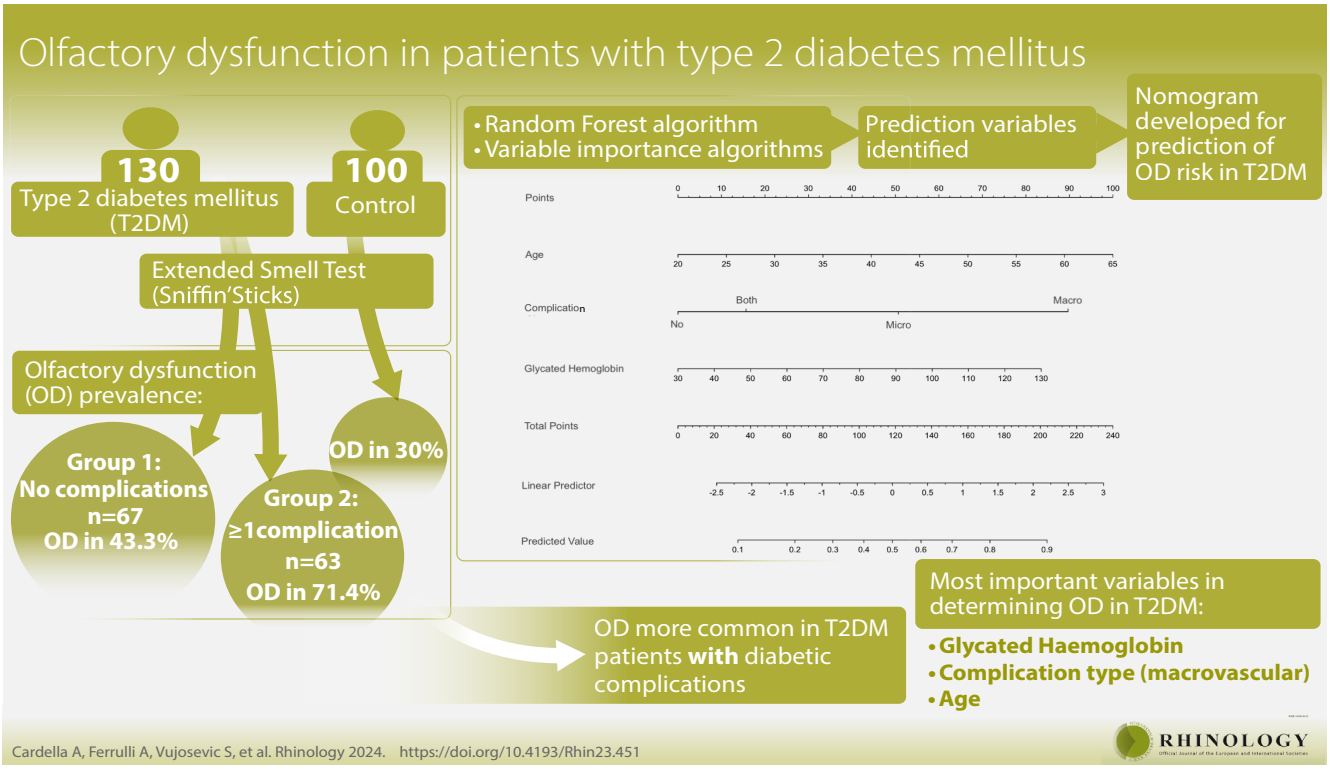
Olfactory dysfunction in patients with type 2 diabetes mellitus

Arianna Cardella[1,2], Anna Ferrulli[2,3], Stela Vujosevic[4,5], Andrea Preti[1], Federico Ambrogi[6], Ileana Terruzzi[2,3], Andrea Cecamore[1,6], Arkadi Yakirevitch[7,8], Antonio Schindler[9], Livio Luzi[2,3], Francesco Mozzanica[1,6]

Rhinology 62: 5, 537 - 547, 2024
https://doi.org/10.4193/Rhin23.451



Abstract

Background: diabetic complications and olfactory dysfunction (OD) in patients with type 2 diabetes mellitus (T2DM) seem related. This study aims to evaluate the prevalence of OD in T2DM patients and to analyze its relationship with diabetic complications. **Methods**: 130 T2DM patients and 100 comparable controls were enrolled. Olfaction was evaluated using the Extended Smell Test (TDI) and the Italian brief Questionnaire of Olfactory Disorders – Brief-IT-QOD. T2DM patients were divided into: "Group 1", patients with no complications, and "Group 2", patients with at least one diabetic complication. Non-parametric tests were used. Machine learning algorithms were applied to explore which variables were most important in predicting the presence of OD in T2DM. **Results**: The prevalence of OD was significantly higher in Group 2 than in controls (71.4% vs 30%) and in Group 1 (71.4% vs 43.3%). However, when comparing the TDI scores between Group 1 and 2 the only significant difference was found for the discrimination scale and not for the identification and threshold scales. Brief-IT-QOD scores were significantly higher in Group 2 than in controls. The Random Forest and variable importance algorithms highlighted the relevance of LDL, glycated hemoglobin, type of complication (macrovascular) and age in determining OD in T2DM. The last three variables were included in a nomogram for the prediction of OD risk in T2DM. **Conclusions**: T2DM patients with diabetic complications are more frequently affected by OD. Poor glycemic control, LDL values, age and presence of macrovascular complications are the more important factors in determining OD in T2DM patients.

Key words: diabetes complications, diabetes mellitus, olfaction disorders, smell, smell test

Introduction

Olfactory dysfunction (OD) is the reduced or distorted ability to smell during sniffing or eating[1,2]. When the alteration involves the strength of odors' perception (hyposmia, anosmia), OD is quantitative, whereas if the quality of odors' perception is changed (parosmia) or is evocated in the absence of an external odorant stimulus (phantosmia) the dysfunction is qualitative[1,2]. Since olfaction plays a crucial role in nutrition, social behavior and detection of dangerous compounds, OD has profound effects on quality of life (QoL), physical and social function, personal safety and even mortality[2–6]. A review on olfactory disorders and QoL by Croy et al.[4] highlighted patient-reported worries about food intake (increased/decreased quantities, decreased enjoyment, decreased appetite, difficulties in cooking), safety (eating spoiled food, failure to perceive fire, smoke, or gas), personal hygiene, social life, household chores and working life. Pinto et al.[6] analyzed a large population in the US and reported a mortality for anosmic patients four times higher than that of normosmic individuals. In contrast, hyposmic subjects had intermediate mortality, with a "dose-dependent" effect across the age range[6].

