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Olfactory function in patients undergoing hemodialysis as assessed by Sniffin' Sticks testing

M. KAR[1], M. ALTINTAŞ[2], N. BAYAR MULUK[3], C. CINGI[4]

[1]Department of Otorhinolaryngology, Alaaddin Keykubat University, Alanya Training and Research Hospital, Alanya, Antalya, Turkey
[2]Otorhinolaryngology Clinic, Health Sciences University, Antalya Training and Research Hospital, Antalya, Turkey
[3]ENT Department, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkey
[4]ENT Department, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey

Abstract. – OBJECTIVE: This study evaluated olfactory function in patients undergoing hemodialysis. The evaluation utilized the Sniffin' Sticks test.

PATIENTS AND METHODS: The study enrolled 56 individuals undergoing hemodialysis for chronic renal failure alongside 54 healthy controls. The Sniffin' Sticks battery was used to assess olfactory function in all subjects. The battery included 12 separately identifiable odors. A score below 6 was considered anosmia, whilst scores ranging from 7 to 10 were classed as hyposmia. A score of at least 11 indicated normal olfaction.

RESULTS: There was a statistically significant difference in scores between the two groups. The hemodialysis patients scored 9.12±2.77 compared to 10.72±1.94 in the controls. In the hemodialysis patients, scores for males and females did not differ significantly. Furthermore, there was no correlation between score and age, sex or length of renal failure. Some 12.5% of hemodialysis patients were anosmic, whilst 50% were hyposmic. The corresponding rates in the control group were 7.4% and 20.4%.

CONCLUSIONS: Undergoing hemodialysis is associated with a decreased total score on the Sniffin' Sticks battery, with anosmia in 12.5% of patients and hyposmia in 50.0%. Thus, olfactory impairment is present in 62.5% of hemodialysis patients. According to previous research, renal transplantation results in an improved ability to smell, depending on how plastic the neurons involved in olfaction are.

Key Words:
Chronic renal failure (CRF), Hemodialysis (HD), Sniffin' Sticks test, Odor, Olfactory impairment.

Introduction

Olfactory function becomes less effective with increasing age and may be altered by pharmacotherapy, malnutrition and certain disorders, notably diabetes mellitus. It is known from the literature that abnormal function of the olfactory system frequently occurs in patients with chronic renal disorders. Age alters the ability to smell, as do a variety of disorders, including diabetes mellitus, disorders involving neurodegeneration, respiratory disorders and neoplasia. Furthermore, traumatic injury, side effects of drugs, toxic effects of pesticides, solvents and exposure to radiation can also impair olfaction. Malnutrition is also a recognized cause of olfactory dysfunction[1,2].

All forms of olfactory dysfunction, such as anosmia, hyposmia and dysosmia may commonly be noted in patients with chronic renal disorders. Usually, the ability to smell accurately is diminished in renal patients, irrespective of treatment by dialysis. It is an unresolved matter in the literature whether dialysis can restore olfactory ability. The abnormalities in olfaction observed in patients undergoing dialysis do not differ according to the method of dialysis (peritoneal or hemodialysis). Being the recipient of a donor's kidney results in increased olfactory perceptual ability, with the important result that patients may attend more carefully to an adequate diet[1].

According to Vreman et al[3], male patients had a lower ability to perceive smells than females. There was no relation between this reduced ability and zinc levels as quantified in the circulation and in hair samples.

According to a study by Griep et al[4] undertaken in 101 patients with chronic renal disorders, the olfactory threshold was lowered in cases where peritoneal or hemodialysis was ongoing or where the glomerular filtration rate (GFR) was no higher than 30 mL.min^{-1}. The group consisted of

Corresponding Author: Nuray Bayar Muluk, MD; e-mail: nbayarmuluk@yahoo.com; nurayb@hotmail.com

38 individuals undergoing hemodialysis, 16 undergoing peritoneal dialysis, 28 having received a transplanted kidney and 19 having a GFR no higher than 30 $mL.min^{-1}$. Olfactory function in kidney recipients was not significantly different from healthy controls and neither dialysis method was superior in terms of being associated with higher olfactory ability. When hemodialysis patients were tested before and after the dialysis session to compare the effects of dialysis, their olfactory abilities did not differ. On the other hand, there was an inverse correlation between the blood level of urea and phosphate and olfactory perception, which may imply that higher levels do decrease the ability to smell.

