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Original Article

Odor olfactory dysfunction in chronic kidney disease and diabetes mellitus and its association with nutritional factors

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Abstract

Background: Olfactory changes connection to deteriorated quality of life in chronic kidney disease cases (CKD) and diabetes mellitus (DM). The nutritional status is altered in CKD and DM and it closely interconnected with olfactory function. We aimed to study the olfactory dysfunction in these populations.

Methods: We conducted a cross-sectional research on CKD and DM cases aged 20-50 (27 healthy controls, 77 CKD patients, and 36 DM patients). We used the Iran Smell Identification Test (Iran-SIT) version of the University of Pennsylvania Smell Identification Test (UPSIT) to evaluate the olfactory function. The significant level was set as <0.05.

Results: Our 140 cases included 51.4% of men (mean age of 46.7±10.6 years). The total score of the Iran-SIT test indicated that olfactory impairment in the CKD was higher (16.2±4.2) than in the DM (18.8±2.1) and control groups (20.4±1.2) (P=0.001). It was determined that 54.5% of CKD patients and 38.9% of the DM group had olfactory dysfunction compared to 7.4% of the controls (P=0.001). Multiple regression analysis indicated that being men and low-density lipoprotein cholesterol (LDL-C) were related to olfactory dysfunction in the total population (OR: 4.55, P=0.037, and OR: 0.94, P=0.037). Still, it was only associated with LDL-C in the CKD group (OR: 0.93, P=0.013).

Conclusion: Based on the findings of this study, CKD and DM patients had a higher prevalence of olfactory dysfunction than the controls, which could be associated with some preventive nutritional factors. This information may help perform a screening program and early intervention on olfactory dysfunction in these systematic diseases.

Keywords: Chronic kidney disease, Diabetes mellitus, Hyposmia, Olfaction disorders, Uremia

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Olfactory dysfunction is frequent in people, especially the elderly, but they are not usually unknowing of this problem (1, 2). The prevalence of olfactory loss was reported as 1-20% (3). Several conditions may play a role in this dysfunction, as nasal infections, head injury, neurodegenerative diseases, chemical contact, aging, post-viral olfactory loss, and some chronic disorders, including chronic kidney disease (CKD) and diabetes mellitus (DM) (4-6). CKD is a significant health problem, mainly in developing countries; (7), as previously described, we have a notable CKD distribution (8, 9). Impaired olfactory function has recently been shown in CKD patients, as a common problems in these patients (1, 5). It can be due to uremic toxins, neuropathy, inflammation-oxidative stress, and malnutrition (1, 10-14). Our understanding of olfactory impairment is inadequate, so a broad explanation of the olfactory problem in CKD patients is needed (5). In addition, DM is a chronic disease associated with significant health-related complications (15, 16).

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Among the DM patients, olfactory dysfunction may occur secondary to some disorders like hyperglycemia, neuropathy, and nutritional status (3, 6, 17-21). So, olfactory testing can be useful in the diagnosis of early complications (22, 23). It has been shown that olfactory dysfunction affects the quality of life due to impaired smell and resulting taste functions that could affect nutritional intake (5). Olfactory dysfunction also affects personal and social activities by impairing the detection of the flavor of foods and notice for hazardous conditions as spoiled food or gas leakage (5, 24, 25). Clinical evaluation of olfactory function is needed to diagnosing and treating olfactory dysfunction (26). On the other hand, it has been revealed that some interventions might make better olfactory function in these groups (27, 28), so addressing this issue can benefit the patients concerned. In this study, we intended to examine the olfactory dysfunctions in non-diabetic CKD and DM patients compared to the general population and detect any differences between these patients. We also investigated any association between some nutritional factors and olfactory dysfunction in CKD and diabetic cases.

