

Effect of Intranasal Insulin on Olfactory Recovery in Patients with Anosmia

Khalaf Hamead Mohammed, Amr Adel Abdel Monem, Soad A. Mohamad,
Abdel Rahim Ahmed Abdel Karim, Mostafa Ismail Ahmed

Department of Otorhinolaryngology, Faculty of Medicine, Minia University, Minya, Egypt

Received: 08th July, 2024; Revised: 12th August, 2024; Accepted: 25th August, 2024; Available Online: 31st August, 2024

ABSTRACT

Olfactory dysfunction, defined as either a complete or partial impairment of smell, is a common condition that may substantially affect a person's quality of life and is frequently difficult to treat. Physical activity, heredity, nutrition, smoking, head trauma, medical treatments, and virus exposure all influence one's capacity to smell. Hyposmia or anosmia, or loss of smell, affects 3% to 20% of the population. Intranasal insulin can improve cognitive performance, reduce food intake, and boost olfactory thresholds in healthy individuals. As people age, they are more likely to experience olfactory dysfunction, which may be affected by a variety of reasons, such as acute and chronic sino-nasal illness, upper respiratory infections, toxic chemical exposure, and degenerative diseases. About ten percent of those over 65 develop olfactory impairment, which can range from mild loss to total anosmia. Insulin resistance in the central nervous system has been linked to conditions like type II diabetes, Alzheimer's disease, obesity, and poor odor identification. Reduced odor perception may contribute to reduced olfactory function in anosmic patients.

Keywords: Intranasal insulin, Olfactory recovery, Anosmia.

International Journal of Pharmaceutical Quality Assurance (2024); DOI: 10.25258/ijpqa.15.3.92

How to cite this article: Mohammed KH, Monem AAA, Mohamad SA, Karim ARAA, Ahmed MI. Effect of Intranasal Insulin on Olfactory Recovery in Patients with Anosmia. International Journal of Pharmaceutical Quality Assurance. 2024;15(3):1703-1706.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Impaired olfaction has a substantial negative influence on quality of life, affecting food satisfaction, personal hygiene, and social connections, as well as contributing to more severe depressive symptoms and overall physical and mental well-being.¹

Furthermore, impaired smell function may limit one's ability to detect warning aromas, raising the risk of harm from fires, environmental contaminants, natural gas leaks, and contaminated food. Less than 25% of people with olfactory impairment are aware of their condition, and confusion rates for warning odors are high among those over 70 years old, raising public health concerns.¹

Olfactory dysfunction is more common in older adults and could be brought on by several conditions, including degenerative diseases, upper respiratory infections, acute and chronic sinus infections, and exposure to hazardous chemicals. Olfactory impairment affects approximately ten percent of people over 65 and can vary from partial loss to complete anosmia. The correlation between neurodegenerative diseases and olfactory impairment has garnered recent interest because

of the correlation's high incidence, early onset, persistence across the course of the disease, and accessibility of olfactory testing.²

The sense of smell is linked to neurological illnesses like multiple sclerosis and epilepsy and is thought to be a main predictor of Alzheimer's and Parkinson's disease. Population-based studies of olfactory loss show a prevalence of twenty-two percent among the ages of 25 and 75, 19% for those over the age of 20, and 24% for those over the age of 53, with the highest frequency among older men. Infections of the upper respiratory tract, plus inflammatory disorders of the nose and sinuses (fifty-three percent), respiratory dysfunction (nineteen percent), and post-viral conditions (eleven percent), are the leading causes of olfactory loss and dysfunction.³

The loss of sense of smell occurs when there are problems in the nasal cavity, nasal structure, olfactory nerve (the neural system responsible for the sense of smell), as shown in Figure 1, or brain problems. Most of us have experienced a loss of sense of smell, especially when we have a fever and runny and stuffy nose. In most cases, the problem is temporary. Those who suffer from smell disorders experience taste disturbances as well.³

