Dermatology Practical & Conceptual

Effects of Oral Isotretinoin on Taste and Olfactory Functions in Acne Vulgaris: A 6-Month Follow-Up Study

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ABSTRACT

Introduction: Acne vulgaris is a common multifactorial inflammatory skin disease of the pilosebaceous unit. Oral isotretinoin is one of the most effective choices among available treatments, and the most common and known side effects are mucocutaneous changes. However, few studies have investigated the smell and taste functions secondary to nasal and oral mucosal alterations.

Objective: This study aimed to evaluate the changes in taste and smell functions before and after systemic isotretinoin treatment during a six-month period.

Methods: The study included 48 patients with acne vulgaris aged over 18 years who were indicated for treatment with isotretinoin. Taste and smell functions were measured in patients at three different time points: before treatment, at the third month, and at the sixth month of treatment.

Results: Among 48 patients, 35 (72.9%) were female, and 13 (27.1%) were male. The mean age was 21.02 ± 3.42 years. The mean dose was 0.56 ± 0.08 mg/kg. The median taste scores were 14.5 (11–16) before treatment, 13.0 (10.5–16) at the third, and 12.0 (9–14) at the sixth month of therapy ($P<0.001$). A positive correlation was found between the decrease in taste scores and the mean dose (r=0.418, $P=0.003$). No significant change was observed in olfactory scores ($P>0.05$).

Conclusions: Although isotretinoin is known to be a safe and effective treatment method for acne vulgaris, informing patients about changes in taste functions before starting the medication and during follow-up visits could make a significant difference in their quality of life.

Introduction

Acne vulgaris is a common, multifactorial inflammatory skin disease of the pilosebaceous unit. The four primary pathogenic mechanisms involved in the development of acne are increased sebum production, follicular hyperkeratinization, bacterial colonization, and inflammation [1]. Acne vulgaris lesions are most commonly present in areas with a higher density of pilosebaceous glands such as the face, chest, and upper back. Clinically, acne vulgaris presents with noninflammatory lesions like open and closed comedones and inflammatory lesions such as papules, pustules, nodules, and cysts. In some cases, lesions may resolve with varying degrees of scarring or pigmentation [2].

Among systemic treatment options for acne vulgaris, oral isotretinoin is preferred in patients with severe nodulocystic acne, in cases resistant or unresponsive to long-term oral and topical therapies in mild-to-moderate acne, and in severe or scarring acne [3]. Clinical and laboratory side effects of isotretinoin include xerosis, cheilitis, epistaxis, dry eyes, abnormal serum lipid profile, elevated liver enzymes, gastrointestinal upset, back pain, and arthralgia [4].

The senses of taste and smell play a crucial role in quality of life and nutritional behavior. These senses can be affected by various systemic diseases such as renal failure, hepatic failure, and diabetes mellitus as well as by infections and certain medications, including chemotherapeutics and antimicrobials [5]. Dryness of mucous membranes during isotretinoin treatment may involve the nasal mucosa, leading to changes in olfactory perception. Additionally, previous studies have shown that isotretinoin use may reduce salivary gland function [6].

Objectives

There have been cases of taste and smell dysfunction or loss in acne vulgaris patients previously treated with isotretinoin [7,8]. However, the available literature on both taste and smell function in this context is limited. This study aimed to investigate the changes in taste and smell functions in patients diagnosed with acne vulgaris before and at the third and sixth months of isotretinoin treatment.

Methods

Study Design and Selection Criteria

This prospective cohort study included 51 acne vulgaris patients initiating systemic isotretinoin treatment between September 2023 and June 2024. The study was approved by the clinical studies ethical review committee (approval number: E2-23-4891). Informed consent was obtained from all participants prior to participation in the study.

Participants who had chronic conditions such as kidney or liver disease, oncological, endocrinological, or rheumatological disorders, known psychiatric or neurological illnesses, salivary gland diseases, or a history of glossitis, oral aphthae, or other oral mucosal disorders were excluded. Additional exclusion criteria included regular use of mouthwash, recent upper respiratory tract infection or otitis media within the preceding three months, any condition affecting the nasal mucosa or middle ear, smoking, asthma, and a positive COVID-19 test within the previous six months.

In addition to the routine clinical evaluation of acne vulgaris, all patients underwent monthly follow-up for their acne severity, isotretinoin-related side effects, and diseases that may have developed during the study period. Demographic data such as age, disease and medication history, and BMI were also collected. Taste and smell evaluation were applied before the therapy, at third month, and at sixth month of therapy.