The study presented here involves assessing the olfactory abilities of patients undergoing hemodialysis. It utilizes the Sniffin' Sticks battery. The results obtained are compared with those obtained in healthy volunteers. The literature on this subject is reviewed to set the results we obtained in context.

Patients and Methods

This study was undertaken at Serik State Hospital in accordance with the principles of the Declaration of Helsinki. Ethical approval was granted by SBÜ Antalya Training and Research Hospital Clinical Research Ethics Committee on 17.02.2022 with decree number 4/4.

Subjects

There were two groups: cases (group 1) and a control group (group 2) for the study. Group 1 consisted of 56 patients with chronic renal failure and registered with Serik State Hospital. The mean duration for which they had been on hemodialysis was 3.98±3.59 (range: 1-18) years, whilst the mean age was 58.66±14.65 (range: 22-81) years. In group 2 there were 54 healthy individuals with a mean age of 39.75±12.64 (range: 18-63) years. Verbal consent was obtained from all participants before the study began.

The exclusion criteria for the study were as follows: an infection affecting the upper respiratory tract within the preceding 3 weeks, those with congenital abnormalities of gustation or olfaction, a history of traumatic injury to the head, disorders of the nervous system (in particular Alzheimer or Parkinson disease or epilepsy), metabolic or endocrine conditions (particularly diabetes mellitus).

Assessment Of Olfactory Function

Olfactory function was assessed in all subjects enrolled in the study by using the Sniffin' Sticks odoriferous felt type pens, manufactured by Sniffin' Sticks (Burghart GmbH, Wedel, Germany)[5-7]. The pens form a battery of tests which assess psychophysical aspects of the sense of smell. The method of administering the test was as follows: the cap was removed from a pen and it was presented to the subject's nostril, remaining 1-2 cm from the nose. The odors presented should be well-known to participants. The subject was asked to select which of four descriptive terms best described the odor. The pens were presented at intervals of at least 30 seconds to prevent desensitization from occurring. It was left up to the subject to decide how long they wished to smell the pen before making a choice of descriptive term. To calculate the final score, the assessors counted how many odors the test subject had correctly described[5-7].

The pens constituting the test battery bore the following odors: Orange (Pen 1), Leather (Pen 2), Cinnamon (Pen 3), Peppermint (Pen 4), Banana (Pen 5), Lemon (Pen 6), Liquorice (Pen 7), Coffee (Pen 8), Clove (Pen 9), Pineapple (Pen 10), Rose (Pen 11) and Fish (Pen 12).

The scoring scheme was as follows: a score below 6 was considered anosmia, whilst scores ranging from 7 to 10 were classed as hyposmia. A score of at least 11 indicated normal olfaction.

Statistical Analysis

All statistical analysis for this study was performed using the SPSS for Windows 16.0 software (SPSS Inc., Chicago, IL, USA). Statistical testing was made using the Chi-square test, Mann-Whitney U test, Pearson correlation test and Spearman's rank correlation rho efficient test.

A p-value below 0.05 was set as the level of statistical significance.

Results

Within group 1 (cases), 57.1% (n=32) were male, whilst 42.9% (n=24) were female. In group 2 (controls), 42.6% (n=23) were male and 57.4% (n=31) were female. Thus, they do not have a statistically significant difference (p=0.127, χ^2=2.328).

The results of olfactory testing are shown in Table I, which lists the scores for each of the odors presented. The scores obtained for odors 2, 7, 10, and 12 by the cases group were lower

Table I. Sniffin' Sticks test results for 12 odors.