The prevalence of OD in the general population is high (1.5% to 25%) and increases to about 60% in individuals older than 65 years[1,2,7–10]. This is not surprising since numerous etiologies can determine an impairment of olfaction, the most common being sinonasal disease and upper respiratory infection, followed by head trauma, exposure to toxins/drugs, and congenital anosmia[1,4]. Nevertheless, up to 16% of patients screened at smell and taste centers are diagnosed with idiopathic OD[1].

Emerging evidence supports the hypothesis of a link between type 2 diabetes mellitus (T2DM), a chronic, non-communicable, multi-systemic pathology, and the development of OD[11-20]. However, results are limited or inconsistent, and the pathogenesis of OD in T2DM remains unclear. While some works have highlighted an association between T2DM and OD[12,13,17,20], and even between OD and microvascular[13] or macrovascular[11] diabetic complications, others have failed to identify these relationships[14,18,21,22]. It should be noted that these studies differ in the methodology for assessing olfaction, which is sometimes even self-reported; moreover, the type of diabetes affecting participants is not always clear, nor are exclusion criteria (i.e., factors potentially determining OD) adequately defined. Consequently, little is known regarding the relationship between OD and T2DM and its complications.

This study aims to assess the olfactory function (through psychophysical testing and subjective evaluation) in a representative sample of T2DM patients and to compare it with a control group of individuals without diabetes but comparable for sex, age, socio-demographic characteristics, and comorbidities (except for diabetes); and to evaluate the differences in OD within T2DM patients according to the presence of diabetic complications.

The relevance of this study lies in the fact that a more profound knowledge of the relationship between OD, T2DM, and the presence of diabetic complications might be helpful in clinical practice, as OD might be associated with a noticeable reduction in QoL. In addition, OD could interfere with metabolic control through changes in dietary habits and/or desire for certain foods that accompany altered olfaction[16]. Finally, a better awareness of the associations between diabetic complications and OD might be helpful to understand the mechanisms underlying the development of OD in T2DM.

Materials and methods

Study population

A group of 130 T2DM patients and a control group of 100 healthy individuals without T2DM and comparable for sex, age, socio-demographic characteristics, and comorbidities were enrolled. Exclusion criteria for both groups were: use of drugs affecting nasal mucosa, previous head trauma, congenital abnormalities of facial growth, systemic granulomatous disease, mucociliary clearance disorders, head and neck malignancies, radiotherapy to the head and neck, previous nasal surgery, cognitive function deterioration, neurodegenerative disorders, history of alcoholism, endocrine disorders, presence of major depression or anxiety disorder, inability to give informed consent, pathologies potentially affecting the sense of smell (such as COVID-19, acute or chronic sinusitis), age over 65 years. Additional exclusion criteria for the T2DM group were: fasting serum glucose ≤126 mg/dL, oral glucose tolerance test ≤200 mg/dL, or glycated hemoglobin (HbA1c) levels ≤6.5% at diagnosis of T2DM(24); decompensated diabetes or diabetic ketoacidosis at enrollment; variations in anti-diabetic therapy in the three months prior to enrollment.

Data were gathered from the multidisciplinary evaluation of T2DM patients, which represents the standard of care in our institution. Controls were recruited among volunteer hospital staff and individuals visiting the ENT outpatient clinic for non-rhinological issues. The study was conducted following the principles stated in the Declaration of Helsinki and was previously approved by the Ethical Committee of our hospital (Comitato Etico Indipendente IRCCS Multimedica; Protocol n. 506.2021). Informed consent was obtained by all enrolled individuals before the study.

Power analysis

Sample size calculation was based on data from our pilot study[20]. According to previous results, T2DM patients were significantly more at risk of developing OD than control subjects with an OR of 5.829. A sample size of 45 individuals per group reaches a power of 90% with an alpha level of 5% using a two-sided Z test.

Clinical evaluation

• *Otorhinolaryngological (ENT) examination*

Each of the enrolled subjects underwent an ENT examination, including nasal endoscopy (30-degree rigid endoscope, 2.7 mm in diameter), psychophysical olfactory testing, and self-assessment of olfactory-related QoL. Nasal endoscopy allowed to assess olfactory cleft patency and to rule out the presence of factors contributing to OD (acute or chronic rhinosinusitis or nasal polyps). The Extended Smell Test by "Sniffin' Sticks" (Burghart Messtechnik GmbH, Germany) was used for psychophysical olfactory testing. This is a validated method[25], which assesses the three domains of olfaction: odor threshold, discrimination and identification. Threshold testing involves determining the lowest concentration at which a particular odorous substance (n-butanol) can be discerned correctly from two negative controls. In odor discrimination testing, the participant is presented with 16 triplets composed of two identical odorants and a third, different one, and is required to indicate the latter. Finally, odor identification requires the subject to correctly name 16 common odors from a list of four verbal descriptors in a multiple forced-choice format for each pen. A total score is generated by the sum of the marks of each assessment, the TDI score (T = threshold; D = discrimination; I = identification), which ranges from 1 to 48. A TDI score ≥ 30.75 indicates normal olfactory function (normosmia), while scores below this mark indicate the presence of hyposmia[26]. During olfactory evaluation, stimuli were presented birhinally at about 5 cm under the nose with an interstimulus interval of at least 20 seconds to avoid adaptation.

For subjective evaluation of olfactory function, each enrolled individual filled in the validated Italian adaptation of the Brief Questionnaire of Olfactory Disorders (Brief-IT-QOD)[27]. This consists of 4 items concerning parosmia (QOD-P) and 7 items on quality of life (QOD-negative statements; QOD-NS); higher scores imply greater difficulties in daily life related to olfaction.

