Original Article

American Journal of Rhinology & Allergy
2025, Vol. 39(3) 237–244

DOI: 10.1177/19458924251322058
journals.sagepub.com/home/ajr
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Therapeutic Potential of Chitosan Nasal Gel in Addressing Olfactory Dysfunction: A Clinical Trial and Mechanistic Study

Majed A. Algarni, PhD[1], Mohamed H. Abdelazim, MD[2], Fahad T. Alsulami, PhD[1], Abdulaziz Ibrahim Alzarea, PhD[3], Adnan Alharbi, PhD[4], Abdullah H. Altemani, MD[5], Abdullah S. Alshammari, Pharm.D[4], Faisal Alsenani, PhD[6], and Ahmed H. Abdelazim, PhD[7]

Abstract

Background: Olfactory dysfunction significantly impacts daily life, affecting safety, appetite, and sensory enjoyment. Olfactory receptor neurons (ORNs) are essential for odor detection, but environmental exposure can lead to dysfunction. Regeneration of these neurons is crucial for maintaining olfactory function, and elevated calcium levels in nasal mucus are linked to this dysfunction.

Objective: The study evaluated chitosan nasal gel for persistent olfactory dysfunction lasting over 6 months, focusing on ORNs regeneration and reduced calcium levels in nasal mucus.

Methods: A randomized, double-blind trial included 215 participants with persistent olfactory dysfunction lasting over 6 months. Participants were divided into two groups: 116 received nasal chitosan gel, and 99 received a control sodium chloride gel. Over 3 months, 11 participants in the chitosan group and 9 in the control group were lost to follow-up. Olfactory function was assessed with the Sniffin' Sticks test, and calcium levels were measured before and after treatment.

Results: Patients treated with chitosan nasal gel showed an increased composite threshold, discrimination, identification (TDI) score, indicating improved olfactory function. Discrimination and identification scores improved, while threshold scores showed no significant change. Notably, while the total TDI score improved by 4.55 points, it did not reach the threshold for clinical significance (5.5 points). Furthermore, chitosan nasal gel significantly reduced calcium levels in nasal secretions compared to the control group. No improvement was observed in the placebo group, likely due to the strict inclusion criteria targeting individuals with treatment-resistant olfactory dysfunction persisting over 6 months.

Conclusion: This small-scale pilot study highlights the potential of chitosan nasal gel to improve specific domains of olfactory dysfunction and reduce nasal calcium levels. However, further studies with larger sample sizes, diverse populations, and longer follow-up periods are required to confirm these preliminary findings.

Keywords

olfactory function, chitosan, Sniffin' Sticks, olfactory dysfunction, randomized trial, odor, regeneration, calcium, nasal gel, paper sensor

[1]Department of Clinical Pharmacy, College of Pharmacy, Taif University, Taif, Saudi Arabia
[2]Department of Otolaryngology, Faculty of Medicine, Al-Azhar University, Damietta, Egypt
[3]Clinical Pharmacy Department, College of Pharmacy, Jouf University, Sakaka, Saudi Arabia
[4]Pharmaceutical Practices Department, College of Pharmacy, Umm Al-Qura University, Makkah, Saudi Arabia
[5]Department of Family and Community Medicine, Faculty of Medicine, University of Tabuk, Tabuk, Saudi Arabia
[6]Department of Pharmaceutical Sciences, College of Pharmacy, Umm Al-Qura University, Makkah, Saudi Arabia
[7]Pharmaceutical Analytical Chemistry Department, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt

Corresponding Author:
Ahmed H. Abdelazim, Pharmaceutical Analytical Chemistry Department, Faculty of Pharmacy, Al-Azhar University, 11751, Cairo, Egypt.
Email: ahmed.hussienabdelazim@hotmail.com

