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Olfactory function in diabetes mellitus

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ABSTRACT

Diabetes mellitus (DM) is an increasingly common disease in both children and adults. In addition to neuronal and/or vascular disorders, it can cause chemosensory abnormalities including olfactory deterioration. The purpose of this article is to summarize current knowledge on olfactory function in DM, highlighting the impact of co-morbidities, especially obesity, thyroid dysfunction, chronic kidney disease and COVID-19 on olfactory outcomes. Research to date mostly shows that olfactory impairment is more common in people with diabetes than in the general population. In addition, the presence of concomitant diseases is a factor increasing olfactory impairment. Such a correlation was shown for type 1 diabetes, type 2 diabetes and gestational diabetes. At the same time, not only chronic diseases, but also DM in acute conditions such as COVID-19 leads to a higher prevalence of olfactory disorders during infection. Analyzing the existing literature, it is important to be aware of the limitations of published studies. These include the small number of patients studied, the lack of uniformity in the methods used to assess the sense of smell, frequently relying on rated olfactory function only, and the simultaneous analysis of patients with different types of diabetes, often without a clear indication of diabetes type. In addition, the number of available publications is small. Certainly, further research in this area is needed. From a practical point of view decreased olfactory performance may be an indicator for central neuropathy and an indication for assessing the patient's nutritional status, examining cognitive function, especially in older patients and performing additional diagnostic tests, such as checking thyroid function, because all those changes were correlated with smell deterioration.

Introduction

Diabetes mellitus (DM) is a common illness affecting 422 million people worldwide [1]. It may result from autoimmune or idiopathic destruction of beta-cells in the pancreas, insulin resistance, genetic defects, diseases of the pancreas, endocrinopathies, infections, drug use, or pregnancy. Depending on the etiology, DM can be classified as type 1 (T1DM), type 2 (T2DM) (the most common), gestational and other specific, less common types [2]. DM is characterized by hyperglycemia, which in the long term can disrupt the functioning of various organ systems, especially the urinary system, cardiovascular system and nervous system [3]. In addition to the damage in major organ systems, changes in chemosensory function were observed. Those changes may result from neuronal and/or vascular damage, or be a manifestation of persistent insulin resistance [4].

A systematic review and meta-analysis showed that patients with diabetes may have a 1.58 greater risk for developing olfactory impairment [5]. This relationship was also suggested in recently published studies, where DM was identified as one of the factors associated with smell deterioration in various populations [6–8]. What is also important to mention is the fact that although patients diagnosed with DM tend to olfactory dysfunction, the latter cannot be used as a predictor for diabetes development [9].

Although smell disorders were connected with disturbances in food intake, social communication and harm avoidance, data regarding mechanisms behind this phenomenon in DM is scarce [10]. Hence, learning more about those mechanisms and evaluation of possible therapeutic options is important.

This review aims to summarize current knowledge on olfactory function in DM, highlighting the impact of co-morbidities especially obesity, thyroid dysfunction (TD), chronic kidney disease (CKD) and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection on olfactory outcomes.

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Impact of DM on the sense of smell – state of the art

Previously published studies found that smell deterioration appears more frequently in patients with DM, especially T2DM, presenting in relation to the presence of co-morbidities [11]. Loss of smell is not correlated with the duration of the illness, but rather with the presence of other concomitant diseases, like obesity, insulin resistance, thyroid dysfunction, or recently also, COVID-19 [11–15]. Various studies showed no correlation between fasting blood glucose, and HbA1c, being measures for glycemic control and smell deterioration in diabetic patients [16–20]. Therefore, it may be assumed that diabetes alone is not responsible for smell deterioration, but rather the summation of illness related factors additional complication and resulting from it, and coadministration of drugs, that in some cases, may also alter olfactory function [9].