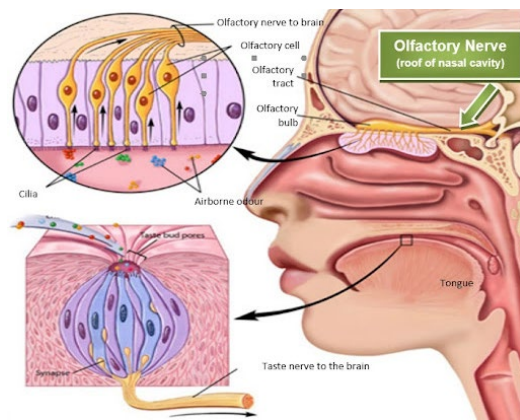


Figure 1: Neural system responsible for the sense of smell

Intranasal Insulin's Mechanism of Action

A possible regulator of olfactory function is insulin, a hormone involved in glucose regulation. Research has indicated that insulin receptors have been extensively distributed in the human brain; nevertheless, the brain's olfactory bulb has the highest concentration of both insulin and insulin receptors, indicating that insulin has a direct role in olfactory processes and signaling. The olfactory bulb's mitral cells and other brain regions are the primary locations of IN receptors. Additionally, they are widely dispersed throughout tiny arterial walls and capillaries, which affects regional perfusion.⁴

Since sustentacular cells also have IN receptors, this patient group may benefit from intranasal IN administration. IN stimulates the maturity of recently formed olfactory sensory neurons (OSN) and increases their electrical activity, promoting olfactory mucosa (OM) regeneration.⁵

Impaired insulin signaling is thought to influence the development and neurodegeneration of Parkinson's disease. In contrast, insulin's neuroprotective properties have been considered crucial for the upkeep and repair of the olfactory mucosa.⁵

Numerous investigations have supported this theory, showing that intranasal insulin effectively enhances olfactory performance. More recent studies have demonstrated that IN affects not just neurons but astrocytes and other brain cell types, such as tanycytes, microglia, and oligodendrocytes.⁵

When olfactory performance had been reevaluated 30 minutes after intranasal insulin administration, a 2015 study that looked at the impacts of the medication on ten participants with post-infectious anosmia discovered that odor threshold and sensitivity improved by sixty percent, compared to only twenty-eight percent in the intranasal saline control group.⁶

Researchers examined the impacts of administering insulin gel foam endoscopically inserted twice a week in the olfactory cleft of studied cases with mild to severe hyposmia in a double-masked randomized controlled trial conducted in 2018. The experiment's findings demonstrated that, after four weeks, the insulin-treated group's mean scores for odor recognition and smell threshold were significantly higher than those of the saline-treated control group ($p = 0.01$).⁷

While intranasal application is generally regarded as a safe method of administering IN, some authors note that more work needs to be done to address adverse drug reactions associated with this mode of administration, such as respiratory symptoms (cough, sinus pain/irritation, coryza) or nasal irritation, burning, pain, epistaxis). Using fast dissolving films, which provide accurate dosage, quick IN release, and improved application qualities, is a novel strategy to solve this issue.⁸

Influence of Intranasal Insulin on Olfactory Recovery in Studied Cases with Hyposmia

Patients with hyposmia experience a reduction in their sense of smell. Nevertheless, there have been no effective treatment plans for this illness. According to certain research, an intranasal insulin injection (40 IU) may enhance smell perception and doesn't seem to have any serious side effects.⁹

Role of intranasal insulin in olfactory performance in anosmic patients.

This clinical pilot study aimed to examine the effects of intranasal insulin on olfactory performance measures in anosmia-studied cases. Subjective ratings of odor intensity increased dramatically, and 60% of studied cases receiving insulin had a rapid improvement in olfactory sensitivity. Following insulin delivery, identification scores declined, according to a descriptive analysis of the individual evaluations. The fact that studied cases showed improvements in sensitivity and declines in identification and discrimination ratings may make this seem contentious. Nonetheless, this makes sense, given the varying levels of task complexity. Furthermore, it is suggested that odor identification and discrimination are more core and a component of higher cognitive olfactory processes. In contrast, odor sensitivity is a more peripheral measure of olfactory processing. It is plausible that an intranasal administration of insulin influences the various processing processes in distinct ways. This may be related to prolonged illness durations that make it harder to identify and distinguish between odors because the clinical test battery requires excessive odorous impressions. However, the influence of intranasal insulin on olfactory function in our sample was not influenced by the length of the disease.^{6,10}

