Association of olfactory function with the intensity of self-reported physical activity in adults with type 1 diabetes

Bogusz Falkowski, Maciej Chudziński, Ewa Jakubowska, Anna Duda-Sobczak

Department of Internal Medicine and Diabetology, Poznan University of Medical Sciences, Poznań, Poland

KEY WORDS

chronic complications, diabetic neuropathy, olfactory function, physical activity, type 1 diabetes

ABSTRACT

INTRODUCTION Olfactory function is impaired in patients with type 1 diabetes and can be recognized as a form of diabetic neuropathy. Physical activity has various beneficial effects on type 1 diabetes.

OBJECTIVES The aim of this study was to assess a relation between physical activity and olfactory function in patients with type 1 diabetes.

PATIENTS AND METHODS We enrolled 120 patients with type 1 diabetes referred to an outpatient diabetes clinic. Patients with diabetes duration of less than 5 years, age above 65 years, concomitant diabetic ketoacidosis, and those using drugs affecting nasal mucosa were excluded. The final study sample included 90 patients. A control group comprised 22 healthy participants. Olfactory function was assessed using 12 odor-emitting pens called Sniffin' Sticks. Physical activity was measured using the short version of the International Physical Activity Questionnaire (IPAQ-SF).

RESULTS There was a significant difference in the occurrence of hyposmia between diabetic patients and healthy controls (70.0% vs 45.5%, respectively; $P = 0.03$). There were no significant differences in IPAQ-SF results between the groups. Moreover, IPAQ-SF results correlated positively with olfactory test scores ($r = 0.25$; $P = 0.02$) and negatively with age. Additionally, patients with retinopathy and autonomic neuropathy obtained lower IPAQ-SF scores than patients without those complications. A stepwise multivariable linear regression analysis indicated IPAQ scores, body mass index, and peripheral neuropathy as predictors of the olfactory test score ($R = 0.2$).

CONCLUSIONS Our study confirms the beneficial role of physical activity in type 1 diabetes within the structures of the central nervous system.

Correspondence to:
Anna Duda-Sobczak, MD, PhD, Katedra i Klinika Chorób Wewnętrznych i Diabetologii, Uniwersytet Medyczny im. K. Marcinkowskiego w Poznaniu, ul. Mickiewicza 2, 60-834 Poznań, Poland, phone: +48 61 224 52 70, e-mail: a_sobczak@onet.pl
Received: April 27, 2016.
Accepted: April 28, 2016.
Published online: August 3, 2017.
Conflict of interest: none declared.
Pol Arch Intern Med. 2017; 127 (7-8): 476-480
doi:10.20452/pamw.4073

* The authors won the first award of the Editor-in-Chief for the best student paper in 2017. For more information, go to www.pamw.pl.

INTRODUCTION Type 1 diabetes is an autoimmune disease leading to absolute insulin deficiency and its metabolic consequences. The incidence of type 1 diabetes shows an increasing trend, and by 2020, the number of newly diagnosed patients under 5 years old will have doubled in comparison with 2005.[1] Importantly, a wide range of neurovascular complications is recognized as a result of inadequate metabolic control of diabetes. The most common complication of type 1 diabetes is diabetic polyneuropathy; however, intensive insulin treatment reduced its overall risk by 60%.[2] In some patients with diabetes, central forms of neuropathy may also be diagnosed.

Olfactory dysfunction frequently occurs together with neurodegenerative diseases such as Alzheimer disease or Parkinson syndrome.[3] Currently, it is known that olfaction is impaired also in patients with type 1 diabetes. Not only the sensitivity of olfaction is impaired but also the capacity for distinction of particular smells in comparison with controls.[3] Moreover, olfactory dysfunction is related to the presence of diabetic neuropathy.[3,4] It is highly probable that mild olfactory dysfunction unveils central neuropathy at an early stage.[5]

In the past, physical activity constituted a great therapeutic challenge both for patients and for doctors, owing to higher risk of hypoglycemia. Nowadays, with advances in the therapy of type 1 diabetes and with increased knowledge of the importance of safe physical activity