• *Diabetologic evaluation*

Complete physical examination with screening for neuropathy (evaluation of overall muscle strength and tone, tendon reflexes, sensitivity to touch and vibration through filament test and sensory testing) and peripheral artery disease (legs and feet pulses, doppler, measurement of leg blood pressure at ankle). In addition, laboratory tests for the measurement of lipids, HbA1c, glycemia and renal function (creatinine, estimated Glomerular Filtration Rate – eGFR, and urinalysis for microalbuminuria) were noted; measurement of body weight and height and computation of body mass index (BMI) were also performed. Finally, considering that metformin seems to be associated with lower odds of olfactory dysfunction in T2DM[28,29], also this variable was collected.

• *Ophthalmologic examination to ascertain the presence of diabetic retinopathy.*

• *Cardiologic examination to identify coronary artery disease or carotid artery pathology.*

According to the presence of diabetic complications, the cohort of T2DM patients was divided into two groups: Group 1 – patients without diabetic complications, and Group 2 – patients affected by at least one micro- or macrovascular diabetic complication[30]. Atherosclerotic Cardiovascular Disease (ASCVD) was considered a macrovascular complication according to the Standard of Care in Diabetes of the American Diabetes Association (2023)[31]. It includes coronary heart disease, cerebrovascular disease (e.g. stroke), or peripheral arterial disease (PAD) (e.g., obliterative arterial disease in the lower limbs), presumed to be of atherosclerotic origin. Coronary artery disease was detected on the basis of the electrocardiogram, while PAD was defined as ankle- brachial index ≤ 0.9 measured with a Doppler apparatus, as in the study of Gouvery et al.[13].

Diabetic nephropathy, a microvascular complication, was diagnosed by presence of albuminuria and/or reduced eGFR in the absence of signs or symptoms of other primary causes of kidney damage[31]. Specifically, normal albuminuria was defined as <30 mg/g creatinine, moderately elevated albuminuria was defined as ≥30–300 mg/g creatinine, and severely elevated albuminuria was defined as ≥300 mg/g creatinine. Taking into account also eGFR, Stage 1 and stage 2 chronic kidney disease (CKD) were defined by evidence of high albuminuria with eGFR ≥60 mL/min/1.73 m^2, and stages 3–5 CKD by progressively lower ranges of eGFR[31].

Diagnosis of diabetic peripheral neuropathy (DPN), a microvascular complication, was based on the physical examination by evaluating temperature or pinprick sensation and vibration. A Diabetic Neuropathy Index (DNI)(32) >2 was considered suggestive of DPN (AMD-SID, Italian standards for the treatment of diabetes mellitus, 2018)[33]. A diagnosed Diabetic Autonomic Neuropathy (e.g., gastroparesis, cardiovascular autonomic neuropathy) was also considered a diabetic complication.

Diagnosis of diabetic retinopathy, a microvascular complication, was diagnosed in presence of at least 1 microaneurysm and/or retinal hemorrhage and/or other signs of retinal damage[34].

Statistical analysis

Data were presented as median and interquartile ranges (IQR) for continuous variables or frequency and percentage for categorical variables. The normality of the distribution and the equality of variances were preliminarily tested using Kolmogorov–Smirnov's and Levene's tests, respectively. In evidence of non-normal distribution, non-parametric tests were used (Kruskal-Wallis and Mann-Whitney tests as appropriate). Categorical variables were compared using the Fisher test. This was used to evaluate the associations between the presence of T2DM (with or without complications) and OD. Odds ratios (OR) and their 95% CI were reported. A random forest model[35] for classification was used to determine which variables contribute

Table 1. Clinical and demographic characteristics of the enrolled subjects.

	T2DM patients (n=130)	Control subjects (n=100)	p
Age (years)	59 (54 – 63)	58 (52 – 61.5)	0.117
Sex			
Males	71 (54.6%)	43 (43%)	0.086
Females	59 (45.4%)	57 (57%)	
Smoking			
Non-smokers	80 (61.5%)	73 (73%)	0.154
Active and former smokers	50 (38.5%)	27 (27%)	
Alcohol			
No	113 (86.9%)	92 (92%)	0.287
Yes	17 (13.1%)	8 (8%)	
Allergy			
None	94 (72.3%)	63 (63%)	0.204
Allergic	36 (27.7%)	37 (37%)	
BMI (kg/m^2)	28.2 (24.7 – 32.2)	24.5 (22.6 – 28.6)	0.001
Diabetic complications			
None	67 (51.5%)	/	/
Retinopathy	33 (25.4%)		
Nephropathy	19 (14.6%)		
Neuropathy	15 (11.5%)		
Coronary artery disease	12 (9.2%)		
Stroke	2 (1.5%)		
Carotid artery disease	8 (6.2%)		
Peripheral artery disease	7 (5.4%)		

Results are reported as median and confidence interval (in brackets) and frequencies. The results of Mann–Whitney and Fisher tests are reported. Statistically significant differences are highlighted in bold. T2DM = Type 2 Diabetes Mellitus; BMI = Body Mass Index.

the most in predicting the outcome of OD in T2DM. Random forests are collection of binary trees estimated on bootstrap samples of the data. Results of the different trees are aggregated for obtaining stable predictions. Demographic (age; sex), clinical (smoking; alcohol consumption; allergy; BMI; type of diabetic complication; disease duration; metformin use) and biochemical variables (HbA1C; triglycerides; total cholesterol; high and low density lipoprotein cholesterol; glycemia) were considered and ranked according to two criteria[36]: 1) variable importance (VIMP): first the prediction error is computed for each tree on the data out of the bootstrap sample, then the prediction error is recalculated after permuting the variable of interest (shuffling its values). A variable that is associated with the outcome, after a random shuffle of the values will cause an increase in the prediction error while a variable not associated will have a minimal impact; 2) Minimal depth, which measures the average depth of the first split over all the trees of the forest. A logistic regression model was then fitted for the estimation of the risk of OD in T2DM according to the most important variables for both algorithms, and a nomogram was proposed[37,38].

All statistical tests were performed using the SPSS Statistics 24.0 software (SPSS Inc, Chicago, IL, USA).

Table 2. Frequency of OD and results of the Extended Smell Test by "Sniffin' Sticks" (TDI) in the group of patients with type 2 diabetes (T2DM) and controls.