Introduction

The olfactory process plays a crucial role in human daily life. Olfactory dysfunction not only impairs the ability to detect environmental hazards but also affects the quality of life by diminishing appetite, and the appreciation of scents and sexual function.[1–3] Olfactory receptor neurons (ORNs) in the neuroepithelium of the olfactory cleft detect odors by binding odor molecules, triggering neural signals to the brain for odor perception and identification.[4–6] Due to their direct exposure to the external environment, ORNs may degrade when exposed to pathogens or toxins, potentially leading to alterations in olfactory bulb volume. The olfactory system has a regenerative capacity, with the neuroepithelium generating new ORNs. Failure in this process leads to olfactory dysfunction, while specific signaling pathways are known to regulate regeneration, though their mechanisms remain partially understood.[7,8] Additionally, the calcium elevation in nasal mucus can desensitize ORNs, while decreased levels can enhance sensitivity and overall olfactory function. Several reports have highlighted that patients with olfactory dysfunction often have increased calcium levels in their nasal mucus.[9–11]

Chitosan is a cationic polysaccharide molecule that has common applications in the pharmaceutical and medical fields, including biocompatibility and biodegradability.[12] Chitosan can mediate the differentiation of ORNs, increase the thickness of the olfactory epithelium, and offer regenerative potential impact.[13,14] Furthermore, it possesses a unique chelating ability for various metal ions, including calcium,[15] the elevation of which has been reported to exacerbate olfactory dysfunction.

The primary objective of this research is to investigate the therapeutic potential of chitosan nasal gel in addressing olfactory dysfunction, a condition that significantly impacts daily life. Chitosan's regenerative properties and its ability to reduce elevated calcium have been linked to improvements in olfactory function. By assessing the effects of chitosan nasal gel on olfactory performance, this study aims to contribute to the development of effective treatments for olfactory dysfunction.

Methods

Study Design and Sample Size Determination

A prospective, randomized, double-blind clinical trial was conducted from January 2023 to February 2024. The sample size was determined based on practical considerations, as no preliminary data or information regarding effect size was available. Following the specified selection criteria, a total of 238 participants were screened, resulting in the enrollment of 215 patients with 215 participants with persistent olfactory dysfunction lasting longer than 6 months. Participants were divided into two groups: one group received nasal chitosan gel (n = 116), while the other group received a sodium chloride gel (n = 99). Follow-up assessments were performed over a 3-month treatment period, during which 11 participants from the chitosan gel group and 9 from the control group were lost to follow-up. Figure 1 illustrates the study design and the procedure for participant inclusion.

Ethical Considerations

The study adhered to the ethical principles of the Declaration of Helsinki, with approval from the institutional review board. All participants provided written informed consent before inclusion.

Inclusion and Exclusion Criteria

The following inclusion criteria were applied: Adults must be 18 years of age or older, exhibit olfactory dysfunction for longer than 6 months, and have a threshold, discrimination, and identification score (TDI score) of less than 16, which is exclusively indicative of anosmia, on Sniffin' Sticks.

Furthermore, the following participants were excluded from this study: (1) Patients with congenital, surgical, or trauma-related olfactory impairment; (2) people who have had nasal polyps before, who have had anterior skull base or Sino nasal surgery in the past, who have neurodegenerative disorders or any other sort of arrhythmia in the past; and (3) people who are using active drugs to address olfactory dysfunction; and (4) women who were expecting or breastfeeding.

Entry into the Study

An assigned member explained the study's goals, benefits, and risks to participants before they voluntarily signed informed consent forms. Treatment began after consent was obtained.

Randomization Process

A computer-generated randomization list that was created and securely maintained by an independent study chemist was used to randomly allocate participants to study arms. All participants and study team members were unaware of their randomization assignment, with the exception of the study chemist who had access to this information. The study's researchers rigorously adhered to the specified strategy and the computer-generated list's randomization procedure.

Treatment Regimen Procedures

A total of 215 volunteers with 215 participants with persistent olfactory dysfunction lasting longer than 6 months