TABLE 1 Characteristics of the study participants

Parameter	Study group (n = 90)	Control group (n = 22)	*P* value
Age, y, median (IQR)	35.5 (29–42)	38.5 (30–45)	0.3[a]
Female sex, n (%)	47 (52.2)	17 (77)	0.03[b]
IPAQ, score, median (IQR)	1556 (960–3291)	1968 (1257–3573)	0.2[a]
Hyposmia, yes, n (%)	63 (70)	10 (45.5)	0.03[b]
Smoking, yes, n (%)	21 (23.3)	2 (9.1)	0.1[b]
Type 1 diabetes duration, y, median (IQR)	18 (13–26)	–	–
HbA_{1c}, %, median (IQR)	8.2 (7.3–9.0)	–	–
BMI, kg/m^2, median (IQR)	25.0 (22.6–27.3)	24.0 (22.0–24.7)	0.2[a]
Retinopathy, yes, n (%)	46 (51.1)	–	–
Neuropathy, yes, n (%)	25 (27.8)	–	–
Chronic kidney disease, yes, n (%)	12 (13.3)	–	–

a Mann–Whitney test; **b** Fisher exact test

Abbreviations: BMI, body mass index; HbA_{1c}, glycated hemoglobin A_{1c}; IPAQ, International Physical Activity Questionnaire; IQR, interquartile range

in these patients, physical exercise should no longer be avoided; quite the opposite, it has become increasingly prescribed in this group of patients.[6] We notice the same positive effects of physical exercise in patients with diabetes as in the group of healthy controls. Sport lowers blood pressure, improves serum lipid levels, and reduces abdominal fat.[7] Additionally, physical activity decreases insulin resistance, which in turn lowers insulin needs and decreases glycated hemoglobin A_{1c} (HbA_{1c}) levels.[8] The mechanisms of the healthy impact of physical activity include the phosphorylation of AMP-activated protein kinase (AMPK) that activates the enzyme. Subsequently, the activated AMPK elicits glucose transport and desirable lipid metabolism.[8] An inverse association between physical activity and retinopathy or microalbuminuria has been reported among adults with type 1 diabetes.[9] Moreover, a positive effect of regular aerobic exercise on laboratory parameters in type 2 diabetes patients with diabetic peripheral neuropathy was noted already after 8 weeks.[10] To our knowledge, no such research has been conducted for type 1 diabetes. Therefore, the aim of this study was to assess olfactory function in relation to the intensity of self-reported physical activity in patients with type 1 diabetes.

PATIENTS AND METHODS

The study was performed in the Department of Internal Medicine and Diabetology at the Poznan University of Medical Sciences, Poznań, Poland, in cooperation with the Department of Otorhinolaryngology of the Raszeja City Hospital in Poznań. It was conducted in accordance with the guidelines of the Declaration of Helsinki on biomedical research involving human subjects and was approved by the Bioethical Committee of the Poznan University of Medical Sciences. All participants provided written informed consent before enrollment to the study.

Study population

We enrolled 120 patients with type 1 diabetes referred to an outpatient clinic. The exclusion criteria were as follows: diabetes duration of less than 5 years, age above 65 years, diabetic ketoacidosis at enrollment, use of drugs affecting nasal mucosa (antihistamines, local steroids). We excluded 14 patients owing to nasal pathologies potentially affecting the sense of smell (acute or chronic sinusitis, rhinitis, nasal polyposis, severe nasal septum deviations). Another 16 patients refused to participate in the study. The final study sample included 90 patients. The control group consisted of 22 healthy individuals.

Data collection

All patients underwent a full physical examination, including anthropometric measurements. We used standard diagnostic criteria to assess the metabolic control of diabetes and the presence of diabetic retinopathy (DR), peripheral neuropathy, and diabetic kidney disease.[11-13]

The assessment of cardiac autonomic neuropathy was performed using the ProsciCard III program (Medi-Syst GmbH, Linden, Germany). An electrocardiogram recording with the use of selected standardized stimuli such as the Valsalva maneuver, orthostatic test, and deep breathing was used to calculate heart rate variability and associated parameters. The results were then compared with the standard values for age and sex. Cardiac autonomic neuropathy was diagnosed if 2 of the 4 tests yielded abnormal results.

Blood samples were obtained after overnight fasting. The levels of HbA_{1c}, serum lipids, and creatinine were measured using standard techniques. The clinical characteristics of the study group are presented in TABLE 1. Additionally, an ear, nose, and throat examination was performed with nasal endoscopy (patients were asked not to drink or eat anything but water and restrain from smoking cigarettes for at least 1 hour prior to examination).