	T2DM patients (n=130)	Control subjects (n=100)	p
OD			
No	56 (43.1%)	70 (70%)	0.001
Yes	74 (56.9%)	30 (30%)	
TDI	29.0 (26 – 31.75)	31.25 (29.5 – 33.5)	0.001
Threshold	6.0 (4.75 – 7.125)	6.25 (5 – 7.75)	0.746
Discrimination	12 (9 – 12)	12 (10 – 13)	0.005
Identification	12 (11 – 13)	13 (12 – 14)	0.003

Results are reported as frequency and percentage for OD and median and interquartile range for TDI scores. The results of Mann-Whitney and Fisher test are also reported. OD: olfactory dysfunction.

Results

A total of 130 T2DM patients and 100 control subjects were enrolled. The T2DM group was composed of 71 males and 59 females with a median age of 59 years (IQR = 54 – 63), while the control group comprised 57 males and 43 females with a median age of 58 years (IQR = 52 – 61.5). The clinical and demographic characteristics of the enrolled individuals are reported in Table 1. No difference in the distribution of age, sex, smoking habit, alcohol consumption, and allergy was demonstrated between the two groups. On the other hand, the distribution of BMI was significantly different between the two groups (p = 0.001 at Mann-Whitney test), with T2DM patients having higher BMI scores than control subjects.

Among patients, the median duration of T2DM was nine years (IQR = 4 – 15 years) and 77 of them were under metformin treatment. The presence of diabetic complications was detected in 63 patients out of 130 (48.5%). Retinopathy was the complication most frequently encountered (33/63 cases). Thirteen patients suffered from two or more diabetic complications. The distribution of diabetic complications is reported in Table 1.

Psychophysical olfactory testing

The olfactory assessment was performed with the Extended Smell Test by "Sniffin' Sticks". According to their TDI score, subjects were categorized as normosmic or not. A significant difference in the frequency of OD was demonstrated between T2DM patients and controls. Specifically, OD was observed in 74 of 130 T2DM patients (56.9%) and 30 out of 100 controls (30%) (OR = 3.083; CI: 1.777 –5.349; p = 0.001 at Fisher test). Furthermore, the median TDI total score for T2DM patients was 29 (CI: 26 – 31.75), while that of control subjects was significantly higher at 31.25

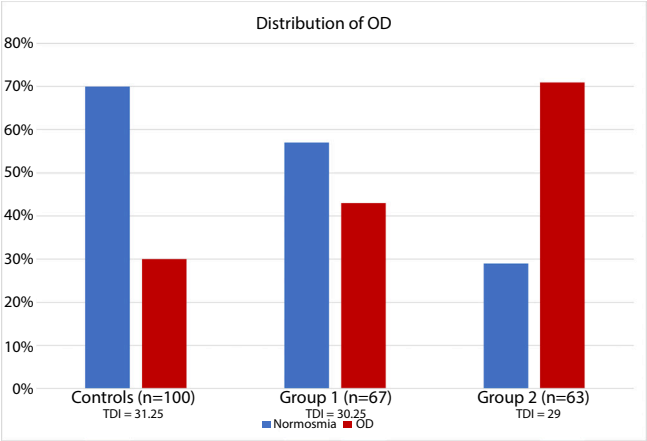


Figure 1. Distribution (in percentage) of olfactory dysfunction (OD) in the studied population. Group sizes in absolute numbers are indicated in brackets. Median TDI score per group is also shown. Controls: control subjects; Group 1 = Type 2 Diabetes Mellitus patients without diabetic complications; Group 2 = Type 2 Diabetes Mellitus patients with diabetic complications.

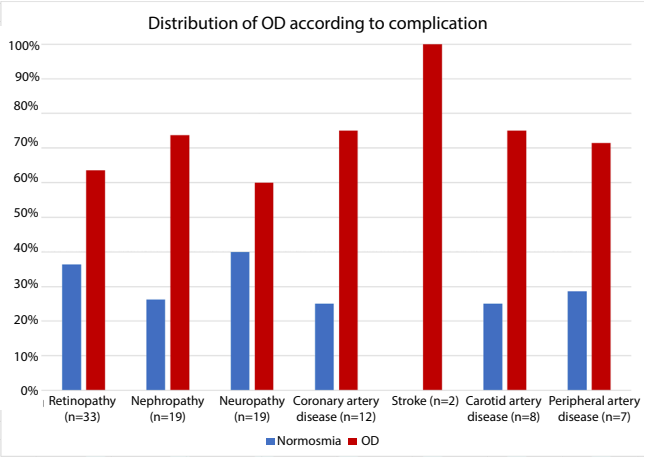


Figure 2. Distribution (in percentage) of olfactory dysfunction (OD) in Type 2 Diabetes Mellitus patients according to type of complication. Group sizes in absolute numbers are indicated in brackets.

(CI: 29.5 – 33.5; p =0.001 at Mann-Whitney test). The comparison of the TDI subscale scores between T2DM patients and controls is reported in Table 2. No differences were found between the threshold scores obtained in patients and controls.

There was no evidence of association between the use of metformin and OD (OR: 1.02, 95%CI: 0.50-2.07, p=1.00) or complications (OR: 1.18, 95%CI: 0.59-2.38, p=0.72). On the other hand, OD was found in 29 out of 67 uncomplicated patients (43.3% - Group 1) and 45 out of 63 patients with complications (71.4% - Group 2) (Figure 1). This difference was found to be significant at Fisher test, and Group 2 was significantly at higher risk of developing OD than Group 1 (OR = 3.276; CI: 1.579 – 6.795; p = 0.001). Table 3 reports the results of the comparison of the frequency of OD among the Groups 1 and 2 and control subjects: there was no difference between Group 1 and control subjects (p = 0.078 at Fisher test); on the other hand, a statistically significant difference in the frequency of OD between Group 2 and controls (p = 0.001) was found. Results of the Extended Smell Test are also shown in Table 3.

The median TDI scores were 30.25 (CI: 27 – 33) for Group 1, 28 (CI: 25.5 – 31) for Group 2, and 31.25 (CI: 29.5 – 33.5) for control subjects. The Kruskal Wallis test for the comparison of the medians TDI among controls, Group 1 and Group 2 was significant (p < 0.001). Post-hoc analysis with Dunn's test, showed a significant difference between Group 1 and 2 (p = 0.014) and between Group 2 and controls (p < 0.001), while the median TDI score of Group 1 was not significantly different from the median score of control subjects (p = 0.092).

