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Effect of vitamin D on olfactory function

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ABSTRACT

Objective: In this study, we evaluated the olfactory function in individuals with vitamin D insufficiency and the effect of replacement therapy on olfactory function.

Methods: A total of 91 individuals with vitamin D insufficiency and 91 controls were assessed. Smell capacity was assessed with the Connecticut Chemosensory Clinical Research Center (CCCRC) test. An olfactory test was applied before and after replacement therapy. The olfactory test scores of both groups were compared with each other.

Results: The mean 25-hydroxy vitamin D levels in the pre-replacement, control, and post- replacement groups were 12.88±5.90, 35.76±6.13, and 42.99±4.89 ng/mL, respectively. In the post-replacement group, mean threshold test scores (pre-replacement 3.75±1.2; 12th week post-replacement 5.29±1.02), mean identification test scores (pre-replacement 6.6±0.85; 12th week post-replacement 6.94±0.22), and mean total test scores (pre-replacement 5.17±0.89; 12th week post-replacement 6.12±0.54) demonstrated statistically significant increases when compared with the pre-replacement group ($p<0.001$). The mean total test scores of the pre-replacement group was significantly lower than the control ($p<0.001$). There was no considerable difference statistically between the mean total test scores of the post-replacement and control groups ($p=0.4$).

Conclusion: Low blood vitamin D levels can be associated with olfactory dysfunction. Vitamin D replacement therapy can improve olfactory function in patients with vitamin D insufficiency.

Keywords: Olfactory function, vitamin-D, smell test

Introduction

Olfaction plays an important role in our daily lives, and olfactory dysfunction causes a significant decrease in the quality of life. Almost 20% of the general population complains about olfactory dysfunction, and 5% of these individuals are anosmic (1). Psychophysical and electrophysiological tests are often used to evaluate olfaction. Although psychophysical tests are generally used for the clinical assessment of people with smell dysfunction, electrophysiological tests are mostly used for further investigation (2). The Connecticut Chemosensory Clinical Research Center (CCCRC) olfactory test evaluates the butanol threshold and odor identification (3). It is validated for the analysis of smell capacity in the Turkish society (4). It is easy to prepare, cheap, and simple to administer (4).

Vitamin D plays an important role in the conservation of mineral balance and bone metabolism (5). It also has various effects on the extra-skeletal systems. It appears to have a neuroprotective effect on the nervous system, supporting an increase in the synthesis of neurotrophic agents that leads to the acceleration of neuronal progress in the nervous system and the reduction of oxidative stress (6, 7).

Vitamin D has been reported to have many targets mediated by its receptor (8). It binds to receptors in the olfactory system and the brain as a neurosteroid hormone (9, 10). Vitamin D insufficiency was demonstrated to be associated with various neurological problems (8, 11, 12). As a potential example of vitamin D insufficiency leading to symptoms within the central nervous system, hypoacusis has been documented in rodents deprived of functional vitamin D receptors (13).

In this study, we aimed to analyze the olfactory function with the CCCRC olfactory test in individuals with isolated vitamin D insufficiency and to reveal the changes in the olfactory level after vitamin D replacement therapy.

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Methods

This study included 91 patients with 25-hydroxy (OH) vitamin D insufficiency and 91 controls and was conducted between May and December 2019. The participants were selected from the internal medicine clinic on the basis of their vitamin D testing and then referred to the ENT clinic for olfactory testing. After the exclusion of the secondary causes of vitamin D insufficiency (e.g., liver or kidney diseases, malabsorption, and inflammatory bowel abnormality), the deficiency was deemed as primary because of insufficient oral intake and reduced sun exposure. A detailed history was taken from all the patients, and a routine ear, nose, and throat examination was also performed. Patients with nasal septum deviation, acute or chronic rhinosinusitis, active upper respiratory tract infection, nasal polyposis, history of nasal surgery, allergic rhinitis, smoking, systemic diseases (e.g., diabetes mellitus, hypothyroidism, hypertension, chronic renal failure, and chronic liver failure), neurological diseases, <18 years of age, pregnancy, female menopause, and a history of head trauma were excluded. Participants using drugs (e.g., diuretics, calcium channel blockers, statins, angiotensin-converting enzyme inhibitors, antidepressants, and local or systemic steroids) that could affect olfactory function were also excluded. The control group involved healthy volunteers with normal vitamin D levels and without any of the rhinological and systemic abnormalities mentioned earlier.

Both groups were evaluated according to serum 25 (OH) vitamin D levels, with values <30 ng/mL considered as 25 (OH) vitamin D insufficiency. After administering the olfactory test to patients, we used a weekly 50,000 IU vitamin D3 capsule for eight weeks' protocol, and after 12 weeks, reassessed the 25 (OH) vitamin D levels.