Evaluation of olfactory function

Sniffin' Sticks (Burghart®, Wedel, Germany) were used to assess odor identification and, using extrapolation, estimate olfactory function. The test consisted of 12 pens emitting different well-known odors. After removing the cap, the tip of the pen was placed 2 cm below the patient's nostrils for 2 seconds. Each odor was presented with the list of 4 possible answers from which only 1 was correct (best describing the smell). The procedure was repeated for every 12 odors. The score ranged from 0 to 12 points: a range of 11 to 12 points denoted normal olfactory function (normosmia), and of 0 to 10 points—significant olfactory dysfunction.

Assessment of physical activity

Physical activity was assessed using a questionnaire survey. Questions were asked according to the short version of International Physical Activity Questionnaire

TABLE 2 Correlations between laboratory parameters and olfactory function and International Physical Activity Questionnaire score (Spearman rank correlation analysis)

Parameter	*r*	*P* value
Bilateral olfactory test score		
Age	–0.2	0.12
IPAQ	0.3	0.02
Type 1 diabetes duration	–0.1	0.20
HbA_{1c}	–0.1	0.27
BMI	–0.2	0.03
LDL cholesterol	–0.1	0.2
HDL cholesterol	0.2	0.08
TG	–0.2	0.04
IPAQ		
Age	–0.3	0.02
Bilateral olfactory test score	0.3	0.02
Type 1 diabetes duration	–0.2	0.1
HbA_{1c}	–0.1	0.5
BMI	–0.04	0.7
LDL cholesterol	–0.06	0.6
HDL cholesterol	–0.1	0.3
TG	–0.1	0.4

A *P* value of less than 0.05 was considered significant.

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; others, see TABLE 1

TABLE 3 Predictors of bilateral olfactory test score in a linear regression analysis; multivariable regression model performance: $R^2 = 0.2$; $P < 0.05$

Predictors	Univariable analysis		Multivariable analysis	
	β	*P* value	β	*P* value
IPAQ	0.3	0.008	0.2	0.03
BMI	–0.2	0.03	–0.2	0.03
Age	–0.2	0.05	–	–
Type 1 diabetes duration	–0.07	0.5	–	–
HbA_{1c}	–0.03	0.7	–	–
LDL cholesterol	–0.1	0.5	–	–
HDL cholesterol	0.2	0.06	–	–
TG	0.1	0.2	–	–
Chronic kidney disease	–0.2	0.1	–	–
Retinopathy	–0.2	0.02	–	–
Peripheral neuropathy	–0.3	0.002	–0.3	0.007
Autonomic neuropathy	–0.3	0.009	–	–

The result of the univariable analysis did not exclude predictors from including them in the multivariable analysis. All variables entered the multivariable model. Candidate predictors were consecutively excluded according to statistical significance until all variables in the model were significant ($P < 0.05$).

Abbreviations: see TABLES 1 and 2

(IPAQ-SF), following the principles outlined in the "Guidelines of Data Processing and Analysis of IPAQ short version".[14] The questionnaire evaluates physical activity seperately for 3 specific types of activity according to a metabolic equivalent score (MET, a unit that is applied to estimate the amount of oxygen used by the body during exercise): walking (3.3 METs), moderate-intensity activities (6.0 METs), and vigorous-intensity activities (8.0 METs). Participants were asked about the activities they were involved in according to their intensity, domain type (eg, work, transportation, domestic, garden, leisure time), and duration in the past 7 days. For each category, MET minutes per week were calculated by multiplying the MET score by the minutes and days of engagement; then, the scores for each type of activity were summed up to measure the total MET minutes per week. Previous studies showed that the IPAQ-SF has acceptable reliability and validity.[15]

Statistic analysis A statistical analysis was conducted using STATISTICA 12 (StatSoft Inc., Tulsa, Oklahoma, United States). The results were presented as medians of numerical variables and number of patients for categorical variables. The Mann–Whitney test was performed to compare median IPAQ scores in the study and control groups as well as in the groups with diabetic complications. The Fisher exact test was used to compare the proportions of hyposmic patients in the respective groups. Correlations between IPAQ scores, olfactory test scores, and laboratory findings were assessed by a Spearman rank correlation analysis. A *P* value of less than 0.05 was considered significant. We evaluated the variables correlating with olfactory test scores and subsequently included them in a stepwise multivariable linear regression model. A *P* value of less than 0.05 was accepted as the threshold for inclusion.