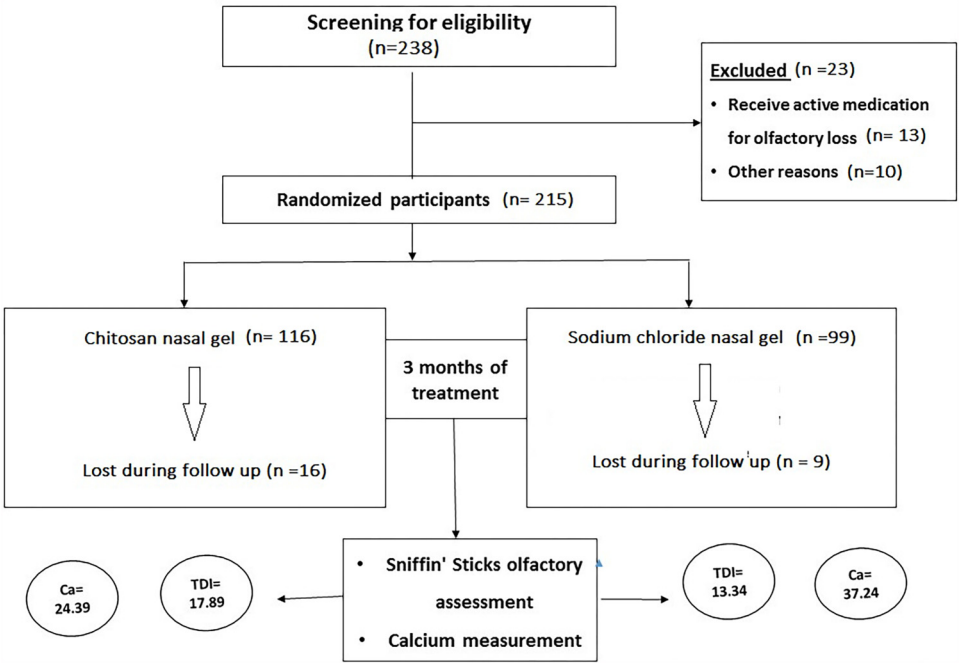

Figure 1. The consort diagram of the proposed study.

were included in the study and randomly assigned to two groups. One group, consisting of 116 individuals, received a nasal gel treatment containing 1% chitosan, prepared in a phosphate buffer solution with a pH of 7.5. In contrast, the second group, comprising 99 patients, received a 1% sodium chloride nasal gel, also prepared in a phosphate buffer solution with a pH of 7.5. Participants were instructed to apply the nasal gel, three times daily for 3 months, in the anterior nasal cavity while in a reclining position to facilitate diffusion toward the olfactory mucosa. The gel's bioadhesive properties were specifically designed to maximize mucosal contact and support gradual diffusion to more posterior regions, including the olfactory area. The formulations were dispensed in identical gel tubes, each labeled with a unique sealed code, which was unknown to the study team. The concealment of these codes was maintained unless disclosure was deemed necessary due to any adverse effects.

Study Outcomes

Olfactory Function Evaluation. The participants' olfactory abilities were assessed using the "Sniffin' Sticks" test after a structured medical history and examination of the ear, nose, and throat. This evaluation was conducted both before and following the full course of therapy. Three levels of evaluation were given for each individual's olfactory functions: threshold (T), discrimination (D), and identification (I). Additionally, composite scores (TDI) resulting from these assessments were used to determine the overall function and dysfunction of the olfactory system.[16–19] Anosmia was defined as having a TDI score below 16.5, normosmia as having a TDI score above 30.5, and hyposmia as having a score in the middle of these two ranges. When the threshold score rose by 2.5, the discrimination or identification score rose by 3 points, or the composite TDI score rose by 5.5, clinical improvement was taken into account.[20]

Determination of Calcium in the Nasal Secretions. Before and 3 months after the course of treatment, nasal secretions were taken right after sneezing. The secretions were collected using a tiny clamp made of stainless steel that measured roughly 10 mm by 5 mm by 2 mm and was placed on the septum in the space between the nostrils.[21] A 2 mL phosphate buffer solution with a pH of 7.5 was added to the secretions to dilute them, and 3 mL of acetonitrile was added to denature the protein content. The solutions were then evaporated until they were completely dry, and the leftovers were then diluted with phosphate buffer solution. A paper-based analytical sensor, modified with nanotechnology, was developed to measure calcium in nasal secretions, Figure 2. The sensor consists of two rectangular filter paper strips with orifices for a calcium-selective electrode and a reference electrode.