Olfaction in T1DM

For T1DM it was suggested that, if non-complicated, there is no difference between olfactory function in comparison to healthy subjects [21]. A more recent study found that coexisting neuropathy or retinopathy is correlated with worse olfactory performance in patients with T1DM. The authors even proposed olfactory impairment as an indicator for the central neuropathy in T1DM [22]. Furthermore, insulin resistance may lead to smell deterioration in T1DM patients. A link between markers for insulin resistance (bioelectrical impedance analysis, waist to hip ratio, triglyceride to high-density lipoprotein cholesterol (TG/HDL) ratio, estimated glucose disposal rate, visceral adiposity index) and olfactory function was detected [23]. For T2DM the results are more conflicting. Gouveri et al. showed a correlation between olfactory dysfunction and diabetic peripheral neuropathy as well as retinopathy [24]. Le Floch et al. associated olfactory dysfunction with microalbuminuria and peripheral neuropathy [25]. Weinstock et al. correlated the presence of macrovascular disease with olfactory dysfunction [20]. On the other hand Naka et al. and Seraj et al. failed to demonstrate those correlations [11,18]. It is important to notice that the duration of diabetes and glycemic control demonstrated by fasting blood glucose, and HbA1c is not necessarily connected with the appearance of disease complications. Newer studies highlight the importance of glycemic variability, as a risk predictor for micro- and macro-angiopathies in patients with DM [26,27]. It has been also shown that glucose variability appears more often in patients with T1DM and that HbA1c is not enough for evaluation of diabetes control in those patients [28,29]. This may at least to some extent explain why duration of diabetes is not linked to smell deterioration. In patients presenting more stable blood sugar values, complications may be delayed in time, or even not appear. Micro- and microangiopathies may occur with different prevalences making it difficult to draw conclusions on olfactory deterioration. On the other hand as T1DM patients tend to exhibit hypoglycemia more often than T2DM patients the correlation between neuropathy or retinopathy may be more evident.

Thyroid dysfunction

Thyroid dysfunction and DM often occur at the same time. In the case of T1DM, there is an association between thyroid autoimmune disease (AITD) with the illness on the basis of the same pathophysiological mechanism [30,31]. AITD is prevalent in children and adults with T1DM leading to poorer glycemic control and more aggressive disease in its early stages [32,33]. In adults thyroid dysfunction was linked to smell deterioration, and the treatment of the condition led to its improvement [34]. Interestingly, in a study evaluating the influence of chronic diseases including T1DM and hypothyroidism on the olfactory function in children, no correlation with olfactory performance was observed [35]. This is certainly a field for further investigation, as T1DM affects predominantly young people.

COVID-19

To our knowledge, for T1DM, no studies have been performed specifically aimed towards the relation to olfactory function and COVID-19. However, one study describing clinical manifestations of the infection in children, adolescents, and young adults with established T1DM showed that olfactory deterioration was one of the main symptoms of the SARS-CoV-2 infection. It was a clinical manifestation of COVID-19 in 85 % of the patients with symptomatic SARS-CoV2 infection. Comorbidities (among others AITD, hyperlipidemia, asthma, allergy and combined T1DM and T2DM) and elevated glucose levels were correlated with a greater risk for symptomatic infection. They raised the odds of having symptomatic infection by 8.21 times, and elevated glucose levels during infection by 5.23 times. At the same time temporary deterioration in glycemic control during the short infection period was observed [36].

Olfaction in T2DM

Similarly to patients with T1DM, T2DM is also connected with smell deterioration, in particular when comorbidities exist [26–28]. In this sense, it is understandable why olfactory disorders are more common in patients with T2DM than in patients with T1DM or other types of the illness. **First** T2DM, due to civilizational changes, affects more people [29]. **Second** T2DM, although trends are changing, is frequently observed in older people, predominantly with comorbidities. **Third**, some co-existing conditions with DM can also affect the sense of smell (e.g. obesity, hypertension, thyroid dysfunction, chronic kidney disease, chronic obstructive pulmonary disease) [11,37–43].

Obesity

In a study analyzing data from the National Health and Nutrition Examination Survey, the prevalence of smell impairment in patients with diabetes was 7 % higher, compared to people without DM. Furthermore it showed that smell impairment in diabetics led to lower daily calorie intake compared to patients with DM and normal smell function [12].

On the other hand it is worth noting that obesity, which is most often due to dietary errors, is one of the risk factors for diabetes, which again can cause olfactory disorders, which in turn can affect food intake. These diseases are therefore inextricably linked and can influence one on the other [44].

