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Effect of neuropathy on pupillary response measured with infrared static pupillography in type 2 diabetes mellitus patients

Tip 2 diyabetes mellitus hastalarında infrared statik pupillografi yardımıyla nöropatinin pupil cevabı üzerine etkisi

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Abstract

Aim: Diabetic autonomic neuropathy is manifested by pupillary dysfunction in the eye; so pupillary assessment can be vital for early detection. We aim to determine the relationship between diabetic polyneuropathy and pupil response for evaluating the presence of neuropathy via static pupillometer that is a non-invasive and quantitative method. This method could be used as an indicator for early diagnosis of neuropathy in diabetic patients.

Methods: This case-control study was planned on 420 patients. All participants have been diagnosed with Type 2 Diabetes Mellitus and were referred to Neurology Department. The first group includes 60 patients who have type 2 diabetes mellitus with distal symmetric polyneuropathy (DPN). Second group includes 212 diabetic patients who don't have polyneuropathy. Besides, age-sex matched 208 non-diabetic controls were included in the study. Mesopic, scotopic and photopic pupil measurements were recorded via infrared static pupillography.

Results: The photopic pupil diameter was 3.72 (0.86) mm, 3.64 (0.78) mm, 3.74 (0.78) mm and mesopic pupil diameter were 4.06 (0.76) mm, 4.22 (0.80), 4.39 (0.83) mm and scotopic pupil diameter was 4.58 (0.76) mm, 4.56 (0.84) mm, 4.77 (0.85) mm respectively in DPN group, non-neuropathic diabetic group, and control group. There was no statistically significant difference in groups (P>0.05) except for mesopic and scotopic pupil diameters between control and non-neuropathic diabetic group (P=0.03 and P=0.01, respectively).

Conclusion: Pupillographic methods are not as reliable as diabetic autonomic neuropathy in the early diagnosis of DPN.

Keywords: Diabetes mellitus, Pupillography, Polyneuropathy, Diabetic complications

Öz

Amaç: Diyabetik otonomik nöropati pupil disfonksiyonu ile karşımıza çıkabildiği için erken tanıda pupil değerlendirmesi önemli olabilir. Bu çalışmada statik pupilometre aracılığıyla diyabetik polinöropatinin pupil cevabına etkisini araştırmayı amaçladık.

Yöntemler: Vaka kontrol çalışmamız 420 katılımcı üzerinde gerçekleştirildi. Tüm hastalar nöroloji departmanına konsülte edilen tip 2 diyabetes mellitus hastalarıydı. Birinci grupta Tip 2 Diyabetes Mellitus u bulunan 60 distal simetrik polinöropatili hasta bulunmaktaydı. İkinci gruba 202 polinöropatisi olmayan diyabetik hasta dahil edildi. Ayrıca diyabetik olmayan 208 hasta da kontrol grubu olarak çalışmaya dahil edildi. İnfrared statik pupillografi cihazı ile mezopik, skotopik ve fotopik şartlarda ölçümler alındı.

Bulgular: Diyabetik Polinöropatili , nöropatisi olmayan diyabetik ve kontrol gruplarındaki cevaplar sırasıyla; fotopik şartlarda 3,72 (0,86) mm, 3,64 (0,78) mm, 3,74 (0,78) mm, mezopik şartlarda 4,06 (0,76) mm, 4,22 (0,80), 4,39 (0,83) ve skotopik şartlarda 4,58 (0,76) mm, 4,56 (0,84) mm, 4,77 (0,85) mm idi. Kontrol grubu ile nöropatisi olmayan diyabetik hastalardaki mezopik ve skotopik pupil çapları dışında (sırasıyla P=0,03 ve P=0,01) gruplar arasında istatiktiksel olarak anlamlı (P>0,05) bir farklılık bulunamadı.

Sonuç: Pupillografik metodlar diyabetik polinöropati nin erken tanısında diyabetik otonomik nöropati kadar güvenilir sonuçlar vermemektedir.