Data Integrity and Monitoring. This trial adhered to rigorous protocols to ensure data integrity and eliminate potential bias. Randomization and study gel preparation were managed by an independent chemist who was not involved in the assessment process. The study followed a double-blind design, ensuring that neither the participants nor the

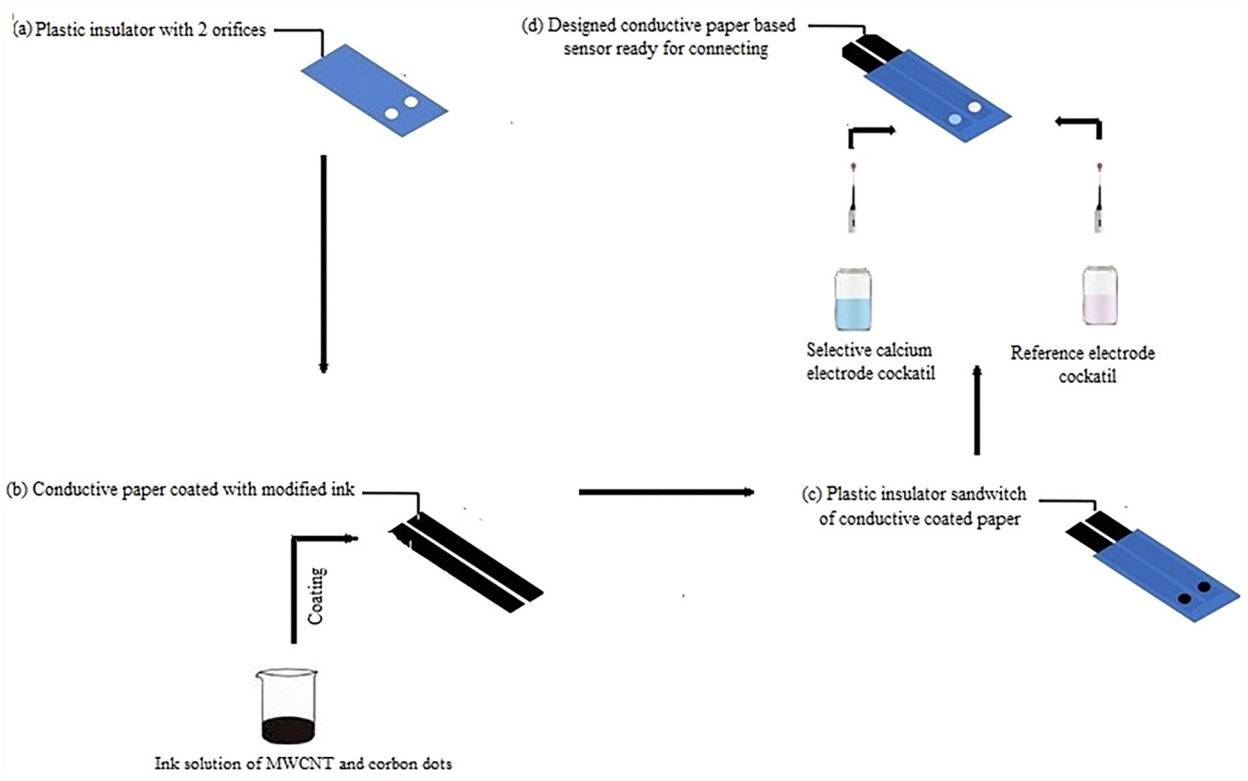

Figure 2. Schematic diagram for designing paper-based sensor for calcium determination.

Table 1. Patient Demographics.

Character	Chitosan	Sodium chloride	*P*
Sample size, n	116	99	
Age (years), mean ± SD	44.45 ± 8.58	45 ± 7.23	
Duration of disorder (at first visit in months: mean; SD)	6.4 ± 1.3	6.4 ± 1.2	
Sex (F; M), n	60:56	58:41	
Smokers (current/never), n	6/111	7/92	0.70
Comorbidities, n			
Diabetes	15	14	1.00
Asthma	4	3	1.00
Migraine	4	3	0.70
Hypertension	13	14	1.00
Current medication	B- blocker	Amlodipine	
	Metformin	Glipizide	
	Anti-histamine	Anti-histamine	
	Paracetamol	ACE inhibitor	
	ACE inhibitor	Paracetamol	

researchers conducting the assessments were aware of the group allocations. These measures, along with adherence to ethical research principles, affirm the reliability of the results.