A study in mice showed that even short-term loss of smell improves metabolic health and contributes to weight loss, regardless of the effects of a high-fat diet [45]. However, olfactory loss in humans does not uniformly produce weight loss but, depending on context, often is accompanied by weight gain [46]. Standing in line with the previously mentioned result from the study by Rasmussen et al., smell deterioration in the group of obese, diabetic patients may serve as a protective mechanism against further weight gain [12]. However, a second study performed among mice revealed that anosmia does not protect against diet induced obesity and has no influence on food choice. Olfactory information was neither sufficient nor necessary for the type of food selection [47].

Interestingly, a recent study performed among normal weight and overweight/obese adolescents revealed that olfactory sensitivity is related to pubertal stage. Differences exist between stimulants selectively activating the olfactory system and both, the olfactory and the trigeminal systems, in accordance to BMI. Obrębowski et al. reported that “bimodal odors” stimulating both the olfactory and trigeminal systems were less likely to be detected in obese teens than in more selective olfactory stimulants [48]. In a study by Herz et al. adolescents with high BMI scores were found to have a greater sensitivity to a pure olfactory stimulus than adolescents with normal BMI values. It was also found that adolescents in early puberty present greater odor sensitivity than adolescents in late puberty [49]. These findings are particularly important when examining adolescents with T1DM as well as T2DM, as it may contribute to proper evaluation of achieved results.

Changes in olfaction connected with T2DM influence not only food intake in different manners among different populations. There is also a relationship between olfactory dysfunction and cognitive impairment in elderly patients with T2DM [50].

According to the previously mentioned findings by Sanke et al., a study performed among obese adults with diabetes showed lower general cognition and olfactory deterioration in comparison to normal weight diabetics. Furthermore, decreased left hippocampal activation, and disrupted functional connectivity with right insula were observed, providing insights into cognition-associated olfactory network and brain insulin resistance in patients with T2DM [51].

Obesity is also connected with a greater prevalence of insulin resistance, negatively influencing olfaction [52]. A study published in 2018 demonstrated that high values of the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) are connected with even a two-fold increase in odds of smell dysfunction. The same study failed to find a correlation between the sense of smell and other DM-related biomarkers; fasting blood glucose, HbA1c and serum insulin [16]. Importantly, insulin resistance is present not only in obese patients [52].

Thyroid dysfunction

The prevalence of thyroid dysfunction among patients with T2DM is estimated between 16.2 and 17.5 %, leading to poorer diabetes control [13,14]. Unfortunately, to our knowledge there are limited studies regarding olfactory function in patients presenting with TD and T2DM. Naka et al. showed that diabetics developing severe complications, also including hypo- or hyperthyroidism are at greater risk of smell deterioration than patients with uncomplicated diabetes [11]. Research performed among individuals only with hypothyroidism and subclinical hypothyroidism, suggest that proper treatment leads to restoration of olfactory function [34,53]. Further research is needed to show whether this observation will be reproduced in the group of T2DM patients with thyroid dysfunction.

Chronic kidney disease

In a limited number of studies, CKD was connected with olfactory deterioration in adults [54,55]. Decreased GFR values correlated with decreased olfactory performance [56]. Interestingly, this association was not observed in children with CKD, where only BMI values were correlated with olfactory deterioration [57]. Data on causes for olfactory impairment in adult patients with CKD are unconcise. One case-control study suggested that smell deterioration in patients with CKD is connected with changes in the central olfactory pathway [43]. Landis et al. suggested a mixed peripheral and central mechanism for olfactory deterioration in CKD, and Nigwekar et al. hypothesized peripheral changes as explanation for olfactory impairment in those patients [58,59].

Similarly to TD, it is difficult to draw conclusions on consequences of coexistence of CKD and T2DM in patients on their olfactory function, as to our knowledge no studies were performed exclusively addressing this topic. Two studies evaluating the impact of CKD on olfaction declared including patients with T2DM. In a study by Nigwekar et al. diabetic patients made up 8 % of the control group and 50 % of the intervention groups. The first intervention group gathered patients with CKD and the second patients with end-stage renal disease (ESRD). The study showed that approximately 70 % of patients with CKD and 90 % of patients with ESRD had olfactory detection thresholds than CKD patients [58]. Raff et al. performed a study aiming to examine the relationship between olfactory impairment in ESRD to malnutrition and uremic toxins. Diabetic patients comprised 52 % of the studied population. Interestingly the study showed that patients with ESRD presenting with greater C-reactive protein (CRP) values and worse nutritional status had worse olfactory performance than end-stage renal disease patients with low CRP values and with better nutritional status. Patients without malnutrition even presented olfactory outcomes similar to healthy controls. On the other hand it has to be mentioned that the study group included only 31 patients and 18 healthy controls [60].