Similarly, the median discrimination scores were 12.00 (CI: 10 – 14) for Group 1, 10.00 (CI: 9 – 11) for Group 2, and 12.00 (CI: 10 – 13) for control subjects. The Kruskal Wallis test for the comparison of the median discrimination scores among controls, Group 1 and Group 2 was significant (p < 0.001). Post-hoc analysis with Dunn's test, showed a significant difference between Group 1 and 2 (p = 0.003) and between Group 2 and controls (p < 0.001), while there was no significant difference between Group 1 and control subjects (p = 0.392).

Similarly, the median identification scores were 12.00 (CI: 11 – 13) for Group 1, 12.00 (CI: 9.75 – 14) for Group 2, and 13.00 (CI: 12 – 14) for control subjects. The Kruskal Wallis test for the comparison of the median discrimination scores among controls, Group 1 and Group 2 was significant (p = 0.003). Post-hoc analysis with Dunn's test, showed a not significant difference between Group 1 and 2 (p=0.638) and a significant difference between Group 2 and controls (p=0.007), and between Group 1 and control subjects (p = 0.016).

On the other hand, no significant difference was found in the threshold test for Group 1, Group 2, and control subjects (p = 0.157 at Kruskal Wallis test).

Concerning diabetic complications, 39 patients suffered from microvascular diseases, 11 from macrovascular complications and 13 from both. The distribution of OD among these categories is reported in Table 4, and the differences were not significant at the Fisher test (p = 0.703). The distribution of OD according to the specific type of complication is reported in Figure 2. No differences were demonstrated at the Fisher test (p = 0.946). Specifically, OD was present in 21 out of 33 retinopathic patients (63.6%), 14 out of 19 patients affected by nephropathy (73.7%), 9 out of 15 patients suffering from neuropathy (60%), 9 out of 12 patients with coronary artery disease (75%), both patients with

Table 3. Frequency of OD and results of the Extended Smell Test by "Sniffin' Sticks" in the two groups of patients with type 2 diabetes (with and without diabetic complications) and controls.

	Control Subjects (n = 100)	Group 1 (n = 67)	Group 2 (n = 63)
OD			
No	70 (70%)	38 (56.7%)	18 (28.6%)
Yes	30 (30%)	29 (43.3%)	45 (71.4%)
TDI	31.25 (29.5 – 33.5)	30.25 (27 – 33)	28 (25.5 – 31)
Threshold	6.25 (5 – 7.75)	6.25 (5.25 – 7.5)	5.625 (4.4375 – 7)
Discrimination	12 (10 – 13)	12 (10 – 14)	10 (9 – 11)
Identification	13 (12 – 14)	12 (11 – 13)	12 (9.75 – 14)

Results are reported as frequency and percentage for OD and median and interquartile range for TDI scores. OD: olfactory dysfunction. Group 1: Type 2 Diabetes Mellitus patients without complications. Group 2: Type 2 Diabetes Mellitus patients with complications.

previous stroke (100%), 6 out of 8 patients affected by carotid artery disease (75%), and in 5 out of 7 patients suffering from peripheral macroangiopathy (71.4%).

Subjective olfactory assessment

The subjective olfactory assessment was performed with the Brief-IT-QOD.

The median QOD-P scores were 1.50 (CI: 0.00 – 3.25) for Group 1, 3.00 (CI: 0.00 – 4.00) for Group 2, and 0.50 (CI: 0.00 – 3.00) for control subjects. The Kruskal Wallis test for the comparison of the medians QOD-P among controls, Group 1 and Group 2 was significant (p = 0.003). Post-hoc analysis with Dunn's test, showed a significant difference between Group 2 and controls (p=0.014) while the difference between Group 1 and controls, and Group 1 and Group 2 were not significant (p=0.114 and p = 0.144, respectively).

Regarding QOD-NS, the median QOD-NS scores were 0.00 (CI: 0.00 – 2.00) for Group 1, 0.00 (CI: 0.00 – 3.00) for Group 2, and 0.00 (CI: 0.00 – 0.00) for control subjects. The Kruskal Wallis test for the comparison of the medians QOD-NS among controls, Group 1 and Group 2 was significant (p = 0.002). Post-hoc analysis with Dunn's test, showed a significant difference between Group 2 and controls (p = 0.001) while the difference between Group 1 and controls, and Group 1 and Group 2 were not significant (p = 0.077 and p = 0.160, respectively).

Variable ranking and risk prediction

The Random Forest and the variable importance algorithms were used to explore which demographic, clinical and biochemical variables were most important to predict the presence of OD in T2DM patients (Figure 3). According to VIMP, LDL values, HbA1c values, type of complication (macrovascular) and age were the important variables for the presence of OD in T2DM. Minimal depth also suggested the last two as having the greatest weight in predicting the outcome.

A logistic regression model considering age and type of complication together with HbA1c, which was the third ranked variable according to VIMP and deemed clinically important to explain complications in diabetic subjects, was developed. A nomogram for the prediction of the risk of OD in T2DM was also created (Figure 4). The bootstrap corrected c-index is equal to 0.69. The correction does not consider the variable selection algorithm.

The measures of model fit (Akaike and Bayesian information criterion), odds ratio, 95% confidence interval, and p-values for every variable of the multivariable model are reported in Table 5. Although the association with age and HbA1c is not statistically significant, these variables were retained in the regression model for their clinical importance and as age was strongly suggested by Minimal Depth criterion. The association with type is significant (p=0.025 at Likelihood ratio test) and type appears the most important variable in the model for discriminating OD.

Table 4. Frequency of olfactory dysfunction (OD) according to type of diabetic complication.

	Microvascular complications	Macrovascular complications	Both
OD			
No	12 (30.8%)	2 (18.2%)	4 (30.8%)
Yes	27 (69.2%)	9 (81.8%)	9 (69.2%)

Results are reported as frequency and percentage.

Table 5. The measures of model fit (Akaike and Bayesian information criterion, AIC and BIC, respectively), odds ratio, 95% confidence interval, and p-values for every variable of the multivariable model are reported.