Anahtar kelimeler: Diabetes mellitus, Pupillografi, Polinöropati, Diabet komplikasyonları

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Introduction

Diabetes mellitus is a public health issue that has been increasing rapidly in our country and the world in recent years [1]. It is essential to diagnose diabetes mellitus in the early period and adjust the lifestyle changes with/without medical treatment for prevention of development of possible complications in patients. In ophthalmology department, the majority of patients, especially those who are followed up in the retina, have vision problems related to diabetic retinopathy. Therefore, it is essential to diagnose the disease as soon as possible and apply the appropriate treatment. Another significant complication of diabetes, neuropathy is related to the duration of diabetes, not having proper control of hyperglycemia similar to other complications such as retinopathy, nephropathy, cardiovascular disease.

Diabetic autonomic neuropathy is manifested by pupillary dysfunction in the eye; so early recognition is vital for this [2]. For this reason, sequential autonomic dysfunction screening is necessary. Studying pupillary tests may be a way to diagnose this as early as possible, and abnormalities in pupil function may be detected before cardiovascular autonomic function abnormalities and may be the earliest finding of diabetic autonomic neuropathy [3]. It has been observed, however, that autonomic changes cause an increase in mortality [4]. In this study, we aimed to evaluate the existence of similar relation with diabetic polyneuropathy (DPN) and pupillary dysfunction as if it has been identified in autonomic neuropathy. So, we objected that to determine whether polyneuropathy can be detected at an early stage by pupillography and to investigate whether any changes consist of pupil responses in diabetic patients that no complications have occurred yet. Until this time, all studies have been focused on the relationship between diabetic autonomic dysfunction and pupil responses. Unlike this, we believe that this pupillary response dysfunction may occur in polyneuropathy through different pathophysiological pathways.

Materials and methods

The study was conducted with adherence to the tenets of the Helsinki declaration and under the approval of the institutional ethics committee. Informed consent from each participant was also gathered. Patients that have been just diagnosed with Type 2 Diabetes Mellitus and has been identified previously were referred from the Internal Medicine Department to the Ophthalmology Department for detailed ophthalmological examination and healthy control participants who were admitted for a routine visit to Ophthalmology Department without any retinal complaints between July 2013 and January 2015 were enrolled prospectively in the study. All subjects underwent detailed ophthalmological examination including best-corrected visual acuity (BCVA), intraocular pressure measurement, slit-lamp biomicroscopy. Exclusion criteria were the presence of ametropia more than 3 diopters (D), axial length (AL) less than 22mm or more than 25mm, previous glaucoma diagnosis, age-related macular degeneration, uncontrolled hypertension, previous intraocular surgery or intervention, macular diseases and media opacities that limit to obtain pupillometry measurements. All participants in all groups have been recorded with detailed ophthalmologic examination and in addition to this optical coherence tomography (OCT) (Cirrus HD Spectral domain-OCT Model 4000; Carl Zeiss Meditec, Inc., Dublin, CA, USA) and pupillography measurements. (CSO-Schwind Sirius, SCHWIND eye-tech-solutions GmbH, Kleinostheim, Germany)Pupil diameter size measurements in photopic (40 lux) condition simulating the day-time, in mesopic (4 lux) condition and in scotopic (0.04 lux) condition simulating the level of light encountered at night; recorded via using Scheimpflug/Placido photography-based topography system in the pupillometer mode (Sirius, Italy) by the same technician preoperatively. The integrated pupillometry captures the pupil diameter either dynamically or statically according to the defined lighting conditions. Participants were instructed not to consume caffeine or smoke cigarettes during the measurement day until the measurement time. After pupillographic measurements were completed, the fundus examination was completed by diluting the pupil with 0.5% tropicamide. Patients that have been diagnosed with diabetic retinopathy on dilate fundus examination (except for background diabetic retinopathy), systemic disease that may affect the pupillary function, using medical therapy, previous anterior segment or retinal surgery history and any ocular or systemic disease that able to affect pupillary parameters (pseudoexfoliation syndrome, previous uveitis, active or passive rubeosis iridis) were not included in the study. Age, sex, Hemoglobin A1c (HbA1c) levels, diabetes duration, medications, and concomitant systemic diseases were noted for each participant. Results of blood glucose samples were taken simultaneously with an ophthalmologic examination from all participants that have been identified with Type 2 Diabetes Mellitus and have been studied glycosylated HBA1c values by HPLC (high-performance liquid chromatography) method.