COVID-19

Despite chronic comorbidities, also acute conditions, like COVID-19, coexisting with DM may worsen olfactory outcome [15]. In a study performed among patients suffering from mild pneumonia during COVID-19, those with T2DM, presented higher incidences of hyposmia. The authors showed that this phenomenon may be connected with diabetes impaired nasal immunity resulting from upregulation of ACE2 expression in the lamina propria and nasal-associated lymphoid tissue lymphocyte reduction [61]. Another study particularly addressing the impact of comorbidities on olfactory disorders during COVID-19 pandemic showed that there is a statistically significant correlation between smell deterioration and diabetes, hypertension, asthma, chronic liver disease, hypothyroidism and chronic renal disease [62]. All of those conditions were to some extent also linked with higher odds for smell disorders in the general population, without COVID-19 infection [54,63–65]. The occurrence of olfactory deterioration was related to a mild course of the disease and lower hospitalization rates [62]. At the same time a meta-analysis showed that pre-existing DM had little impact on the recovery of smell after COVID-19 [66]. Certainly further studies are needed to evaluate the mechanism behind olfactory deterioration in diabetes and answer the question whether hyposmia/anosmia observed in diabetics during COVID-19 infection is connected only with damage of the olfactory mucosa or the worsening of an already lower olfactory function in DM.

Olfaction in gestational DM

Olfaction changes in gestational diabetes are not widely studied. To our knowledge there is only one study performed in 1961 evaluating this topic. Jørgensen and Buch noted that about 50 % of participating pregnant women with diabetes had pronounced hyposmia. By comparing the results with a previously performed investigation on non-pregnant women with diabetes the authors link their findings to diabetes rather than to a physiological change resulting from pregnancy [67].

Notably, a recently published study showed a significant increase in tyrosine hydroxylase, and dopa decarboxylase in the olfactory bulb tissue, in the offspring of rats with gestational DM. The authors hypothesize that an increase in (typically inhibitory) dopaminergic neurons count in the olfactory bulb may lead to odor impairment in the offspring [68].

Taking the aforementioned publications into consideration, there is certainly a need for further investigation on this topic, as gestational DM is increasingly prevalent, and the negative effects of the disease on the fetus may also potentially contribute to chemosensory developmental disorders in children.

Therapeutic options for smell deterioration in DM

Although treatment of smell deterioration was studied extensively, and various therapeutic methods were proposed (e.g. olfactory training or more recently intranasal insulin), options regarding treatment of olfaction disorders in diabetes is scarce [63,69,70]. A recently published review detected only 3 articles covering this topic. Therapeutic interventions included the use of DPP-4 inhibitors, hyperbaric oxygen, and GLP-1 agonists. Of these, only the last two yielded statistically significant improvements in odor identification [51,71]. Worth noting is, that GLP-1 agonists exhibiting central and peripheral action profiles, may lead to improvement in odor perception, not only by improvement of glucose homeostasis, but also through enhancing weight loss in patients with diabetes [72].

What is also important, and has to be kept in mind are the results of a study showing, that diabetics under insulin treatment experienced phantom odors significantly more frequently and tended to exhibit severe hyposmia/anosmia more often than healthy controls. More

aggressive treatment of DM (oral and insulin treatment) led to significantly poorer olfactory outcomes, compared to patients only on dietary treatment [4].

It should be noted at this point, that improvement in the control of concomitant diseases, can also lead to better outcome in the sense of smell, as it was shown for thyroid dysfunction [34,53].