Statistical Analysis. SPSS v23 statistical software was used to analyze the data statistically. Fisher's exact probability test was used to estimate the subject population size. When P 0.05, statistical significance was considered to exist. All statistical analyses were conducted by a biostatistician blinded to group allocation to ensure objectivity.

Results

The study included 215 participants (118 women and 97 men) diagnosed with persistent olfactory dysfunction

Table 2. Measured Olfactory Scores (Mean; SD) and Calcium Concentrations Pre- and Post-Treatment Regimen.

	Chitosan			Sodium chloride		
	Pre-treatment	Post-treatment	*P*	Pre-treatment	Post-treatment	*P*
Threshold (T)	1.93; 0.11	1.94 ± 0.10	0.319	1.93 ± 0.13	1.93 ± 0.15	0.341
Discrimination (D)	6.21; 0.23	7.51 ± 0.99	**$1.5x\ 10^{-7}$**	6.24 ± 0.23	6.27 ± 1.08	0.425
Identification (I)	5.20; 0.18	8.44 ± 0.24	**$1.1x\ 10^{-6}$**	5.20 ± 0.24	5.28 ± 1.01	0.392
Composite TDI	13.34; 0.32	17.89 ± 0.54	**$2.2x\ 10^{-9}$**	13.37 ± 0.32	13.48 ± 3.24	0.410
Calcium concentration, mM	37.99; 2.06	24.39; 4.52	**$5.2x\ 10^{-9}$**	37.28; 3.04	37.24; 2.64	0.521

Statistical significance is indicated by bold.

lasting more than 6 months. Participants were randomly divided into two equal groups. One group, consisting of 116 patients, received treatment with a 1% chitosan nasal gel, administered three times daily for 3 months. In contrast, the second group, comprising 99 patients, received a 1% sodium chloride nasal gel, also administered three times daily over the same period. The characteristics and demographic information of all participants are presented in Table 1. Analysis of the sample sizes indicated no significant differences between the two groups.

Table 2 presents the average olfactory scores before and after the specified treatment regimen. Figure 3 displays the recorded olfactory scores following the use of nasal sodium chloride gel and nasal chitosan gel. In general, a noticeable difference was observed in the change of TDI scores between patients who were administered nasal chitosan gel (4.55 points) in comparison to non-remarked change for those in the nasal sodium chloride gel group (0.11 points). However, it's worth mentioning that the increase of 4.55 points in the TDI score noted in patients who received nasal chitosan gel did not reach the level of clinical improvement typically considered significant, which is when the TDI score increases by 5.5 points.[20]

Figure 3 illustrates the alteration in threshold scores among all patients who utilized nasal sodium chloride gel and nasal chitosan gel. In both groups, there were no statistically meaningful distinctions or notable clinical improvements in the threshold scores. It is important to highlight that a clinical enhancement in the threshold was defined as an increase exceeding 2.5 points. Additionally, a discernible pattern towards enhanced alterations in discrimination and identification scores was noted in patients who received nasal chitosan gel, with gains of 1.3 and 3.24 points, respectively. In contrast, individuals treated with nasal sodium exhibited non-improvement in the discrimination and identification scores. These findings highlight the substantial improvements in scores among those who were administered nasal chitosan gel. It is noteworthy that the identification score in patients treated with nasal chitosan gel reached both clinical threshold and statistically significant typically associated with a 3-point increase in the identification score.

A paper-based analytical sensor was created and employed to assess calcium in nasal secretions both before and after the prescribed treatment. Figure 3 illustrates the changes in calcium in all patients who used nasal sodium chloride gel and nasal chitosan gel. The average calcium levels before and after the specified treatment are detailed in Table 3. The findings indicated a significant reduction in calcium among patients who were treated with nasal chitosan gel, as compared to those who received nasal sodium chloride gel.

An unpaired t-test compared outcomes between patients treated with chitosan nasal gel and sodium chloride gel, revealing statistically significant differences (low P-values). Chitosan gel was well tolerated, with no severe adverse effects reported.