RESULTS We found no differences in IPAQ scores between diabetic patients and controls (1556 points [interquartile range (IQR), 960–3291] vs 1968 points [IQR, 1257–3573], respectively; $P = 0.2$). Hyposmia was found in 70.0% of diabetic patients and 45.5% of controls ($P = 0.03$). IPAQ scores correlated positively with olfactory test scores ($r = 0.25$; $P = 0.02$). Patients with retinopathy obtained lower median IPAQ scores than those without retinopathy (1306.5 points [IQR, 626.0–1830.0] vs 2442.0 points [IQR, 1070.0–5310.0]; $P = 0.005$). Patients with diabetic proliferative retinopathy showed lower median IPAQ scores than those with nonproliferative retinopathy (1167 points [IQR, 596–1908] vs 1782 points [IQR, 1070–4212]; $P = 0.02$). Moreover, patients with autonomic neuropathy showed lower median IPAQ scores compared with patients without neuropathy (1053.0 points [IQR, 297.0–1422.0] vs 1773.0 points [IQR, 988.5–4239.0]; $P = 0.008$). We found a negative correlation between IPAQ scores and age ($r = -0.3$; $P = 0.02$) (TABLE 2). The stepwise multivariable linear regression analysis indicated the IPAQ score, body mass index (BMI), and peripheral neuropathy as predictors of the olfactory test score ($R^2 = 0.2$) (TABLE 3).

DISCUSSION Regular physical activity improves metabolic control and reduces the risk of chronic diabetic complications.[8] Moreover, patient safety even during high-intensity exercise in type 1 diabetes has been proved in a recent study.[16] Previous studies have shown a relation between olfactory function and DR and neuropathy, suggesting the olfactory impairment as an indicator of central diabetic neuropathy.[4] In our study, the assessment of physical activity was based on a self-reported questionnaire, which is considered to be less precise and to overestimate the results.[17] It is important to emphasize that the obtained results may be difficult to replicate because there is a number of different scoring protocols of physical activity available and there is no consensus in terms of the interpretation and description of data provided by self-reported questionnaires.[14] In our study, patients declaring physical activity of higher intensity, as indicated by the IPAQ-SF, performed significantly better in olfactory tests. Herbst et al[18] reported that physical activity has limited effect on glycemic control in patients with type 1 diabetes.[18] However, regular physical activity improves endothelial function in these patients and thus reduces the incidence of microvascular complications.[19] This may also contribute to maintaining normal olfactory function in type 1 diabetes. Furthermore, physical activity decreases insulin demands by reducing insulin resistance. Insulin resistance is a proven risk factor of microvascular complications in patients with type 1 diabetes.[20] The pathogenesis of decreased olfaction in these patients has not been fully elucidated, thus making it difficult to determine the impact of regular physical activity on olfactory function. We also found that patients with lower BMI tended to have better olfaction, and this observation is consistent with other studies in the field of chemosensory function in patients with diabetes. Naka et al[21] reported a negative correlation of gustatory and olfactory function with BMI.

In our study, we found that patients with autonomic neuropathy had lower IPAQ scores compared with patients without this complication. First, we should emphasize that diabetic autonomic neuropathy (DAN) is a common complication of diabetes, which may affect the cardiovascular, gastrointestinal, and urogenital systems. Its prevalence varies widely depending on diagnostic criteria and differences in a study population.[22] The most common manifestation of DAN is cardiac autonomic neuropathy, and, according to a meta-analysis published in 2014, its prevalence in type 1 diabetes ranges from 1% to 90%.[23] Cardiac autonomic neuropathy is an important problem owing to its contribution to poorer quality of life[24] and even more life-threatening complications such as arrhythmias, silent myocardial ischemia, or sudden unexplained deaths.[25] Lower IPAQ scores in patients with autonomic neuropathy may be a consequence of clinical features of DAN such as orthostatic hypotension, asymptomatic hypoglycemia, resting tachycardia, and exercise intolerance. However, studies showed that aerobic training improves cardiac autonomic dysfunction in patients with type 2 diabetes.[26,27] Therefore, the correlation between neuropathy and IPAQ scores could be significant in both ways: low physical activity could be a risk factor of neuropathy and, on the other hand, clinical features of DAN could result in lower physical activity. When considering cardiac risk, it is necessary to conduct an exercise stress test before recommending an exercise program. Moreover, it is important to monitor blood pressure, heart rate, and blood glucose levels during the first hours of physical activity.