	OR	2.5%	97.5%	z val.	p
intercept	0.01	0.00	0.58	-2.21	0.03
Age	1.06	0.9	1.13	1.77	0.08
Type 1	3.69	1.30	10.47	2.45	0.01
Type 2	10.07	1.16	87.57	2.09	0.04
Type 3	1.50	0.35	6.46	0.54	0.59
Hb gli	1.02	0.99	1.05	1.54	0.12

OR = odds ratio. Type = type of complication: 1 = microvascular complications, 2 = macrovascular complications, 3 = both micro- and macrovascular complications; Hb gli = glycated hemoglobin value. MODEL FIT: AIC = 139.64, BIC = 155.67

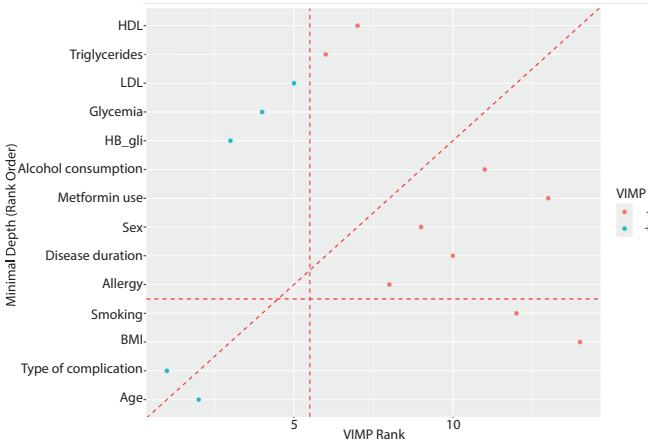


Figure 3. Random forest for variable ranking. Variable Importance (VIMP) and Minimal Depth are two criteria proposed with random forest algorithms to evaluate variable importance in explaining olfactory dysfunction (OD). The variables on the diagonal red line are those ranked equally by the two methods. The vertical line divides variables with positive VIMP (left) from those with negative VIMP (right; unimportant). The horizontal line indicates the minimal depth threshold: important variables are below the line. Hb_gli = glycated hemoglobin value; BMI = body mass index; type of complication, microvascular/macrovascular.

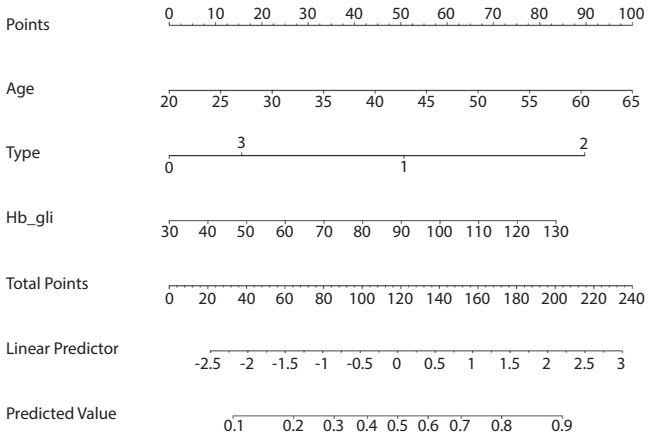


Figure 4. Nomogram for prediction of olfactory dysfunction (OD) in Type 2 Diabetes Mellitus patients. Hb_gli = glycated hemoglobin value; BMI = body mass index; type = type of complication: 0 = no diabetic complications, 1 = microvascular complications, 2 = macrovascular complications, 3 = both micro- and macrovascular complications. To use the nomogram, each variable, represented by a scale, is mapped to the "Points" scale on the top. The points must be summed and then converted into a risk prediction. For example, a patient of age 50 scores 67 points, no diabetic complications scores 0 points, and Glycated Hemoglobin equal to 50 scores about 17 points. The resulting total score is then 84 corresponding to an OD risk of about 30%. A subject of age 50, with macrovascular complications and Hemoglobin equal to 100, will score 67, 90 and 58 points respectively, for a Total Point of 215, corresponding to an OD risk equal to about 90%.

Discussion

In this study the prevalence of OD in T2DM was analyzed and the results suggest that patients with diabetic complications are more frequently affected by OD compared to controls and to patients with T2DM without complications. However, it must be noted that, when comparing the TDI subscales scores between T2DM patients with and without diabetic complications, the only significant difference was found for the discrimination score.

Patients with diabetic complications demonstrated a poorer olfactory-related quality of life. Interestingly, some clinical and demographic factors seem to play a role in determining OD, in particular, patients with macrovascular diabetic complications seem to be more at risk of OD.

Prevalence of OD

T2DM patients were found to be significantly more frequently affected by OD than controls (56.9% vs 30%, p=0.001) and scored significantly lower at TDI total, identification, and discrimination scores (while no differences in the threshold scores were demonstrated between the two groups). These data are only partially in line with previous reports. Gouveri et al.[13] reported that T2DM patients had lower TDI total, identification, discrimination, and, also, threshold scores than control subjects. Similarly Brady et al.[12] found a significant difference in the all the TDI subscales scores between T2DM patients and controls. Yazla et al.[15] found a significant reduction in the olfactory function of T2DM patients compared to controls and reported that also the threshold was significantly lower in patients with T2DM. In our sample the threshold score of the TDI was not significant. It is possible that this difference might be related to the methodology used in the above mentioned studies (Yazla et al.[15] for example did not used the TDI to evaluate the thresholds) and/or to the characteristics of the cohorts of patients included.

In both the studies of Gouveri et al.[13] and Brady et al.[12], a significant percentage of T2DM patients had diabetic peripheral neuropathy (DPN) (32 out of 119 and 18 out of 51, respectively) while in our study only 15 out of 130 suffered from this complication. Heckmann et al.[39], who analyzed the smell function in a group of patients affected by polyneuropathy using the TDI, found that the smell dysfunction was more pronounced for the threshold part of the olfactory test battery, whereas discrimination and identification of odors were relatively preserved. It is consequently possible that the higher prevalence of DPN in the studies of Gouveri et al.[13] and Brady et al.[12] might have influenced the results of the thresholds scale of TDI (in particular, in the study of Gouveri et al.[13] T2DM patients with DPN scored the lowest on threshold scale).