		Group 1 (n = 56)		Group 2 (n = 54)		
		N	%	N	%	*p**
Odor 1	Absent Present	6 50	10.7 89.3	6 48	11.1 88.9	$p = 0.947$ $\chi^2 = 0.004$
Odor 2	Absent Present	33 23	58.9 41.1	13 41	24.1 75.9	$p = 0.000$ $\chi^2 = 13.726$
Odor 3	Absent Present	10 46	17.9 82.1	5 49	9.3 90.7	$p = 0.189$ $\chi^2 = 1.726$
Odor 4	Absent Present	3 53	5.4 94.6	0 54	0.0 100.0	$p = 0.255$ $\chi^2 = 1.297$
Odor 5	Absent Present	13 43	23.2 76.8	7 47	13.0 87.0	$p = 0.163$ $\chi^2 = 1.942$
Odor 6	Absent Present	12 43	21.8 78.2	5 49	9.3 90.7	$p = 0.071$ $\chi^2 = 3.265$
Odor 7	Absent Present	23 33	41.1 58.9	11 43	20.4 79.6	$p = 0.019$ $\chi^2 = 5.517$
Odor 8	Absent Present	5 51	8.9 91.1	3 51	5.6 94.4	$p = 0.754$ $\chi^2 = 0.098$
Odor 9	Absent Present	6 50	10.7 89.3	1 53	1.9 98.1	$p = 0.130$ $\chi^2 = 2.289$
Odor 10	Absent Present	31 25	55.4 44.6	16 38	29.6 70.4	$p = 0.006$ $\chi^2 = 7.436$
Odor 11	Absent Present	8 48	14.3 85.7	2 52	3.7 96.3	$p = 0.110$ $\chi^2 = 2.554$
Odor 12	Absent Present	11 45	19.6 80.4	2 52	3.7 96.3	$p = 0.010$ $\chi^2 = 6.702$
Classification of total odor scores	Anosmia Hiposmia Normosmia	7 28 21	12.5 50.0 37.5	4 11 39	7.4 20.4 72.2	$p = 0.001$ $\chi^2 = 13.597$
Total odor score		Mean 9.12 · Median 10.00 · Std. Dev. 2.77		Mean 10.72 · Median 11.50 · Std. Dev. 1.94		*p*** 0.000

**p*-value shows the results of Chi-square test. ***p*-value shows the results of Mann-Whitney U test.

than those obtained by the control group, and this difference had statistical significance ($p<0.05$). Overall, the score for the cases group was also below that of the controls (9.12±2.77 *vs.* 10.72±1.94, respectively). Again, this result was of statistical significance.

For the cases group, male and female patients scored very similarly (9.15±2.99 *vs.* 9.08±2.50, respectively) and any difference was not at the level of statistical significance ($p=0.395$).

Some 12.5% of hemodialysis patients were anosmic, whilst 50% were hyposmic. The corresponding rates in the control group were 7.4% and 20.4%. This difference between groups was statistically significant ($p=0.001$, $\chi^2=13.597$).

In the case group, there was no significant correlation between olfactory function score and age ($p=0.166$, r=-0.187), nor were correlations found using sex ($p=0.400$, r=-0.115), or period for which chronic renal failure had been present ($p=0.217$, r=-0.168).

Discussion

Identifying impairment of olfactory function is essential to facilitate access to appropriate clinical management as well as for prevention of the complications. They may occur in individuals who are anosmic for lengthy periods, such as lowered quality of life[8], poor dietary intake[9], altered social position[10], mental disorders, in particular depressive disorder[11], anxiety or anorexia[12] and even cognitive decline[10,13].

Chronic renal failure is a systemic disorder with the recognized complication of producing severe dysfunction of the olfactory system[14-16]. Reduced ability to smell is considered to play a part in patients becoming malnourished and lacking the desire to eat, two characteristic features of chronic renal conditions[17-19]. It may be significant that olfactory dysfunction in chronic renal failure affects the ability to identify odors and tell them apart, rather than the level required to detect their presence[3,14,15]. Impairment occurring in this way is suggestive of a cause within the central nervous system. Another important feature is that the impairment appears to be reversible insofar as patients who successfully undergo renal transplantation appear to recover comparable olfactory function to healthy peers[14].