Methods

Current cross-sectional research assessed the olfactory function among CKD and DM patients compared to the controls. Current research was accepted by the local ethics committee (IR.SUMS.REC.1400.139). First, informed consent was obtained. We included cases aged 20-50 years with a duration of illness > 5years. We excluded those who did not want to collaborate and had disorders with probability of disturb olfactory function, as the deviated nasal septum, tight nasal valve, nasal adhesion, sinus disease, history of previous chemo-radiotherapy, history of head trauma, toxic chemical exposure, severe upper respiratory problems, history of nasal surgery, and nasal allergies. According to the objectives and type of study and referring to the previous study in this field (Reference No. 5), error of 5% and power of 80%, the minimum difference in the mean of odor identification score of eight between the 2 groups of patient and control, the standard deviation of 11.4 and 13.1, the ratio of 1:1, and generalizing the results to three groups using the formula:

$$n = \frac{\frac{1+r}{r} s^2 (z_{1-\alpha/2} + z_{1-\beta})^2}{(\partial)^2}$$

114 samples were estimated in total. The sample size increased to 140 to increase sampling accuracy and perform subgroup analysis. The participants included 27 controls and non-diabetic with GFR≥90, 77 non-diabetic patients with CKD (GFR 30-60), and 36 patients with DM (HbA_1c≥6.5 and GFR≥90). The distribution of the demographic characters was similar in the patient and control groups (p>0.05). We selected the subjects using the conventional method based on the physical examination and medical history.

The researcher recruited those using their archive files, checked the inclusion criteria, and contacted them to schedule a voluntary appointment. All factors were extracted from the latest patient's recorded some nutritional factors of laboratory data; some biochemical and nutritional factors: triglyceride (TG), cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting blood sugar (FBS), blood urea nitrogen (BUN), creatinine (Cr), albumin, hemoglobin (Hb), and HbA1c. All laboratory data were assessed using commercial kits. After explaining the research objectives, they were asked to fill out the required information: data gathering form, Iran-SIT, and Persian version of the questionnaire of olfactory disorders negative statements (QOD-NS) (25).

Iran-SIT: The University of Pennsylvania Smell Identification Test (UPSIT) is the first reference for the smell identification test in many countries (5). We used Iran-SIT as a validated version of UPSIT (26). It is a 24-item smell identification test based on a four-choice question. The examiner must scratch labels by a pencil to release the scents, so they sniffed that and select four alternatives. The diagnostic criterion of the olfactory disorder included scores 0-9 for anosmia, 10-13 for severe hyposmia, 14-18 for mild hyposmia, and 19-24 for normosmia (5).

Questionnaire of olfactory disorders: The QOD as a valid olfactory-specific QOL survey, contains a 17 parts (0: disagree to 3: agree, from 0 to 51), which upper numbers means more advanced the olfactory problem (25, 26).

Self-assessment: Patients assessed the olfactory on a scale of 0 to 10.

Definition: Body mass index (BMI) was measured as body weight divided by squared height in meters (29). The MDRD equation calculated the glomerular filtration rate (GFR) (30). Blood pressure was assessed by an aneroid sphygmomanometer.

Statistical analysis: Statistical Package for Social Sciences Version 22 (SPSS Inc, Chicago, IL, USA) was applied for statistical analysis). The continuous variables were displayed by mean±SD, and the quantitative information was presented by number and percentage. Qualitative data

analysis was made by the chi-square test. Independent two-sample t-test and ANOVA test (LSD Post Hoc Tests) were done to associate the means. Moreover, the Pearson correlation coefficient was employed to evaluate the quantitative variables. And logistic regression was done for variables with significance levels of less than 0.25 in one-way analysis. The significant level was set as <0.05.

Results

In current research, 140 participants, including 72 men (51.4). In current research, 140 participants, including 72 (51.4%) men with an average age of 46.7±10.6 years, were recruited, which were divided into a control group (27 cases), a CKD group (77 cases), and a DM group (36 cases). The baseline data did not have significant difference (table 1), except for higher HbA1c (p: 0.023) in DM and lower GFR and higher Cr in the CKD group (p<0.008). The most etiological factors for renal failure in the CKD group were hypertension in 29 (37.6%) and glomerulonephritis in 16 patients (20.8%).