Patients were directed to the Neurology Department for the detection of neuropathy. Diabetic polyneuropathy (DPN) diagnosis was established with the presence of clinical symptoms, Douleur Neuropathique-4 questionnaire (DN-4), neurological examination findings, and electroneurophysiological assessment after other possible causes of peripheral neuropathies were excluded (cancer related, side effect of immunosuppressive drugs, vitamin B12 deficiency, uremic and other metabolic causes, etc.).

Participants in the control group without diabetes mellitus or polyneuropathy has been identified as Group 1 (DM-PNP-); which have Type 2 Diabetes Mellitus without polyneuropathy has been identified as Group 2 (DM+ PNP-) and that have both Type 2 Diabetes Mellitus and polyneuropathy has been identified as Group 3 (DM+ PNP+).

Eventually, 60 eyes of 30 diabetic patients with diabetic polyneuropathy(DPN) (Group 3), 202 eyes of 102 non-neuropathic Type 2 diabetes mellitus patients (Group 2), and 208 eyes of 104 healthy participants (Group 1) those age and sex-matched were included in the study.

Statistical analysis

For the statistical analyses, SPSS (Statistical Package for Social Sciences) FOR Windows 21.0 program was used. One Way ANOVA was used to compare descriptive statistical methods (Mean (Standard deviation)) when study data were

evaluated. The results were evaluated in a 95% confidence interval and a significance level of P <0.05.

Results

The distribution of the gender of the 208 control participants was 109 female (52.40%) and 99 male (47.59%) (Group 1). The mean age of the patients was 57.39 (14.21) (22-85 years) in Group 1. The distribution of the gender of the 202 non-neuropathic diabetic patients was 132 female (65.34%) and 70 male (34.65%) (Group 2). The mean age of the patients was 59.59 (9.60) (32-78 years) in Group 2. The distribution of the gender of the 60 diabetic neuropathic patients was 44 female (73.33%) and 16 male (26.66%) (Group 3). The mean age of the patients was 61.10 (12.30) (29-85 years) in Group 3. Age distributions between groups are shown in Table 1. There was no difference between the mean age and gender distributions of the diabetic group with diabetic neuropathy, diabetic group without diabetic neuropathy, and control group (P=0.06).

The demographic features, systemic diseases according to the groups are shown in Tables 2. Group 1 (n=208) was defined as a control group without diabetes mellitus. The mean duration of diabetes was recorded as 4.26 (5.21) years in Group 2 (n=202), and the mean duration of diabetes was recorded as 7.98 (5.30) years in Group 3 (n=60). In group 2, the number of patients that have been just diagnosed with diabetes mellitus was 66 (32.7%); in group 3, this number was 4 (6.7%). Obviously, this result shows that about 6% of patients with diabetes mellitus do not realize the disease even though neurological complications occur during the development of diabetes mellitus.

HBA1c values of the patients was taken simultaneously with ophthalmologic examinations and recorded as 6.23 (1.00) in Group 2 and 8.83 (1.97) in Group 3. The difference between groups 2 and 3 in terms of HbA1c was significant (p<0.01).

The pupil diameter measured by pupillography in the diabetic group with neuropathy (Group 3) was 3.72 (0.86) mm (2.57-6.12 mm) in photopic conditions; 4.26 (0.76) mm (3.02-6.14 mm) in mesopic conditions; 4.58 (0.76) mm (3.28-6.37 mm) in scotopic conditions. The pupil diameter measured by pupillography in the diabetic group without neuropathy (Group 2) was 3.64 (0.78) mm (2.21-6.79 mm) in photopic conditions; 4.22 (0.80) mm (2.49-6.88 mm) in mesopic conditions; 4.56 (0.84) mm (2.52-6.90 mm) in scotopic conditions. The pupil diameter measured by pupillography in control group (Group 1) with neuropathy was 3.74 (0.78) mm (1.85-6.28 mm) in photopic conditions; 4.39 (0.83) mm (2.79-7.22 mm) in mesopic conditions; 4.77 (0.85) mm (3.22-7.81 mm) in scotopic conditions.

There was no difference in pupil diameters between photopic, mesopic and scotopic conditions between all three groups (P=0.38, 0.09, 0.05, respectively); between Group 2 (DM + PNP-) and Group 3 (DM + PNP+). (P=0.48, 0.72 and 0.84, respectively) and between Group 1 (DM-PNP-) and Group 2 (DM + PNP-) (P=0.17, 0.03 and 0.01, respectively) except for mesopic and scotopic pupil diameters. Likewise, there was no statistically significant difference between photopic pupil diameters in these groups (P=0.17). Distribution of pupil diameters and statistical significance values between groups are shown in Table 3.