In line with previous studies, we observed a lower median IPAQ score in patients with proliferative DR in comparison with patients with nonproliferative DR. Praidou et al[28] showed lower IPAQ scores in patients with type 2 diabetes and proliferative DR compared with patients with nonproliferative DR.[28] Additionally, the occurrence of DR in patients with type 1 diabetes was reported to be associated with lower intensity of total leisure-time physical activity.[29] However, the association was not significant. Maintaining good metabolic control of diabetes expressed by HbA_{1c} levels, lipid profile, and blood pressure remains one of the most important therapeutic goals that prevents the development and progression of chronic complications of diabetes. The study of Danish pediatric cohort indicated high HbA_{1c} levels and elevated blood pressure as risk factors for progression of DR.[25] Owing to its beneficial influence on metabolic control, a regular physical activity is one of the treatment recommendations in diabetes.[8] However, we must emphasize that patients with proliferative DR are advised to avoid intensive physical activity, which is associated with the risk of vitreous hemorrhage, until the completion of laser therapy.

Olfactory function has a considerable effect on the quality of life; therefore, it deserves greater attention. Smell disorders do not only affect taste, but there is also a wide range of less obvious negative consequences of hyposmia or anosmia. In a Korean study,[30] severely impaired olfactory function was associated with lower quality of life and cognitive performance, and higher severity of depression in comparison with controls. Lower quality of life is not the only result of olfactory impairment. Miwa et al[31] showed an increased occurrence of disability in this group of patients. In another study,[32] impaired olfaction was a risk factor for certain injuries because normosmia allows early detection and avoidance of potentially hazardous situations, such as cooking or house fires, delayed detection of gas leaks, and exposure to or ingestion of toxic substances.[32] In our study, higher physical activity was associated with better olfactory function; therefore, we can conclude that it is another argument for recommending physical activity. Accordingly, the evaluation of olfactory function should be considered in patients with type 1 diabetes.

Our study has several limitations. First, it was not a prospective study, and the assessment of physical activity was based on a self-reported questionnaire, which in itself has some limitations. Also investigations using the Sniffin' Sticks have their own specific limitations.

To conclude, a lower IPAQ score, higher BMI, and the presence of neuropathy were predictors of impaired olfactory function. This study confirms the beneficial role of physical activity within the structures of the central nervous system in patients with type 1 diabetes.

Acknowledgments Grant of Diabetes Poland (number, to xx). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Contribution statement MC, EJ, and AD-S contributed to the concept of the study. All authors contributed to data acquisition. BF, MC, and AD-S analyzed and interpreted the data. BF, MC, EJ, and AD-S drafted the manuscript. AD-S revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript to be submitted for publication and any revised version.

REFERENCES

1 Patterson CC, Dahlquist GG, Gyürüs E, et al. EURODIAB Study Group. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet. 2009; 373: 2027-2033.

2 Callaghan BC, Hur J, Feldman EL. Diabetic neuropathy: one disease or two? Curr Opin Neurol. 2012; 25: 536-541.

3 Brady S, Lalli P, Midha N, et al. Presence of neuropathic pain may explain poor performances on olfactory testing in diabetes mellitus patients. Chem Senses. 2013; 38: 497-507.

4 Duda-Sobczak A, Araszkiewicz A, Urbas M, et al. Impaired olfactory function is related to the presence of neuropathy in adults with type 1 diabetes. Diab Vasc Dis Res. 2017; 14: 139-143.

5 Várkonyi T, Körei A, Putz Z, Kempler P. Olfactory dysfunction in diabetes: a further step in exploring central manifestations of neuropathy? Angiology. 2014; 65: 857-860.

6 Riddell MC, Gallen IW, Smart CE, et al. Exercise management in type 1 diabetes: a consensus statement. Lancet Diabetes Endocrinol. 2017; 5: 377-390.

7 Lehmann R, Kaplan V, Bingisser R, et al. Impact of physical activity on cardiovascular risk factors in IDDM. Diabetes Care. 1997; 20: 1603-1611.

8 Horton WB, Subauste JS. Care of the athlete with type 1 diabetes mellitus: a clinical review. Int J Endocrinol Metab. 2016; 14: e36091.

9 Bohn B, Herbst A, Pfeifer M, et al. Impact of Physical Activity on Glycemic Control and Prevalence of Cardiovascular Risk Factors in Adults With Type 1 Diabetes: A Cross-sectional Multicenter Study of 18,028 Patients. Diabetes Care. 2015; 38: 1536-1543.

10 Dixit S, Maiya AG, Shastry BA. Effect of aerobic exercise on peripheral nerve functions of population with diabetic peripheral neuropathy in type 2 diabetes: a single blind, parallel group randomized controlled trial. J Diabetes Complications. 2014; 28: 332-339.