According to a study by Frasnelli et al[15], patients with chronic renal failure failed to recognize deficits in their olfactory abilities. Since the deficits are generally mild or moderate (a decline in perception between 10 and 20%) – following our expectations from a review of the literature related to self-perception of olfactory function – it is usual for mild alterations in olfactory function to pass unnoticed by patients, although anosmic patients do typically observe a problem[20,21].

In our study, we have specifically evaluated olfactory ability by means of the Sniffin' Sticks battery, in patients undergoing hemodialysis. The overall score for the cases group was lower than that of the cases (9.12±2.77 *vs.* 10.72±1.94, respectively), a result that was statistically significant. Within the cases group, the overall score did not differ between men and women. Furthermore, within the cases group neither age, sex nor length of illness correlated with the score.

One other study[22] has also looked at the sense of smell in patients undergoing hemodialysis for chronic renal failure. This study, by Landis et al[22] enrolled 28 dialysis patients together with 24 healthy volunteers. Twenty of the patients were on hemodialysis, whereas 8 were receiving peritoneal dialysis. The data obtained included olfactory identification, the concentration of n-butanol and ethanoic acid necessary to elicit a response, urea fractional clearance, percentage of reduced urea, and body mass prior to and post dialysis. The researchers also obtained a self-report on the participants' olfactory abilities. For patients receiving dialysis, their olfactory function was moderately impaired in comparison with healthy control subjects. Hemodialysis was associated with a greater deficit than peritoneal dialysis. These differences reached statistical significance. Self-reported ability to smell did not differ between groups, indicating that olfactory impairment largely passed unnoticed by the patients. Since there was a significant improvement in the ability to smell after hemodialysis was performed, the authors reasoned that olfactory impairment can be rectified in renal patients through administering hemodialysis.

A further finding from the abovementioned study[22] was that chronic kidney disease most affects the ability to detect peripheral smells. Chronic renal failure alters sensitivity to peripheral odors and may cause a change in olfactory receptors or the olfactory mucosa[23], but does not produce an overall diminution in the ability to smell. One way to explain why renal patients were less able to detect ethanoic acid is that perception of this odor involves nociception by the fifth cranial nerve. Earlier studies[24] that looked at the somatosensory function of the fifth cranial nerve in renal patients showed the peripheral nervous system was more affected than the central nervous system. When patients in chronic renal failure receive a donor kidney[11], they recover the ability to smell normally, indicating that this defect is capable of being reversed[22].

A study undertaken by Koseoglu et al[25] assessed olfactory abilities in patients with chronic renal failure, not due to diabetes mellitus. The researchers looked at an olfactory function in several subgroups (not yet on dialysis, undergoing hemodialysis or on peritoneal dialysis). The largest olfactory impairment was seen in those undergoing peritoneal dialysis. In research by Nigwekar et al[26], patients with chronic renal failure were less able to identify odors and make a distinction between them, but the level at which they could perceive an odor was no different from that noted in healthy volunteers. This study also showed that olfactory dysfunction correlated with the presence of malnutrition.

According to our findings, some 12.5% of hemodialysis patients were anosmic, whilst 50% were hyposmic. The corresponding rates in the control group were 7.4% and 20.4%. According to Frasnelli et al[15], in a study involving 49 participants, 56% of patients with chronic renal failure undergoing hemodialysis had a degree of olfactory impairment. They ascertained that the ability to detect a smell was reduced by 11%, 38% had an impaired discriminatory ability, and 48% were less able to identify particular smells than normal[15]. Our study puts the combined total of anosmic and hyposmic patients at 62.5%, higher than Frasnelli et al[15] found.