Table 1: Age-group distributions of participants

	Group 1		Group 2		Group 3		*P*-value
	n	%	n	%	n	%	
Female	109	52.4	132	65.34	44	77.33	0.06
Male	99	47.59	70	34.65	16	26.66	
Age mean (SD)	57.39 (14.21)		59.59 (9.60)		61.10 (12.30)		0.06
Total	208	100	202	100	60	100	

SD: Standard deviation

Table 2: Distribution of systemic diseases of participants

Systemic disease	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)
Hypertension	58 (27.9)	78 (38.6)	23 (38.3)
Chronic Renal Failure	2 (1.0)	6 (3)	2 (3.3)
Coronary Arterial Disease	6 (2.9)	14 (6.9)	3 (5.0)
Cerebrovascular Disease	0 (0)	2 (1.0)	0 (0)
Dyslipidemia	6 (2.9)	12 (5.9)	4 (6.7)
Thyroidopathy	16 (7.7)	18 (8.9)	2 (3.3)
Diabetes inspidus	2 (1.0)	0 (0)	0 (0)
Tuberculosis	0 (0)	2 (1.0)	0 (0)
Gastroesophageal Reflux Disease (GERD)	2 (1.0)	14 (6.9)	0 (0)
Irritable Bowel Disease	0 (0)	2 (1.0)	0 (0)
Osteoporosis	2 (1.0)	0 (0)	0 (0)
Migraine	2 (1.0)	0 (0)	0 (0)
Parkinsonism	10 (4.8)	0 (0)	2 (3.3)
Hemorrhoids	0 (0)	4 (2.0)	0 (0)
Chronic Obstructive Pulmonary Disease (COPD)	0 (0)	4 (2.0)	0 (0)
Asthma	3 (1.4)	2 (1.0)	1 (1.7)
Benign Prostate Hyperplasia (BPH)	2 (1.0)	4 (2.0)	0 (0)
Urinary Incontinence	0 (0)	0 (0)	0 (0)
Essential Tremor	2 (1.0)	0 (0)	0 (0)
Iron Deficiency Anemics	4 (1.9)	16 (7.9)	0 (0)
B12 Vitamin Deficiency	0 (0)	12 (5.9)	6 (10.0)
Total	208 (100)	202 (100)	60 (100)

Table 3: Distribution of pupil diameters according to groups

	Group 1	Group 2	Group 3	*P*-value[1]	*P*-value[2]	*P*-value[3]
Photopic PD	3.74 (0.78)	3.64 (0.78)	3.72 (0.86)	0.17	0.48	0.38
Min-Max	1.85-6.28	2.21-6.79	2.57-6.12			
Mesopic PD	4.39 (0.83)	4.22 (0.80)	4.26 (0.76)	0.03	0.72	0.09
Min-Max	2.79-7.22	2.49-6.88	3.02-6.14			
Scotopic PD	4.77 (0.85)	4.56 (0.84)	4.58 (0.76)	0.01	0.84	0.05
Min-Max	3.22-7.81	2.52-6.90	3.28-6.37			

Values are given as mean (Standard deviation), Min: Minimum, Max: Maximum, [1] Statistical significance value between Group 1 and Group 2, [2] Statistical significance value between Group 2 and Group 3, [3] Statistical significance value among all groups

Discussion

Pupillary responses can be determined quantitatively by the infrared pupillometry method under the constant light stimulus. In photographic methods, reproducibility and reliability indexes are very low due to manual measurements made by photographers. The likelihood of differences due to the operator, who evaluates them by automatization and quantitative measurements, has also ceased to exist. Other advantages include easy measurement and quick results. In the literature, different pupil response measurement methods have been used to investigate the effects of diabetic autonomic neuropathy on pupil response in most studies [23]. In previous studies, there is some evidence that the presence of diabetes leads to damage in the pupil response, even in the absence of neuropathy. In this study, there was no significant difference in the pupillary response between the control group and diabetic patients without neuropathy except for mesopic and scotopic pupil diameters between the control group and diabetic patients without neuropathy.