11 Fong DS, Aiello L, Gardner TW, et al. Retinopathy in diabetes. Diabetes Care. 2004; 27 Suppl 1: 84-87.

12 KDOQI. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. Am J Kidney Dis Off J Natl Kidney Found. 2007; 49 (2 Suppl 2): 12-154.

13 Tesfaye S, Boulton AJ, Dyck PJ, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care. 2010; 33: 2285-2593.

14 Guidelines for Data Processing and Analysis of the International Physical Acitivity Questionnaire (IPAQ) - Short and Long Forms, November 2015. https://sites.google.com/site/theipaq/questionnaire_links. Accessed December 6, 2016.

15 Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003; 35: 1381-1395.

16 Gawrecki A, Naskret D, Niedzwiecki P, et al. High-intensity exercise in men with type 1 diabetes and mode of insulin therapy. Int J Sports Med. 2017; 38: 329-335.

17 Tomaz SA, Lambert EV, Karpul D, Kolbe-Alexander TL. Cardiovascular fitness is associated with bias between self-reported and objectively measured physical activity. Eur J Sport Sci. 2016; 16: 149-157.

18 Herbst A, Bachran R, Kapellen T, Holl RW. Effects of regular physical activity on control of glycemia in pediatric patients with type 1 diabetes mellitus. Arch Pediatr Adolesc Med. 2006; 160: 573-577.

19 Fuchsjäger-Mayrl G, Pleiner J, Wiesinger GF, et al. Exercise training improves vascular endothelial function in patients with type 1 diabetes. Diabetes Care. 2002; 25: 1795-1801.

20 Chaturvedi N, Sjoelie AK, Porta M, et al. Markers of insulin resistance are strong risk factors for retinopathy incidence in type 1 diabetes. Diabetes Care. 2001; 24: 284-289.

21 Naka A, Riedl M, Luger A, et al. Clinical significance of smell and taste disorders in patients with diabetes mellitus. Eur Arch Otorhinolaryngol 2010; 267: 547-550.

22 Verrotti A, Prezioso G, Scattoni R, Chiarelli F. Autonomic neuropathy in diabetes mellitus. Front Endocrinol. 2014; 5: 205.

23 Dimitropoulos G, Tahrani AA, Stevens MJ. Cardiac autonomic neuropathy in patients with diabetes mellitus. World J Diabetes. 2014; 5: 17-39.

24 Alvarado-Martel D, Velasco R, Sánchez-Hernández RM, et al. Quality of life and type 1 diabetes: a study assessing patients' perceptions and self-management needs. Patient Prefer Adherence. 2015; 9: 1315-1323.

25 Tang M, Donaghue KC, Cho YH, Craig ME. Autonomic neuropathy in young people with type 1 diabetes: a systematic review. Pediatr Diabetes. 2013; 14: 239-248.

26 Liu Y, Liu S-X, Zheng F, et al. Cardiovascular autonomic neuropathy in patients with type 2 diabetes. J Diabetes Investig. 2016; 7: 615-621.

27 Esposito P, Mereu R, De Barbieri G, et al. Trained breathing-induced oxygenation acutely reverses cardiovascular autonomic dysfunction in patients with type 2 diabetes and renal disease. Acta Diabetol. 2016; 53: 217-226.

28 Praidou A, Harris M, Niakas D, Labiris G. Physical activity and its correlation to diabetic retinopathy. J Diabetes Complications. 2017; 2: 456-461.

29 Wadén J, Forsblom C, Thorn LM, et al. Physical activity and diabetes complications in patients with type 1 diabetes: the Finnish Diabetic Nephropathy (FinnDiane) Study. Diabetes Care. 2008; 31: 230-232.

30 Seo HS, Jeon KJ, Hummel T, Min BC. Influences of olfactory impairment on depression, cognitive performance, and quality of life in Korean elderly. Eur Arch Otorhinolaryngol. 2009; 266: 1739-1745.

31 Miwa T, Furukawa M, Tsukatani T, et al. Impact of olfactory impairment on quality of life and disability. Arch Otolaryngol Neck Surg. 2001; 127: 497-503.

32 Pence TS, Reiter ER, DiNardo LJ, Costanzo RM. Risk factors for hazardous events in olfactory-impaired patients. JAMA Otolaryngol Head Neck Surg. 2014; 140: 951-955.