In individuals with vitamin D insufficiency without any systemic disturbances, for every 100 IU of added vitamin D3, the serum vitamin D levels improved by almost 0.7 to 1.0 ng/mL (14). The serum vitamin D concentrations of patients without other underlining diseases were expected to return to normal serum levels in 12 weeks after vitamin D replacement. Therefore, olfactory tests were also administered in the 12th week after the treatment. The olfactory test scores calculated before (pre-replacement group) and after 25 (OH) vitamin D replacement (post-replacement group) were compared with each other and with the control group. The study was approved by the local ethics committee (protocol number: 43, date: 17/04/2019). The patients provided written informed consent.

Smell assessment

The CCCRC test comprises of a butanol threshold and an identification as already reported (4). It was administered pre-treatment and in the 12th week post-treatment.

Main Points:

- Vitamin D insufficiency is associated with olfactory dysfunction.
- Vitamin D replacement therapy can be effective in olfactory dysfunction.
- Vitamin D insufficiency could cause disturbances in olfactory pathways.

Butanol threshold test

The participants were given two glass bottles of the same color and uniform view, one of which contained water and the other a dilute concentration of butanol during the test. They were then ordered to close one nostril and place the tip of the first bottle quickly below the other one. The second bottle was then sampled in a similar manner, and the participant had to select which of the bottles contained something other than water. If the selection was incorrect, a more potent concentration of butanol was submitted along with the bottle having only water. Possible scores ranged from 0–9, but scores ≥7 were scored as 7 per the olfactory test protocol. For the final score, the average of both nostril scores was taken.

Identification test

Cinnamon, Vicks, chocolate, Turkish coffee, peanut butter, carbonate, soap, and baby powder were added to opaque bottles. The ability to sniff out Vicks showed unimpaired trigeminal nerve function, and all the subjects easily recognized it; therefore, it was not added to the final score. Possible scores ranged from 0 to 7. For the final score, the average of both nostril scores was taken.

Total score

Scores for the butanol threshold and identification tests were later averaged to reach a total score, which was classified as defined by Cain et al. (3).

Sampling

Serum 25 (OH) vitamin D levels

Biochemical analysis

The levels of 25 (OH) vitamin D (ng/mL) were measured in the serum samples of the patients. Serum was sampled with the patients in a sitting position between 08.30 and 09.00 in the morning after 10–12 h of fasting. After fibrin formation, it was centrifuged at 1,500 rpm for five min. The serum was studied with a Hitachi Cobas (Indianapolis, IN, USA) device.

Statistical analysis

The Statistical Package for Social Sciences version 22.0 software (IBM Corp.; Armonk, NY, USA). The suitability of the parameters to normal distribution was evaluated by the Shapiro-Wilks test. Descriptive statistical methods (mean, median, and standard deviation) were determined when evaluating the study data. The Wilcoxon test was used in the comparison of non-parametric data between the same groups. The Mann-Whitney U test was used in the comparison of non-parametric data between the groups. The Spearman rho test was used for correlation analysis of non-parametric data. The difference between the scores before and after treatment was used to evaluate the correlation between vitamin D and the total score.

Results

The study included 91 patients and 91 controls. In the study group, 71 patients were women and 20 were men. The ages of women ranged between 21 and 49 years, and their mean

Table 1. Comparison of pre-replacement and control groups

	N	Pre-replacement Median (Min-Max)	Control group Median (Min-Max)	p
Threshold score	91	4 (1–7)	6 (4–7)	0.001
Identification score	91	7 (2–7)	7 (6–7)	0.646
Total score	91	5.5 (1.5–7)	6.5 (5–7)	0.001
25 (OH) vitamin D (ng/mL)	91	11.8 (2.5–26)	32 (31–58.9)	0.001

Mann-Whitney U test, N: number of patients, Min: minimum, Max: maximum
p≤0.05

Table 2. Comparison of post-replacement and control groups

	N	Post-replacement group Median (Min-Max)	Control group Median (Min-Max)	p
Threshold score	91	5 (2–7)	6 (4–7)	0.001
Identification score	91	7 (6–7)	7 (6–7)	0.001
Total score	91	6 (4.5–7)	6.5 (5–7)	0.4
25 (OH) vitamin D (ng/mL)	91	42.8 (34–57.3)	32 (31–58.9)	0.001

Mann-Whitney U test, N: number of patients, Min: minimum, Max: maximum
p≤0.05

Table 3. Comparison of pre-replacement and post-replacement groups

	N	Pre-replacement Median (Min-Max)	Post-replacement Median (Min-Max)	p
Threshold score	91	4 (1–7)	5 (2–7)	0.001
Identification score	91	7 (2–7)	7 (6–7)	0.001
Total score	91	5.5 (1.5–7)	6 (4.5–7)	0.001
25 (OH) vitamin D (ng/mL)	91	11.8 (2.5–26)	42.8 (34–57.3)	0.001