Evaluation of Taste Function

Taste function was examined by the Taste Strips Test (TST) developed by Mueller et al. [9]. TST is a validated method for the evaluation of taste function using 16 filter paper strips impregnated with four different substances, each presented at four concentrations, evoking the four basic taste qualities: sweet (0.4, 0.2, 0.1, 0.05 g/ml sucrose), sour (0.3, 0.165, 0.09, 0.05 g/ml citric acid), salty (0.25, 0.1, 0.04, 0.016 g/ml sodium chloride), and bitter (0.006, 0.0024, 0.0009, 0.0004 g/ml quinine hydrochloride).

Distilled water was used as the solvent, and the taste solutions were prepared freshly at regular intervals. Participants did not eat, drink, or brush their teeth for one hour before the test. After each strip, they rinsed their mouth with water and waited for 30 seconds. The strips were placed on the left and right side of the anterior third of the extended tongue, resulting in a total of 32 trials. The taste strips were presented in a randomized order, with the side of the tongue alternated during application.

With their tongue still extended, patients had to identify the taste from a list of six forced-choice options: sweet, sour, salty, bitter, unsure, and no taste. Incorrect identification of each strip was scored as 0 and correct identification was scored as 1 point. The score on one side of the tongue ranged from 0 to 16, and the average score was calculated from each side of the tongue. An overall score of less than or equal to 9 was considered hypogeusia.

Evaluation of Olfactory Function

The Connecticut Chemosensory Clinical Research Center (CCCRC) Olfactory Test was used to assess olfactory function. The test consists of two components: the odor threshold test and the odor identification test [10]. Patients using

moisturizers for nasal dryness were asked to discontinue topical applications 24 hours before the test.

For the odor threshold test, two transparent containers with identical appearance were used: one containing water and the other containing n-butanol diluted in various concentrations. The concentrations were: 4%, 1%, 0.4%, 0.1%, 0.05%, 0.01%, and 0.005% as seven levels. Participants were asked to occlude one nostril and were then presented with the water and the lowest concentration of n-butanol (0.005%). If the participant reported no detectable smell, the next higher concentration was presented. When the participant correctly identified the n-butanol smell five times consecutively at the same concentration, that level was recorded as the threshold score. The same procedure was repeated for the other nostril, and the average of the two scores was documented. In this scoring system, correct odor detection at the lowest concentration (0.005%) is scored as 7 points, while detection at the highest concentration (4%) is scored as 1 point. Participants who were unable to perceive any odor at any concentration received a score of 0.

For the odor identification test, seven different odorants were placed into containers identical in shape and color. With eyes closed, participants were asked to sniff each sample. The odorants used were mothballs, soap, cinnamon, baby powder, coffee, chocolate, and peanut butter. Participants were presented with a multiple-choice answer sheet listing 14 options, including the seven actual tested odorants plus the following distractors: black pepper, rubber, grape jam, burnt paper, ketchup, wood, and mint. Two additional options were also included: "unknown" and "no odor". Participants were asked to choose one option for each odorant for both nostrils separately. Each correctly identified odor received a score of 1, and incorrect or unrecognized odors were scored as 0, yielding a total identification score ranging from 0 to 7. Additionally, to assess the integrity of the trigeminal nerve, all participants were asked to sniff Vicks (VapoRub) prior to the test. Participants who failed to perceive this stimulus were excluded from the study.

Based on the total scores, the olfactory function was categorized as follows: normosmia: 6–7 points, mild hyposmia: 5–5.75 points, moderate hyposmia: 4–4.75 points, severe hyposmia: 2–3.75 points, anosmia: 0–1.75 points.

Statistical Analysis

Data were analyzed with SPSS 26.0 software (IBM Corp., Armonk, NY). Data are presented as mean ± standard deviation for continuous variables and as numbers and percentages for non-continuous data. The normality of the distribution was analyzed using the Shapiro-Wilk test. Spearman correlation analysis was used for the isotretinoin dose and taste and olfactory correlation. Friedman test was used to assess the changes in taste and olfactory scores during treatment. Post hoc pairwise comparisons were performed using the Wilcoxon signed-rank test with Bonferroni correction. Data were considered statistically significant at the $P<0.05$ level.

Results

Fifty-one patients were eligible for the study. One patient discontinued the treatment due to elevated liver enzymes, one patient dropped out, and one patient was excluded from the study due to newly diagnosed hypothyroidism. In total, 48 patients completed the study.

