second session, each nostril got two puffs of 0.4 ml, or 40 IU, of liquid insulin. Each puff included 0.1 ml of insulin, and after 30 minutes which is the amount of time said to take for insulin to reach its peak concentration in the cerebrospinal fluid, olfactory tests were conducted.

After a year, or a mean of 55 weeks, there was a third olfactory testing session. A week later, there was a fourth session, in which olfactory testing was conducted after two placebo puffs of saline were placed in each nostril.

The findings demonstrated that 60% of patients exhibited improved olfactory sensitivity (decreased threshold) (mean difference = 1) and marginal improvement of discrimination scores (mean = 0.7) when comparing olfactory outcomes following intranasal insulin application in the second session to baseline olfactory outcomes in the first testing session.

The results of our study demonstrated a gradual improvement in the olfactory threshold through the 8 sessions of intranasal insulin application, with the mean reaching 3.4 after the fourth session and 5.7 after the eighth session matching with the results of the previous study regarding improvement of the olfactory threshold after intranasal insulin.

A prospective, double-blinded, randomized controlled experiment was carried out by Rezaeian in 2018 to assess the effectiveness of intranasal insulin in helping hyposmic patients regain their ability to smell. 38 participants joined this study between 2016 and 2017. [8]

Patients between the ages of 18 and 70 who had hyposmic symptoms with a duration longer than six months were included in the study.

Patients were randomized into two groups: (1) the intervention group (n=19), receiving insulin treatment; and (2) the placebo group (n=19), receiving normal saline treatment.

The intervention group received 40 units of neutral protamine Hagedorn insulin by endoscopy. The insulin was placed between the middle turbinate and the nasal septum, impregnated on gel foam, while normal saline was given to the placebo group in place of insulin.

However, in our investigation, we employed Insulin H Mix® (100 I.U./ml) administered endoscopically in the olfactory cleft using a fast-dissolving film. The age, sex, and length of anosmia did not change significantly between the two study groups, according to the results. Following a 4-month follow-up, the intervention group's Connecticut chemosensory clinical research center (CCCRC) score was

considerably higher (P =0.01) than that of the placebo group.
The paired t-test showed a significant difference (P value less than 0.0001) in the intervention group's post-treatment CCCRC score.

However, no such significant change in the CCCRC score was observed in the placebo group (P = 0.26).

This study is similar to ours in that it uses the Butanol threshold test as an objective way to measure the patients' olfactory states before and after intervention. It also has similar patient mean ages of approximately 35 years and intervention durations of twice weekly for four weeks.

Our research mimics that of Mohamad et al., (2021) in which participants were drawn from two groups of twenty patients each in a randomized clinical trial. Intranasal insulin films were administered to the intervention group, whilst plain films were given as a placebo to the control group. [(10)],

The findings of our investigation aligned with those of Mohamad et al. (2021) who discovered no significant changes between the two groups before the intervention in terms of olfactory detection scores as determined by the butanol threshold test. Following treatment, the two groups' average odour detection scores were compared, and it was found that the intervention group's findings were significantly higher than those of the placebo group[(10)].

Regarding the olfactory discrimination test, P value = 1.3 indicates that there was no statistically significant difference found in olfactory discrimination values before intervention between the two study groups. Following the intervention, the average olfactory discrimination values of the intervention group were significantly higher than those of the placebo group (P = 0.0454).

Before and after the intervention, the average olfactory discrimination values in each group were compared. The outcomes demonstrated that, after treatment, these values significantly increased in the intervention group (P = 0.0032), whereas there were no significant differences observed in the placebo group (P = 0.0681).

From January to May 2022, Daniel et al., 2024 performed a prospective investigation on 27 post-COVID anosmic patients.

One of the inclusion criteria was a prior diagnosis of COVID-19, which was defined as a positive SARS-CoV-2 antigen test or a positive RT-PCR before the first intervention. [(26)]

The Sniffin Sticks test was used for olfactory evaluation before and after intervention. Over the course of three sessions with one week between each session and the next one, gelfoam cottonoids soaked with 40 IU of NPH insulin were placed for 15 minutes to the nasal roof of each nostril. Findings indicated that 93% of the group made progress. By the conclusion, the average TDI score had risen to 83% ($p<0.01$).

A randomized clinical trial was conducted by Mohamad et al., in 2022 to assess the impact of insulin fast-dissolving nasal films on enhancing health-related quality of life (HRQOL). The study comprised 40 post-viral anosmic patients who were split into two groups: an intervention group that received insulin-containing fast-dissolving films, and a control group that received intranasal placebo films. Three times a week, one intranasal film is inserted into each nostril. The quantitative performance of scent was investigated using the Sniffin' Sticks test, as previously mentioned. Following four weeks of therapy, the physical, mental, and social health quality of life of the intervention group was significantly (p-value <0.0001) higher than that of the control group. **(9)**

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Conflict-of-interest statement: Hereby, the authors certify that they have no conflicting interests.

Ethical approval: A local faculty of medicine research ethics committee (FMREC) No: 12-183-2021 provided ethical approval. Following an assurance of confidentiality for their information, every patient agreed for his data to be retrieved for research purposes in line with the committee's defined protocols. Consequently, there is no risk to the patient's safety or health resulting from the study.

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