Wilcoxon test, N: number of patients, Min: minimum, Max: maximum
p≤0.05

age was 37.52±7.63 years. The ages of men ranged between 27 and 49 years, and their mean age was 39.55±6.03 years. In the control group, 70 participants were women and 21 men. The ages of women ranged between 19 and 49 years, and their mean age was 37.71±8.84 years. The ages of men ranged between 21 and 51 years, and their mean age was 36.71±10.07 years. The mean 25 (OH) vitamin D levels were 12.88±5.90 ng/mL (2.5–26), 35.76±6.13 ng/mL (31–58.9), and 42.99±4.89 ng/mL (34–57.3) in the pre-replacement, control, and post-replacement groups, respectively. There was a statistically significant difference between the groups in terms of 25 (OH) vitamin D levels (p<0.001).

The mean threshold test score was 3.75±1.2 (1–7), 5.86±0.87 (4–7), and 5.29±1.02 (2–7) in the pre-replacement, control, and post-replacement groups, respectively. The mean identification test score was 6.6±0.85 (2–7), 6.75±0.4 (6–7), and 6.94±0.22 (6–7) in the pre-replacement, control, and post-replacement groups, respectively. The mean total test score was 5.17±0.89 (1.5–7), 6.29±0.54 (5–7), and 6.12±0.54 (4.5–7) in the pre-replacement, control, and post-replacement groups, respectively.

When the pre-replacement group was compared with the control group, there was a statistically significant difference in the mean threshold (p<0.001) and total test scores (p<0.001). In contrast, no statistically significant difference was found in the mean identification scores (p<0.646) (Table 1). When the post-replacement group was compared with the control group, there was a statistically significant difference in the mean threshold (p<0.001) and identification test scores (p<0.001); however, no statistically significant difference was found in the mean total test scores (p<0.4) (Table 2). In the post-replacement group, the mean threshold test scores, the mean identification test scores, and the mean total test scores showed statistically significant increases when compared with the pre-replacement group test scores (p<0.001) (Table 3).

Before treatment, anosmia, severe hyposmia, moderate hyposmia, mild hyposmia, and normosmia values were 1.09%, 7.69%, 13.18%, 60.43%, and 17.58%, respectively; and these values after treatment were 0%, 0%, 2.19%, 24.17%, and 73.62%, respectively. After vitamin D replacement, anosmia, severe hyposmia, moderate hyposmia, and mild hyposmia percentage decreased, and the normosmic percentage increased.

There was no correlation between vitamin D levels and total CCCRC olfactory test scores (p=0.91) (Table 4) (Figure 1).

Table 4: Correlation between vitamin D level and total score

	N	Median (Min-Max)	r	p
25 (OH) vitamin D (ng/mL)	91	30.9 (11.03–48.4)	0.012	0.91
Total score	91	1 (0–5)		

Spearman's rho test, N: number of patients, Min: minimum, Max: maximum, r: correlation value p≤0.05
(In the correlation analysis, the difference in vitamin D levels pre- and post-replacement was used as data. The difference in total olfactory scores pre- and post-replacement was also used as data).

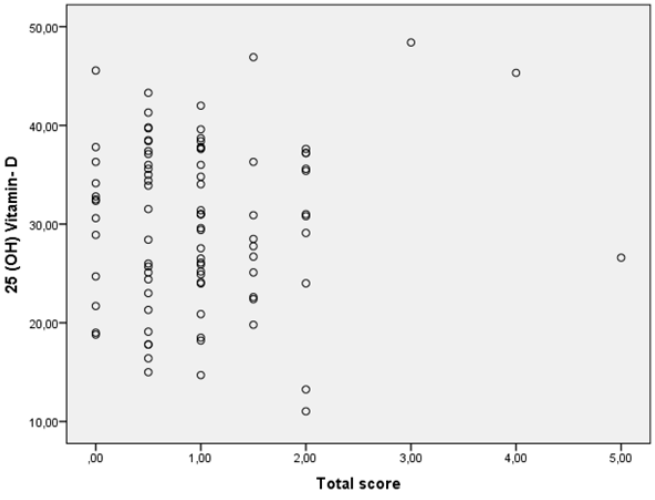

Figure 1. Correlation between vitamin D level and total scores

Discussion

Olfactory dysfunction may occur because of conductive or sensorineural problems. Conductive dysfunction may occur because of nasal pathologies, whereas sensorineural dysfunction may develop owing to the olfactory receptor and subsequent central pathways (15). This study reports that vitamin D insufficiency is associated with smell abnormality. Mean olfactory test scores are significantly increased in people with vitamin D insufficiency after a vitamin D replacement protocol. The number of patients with anosmia and hyposmia decreased after vitamin D replacement therapy. In addition, there was no correlation between vitamin D levels and total CCCRC olfactory test scores.