This result may be caused by the effect of newly diagnosed patients' ratio (n=66, %32.7) on all diabetic groups and an average duration of diabetes was 4.26 (5.21) years in this group. The frequency of diabetic polyneuropathy is closely related to the duration of diabetes. In the meta-analysis, Young et al. have shown that the frequency of diabetic polyneuropathy increases markedly with age. The incidence of diabetic polyneuropathy in the 20-29 age groups is 5% (3.1-6.9%), while it is 44.2% (41.1-47.3%) in the 70-79 age groups. The incidence

of neuropathy is 20.8% (19.1-22.5%) in patients with less than five years of diabetes, and 36.8% (34.9-38.7%) in patients over ten years of age. Diabetic peripheral neuropathy is a common complication associated with diabetes and occurs in patients with Type 2 Diabetes Mellitus over 60 years of age with a 50% excess rate.

The American Diabetes Association recommends that neuropathy screening is performed every five years after diagnosis in Type 1 Diabetes Mellitus patients, and every year after diagnosis in Type 2 Diabetes Mellitus [5]. Therefore, it is not often expected to be affected by pupillary responses even in the absence of polyneuropathy in a population with an average of 4 years of diabetes. In this study, the diabetic patient group was screened for diabetic polyneuropathy, although the change in pupil responses was mostly associated with autonomic neuropathy. This study was designed to show whether changes in pupil responses in the presence of polyneuropathy may be due to autonomic nervous system effects that are predominantly responsible for pupillary response, which is likely to cause deficits in pupillary responses, as well as similar pathophysiological damage pathways. As a matter of fact, the changes in pupil responses in the presence of diabetic polyneuropathy were not statistically significant. Studies in the literature on pupillary reactions of diabetic patients have suggested that pupil changes are often seen in autonomic neuropathic patients, pupillary changes may be present in some polyneuropathic patients, but autonomic neuropathies are also present in these patients simultaneously [6]. It is not likely to declare that pupillary changes are associated with isolated distal somatic polyneuropathy as if autonomic system is not affected. In this study, all participants did not examine for the presence of autonomic neuropathy.

Tentolouris et al. [8] have been conducted another study that investigates the association of diabetic polyneuropathy and autonomic neuropathy; there was a debate on those patients with diabetes were not required to have autonomous and peripheral neuropathy at the same time. Autonomic neuropathy and peripheral neuropathy are found simultaneously in approximately one-third of Type 1 diabetes patients and approximately 45% of Type 2 diabetic patients. Both types of diabetes had a significant group of patients with only autonomic neuropathy or only peripheral neuropathy. polyneuropathy may be presently isolated independently of the presence of autonomic neuropathy in diabetic patients. Pozzessere et al. [9] reported as possible that prediction of fine-fiber neuropathy in diabetic patients. In this study, somatosensory evoked potentials (p-SEP) were recorded after the carbon dioxide laser-mediated painful stimulus were given to participants and values were compared with the monocular pupillometric data (ISCAN, sample rate 50 Hz) taken simultaneously from the participants. Even though the existence of patients with synchronous distal symmetric polyneuropathy and autonomic dysfunction, there was no statistically significant difference between pupillometric values and somatosensory evoked potentials (p-SEP; Pain Induces Somatosensory Evoked Potential). This study revealed that the early, subclinical and selective damage of thin nerve fibers can occur in diabetic patients even with the absence of clinical autonomic dysfunction findings and thick fiber neuropathy proven with electrophysiological methods; also this damage can be evaluated in relation to both autonomic and somatic dysfunction. Another important data reported in the same study shows that the damage appears firstly in the longest nerve pathways of the lower extremity and shows the dysfunction of nerve fibers associated with fiber length. Pupillometry results with changes in pupil response indicate that primarily damage is detected in the longest sympathetic nerve fibers. Therefore, at the beginning of pupillary damage, sympathetic fibers that provide pupillary adaptation in the dark are damaged, and appropriate pupillary response may be encountered after light stimulation. However, if metabolic control is not provided, parasympathetic nerves are also affected by this damage. In this study, any statistically significant difference was found between the pupillometer parameters and somatosensory latencies similar to our study. The main reason for this result could be evaluated as the effects of diabetes on somatic and autonomic nerve fibers occurs in different stages of diabetes. Because of different neural structures of cranial autonomic fibers and peripheral somatic fibers, it is likely that they will be damaged at different stages of the disease. Therefore all studies designed should be designed in such a way as to allow simultaneous assessment of the effects of different nerve fibers [9]. Especially, pupil measurements should be used in clinical practice as a reliable, quantitative method of detecting subclinical diabetic autonomic neuropathy [10].