According to the results of the present study, T2DM patients

were significantly more at risk of developing OD than control subjects, with an OR of 3.083. This is in line with the population-based study of Bramerson et al.[21] who reported an OR of 2.6. On the other hand, Kim et al.[19] reported an OR of 1.58 in their systematic review. It should be noted that the authors calculated the OR considering only the 4 studies which provided this datum. It is possible that methodological differences among the studies included in the meta-analysis might have played a role. For example, Khil et al.[40] did not find a relationship between OD and diabetes (OR = 1.16) but in their study the olfactory function was assessed using only the Sniffin' Sticks– Screen 12-set (which is an identification test used only for screening purposes), they did not differentiate between type 1 and type 2 diabetes and the enrolled patients did not undergo a ENT evaluation before olfactory testing, thus potential other sinonasal causes of OD could not be excluded. Similarly, in the study of Chan et al.[17], who reported a non-significant higher prevalence of severe hyposmia/anosmia in patients with diabetes (OR = 1.57), the olfactory testing was performed with the 8-item pocket smell test, the enrolled patients were not stratified by diabetes subtype, and no ENT evaluation was performed before the olfactory assessment.

Interestingly there was no evidence of association between the use of metformin and OD. This datum is not in line with the results of Vohra et al.[29]. The authors found that metformin treatment was associated with a significantly lower odds of OD (OR = 0.26) in a group of 226 patients with diabetes (119 matched pairs). Similarly, Assi et al.[28] found that metformin users had 58% lower odds of impaired olfactory identification and 67% lower odds of impaired olfactory sensitivity and suggested that metformin might play a protective effect on olfaction. It is possible that the diverging results of our study might be related to differences in the studied population and in the methods used to assess the olfactory function. In our study the mean age of the participants is lower (median age of 59 years) than in the study of Vohra et al.[29] (mean age of 64.4 years) and in the study of Assi et al.[28] (mean age of 70 years). In addition, we included only patients with T2DM. Finally, we used the Extended Smell Test by "Sniffin' Sticks" for psychophysical olfactory testing while in the above-mentioned papers the eight-item Pocket Smell Test was used. It is possible that these differences might explain the different results reported in our study. For this reason, further investigations are necessary to better understand this point.

Olfactory-related quality of life

Group 2 patients expressed significantly higher scores in the two subdomains of the Brief-IT-QOD than control subjects, implying greater difficulties in daily life related to olfaction. Group 1 individuals, on the other hand, only had scores significantly higher than controls in the NS subdomain, while no significant difference was found regarding the questions about parosmia. These results reflect OD's burden on QoL, as described in literature[3-6]. Specifically, in their review on olfactory disorders and quality of life, Croy et al.[4] concluded that about a third of the patients suffering from OD express a noticeable reduction in QoL and enhanced depression. We showed that the population of T2DM patients who suffered from a higher rate of OD, i.e. Group 2, complained of greater difficulties in daily life.

OD and diabetic complications

When comparing T2DM patients with and without diabetic complications, OD was far more frequent among patients with complications. Only a few studies analyzed the association between diabetic complications and OD, and the results available so far are inconsistent. In a pilot study performed by our group, patients with T2DM were found considerably more at risk of developing OD than control subjects[20]. Le Floch et al.[41] and Weinstock et al.[11] found an association between diabetes and micro- and macrovascular complications respectively but in both studies the analyzed population was not stratified by diabetes subtype. Gouveri et al.[13] showed that the number of diabetic complications was inversely associated with the TDI score, and that diabetic peripheral neuropathy and retinopathy were significantly associated with lower olfactory scores. In contrast to our results, other authors[14,15,18,22,23] did not find any association between OD and complications of diabetes. It is possible that these diverging results might be related to differences in the methodology of the studies. For example, in the study of Naka et al.[23], who did not find any difference in OD among patients with complicated and uncomplicated diabetes, and controls, the smell function was only screened using a five-item smell identification test, in addition the number of enrolled patients[67] and controls[29] is lower than in our study. In the work of Yazla et al.[15] the only diabetic complication taken into consideration was the diabetic peripheral neuropathy and no information regarding the association of OD with the other micro- and macrovascular complications have been provided. Finally, Kaya et al.[22] did not detect any significant difference in olfactory test scores of T2DM patients with and without micro-vascular complications but did not provide any information regarding the relationship between OD and macrovascular ones. In our study we included 130 T2DM patients and 100 controls. Each patient underwent an ENT, diabetologic, and ophthalmologic examination to detect the presence of both micro- and macrovascular complication. In addition, the olfactory abilities were assessed using the Extended Smell Test by "Sniffin' Sticks", a validated method able to assess the three domains of olfaction: odor threshold, discrimination and identification[25].

Interestingly, in our work, uncomplicated diabetics did not have a significantly lower TDI score than controls, as was also shown by Brady et al.[12]. On the other hand, Yazla et al.[15] found a significant difference between the scores of these two populations.

Nevertheless, it is worth mentioning that the two cited studies only analyzed patients affected by diabetic peripheral neuropathy as a complication.

In our work, Group 1 had a median TDI of 30.25, which is just 0.25 point below the normative value for normosmia[26], indicating the possibility of a continuous spectrum of decreasing olfactory function with worsening T2DM. Our results also suggest that diabetic complications and OD are somewhat related. Even if no definitive conclusion may be formulated on the basis of the results reported here, it is possible to hypothesize that, since the onset and progression of diabetic complications are linked to hyperglycemia, glucose toxicity and oxidative stress[16], the same mechanisms may come into play in the development and progression of OD in T2DM patients. For example, orexin, a neuropeptide that regulates appetite, has been shown to increase olfactory sensitivity thanks to stimulation of the olfactory bulb (OB) by glucose-sensitive orexin-secreting neurons in the lateral hypothalamus[42]. Since this cell population is inhibited by glucose, it may be possible that hyperglycemia in diabetic patients affects olfactory function through inhibition of the lateral hypothalamus, which in turn depletes the OB of orexin stimulation[16]. Furthermore, thinning in the insular, cingulate, and orbitofrontal cortices determined by hyperglycemia may facilitate the development of OD[17,43].