Assessment of olfactory function by Iran-SITL: The Iran-SIT test indicated that the score of olfactory function in the CKD and DM groups were 16.2±4.2 and 18.8±2.1 compared to 20.4±1.2 in the control cases (p: 0.001, table 2).

Pairwise comparison showed that this difference was significant among the control and CKD groups and between CKD and DM groups (p<0.001). There was a significant difference among our groups in the classification of olfactory function (p: 0.001).

Table1. Baseline characteristics of our studied groups

Characteristics	Studied Groups, N:140			P-value
	Control n:27	CKD n:77	DM n:36	
Age, (year), Mean±SD	46.2±3.6	48.7±5.9	46.6±5.5	NS
Gender, Men, n (%)	12 (44.4)	45 (58.4)	15 (41.7)	NS
Body mass index, (kg/m2), Mean±SD	25.8±7.6	24.5±3.2	27.5±5.1	NS
Marital status, n (%)				
Married	23 (85.2)	69 (89.6)	29 (80.6)	NS
Divorced	3 (3.7)	6 (7.8)	5 (13.9)	
Single	1 (11.1)	2 (2.6)	2 (5.6)	
Level of education, n (%)				
Illiterate and under-diploma	16 (59.3)	48 (62.3)	20 (55.6)	
Diploma	10 (37.0)	16 (20.8)	11 (30.6)	NS
Associate degree	1 (3.7)	9 (11.7)	4 (11.1)	
Bachelor and higher	0 (0.0)	4 (5.2)	1 (2.8)	
Occupation, n (%)				
Unemployed	2 (7.4)	6 (7.8)	4 (11.1)	
Housekeeper	12 (44.4)	23 (29.9)	14 (38.9)	NS
Self-employed	5 (18.5)	26 (33.8)	8 (22.2)	
Employee	8 (29.6)	22 (28.6)	10 (27.8)	
Current smoker, n (%)	3 (11.2)	6 (7.7)	4 (11.1)	NS
Disease duration, (year), Mean±SD	-	7.6±4.7	8.7±3.6	NS
Primary cause of renal failure, n (%)				
Hypertension		29 (37.6)		
Glomerulonephritis	-	16 (20.8)	-	NS
Renal stone		12 (15.6)		
Others/unknown		20 (26.0)		

Comorbidities, n (%)				
Hypertension	-	41 (53.2)	7 (19.4)	0.142
History of CVD	-	6 (7.8)	2 (5.6)	
GFR, (ml/min/m2), Mean±SD	90.5±9.9	54.4±33.9	89.7±10.6	NS
Serum creatinine, (mg/dL), Mean±SD	0.7±0.4	3.6±1.9	0.8±0.6	NS
Blood urea nitrogen, (mg/dL), Mean±SD	13.9±4.8	31.6±10.9	12.7±3.5	NS
Total cholesterol, (mg/dL), Mean±SD	159.0±40.2	153.2±34.9	158.8±57.1	NS
Low-density lipoprotein cholesterol, (mg/dL), Mean±SD	90.1±40.2	79.4±28.2	85.8±30.1	NS
High-density lipoprotein cholesterol, (mg/dL), Mean±SD	45.0±12.7	43.7±12.2	45.7±15.3	NS
Triglycerides, (mg/dL), Mean±SD	175.4±92.2	163.5±92.9	184.4±85.2	NS
Hemoglobin, (g/dL), Mean±SD	14.2±2.1	12.2±1.6	13.3±1.2	NS
HbA1c, Mean±SD	5.2±1.8	5.7±1.5	7.1±2.3	0.023
Systolic blood pressure, mm Hg	128.8±18.2	138.8±18.2	135.2±17.6	NS
Diastolic blood pressure, mm Hg	76.6±7.8	82.3±6.6	81.6±11.4	NS

CKD: Chronic kidney disease, DM: Diabetes mellitus, GFR: Glomerular filtration rate, NS: not significant.