Vitamin D has neuronal cell differentiation and neuroprotective effects through several systems, such as antioxidant effects, detoxification, immunomodulation, neural calcium regulation, and improved nerve conduction (16, 17). It has been shown to affect the transmission rate of the peripheral nervous system (18). Hence, vitamin D insufficiency may lead to disturbances in neurological activity in the central and peripheral nervous systems, and, as a result, disrupt the transmission of the cranial nerves.

The active form of vitamin D performs its transcriptional function through vitamin D receptors (VDR). VDR belongs to the family of nuclear steroid receptors, found in a large variety of tissues (19, 20). Several studies have documented that vitamin D may be a neurosteroid important for brain development (21, 22). It also has important neuroprotective functions and nerve growth (21, 23). VDR and vitamin D binding protein were expressed in the rat vomeronasal organ and also detected in the rat olfactory mucosa and bulb (24). The neuroprotective effect of vitamin D against degenerative processes in the olfactory system is thought to be mediated by the intracellular signaling system via VDR. It may affect the smell transduction pathway or calcium signaling system in smell neurons (25).

Vitamin D is believed to have immunomodulatory effects on autoimmune and inflammatory diseases (26-28). Nasal mucociliary clearance time in people with vitamin D insufficiency was found to be prolonged, and clearance duration was shortened after vitamin D treatment (29). It is also thought that prolongation of mucociliary clearance time in patients with vitamin D insufficiency may be associated with increased pathophysiology of upper respiratory tract infections, sinonasal infections, and ear infections (29-31). Because vitamin D replacement therapy is useful in some conditions characterized by inflammation and infection, it can be speculated that vitamin D also improves olfaction by reducing intranasal inflammation and congestion.

Parkinson's disease (PD) is an important neurological illness associated with olfactory dysfunction (32). Studies have shown that smell abnormality in PD is associated with cognitive abnormality and brain atrophy. The extent to which olfactory abnormality occurs in the early stage of PD may help in the early detection and management of olfactory dysfunction (33, 34). High levels of vitamin D in patients with non-demented PD are associated with good cognitive performance, and its level may be a biomarker of future cognitive dysfunction in PD (35). Serum 25 OH vitamin D levels were also associated with the severity of smell dysfunction in patients with PD (36). In our study, we examined the smell ability before and after treatment in people with isolated vitamin D insufficiency who did not have any neurological disease. In this study, there was a significant increase in olfactory test scores of patients after replacement therapy.

There are a limited number of studies in the literature investigating the relationship between vitamin D levels and olfactory loss. Two patients were reported in which the olfactory function was significantly reduced but possibly recovered with supplementation of vitamin D (37). Both patients described a significant recovery in their olfactory function after eight weeks of vitamin D replacement therapy. The second patient did not return to her doctor for more than one month after eight weeks of treatment and stated that she had lost her sense of smell again during this time. Her doctor ordered another eight weeks of vitamin D replacement therapy, and she observed the same situation of progressive healing of smell function, most marked in the two days after taking the vitamin D (37). The most important limitation of this study was that olfactory tests were not used to evaluate olfactory dysfunction. Another limitation was that there were only two patients in the study. In our study, we demonstrated olfactory dysfunction with an olfactory test in people with isolated vitamin D insufficiency. We found that olfactory function improved after vitamin D replacement therapy.

Although various possible mechanisms that explain the effects of vitamin D on the olfactory pathway have been revealed, the

relationship between vitamin D and olfactory dysfunction has not been exactly explained yet. Further studies are needed to explain the exact role of vitamin D in pathogenesis. One of the limitations of our study was that the long-term results of patients' olfactory functions were not investigated after vitamin D treatment was completed. Another limitation was that the effects of vitamin D at the molecular level were not investigated. Further studies should be designed to investigate the relationship between vitamin D insufficiency and olfactory dysfunction at the tissue level.

In conclusion, this study demonstrates that vitamin D replacement therapy could improve olfactory function in patients with vitamin D insufficiency in the short term. Vitamin D insufficiency may be associated with olfactory dysfunction; however, its role in the pathogenesis of olfactory abnormality or the long-term impact of vitamin D replacement therapy is still unclear.

Ethics Committee Approval: This study was approved by Ethics committee of Zeynep Kamil Women's and Children's Diseases Training and Research Hospital, (Approval No: 43).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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Conflict of Interest: The authors have no conflict of interest to declare.

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