Of the 48 patients, 72.9% (N=35) were female, and 27.1% (N=13) were male. The mean age was 21.02 ± 3.42 years (range 18–32), and the mean BMI was 21.02 ± 3.42 kg (range 18–32). Forty-one patients (85.4%) had no chronic conditions, two had chronic urticaria, two had gastritis, one had ulcerative colitis, one had vitiligo, and one had mitral regurgitation. The mean dose over six months was 0.59 ± 0.08 mg/kg (range: 0.44-0.76 mg/kg).

Among the taste function subgroups, sweet taste did not show a significant decrease, in contrast with the salty, bitter, and sour taste subgroups (Table 1). Total median taste scores were 14.5 (range 11–16) before treatment, 13.0 (range 10.5–16) after the third month, and 12.0 (range 9–14) after the sixth month of isotretinoin treatment, which showed a statistically significant decrease ($P<0.001$) (Figure 1). One patient (2.1 %) developed hypogeusia. In addition to this finding, a moderate positive correlation was found between the decrease in taste scores and the mean isotretinoin dose in patients (r=0.418, $P=0.003$).

The odor threshold test showed an increase during treatment; however, this was not statistically significant ($P=0.606$). The odor identification test showed an increase

Table 1. Pre- and posttreatment changes in taste function subcategories.

	Before Treatment	Third Month	Sixth Month	p-value
Sweet	4 (2-4)	4 (2.5-4)	4 (2-4)	1.000
Salty	3.5 (1.5-4)	3 (1.5-4)	3 (1-4)	< 0.001
Sour	4 (2.5-4)	3 (1.5-4)	3 (1-4)	< 0.001
Bitter	3 (1-4)	3 (1.5-4)	3 (1-4)	0.009

Data are presented as median (minimum-maximum). Taste scores are based on a 0–4 scale.

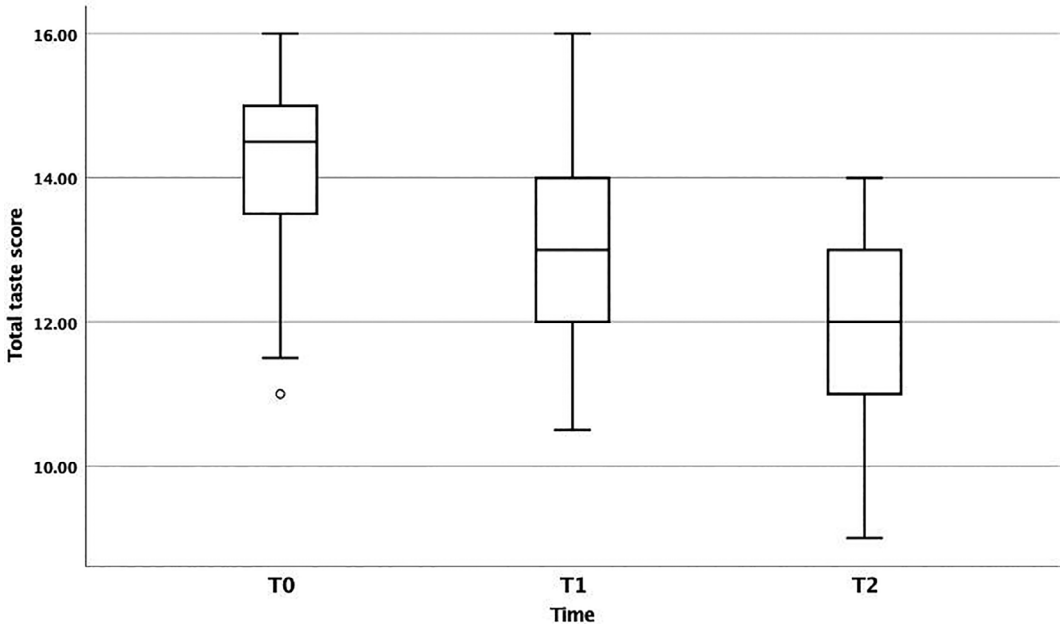

Figure 1. Changes in total taste scores before and after isotretinoin treatment. Legend: T0: Before treatment; T1: Third month; T2: Sixth month.

at the third month, and a decrease at the sixth month, which was also not statistically significant (Table 2).

The total mean olfactory scores were 5.89 (range 4.5–7) before treatment, 5.98 (range 4.75–7) at the third month, and 6.02 (range 5–7) after the sixth month of isotretinoin treatment, showing no statistically significant increase (P=0.336) (Figure 2). Six patients with mild hyposmia before treatment had normosmia after treatment, three patients with moderate hyposmia improved to mild hyposmia, and three patients with normosmia developed mild hyposmia.