Discussion

Although, there is no standard proposal treatment protocol for persistent olfactory dysfunction, the commonly used is intranasal corticosteroids and olfactory training.[22] This study is the first to examine the use of chitosan nasal gel for olfactory dysfunction persisting for more than 6 months. Chitosan may promote ORNs maturation, increase olfactory lining thickness, support regeneration, and modulate sensory perception by affecting signaling pathways. It also reduces elevated calcium levels through calcium binding.

Previous study investigated the use of intranasal chitosan in rats with induced anosmia. The researchers found that rats treated with chitosan showed a significant increase in the thickness of their olfactory epithelium compared to control groups.[23] In addition, chitosan films were shown to enhance the growth and differentiation of olfactory neuro spheres and promote the development of ORNs. Furthermore, it suggests that chitosan films could be a valuable substrate for culturing and differentiating ORNs, potentially offering therapeutic solutions for olfactory dysfunction.[14]

Based on "Sniffin' Sticks" test, chitosan nasal gel achieved meaningful change of discrimination and identification scores contributing to central impact of the pathophysiology of olfactory dysfunction. On the other hand, the

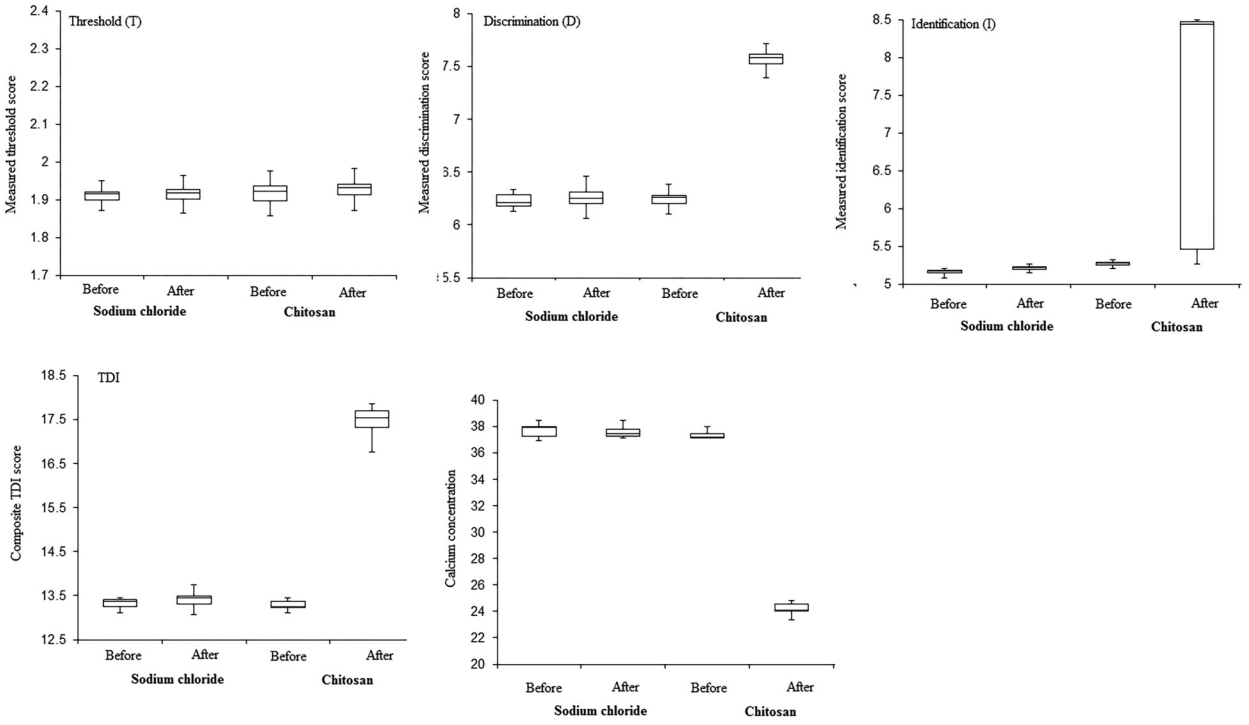

Figure 3. Graphical representation for the assessed olfactory scores and measured calcium levels for group received nasal sodium chloride gel and group received nasal chitosan gel.

Table 3. Un Paired t-statistical Test Comparing the Measured Olfactory Scores and Calcium Concentrations Scores Post Using the Treatment Regimen of the Two Groups.