These findings contradict those of earlier investigations conducted on healthy individuals, wherein intranasal insulin administration reduced olfactory sensitivity relative to the placebo condition.^{11,12}

Thanarajah *et al.* discovered that administering insulin intranasally enhanced olfactory threshold function but did not impact odor discrimination⁴

In contrast, Rodriguez-Raecke *et al.*'s research evaluated susceptibility to peanut and n-butanol scents. It showed that n-butanol olfactory sensitivity was significantly reduced in females but not in males following intranasal insulin delivery. However, not all subjects' olfactory sensitivity to peanuts was affected considerably by intranasal insulin.¹³

Inconsistent with Rodriguez-Raecke *et al.*'s research, Brünner *et al.* have investigated the possibility of modulating

human olfactory processing through increased brain insulin signaling. Compared to the placebo condition, respondents' sensitivity to the odorant n-butanol had significantly reduced ($p=.025$). However, there had been no discernible change in the capacity of the two conditions for olfactory discrimination.¹¹

In research by Mohamad *et al.*, both before and after insulin treatment, the average olfactory discrimination values were measured. After treatment, it was discovered that the intervention group's values increased significantly ($p=.0032$), but the placebo group showed no discernible improvement.³

Furthermore, Thanarajah *et al.* said that the dose-dependent effects of intranasal insulin on olfactory threshold performance were particularly notable when administered at 100 and 160 IU.⁴

Rezaeian's research showed that odor recognition improved after 40 IU of insulin on gel foam was administered. He discovered that compared to the placebo group, the intervention group's Connecticut Chemosensory Clinical Research Centre score was considerably higher ($p=.01$), indicating enhanced olfactory function.⁹

The clinical assessment of insulin fast-dissolving film in the treatment of post-infection anosmia research is another clinical trial looking into the possible use of insulin treatment for olfactory impairment. The clinical study's results showed that the intervention group's olfactory detection scores and olfactory discrimination values increased significantly (7.9 ± 1.2 , 6.7 ± 0.5 , respectively) in comparison to the placebo group's 3 ± 0.8 , 2.8 ± 1 values).¹⁴

Role of intranasal IN on diabetic olfactory dysfunction

Diabetes mellitus is a disease that is becoming more and more common in both adults and children. Apart from neurological and vascular conditions, it can result in chemosensory irregularities, such as declines in smell. Thus far, most research indicates that individuals with diabetes are more likely than the general population to experience olfactory impairment. Concurrent medical conditions are another effective factor because they exacerbate olfactory impairment. For type 1 diabetes, type 2 diabetes, and gestational diabetes, this association has been demonstrated. In addition, DM in acute illnesses like COVID-19 increases the incidence of olfactory abnormalities throughout infection and chronic diseases.¹⁵

This method exhibits the most convenient profile since IN can be administered intranasally and immediately reaches the central nervous system. Previously thought to be an organ unresponsive to insulin, the brain is now understood to be a crucial insulin target. Nevertheless, it appears that the precise function of insulin inside the various brain areas is rather intricate and not well understood. Insulin receptors are abundant in the olfactory bulb, hypothalamus, cerebellum, and memory-related regions such as the limbic system and hippocampus. Transdermal insulin delivery is useful for improving our comprehension of insulin's true role in these processes and possible treatment targets.¹⁵

Role of Intranasal Insulin on Anosmic Patients with Alzheimer's Disease

Based on estimates from more than 200 studies, there were around fifty million dementia patients sufferers globally in 2015. Estimates indicate that the number will rise to 75 million by 2030 and 132 million by 2050. The primary reason for dementia is Alzheimer's disease, for which there are currently no effective cures. According to a recent study, insulin activity in the brain may play a significant role in the etiology of this debilitating condition and be a target for therapies aimed at treating and preventing it. In this regard, most recent studies have successfully used the intranasal method to improve the availability of insulin in the central nervous system.¹⁶

CONCLUSION

Intranasal administration of insulin improves the sense of smell and appears to have no significant adverse effects. However, due to limited existing studies, further research with a larger population is needed.