Discussion

Oral isotretinoin has been used for acne vulgaris treatment as an FDA-approved drug since 1982. The most common side effects of isotretinoin treatment are mucocutaneous findings, and among these, significant changes affecting the nasal mucosa include dryness, epistaxis, nasal obstruction, and decreased mucociliary clearance [11]. Additionally, it is known that a decrease in mucociliary clearance can lead to impaired olfactory functions [12].

However, departing from existing findings in the literature, an animal model study by Karen et al. demonstrated that mice with induced olfactory nerve injury regained their previous olfactory functions by day 16 following oral retinoic acid administration [13].

In another study, by Kartal et al., it was shown that acne vulgaris patients receiving oral isotretinoin had significantly higher olfactory test scores at the third month of therapy compared to baseline [14]. However, the previous study was limited to a three-month follow-up and did not include further observations, which constitutes a key distinction from our study. The improved olfactory function observed in these studies may be attributed to the role of retinoic acid in the development and morphogenesis of the fetal olfactory system and its potential effects on the adult olfactory system, where components of the retinoid signal pathway are expressed in the olfactory mucosa [15,16].

In our study, although an increasing trend was observed in olfactory threshold and identification scores at the third and sixth months of isotretinoin treatment, these changes were not statistically significant. It is possible that the slight improvements, such as cases of mild hyposmia progressing to normosmia, reflect natural variability in olfactory testing or a potential placebo effect rather than a true pharmacological outcome. However, considering earlier evidence suggesting retinoic acid's role in neural regeneration, particularly in olfactory pathways, the possibility of a genuine isotretinoin -induced benefit cannot be entirely ruled out. The differences observed in our study may also be explained by the use of a different olfactory test than in the previous literature, as there is currently no single standardized method for olfactory testing. Additionally, factors such as the inclusion of a younger age group, who may have inherently better olfactory function, and the longer follow-up period of six months instead of three months compared to previous studies, may also have contributed to these discrepancies [17].

In a recent case-control study by Kondo et al., the University of Pennsylvania Smell Identification Test (UPSIT) was used, and it was reported that acne vulgaris patients under isotretinoin treatment had significantly lower olfactory identification scores compared to healthy controls [18]. However,

Table 2. Pre- and posttreatment changes in olfactory function subcategories.

	Before Treatment	Third Month	Sixth Month	p-value
Odor Threshold	6.5 (4–7)	6.5 (4–7)	6.5 (5–7)	0.606
Odor Identification	5.5 (4–7)	6 (4–7)	6 (4–7)	0.216

Data are presented as median (minimum-maximum). Odor threshold and odor identification scores are based on a 0–7 scale.

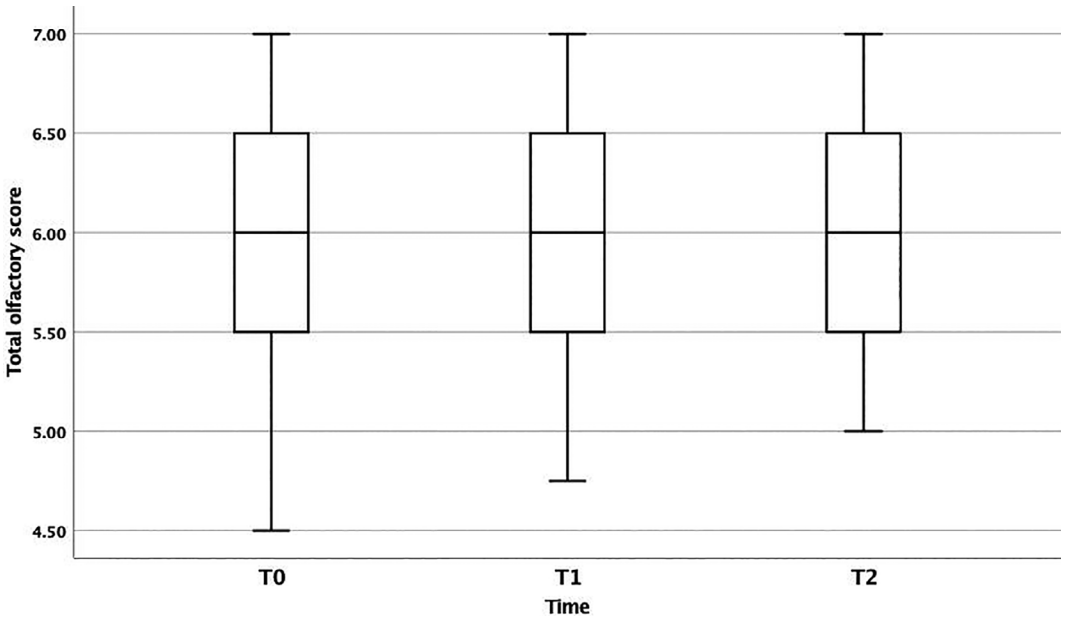

Figure 2. Changes in total olfactory scores before and after isotretinoin treatment. Legend: T0: Before treatment; T1: Third month; T2: Sixth month.