Variable importance and risk prediction

To the best of our knowledge, only the paper of Lotsch et al.[44] used machine learning algorithms to study smell function. In particular, the authors tried to evaluate if the risk of developing diabetes in the next 10 years was somehow related to the olfactory function and concluded that the sense of smell is not a good predictor of diabetes.

In the present study, the random forest, a machine learning model, was applied to establish which demographic, clinical and biochemical variables are important in determining the occurrence of OD in T2DM. Our results highlighted the relevance of age, diabetic complications, HbA1c values and LDL cholesterol values. Olfactory function is known to decrease with age, and it has been shown that about 60% of the population older than 65 is affected by some degree of olfactory deficit[8,10]. It is, therefore, not surprising that even in a population younger than 65, age appears as an important predictor of OD. The presence of macrovascular complications was also relevant in determining OD. This result is more challenging to interpret because even if some previous studies demonstrated an association between diabetic complications and OD[11,13], only in the study of Weinstock et al.[11] a significant correlation between OD and macrovascular complications was found. Furthermore, it is interesting that also higher LDL values, which are strongly implicated in the atherosclerotic process at the basis of the development of macrovascular complications themselves[45], were relevant for the presence of OD. However, this datum should be taken with extreme caution because in our sample there were only 11 patients suffering from macrovascular complications and 13 having both microvascular and macrovascular complications. We believe further studies are necessary to shed more light on these points. Finally, the role of HbA1c is interesting. Sanke et al.[46] showed that olfactory test scores independently correlated with Mini-Mental State Examination score, education level, HbA1c and serum adiponectin levels in 250 elderly Japanese people with T2DM. On the other hand, Min et al.[47] failed to find an association between smell dysfunction and blood glucose, HbA1c, and serum insulin levels. Still, they observed a significant dose-response trend in the odds of smell dysfunction and increasing blood glucose quintile and demonstrated an association between smell dysfunction and insulin resistance in US adults older than 50. HbA1c reflects the average blood sugar level of the previous three months. A higher HbA1c means consistent hyperglycemia over a long period and signifies inadequate disease control. In a similar – and consequential – manner, the presence of diabetic complications implies low control of T2DM and a more severe diabetes phenotype. The risk of developing diabetic complications is proportional to the magnitude and duration of hyperglycemia[48-51]. Considering this, it is possible to hypothesize that the onset and progression of OD are linked to chronic hyperglycemia by a mechanism that might be the same which drives the appearance of diabetic complications. Further studies are needed to verify this hypothesis.

A nomogram is the graphical representation of a mathematical formula, making the use of the predictive tool easier. To the best of our knowledge, this is the first study to develop a nomogram to estimate the risk of OD in T2DM. The possibility of predicting the presence of OD in diabetic patients is intriguing because the problems associated with OD itself may extend beyond a reduction in QoL. As olfaction is believed to alter feeding states[51], the changes in dietary habits and/or desire for certain foods that accompany altered olfaction could affect metabolic control, with long-term consequences for T2DM natural history.

The main limitation of this study resides in the restricted number of diabetic patients affected by complications. A larger sample of individuals with complications in general and for each diabetic complication specifically, would have allowed to evaluate their role in determining OD. However, it should be noted that the aims of this study were to assess the olfactory function in a representative sample of T2DM patients and to evaluate the differences in OD within T2DM patients according to the presence of diabetic complications and not to evaluate the influence of a specific diabetic complication in determining OD. In addition, it should be considered that only 0.25 points can separate between hyposmia and normosmia. Therefore, although the diagnostic categories here applied are widely used in this field, the data reported should be considered with caution conside-

ring that when comparing the TDI scores between Group 1 and 2 (and consequently the focus is shifted from the frequency of OD to the olfactory function) the only significant difference was found for the discrimination scale and not for the identification and threshold scales.

Conclusion

Our study showed that patients with complicated T2DM are more frequently affected by OD compared to controls and to patients with T2DM without complications. Moreover, patients with diabetic complications demonstrated a poorer olfactory-related quality of life.

The Random Forest, a machine learning algorithm, was used for the first time to evaluate the relevance of clinical and demographic factors in determining OD in patients with T2DM. Age, presence of diabetic complications, glycated hemoglobin values and LDL cholesterol values were the more important variables in determining OD. Patients with macrovascular diabetic complications seem to be more at risk of OD, however, more data are needed to confirm this preliminary finding.

Acknowledgement

None.

Authors' contributions

Conceptualization: AF, SV, LL and FM; methodology: ACa, FA, IT and AS; formal analysis: ACa, FA, FM; data curation: ACa, AP and ACe; writing - original draft preparation: ACa, AP and ACe; writing - review and editing: AF, SV, IT, AY, AS and FM; supervision: LL and FM. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Conflicts of interest

None to declare.

Data availability

None to declare.

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Arianna Cardella, MD
Department of Biomedical Sciences for Health
University of Milan
and
Department of Otorhinolaryngology
IRCCS Multimedica
Via San Vittore, 12, 20123
Milan
Italy

Tel: +39-0285994832
E-mail: arianna.cardella@unimi.it

Arianna Cardella[1,2], Anna Ferrulli[2,3], Stela Vujosevic[4,5], Andrea Preti[1], Federico Ambrogi[6], Ileana Terruzzi[2,3], Andrea Cecamore[1,6], Arkadi Yakirevitch[7,8], Antonio Schindler[9], Livio Luzi[2,3], Francesco Mozzanica[1,6]

[1] Department of Otorhinolaryngology, IRCCS Multimedica, Milan, Italy
[2] Department of Biomedical Sciences for Health, University of Milan, Milan, Italy
[3] Department of Endocrinology, Nutrition and Metabolic Diseases, IRCCS Multimedica, Milan, Italy
[4] Eye Clinic, IRCCS Multimedica, Milan, Italy
[5] Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy
[6] Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy
[7] Department of Otolaryngology-Head and Neck Surgery, Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel
[8] Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[9] Department of Biomedical and Clinical Sciences "Luigi Sacco", University of Milan, Milan, Italy

Rhinology 62: 5, 537 - 547, 2024
https://doi.org/10.4193/Rhin23.451

Received for publication:
November 22, 2023
Accepted: May 31, 2024

Assocociate Editor:
Basile Landis