Limitations of current knowledge on olfactory function in DM

An important limitation of our current knowledge on olfactory function in DM is the low number of studies performed on this topic. Scientific data usually relates to patients presenting with T2DM. Olfactory deterioration is studied less frequently in patients with T1DM and almost not studied in patients with gestational DM. Although most of the research performed detects a relationship between diabetes (especially, complicated DM) and smell deterioration, study results are inconsistent. For example Kaya et al. detected no statistically significant difference in odor test classification between diabetic patients with complications (nephropathy, retinopathy, and microalbuminuria) and patients without complications [44,73]. Furthermore there are also limited studies addressing the topic of smell loss in patients presenting with DM and comorbidities. This is particularly so when searching for studies on the topic of olfactory deterioration in DM patients presenting with thyroid dysfunction, chronic kidney disease or even acute conditions like COVID-19.

Another limitation is the methodology of published studies: most of them are short-term, case-control or cross-sectional studies, with relatively low numbers of participants. Also the methods used in olfactory testing are not homogenous ranging from self-assessment to variously measured olfactory performance. It is important to mention that self-assessment of olfaction is based in various ways, so that it cannot replace psychophysical olfactory testing [5,74]. Moreover, in some research, patients with different types of DM are studied together without clear indication of the diabetes type. This makes it difficult to draw conclusions [5,44]. Certainly, an interesting approach would be the analysis of glycemic variation on olfactory performance, as this index was mostly associated with micro- and macrovascular complications in DM.

Conclusions

Olfactory deterioration is frequently observed among patients with DM and comorbidities, however little is known on the molecular mechanism behind this phenomenon. In our review we focus on current knowledge on olfactory function in different types of DM and on the impact of most commonly reported diabetic comorbidities on the sense of smell. At the same time we point out limitations of the performed studies indicating that future large scale multicenter randomized control studies are needed, to reveal the mechanisms and correlations between olfaction, diabetes, comorbidities (thyroid disease, obesity, insulin resistance, chronic kidney disease) and acute conditions like SARS-CoV-2 infection. The most important findings, providing insights into current base of knowledge, are summarized in Table 1 [12,13,14,17,21–23,30–33,35,36,50,52,62,67,75].

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Competing interests

Beata Sienkiewicz-Oleszkiewicz and Thomas Hummel report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Table 1
Most important findings on olfaction in DM.

	Diabetes type 1	Diabetes type 2	Gestational diabetes
Impact of uncomplicated DM on the sense of smell	–	+ Treatment of DM ↓ OP	+/- ↑ frequency of hyposmia
Impact of DM duration on the sense of smell	-*	–	–
Impact of comorbidities on the sense of smell	+	+	-**
Consequences of smell impairment	↓QoL	↓ daily calorie intake ↓QoL	N/A
Comorbidities connected with smell deterioration			
neuropathy	+	+/-	N/A
insulin resistance	+	+	N/A
thyroid dysfunction	+***	+/-	N/A
Obesity	–	+/-	N/A
cognitive impairment	N/A	+	N/A
chronic kidney disease	N/A	N/A****	N/A
COVID-19	N/A*****	+******	N/A
Recommendations for the general practitioner	consider evaluation of the sense of smell, as it may be an early indicator for central neuropathies	consider evaluation of the sense of smell especially in patients presenting with comorbidities if ↓ OP detected: • cognitive assessments in older patients recommended • assessing patient's nutritional status recommended • consider thyroid function tests	–

*DM duration, associated with neuropathy and retinopathy.
**No correlation with severity of DM and degree of retinopathy found.
***In adults, not proven in children.
****No directly performed studies addressing OF in diabetics with CKD.
*****Mild symptoms, predominant manifestation: smell deterioration, elevated glucose levels during infection and older age connected with longer disease duration.
******Smell deterioration during infection related to a mild course of the disease and lower hospitalization rates. Correlation between smell deterioration and diabetes, hypertension, asthma, chronic liver disease, hypothyroidism and chronic renal disease.
OP-olfactory performance, N/A- not accessed, QoL-quality of life.

CRediT authorship contribution statement

Beata Sienkiewicz-Oleszkiewicz: Writing – review & editing, Writing – original draft, Conceptualization. **Thomas Hummel:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Beata Sienkiewicz-Oleszkiewicz and Thomas Hummel declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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