Table 2. Descriptive characteristics of olfactory function in our population

Olfactory function	Studied Groups, N:140			
	Control n:27	CKD n:77	DM n:36	P-value
Iran smell identification test (Iran-SIT)	20.4±1.2	16.2±4.2	18.8±2.1	0.001*,**
Olfactory dysfunction groups based on SIT				
Anosmia	-	7 (9.1)	-	
Severe hyposmia	-	12 (15.6)	2 (5.6)	0.001
Mild hyposmia	2 (7.4)	23 (29.9)	13 (36.1)	
Normosmia	25 (92.6)	35 (45.5)	21 (58.3)	
Olfactory dysfunction groups based on SIT				
Anosmia/Hyposmia	2 (7.4)	42 (54.5)	14 (38.9)	0.001
Normosmia	25 (62.6)	35 (45.5)	22 (61.1)	
Questionnaire of olfactory disorders (QOD)	8.5±5.1	24.3±10.7	20.7±7.6	0.001*
Self-assessment of olfactory dysfunction	9.4±0.9	8.2±2.1	8.6±1.6	0.027*,**,+

When looking from a different angle, we determined olfactory dysfunction in 42 (54.5%) CKD patients, 14 (38.9%) in the DM group, and 2 (7.4%) in the control group (p: 0.001). In addition, age had revers relation with the Iran-SIT score (r:-0.2, p: 0.045). Also, men scored worse than women (16.8±4.1 vs. 18.7±3.0, p: 0.002). We found no associations between the odor function and renal or nutritional parameters, except LDL-C in the whole population (r:-0.4, p:0.003), in CKD patients (r:-0.3, p: 0.025), and among DM patients (r:-0.5, p: 0.02); HbA1c and FBS were not relative to the Iran-SIT score (p>0.05); compared with normosmia, hyposmic patients were older (47.5±3.7 vs. 45.3±4.2, p: 0.045) and had lower total cholesterol (144.6±27.1 vs. 164.9±50.5, p: 0.045) and LDL-

C (71.8±23.5 vs. 90.0±31.2, p: 0.011); also, hyposmic patients in the CKD and DM groups had lower LDL-C than normosmic cases (72.6±25.7 vs. 86.9±30.2, p: 0.041 and 69.0±14.4 vs. 95.7±33.5, p: 0.029).

Questionnaire of olfactory disorders (QOD): QOD scores differed among CKD, DM, and control groups (24.3±10.7, 20.7±7.6, and 8.5±5.1, respectively, p: 0.001). Pairwise comparison showed this difference was significant among the control and CKD groups (p<0.001). We found an association between olfactory disorder and male gender in total patients (15.8±9.1 vs. 11.6±10.0, p: 0.06). Age was negatively associated with olfactory disorders in CKD patients (r:-0.3, p: 0.036). There were significant associations between some nutritional parameters: total cholesterol (r:-0.3, p: 0.05 in CKD and r:-0.5, p: 0.034 in DM), TG (r:-0.4, p: 0.008 in CKD and r:-0.7, p: 0.004 in DM), and BMI (r:-0.4, p: 0.004 in CKD and r:-0.6, p: 0.001 in DM).

Self-assessment of olfactory dysfunction: This score differed among CKD, DM, and control groups (8.2±2.1, 8.6±1.6, 9.4±0.9, respectively, p: 0.027), which Post Hoc test showed it was significant among the control and CKD groups (p<0.001), and control and DM groups (p: 0.001). We found an association between odor function and Cr in the whole population (r:-0.3, p: 0.035) and the CKD group (r:-0.4, p: 0.003). There was a relationship between smell function and TG in the DM group (r:-0.6, p: 0.011). In the study population, Iran-SIT correlated with self-assessment and QOD (r: 0.5, p: 0.001 and r:-0.2, p: 0.021). QOD was correlated with self-assessment (r:-0.3, p: 0.008). Also, in the CKD group, Iran-SIT was correlated with self-assessment (r: 0.5, p: 0.001).