unlike our study, baseline smell identification scores were not evaluated, and additional olfactory test subcategories such as olfactory threshold or olfactory discrimination tests were not included in that study.

To date, studies investigating the effects of isotretinoin-induced mucocutaneous side effects on the oral mucosa are limited. In a study conducted by Erdemir et al., it was demonstrated that patients receiving isotretinoin had significantly reduced salivary flow rate, salivary buffer capacity, and higher caries lesion activity scores compared to healthy controls [19]. Orsal et al. investigated the changes in salivary gland flow scintigraphically before treatment and at the third and sixth months of isotretinoin therapy, observing a significant decrease in salivary gland function compared to the pretreatment values [6]. In another study, Kumral et al. found that the nasal obstruction and the mucociliary clearance started to decrease after the first week of isotretinoin treatment, and they found that significant taste loss occurred at the third month [20]. In our study, although only one patient developed hypogeusia, the observed decline in mean taste scores across the group may still hold clinical relevance. Subclinical alterations in taste function, while not meeting the diagnostic threshold for hypogeusia, can influence dietary preferences, appetite, and overall treatment satisfaction. An additional analysis revealed a moderate positive correlation between higher mean daily isotretinoin doses and greater reductions in taste scores, suggesting a possible dose-dependent effect. While our study design did not allow for establishing causality, this finding supports the hypothesis that higher cumulative exposure to isotretinoin may increase the likelihood or magnitude of taste alteration. Given these potential implications, we suggest that clinicians consider brief taste assessments during follow-up visits, particularly in patients on higher doses or prolonged therapy. Early counseling on possible sensory changes may help manage expectations and mitigate any negative impact on quality of life.

While retinoic acid signaling is essential during embryogenesis, it also contributes to the maintenance of adult salivary gland function. In particular, it regulates keratin expression (Krt5 and Krt14) in the submandibular epithelium, supporting epithelial integrity and function [21]. Disruption of this pathway by isotretinoin may impair salivary gland homeostasis and thereby contribute to taste alterations in adults.

In addition to isotretinoin-induced dryness, systemic autoimmune diseases can also lead to significant oral mucosal dryness. Among these, Sjögren's syndrome is one of the most

studied diseases. The lymphocytic infiltration in the ducts of the salivary glands is thought to be the main mechanism responsible for the decrease in taste sensation [22]. However, further studies are needed to identify which units of the salivary glands are affected by the isotretinoin-induced decrease in salivary secretion.

In our study, baseline taste function was assessed in acne vulgaris patients initiating isotretinoin, and these findings were compared with scores obtained at the third and sixth months of therapy. A statistically significant decrease was observed in total taste scores at both time points.

While a previous study demonstrated more than a 50% improvement in quality of life and reduced psychosocial burden by the second month of isotretinoin treatment in acne patients [23], our findings showed a decrease in taste function without a significant change in olfactory function. Although olfactory deficits did not show a measurable impact, it is known that impairments in taste and smell can negatively affect quality of life, appetite, mood, and even the feeling of safety [24]. Whether this taste decline translates into a measurable reduction in quality of life remains to be investigated in future studies.

This study has some limitations. Most notably, the lack of a healthy control group limits determining whether the observed changes are directly attributable to isotretinoin or simply reflect normal variation over time. While our within-subject design allowed for individual longitudinal assessments, inter-group comparisons would have enhanced the robustness of the findings and provided stronger evidence regarding causality. Another unanswered question is whether the decline in taste and smell functions is reversible after treatment cessation, which should be addressed in future research.

Conclusions

Informing patients about potential changes in taste and smell functions that may affect daily life before initiating treatment and evaluating these changes during follow-up visits could make a meaningful difference in patients' quality of life. Future studies involving healthy control groups are warranted to validate our findings and to distinguish treatment-related effects from baseline variability or external influences.

Abbreviations: CCCRC: Connecticut Chemosensory Clinical Research Center Olfactory Test; TST: Taste Strip Test; UPSIT: University of Pennsylvania Smell Identification Test.

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