	Threshold (T)	Discrimination (D)	Identification (I)	Composite TDI	Calcium concentration
t	1.24	1.41	**8.10**	**10.14**	**11.25**
df	25	25	25	25	25
P	0.420	0.399	**2.12×10^{-6}**	**1.81×10^{-9}**	**5.77×10^{-9}**

Statistical significance is indicated by bold.

threshold scores not improved as the threshold assessment reflects peripheral disease. Thus, the use of a composite "TDI" score provides precise diagnostic sensitivity.[16–19] While the observed improvement in TDI scores in the chitosan nasal gel group was significant, the total TDI score did not meet the threshold for clinical improvement (a 5.5-point increase). However, a notable improvement in smell identification was observed, indicating the targeted efficacy of the intervention in specific olfactory functions. These findings highlight the complexity of olfactory recovery, as different subdomains such as identification, discrimination, and threshold respond variably to treatment. Although the results may be considered preliminary, the significant improvement in smell identification provides valuable insights into the potential utility of chitosan nasal gel and underscores the need for further studies to validate these findings in larger cohorts.

Furthermore, the lack of a placebo effect in the control group is a rare finding in olfactory trials. This could be explained by the tight inclusion criteria, which targeted people with chronic olfactory impairment lasting more than 6 months and resistant to previous therapies. Even in the placebo group, these persons' ability to recover spontaneously may have been limited. Furthermore, the placebo treatment of 1% sodium chloride gel might not have had any significant physiological or placebo-enhancing effects compared to the 1% chitosan gel utilized in the intervention group. Future studies should consider a crossover design or extended follow-up periods to determine whether the control group exhibits similar changes over time. Such designs would provide further validation of the limited placebo effect observed in this study and offer additional insights into the long-term efficacy and durability of the intervention.

The paper-based analytical sensor used to assess calcium in the nasal secretion with remarked evidence for its decrease in patients received nasal chitosan gel which associated with the strong chelation ability of calcium.

A limitation of the proposed study is the lack of systematic documentation regarding the etiology of olfactory dysfunction. While the trial included participants with chronic anosmia, details such as whether their condition was post-viral (eg, post-COVID) or idiopathic were not collected. Future studies should stratify participants by etiology to better understand the specific contexts in which the treatment may be most effective. Although the results of this trial demonstrate significant promise, it is important to interpret them cautiously. In addition, the current study does not provide direct evidence that calcium chelation occurs specifically at the olfactory mucosa. Future studies using advanced imaging or localized sampling, larger sample sizes, diverse populations, and extended follow-up periods are needed to confirm these findings and investigate the mechanisms, long-term efficacy, and safety of chitosan nasal gel.

Conclusion

This study highlights the potential of chitosan nasal gel in improving specific aspects of olfactory dysfunction, particularly in smell identification, and in reducing calcium levels in nasal secretions. However, it should be noted that the improvement in the total TDI score did not meet the threshold for clinical significance, and no placebo effect was observed in the control group. These findings emphasize the exploratory nature of this study, which serves as a pilot investigation. Further research with larger sample sizes, diverse populations, stratification by the etiology of olfactory dysfunction, and longer follow-up periods is necessary to validate the proposed findings.

Acknowledgements

The authors extend their appreciation to Taif University, Saudi Arabia, for supporting this work through project number (TU-DSPP-2024-175).

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The Damietta Faculty of Medicine's Ethical Committee of Al Azhar University in Egypt granted the study approval (DFM-IRB00012367-23-07-007).

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Taif University, (grant number TU-DSPP-2024-175).

ORCID iDs

Majed A. Algarni https://orcid.org/0000-0002-4192-1653
Mohamed H. Abdelazim https://orcid.org/0000-0002-6701-1121
Abdulaziz Ibrahim Alzarea https://orcid.org/0000-0003-0604-6299
Adnan Alharbi https://orcid.org/0000-0002-4825-6596
Abdullah H. Altemani https://orcid.org/0000-0001-7379-2537
Abdullah S. Alshammari https://orcid.org/0000-0002-9994-7266
Faisal Alsenani https://orcid.org/0000-0002-7267-9636
Ahmed H. Abdelazim https://orcid.org/0000-0002-8907-3497

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