There are numerous factors that affect or impair olfactory function in chronic renal failure patients, some of which are molecules taken out of the bloodstream through hemodialysis. It is noteworthy that the olfactory scores obtained by hemodialysis patients after dialysis resemble those obtained by patients undergoing peritoneal dialysis. This is evidence of the effect of chronic renal failure on olfaction[22]. The sense of smell is more intact in those on peritoneal dialysis than in hemodialysis in general, yet improves after dialysis. This finding accords with the observation that renal transplantation following chronic failure is sufficient to restore the recipients' ability to smell normally[22].

In a study undertaken by Raff et al[27], the effect on olfactory function of nutritional status and the accumulation of toxic metabolites in uraemia was studied. The toxins measured were methylamine, ethanamine, indoxyl sulphate, and P-cresol sulphate. There were 31 participants, all with chronic renal failure. Impairment of the sense of smell was found associated with raised C-reactive protein levels and being malnourished. However, the degree of impairment was not correlated with circulating albumin, cholesterol or the toxic metabolites investigated. This study provides evidence linking malnutrition and inflammatory states to the impairments in smell seen in cases of chronic renal failure.

Knowledge of how chronic renal failure impairs olfactory function is still incomplete, but there may be a connection with neurotoxicity. Changes in the ability to smell may be utilized as a non-invasive indicator of neuronal dysfunction. It appears that toxic metabolites which accumulate in uraemia may cause injury to the olfactory epithelial cells, the olfactory bulb and more central neural regions of importance in processing olfactory signals. Besides neurotoxicity caused by uraemic compounds, there are a number of other potential causes for nervous system injury, such as oxidative stress, inflammation and altered permeability of the blood-brain barrier[1].

There are, in addition, several pathological changes affecting the vascular supply to the brain in patients with chronic renal failure. These alterations include a thickened intima within arterioles, abnormal function of the endothelium, calcification within vessels and dysregulation of the intrinsic vascular mechanisms matching supply and demand[28].

When patients with chronic renal failure are successfully transplanted, their ability to smell recovers to a level comparable with healthy controls. This recovery relies on the innate ability of the olfactory mucosal neurons to undergo plastic change and recover function[29]. A potential treatment to boost olfactory function, which is under experimental evaluation, is theophylline. This agent is a phosphodiesterase inhibitor. It works by raising the level of cyclic adenosine monophosphate (cAMP) within cells resulting in greater activity of membrane-bound transporter proteins alongside the activity of vacuolar-type ATPase. A trial involving limited number of participants (n=7) discovered benefits from the administration of theophylline intranasally, which improved respiratory health in 70% of cases. All the participants were on hemodialysis for chronic renal failure[26].

Limitations

The limitation of our study is the ages of the study group being higher than the control group.

Conclusions

There is an association between undergoing hemodialysis and reduced scores for olfactory function as evaluated using the Sniffin' Sticks[30] test battery. Anosmia was detected at a frequency of 12.5% and hyposmia at 50% in this group of hemodialysis patients. Thus, the total frequency of olfactory impairment was 62.5%. The consensus view in the literature is that recovery from olfactory impairment occurs following successful transplantation thanks to the plasticity of the olfactory epithelium.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

SBÜ Antalya Training and Research Hospital Clinical Research Ethics Committee on the date 17.02.2022 and number 4/4.

Informed Consent

All subjects in the study gave consent to participate in the study.

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Authors' Contribution

Murat Kar: Planning, designing, data collection, literature survey, interpretation of the results, active intellectual support Mustafa Altintaş: Planning, designing, literature survey, interpretation of the results, active intellectual support Nuray Bayar Muluk: Planning, designing, literature survey, statistical analysis, interpretation of the results, active intellectual support, writing, submission Cemal Cingi: Planning, designing, literature survey, interpretation of the results, active intellectual support, English editing.

ORCID ID

Murat Kar: 0000-0003-3778-2133; Mustafa Altintaş: 0000-0001-7436-2862; Nuray Bayar Muluk: 0000-0003-3602-9289; Cemal Cingi: 0000-0003-3934-5092.

Availability of Data and Materials

The data are available from the corresponding author upon reasonable request.

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