Most studies have reported that the impairment of the pupil response is associated with autonomic dysfunction in diabetic patients. Dütsch et al. [12] reported the first study that distinguishes the presence of pupillary autonomic dysfunction from cardiac autonomic neuropathy and polyneuropathy. As a result, it has been found that pupillary light reflex responses are independent of polyneuropathy and cardiac autonomic neuropathy, consistent with our clinical results. The frequency of pupillary autonomic dysfunction was similar in patients with or without cardiac autonomic neuropathy or polyneuropathy and any correlation detected between cardiovascular and pupillary parameters. We can predict that cardiac parasympathetic neuropathy should be seen earlier than pupillary dysfunction in the presence of diabetic neuropathy by a pathophysiological approach because of the distal part of the vagal nerve, which is quite long, is more easily damaged than the relatively shorter nerve fibers that provide pupil innervation. Dütsch et al. [12] reported that there is no finding of somatic or cardiac neuropathy in patients with pupillary dysfunction contrary to this pathophysiological assumption. In response, they presented an opinion that autonomic innervation could be damaged more easily than peripheral nerves in diabetic conditions and defended by stating that oculomotor and trochlear neuropathy can also be seen without peripheral and cardiac autonomic neuropathy [13-15]. Apart from this, the ciliary and iris muscles are highly selective, and the number of muscle fibers innerved by a single nerve fiber is very few [16]. For this reason, even in the least severe damage of nerve, pupillary dysfunction is evident which can be seen without cardiac or peripheral neuropathy.

The abnormal pupillary response is associated with the pathology of the afferent and efferent pathways [17-19]. Smith & Smith reported that the reduction in pupillary contraction rate and decreased reflex amplitudes would not be related to the small

pupil diameter and that the disturbances in these parameters were due to parasympathetic dysfunction [20]. Hayashi and Ishikawa have been essayed to prove parasympathetic pupillary denervation in diabetic patients by showing super-sensitivity to cholinergic drugs [21]. Smith et al. found that disturbances in pupil diameter at relaxation were due to sympathetic dysfunction and reduction of sympathetic activity in the iris muscle and they evaluated the sympathetic pupillary denervation that has been demonstrated by pharmacological methods in patients with diabetic autonomic neuropathy [22]. It is thought that the sympathetic nerve fibers are more vulnerable due to the longer length of the sympathetic nerve fibers than the parasympathetic nerve fibers.

Therefore, sympathetic nerve dysfunction could be seen than oculomotor parasympathetic nerve dysfunction [2] and this is resulted in that pupillary dysfunction in resting state or as darkness is seen before the defect in the light reflex [12].

The main limitation of this study is its relatively small sample size, which is due to the elimination of a considerable, because of this reason, that is hard to generalize our findings. Besides, all participants did not undergo a specific diagnostic test to rule out autonomic dysfunction because there is not still a gold standard diagnostic test. Autonomic dysfunction is a complication which is thought to be a quite effective factor in pupil response in diabetic patients and only neurological evaluation and questioning of clinical symptoms such as orthostatic hypotension, orthostatic intolerance, postural orthostatic tachycardia syndrome, also known as postural tachycardia syndrome, syncope, neurogenic bowel (gastroparesis, intestinal dysmotility, constipation), erectile dysfunction and neurogenic bladder were excluded in this study. It is obvious that autonomic dysfunction is entirely independent of polyneuropathy. On the other hand, its prospective, randomized and double-masked design fortifies our study results.

In conclusion, pupillography methods exhibit abnormal pupillary function, but this damage can be a direct indicator of autonomic dysfunction. This autonomic dysfunction is entirely independent of polyneuropathy. Pupillography is recommended to diagnose diabetic autonomic dysfunction more frequently in clinical practice because it is a readily applicable, noninvasive and cheap method. On the contrary, this method cannot be applied for the detection of distal symmetric polyneuropathy in diabetic patients. Finally, strict systemic regulation and close follow-up are required to prevent all these complications in diabetic patients.

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