ACKNOWLEDGMENT

I thank my coauthor for their thoughtful suggestions and remarks while writing this paper.

REFERENCES

1. Marin C, Vilas D, Langdon C, Alobid I, López-Chacón M, Haehner A, *et al.* Olfactory dysfunction in neurodegenerative diseases. *Curr Allergy Asthma Rep* 2018;18:1–19.
2. Boesveldt S, Postma EM, Boak D, Welge-Luessen A, Schöpf V, Mainland JD, *et al.* Anosmia—a clinical review. *Chem Senses* 2017;42(7):513–23.
3. Mohamad SA, Badawi AM, Mansour HF. Insulin fast-dissolving film for intranasal delivery via olfactory region, a promising approach for treating anosmia in COVID-19 patients: Design, in-vitro characterization, and clinical evaluation. *Int J Pharm* 2021;601:120600.
4. Edwin Thanarajah S, Hoffstall V, Rigoux L, Hanssen R, Brüning JC, Tittgemeyer M. The role of insulin sensitivity and intranasally applied insulin on olfactory perception. *Sci Rep* 2019;9(1):7222.
5. Doty RL, Mishra A. Olfaction and its alteration by nasal obstruction, rhinitis, and rhinosinusitis. *Laryngoscope* 2001;111(3):409–23.
6. Schöpf V, Kollndorfer K, Pollak M, Mueller CA, Freiherr J. Intranasal insulin influences the olfactory performance of patients with smell loss, dependent on the body mass index: a pilot study. *Rhinology* 2015;53(4):371–8.
7. Suzuki M, Saito K, Min W, Vladau C, Toida K, Itoh H, *et al.* Identification of viruses in patients with post-viral olfactory dysfunction. *Laryngoscope* 2007;117(2):272–7.
8. Daniel D, Paula LN, Eduardo BM, Daniel GA, Andrea DE, Fernando LN, *et al.* Intranasal insulin for COVID-19-related smell loss. *Eur Arch Oto-Rhino-Laryngology* 2024;281(1):201–5.
9. Rezaeian A. Effect of intranasal insulin on olfactory recovery in patients with hyposmia: a randomized clinical trial. *Otolaryngol Neck Surg* 2018;158(6):1134–9.
10. Hedner M, Larsson M, Arnold N, Zucco GM, Hummel T. Cognitive factors in odor detection, odor discrimination, and odor

- identification tasks. *J Clin Exp Neuropsychol* 2010;32(10):1062–7.
11. Brünner YF, Benedict C, Freiherr J. Intranasal insulin reduces olfactory sensitivity in normosmic humans. *J Clin Endocrinol Metab* 2013;98(10):E1626–30.
 12. Ketterer C, Heni M, Thamer C, Herzberg-Schäfer SA, Häring HU, Fritsche A. Acute, short-term hyperinsulinemia increases olfactory threshold in healthy subjects. *Int J Obes* 2011;35(8):1135–8.
 13. Rodriguez-Raecke R, Brünner YF, Kofoet A, Mutic S, Benedict C, Freiherr J. Odor sensitivity after intranasal insulin application is modulated by gender. *Front Endocrinol (Lausanne)* 2018;9:580.
 14. Soad A, Minia U, Deraya U. Clinical Assessment of Insulin Fast Dissolving Film in Treatment of Post Infection Anosmia. 2021;
 15. Seaquist ER, Damberg GS, Tkac I, Gruetter R. The effect of insulin on in vivo cerebral glucose concentrations and rates of glucose transport/metabolism in humans. *Diabetes* 2001;50(10):2203–9.
 16. Scheltens P, Blennow K, Breteler MMB, De Strooper B, Frisoni GB, Salloway S, *et al.* Alzheimer's disease. *Lancet* 2016;388(10043):505–17.