Multiple regression analysis: The adjusted odds ratio (OR) showed that male gender and low LDL-C as a nutritional factor were related to olfactory dysfunction (OR: 4.55, 95% CI, 1.09–19.00), p: 0.037 and OR: 0.94 (95% CI, 0.89–0.96), p: 0.037). Analysis showed that a reduction in odor dysfunction was associated with lower serum LDL-C in the CKD group (OR: 0.93, 95% CI, 0.88–0.99), p: 0.013) (table 3).

Table 3. Adjusted odds ratio for binary logistic regression in the studied sample

Remained Variables	OR		P-value
	Value	95 % CI	
Age	1.14	0.94-1.38	0.171
Sex	4.55	1.09-19.00	0.037
BMI	1.15	1.00-1.23	0.054
Serum creatinine	0.41	0.86-1.98	0.270
Total cholesterol	1.01	1.01-1.03	0.056
Low-density lipoprotein cholesterol	0.94	0.89-0.96	0.037

CKD: chronic kidney disease, DM: diabetes mellitus, *: Significantly different among Control and CKD groups (LSD tests, p<0.001), **: Significantly different between CKD and DM groups (LSD Post Hoc tests, p<0.001), +: Significantly different between Control and DM groups (LSD Post Hoc tests, p: 0.001).

Discussion

Olfactory disorders are common in the general population (6). Some systemic pathologies have shown to change olfactory function severely (10, 16, 22). In line with that, we also found olfactory impairment in more than half of the CKD and nearly half of DM patients.

Olfactory defects in patients with kidney disease: This study presented a great frequency of olfactory dysfunction in CKD population (55% vs. 7% in control). Prior studies reported olfactory impairment in the CKD population from 30% to 83% (1, 2, 5, 10-12, 16, 31). The present data confirm previous studies that CKD patients have significantly decreased odor perception compared to the healthy control group (1, 5, 10, 11, 16, 32-35). This contrasts with other studies that failed to reveal a significant difference between the controls and dialysis patients (36). Also, some results show that smell function is related to the degree of renal impairment (5, 10, 12, 13, 16, 31).

Several standardized olfactory tests have been developed. To our knowledge, few studies are similar to the current study, using UPSIT in the CKD population before the need for dialysis (5, 31). Nigwekar et al. reported that 70% of CKD cases had an olfactory impairment versus 48% in the control group. Thus, they showed that kidney disease was considered a risk factor among odor deficit patients (OR: 6.0) (5). Also, Chewcharat et al. revealed the olfactory impairment was more seen in CKD cases than the control group (33% vs. 15% and OR: 2) (31). In addition, a study on old adults using UPSIT revealed that anosmia was associated with current and future poor kidney function

(OR: 1.2) (37). Although the olfactory function is affected in CKD, the variance of its prevalence in studies may be due to some reasons, including the use of different olfactory tests (10, 11, 16, 32-34), recruitment of participants with higher limits of age, (6) advanced CKD stages, (11, 14) and concurrent disorders that may affect the olfactory function (1, 5, 6, 10, 16). The moderately more cases with olfactory impairment were seen in controls in some studies (16% to 53%), (6, 11, 24, 35) it might because of the other causes of olfactory deficiency were not excluded before in some studies. Further, they did not have a limit for age. We found some associations between smell dysfunction and renal function markers or low levels of some nutritional parameters (total cholesterol, LDL-C, TG, and BMI).

There may be many reasons for the association between CKD and olfactory dysfunction, including uremic toxins, neuropathy, inflammation-oxidative stress, and malnutrition (1, 10-14, 37). Malnutrition, which affects morbidity and mortality, has been common in CKD patients. Given the rising numbers of CKD patients, the nutrition factors are a clinical challenge. The nutritional condition is changed as a result of diminished kidney function. On the other hand, nutrition and olfactory functioning are closely interconnected (13). Some potential causes for malnutrition in CKD include changes in taste and smell and the effects of polypharmacy (38). The reduction in calorie and protein ingestion is frequently accompanied by malnutrition. In addition, anorexia and nutrition problems may hurt the regeneration of olfactory epithelium cells (13, 38). Poor olfaction may be because of the uremic toxic (12, 13, 16, 39), that progress into uremic neuropathy characterized by olfactory peripheral epithelial neuron alterations and central processing dysfunctions (40).

These findings revealed how function smell improved after dialysis (11, 14) and was completely restored after renal transplantation (11-14, 17); this suggests that poor olfaction is sensitive to changes in uremic toxins (37). On the other hand, biochemical imbalance in CKD stimulates systemic inflammation and oxidative stress, so neurodegeneration and the immune system are activated; subsequently, smell recognition might deteriorate the olfactory epithelium (11, 14, 17, 18). Also, anorexia and malnutrition, as common problems in CKD patients, could limit the regeneration of olfactory epithelium and so contribute to olfactory impairment (11, 34). Moreover, few correlations have been reported between olfactory function and nutritional status, (6, 31) including a study that showed that olfactory identification correlated negatively with BMI and TG (6). Therefore, the olfactory assessment may be used as a part of the routine evaluation in this population and may be considered an early marker for CKD diagnosis (11, 13, 37).

Olfactory defects in patients with diabetes mellitus: We found a higher frequency of olfactory impairment in DM cases than in controls (39% vs. 7%), which is the same with other studies (3, 17-20). However, some studies reported that DM did not show a significant difference in olfactory function compared to the controls (6). Numerous studies also revealed the significant olfactory impairment of DM patients (60-68%) (6, 20, 21). We found associations between smell dysfunction and cholesterol, LDL, TG, and BMI. Instead, we found no correlation between FBS and HbA1c with olfactory scores as in another study (3). Olfactory dysfunctions among DM patients may be explained by hyperglycemia and insulin resistance, peripheral and central neuropathy, vascular disease, and nutritional status (3, 6, 17-21).

Some authors believe that olfactory dysfunction may accrue because of olfactory nerve damage, which should be considered as a new sign of central neuropathy (6, 18). The peripheral and central neurodegeneration may explain at least some of the olfactory dysfunction in DM patients (17). Insulin regulates the olfactory mucosa physiology, and intranasal insulin may improve olfactory function, so insulin resistance might also be part of the cause in olfactory impairment (3). Also, olfactory impairment is a sign of vascular disease, and an ordinary olfactory assessment may early detect microvascular complications in DM requirements to be additional elucidated (3, 19). Our patients' self-assessment of olfactory dysfunction was worse in CKD and DM groups than the controls, although that was statistically significant only among CKD and control groups. Some authors reported similar scores in their studies. A significant correlation between UPSIT, QOD, and subjective assessment was found in this study, which is comparable to others (5).

Additionally, in line with previous studies, we showed men had more olfactory dysfunction (3, 36, 37). In contrast, some studies reported that women with CKD had worse olfactory dysfunction than men; however, it was not significant (3, 6, 24, 35). Our results of olfactory impairment with aging is commonly uncontradictory with the other studies (3, 18, 19, 31, 37) demonstrated that age negatively impacted odor detection and QOL. However, another research did not reveal a significant association among age and smell function (6). One of the limitations of the present study was the inability to compare the CKD stages because we intended to control the effect of dialysis on olfactory impairment in advanced stages of CKD. Another limitation of this study was the absence of an

objective olfactory test. Although UPSIT is the best tool available for smell function assessment, it is a psychophysical test affected by subjective factors. The strength of current research was the evaluation of nutritional parameters that could disturb olfactory function in CKD and DM patients. This study establishes a higher frequency of olfactory impairment in CKD and DM patients compared to controls. Male and low LDL-C levels meaningfully correlated with olfactory dysfunction in CKD and diabetic patients. LDL as a nutritional factor is altered due to impaired renal function significantly related to olfactory functioning. Therefore, some interventions with improving nutritional approach may help with these issues in this population. Current results may help better diagnose, and disease control monitoring warrants further investigations of the mechanisms involved.

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