SHORT-WAVELENGTH AUTOMATED PERIMETRY IN DIABETIC PATIENTS WITHOUT RETINOPATHY

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SUMMARY

Aim: To compare the results of short-wavelength automated perimetry (SWAP) in diabetic patients without retinopathy and healthy subjects and show if it is possible to detect an abnormal function of the retina in diabetic patients before vascular changes on the retina develop. Further, the effect of diabetes duration and long-term glycaemic control on the visual field was examined.
Methods: The study group included 22 patients with diabetes type 1 or 2, without any signs of retinopathy. The control group consisted of 21 healthy subjects. Short-wavelength automated perimetry was performed on the Humphrey Field Analyzer (HFA 860, Carl Zeiss Meditec), SITA SWAP, 24-2 test. In diabetic patients, the duration of diabetes and the level of glycohemoglobin (HbA1c) was registered. The visual field indices MD (mean deviation) and PSD (pattern standard deviation) were compared between both groups by the Mann-Whitney test. The correlation between the visual field indices, HbA1c and duration of diabetes was assessed by the Spearman correlation coefficient.
Results: The mean value of MD in the study and control group was -3.64±3.66 dB and -1.48±2.12 dB respectively, the values in the study group were significantly lower ($p < 0.05$). Mean PSD in the study group was 2.92±1.04 dB and 2.23±0.33 dB in the control group, again the difference was statistically significant ($p < 0.05$). Patients in the study group suffered from diabetes for 17±9.4 years in average. The mean value of HbA1c in the study group was 60.64±16.63 mmol/mol. A significant correlation was found only for PSD and HbA1c ($p > 0.05$). The duration of diabetes had no effect on either of the visual field indices.
Conclusion: Short-wavelength sensitivity of retina seems to be affected in diabetic patients without clinically significant retinopathy suggesting a neuroretinal impairment at early stages of the retinopathy. We found no association between the visual field and the control or duration of diabetes.
Key words: blue-on-yellow perimetry, SWAP, diabetes, diabetic retinopathy, glycohemoglobin

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INTRODUCTION

Blue-on-yellow perimetry (Short-Wavelength Automated Perimetry, SWAP) is a clinical method that was developed to assess the blue-yellow chromatic channel. A blue stimulus is presented on a high luminance yellow background, that helps to saturate the green and red cones, and to simultaneously suppress rod activity, whilst leaving the S-cones (blue cones) largely unaffected. In recent years, considerable interest has been shown in SWAP as a potential means for detecting the presence of visual field loss in glaucoma, prior to that identified by conventional white-on-white (W-W) perimetry. However, despite initial enthusiasm, studies have shown that limitations in the technology make SWAP difficult and impractical in everyday practice. SWAP requires a longer testing time, the results are affected by age-related yellowing of the lens and cataract, and variability in thresholds is greater with SWAP than with conventional W-W perimetry, which makes the evaluation of progression more difficult [1,2,3].

Better usability for practice has been brought about by the later introduction of SITA SWAP on the HFA (Humphrey Field Analyzer). This algorithm has helped to significantly reduce the length of the examination, while preserving sufficient reliability of the test [4]. At the same time, some studies have shown that this method can be useful for the detection of early stages of diabetic retinopathy [5] and diabetic macular oedema [6].

Diabetic retinopathy (DR) is the second most frequent cause of blindness in developed countries [7]. Once sight-threatening vascular changes have developed, laser therapy can substantially reduce the risk of vision loss [8]. To prevent or delay progression of vascular abnormalities, it is necessary to regulate the hyperglycaemia and related metabolic disturbances by systemic drug therapy [9]. The progression of diabetic retinopathy and the effects of drug therapy have been and still are monitored by stereo fundus photographs. The standard for the evaluation of visual function is the ETDRS scale [10]. However, it seems that psychophysical tests, such as perimetry or contrast sensitivity, are more sensitive in detecting early neurodegeneration in diabetic retina than visual acuity.

The application of these methods can be useful in the diagnosis of early diabetic retinopathy and in monitoring its progression, and the effect of pharmacotherapy in stages where morphological changes on the retina are minimal or absent and the visual acuity is normal [11,12,13].

In the present study, we compared the results of SWAP in diabetic patients without retinopathy and healthy subjects. Our primary aim was to show whether SWAP can detect the disruption of retinal function in diabetic patients before morphological changes occur on the retina. A secondary purpose was to find whether the duration and compensation of diabetes have an influence on the parameters of the visual field.

MATERIALS AND METHODS

Patients with diabetes type 1 or 2, with no signs of diabetic retinopathy and a different level of compensation and duration of diabetes were recruited into the study. The control group included age-related healthy subjects without diabetes. The exclusion criteria for both groups were the following: any signs of DR, previous laser treatment of the retina, cataract or any opacity of ocular media, glaucoma, amblyopia, high refractive error, diseases of the retina or the visual pathway, medications that could affect the visual field, and poor cooperation during perimetry.

All subjects underwent a comprehensive ophthalmological examination that included a slit-lamp examination, non-contact tonometry and measurement of uncorrected and best-corrected distance and near visual acuity, indirect ophthalmoscopy and colour fundus photography through a dilated pupil.

Diabetic patients were screened for the duration of diabetes and their level of glycohaemoglobin. Glycohaemoglobin (HbA1c) is formed by an irreversible non-enzymatic reaction between haemoglobin and blood glucose. HbA1c is measured primarily to determine the three-month average blood sugar level and is used as an assessment test for glycaemic control in people with diabetes. HbA1c values lower than 45 mmol/mol indicate excellent compensation of diabetes; values up to 60 mmol/mol an acceptable level and higher values show an insufficient compensation of diabetes.

For the visual field test, the Humphrey Field Analyzer (model HFA 860, Carl Zeiss Meditec) was used. In all cases, visual field was examined by the 24-2 SITA SWAP test, Goldmann stimulus V. This program tests the central 24° of the visual field with 52 points, which corresponds to a great extent to the area covered by standard fundus photographs. The examination of one eye takes about 3 minutes. The subjects were all instructed about the course of the test and necessary cooperation. In the case of the false positive rates exceeding 15%, the test was repeated after a break.

Mean deviation (MD) and pattern standard deviation (PSD) were recorded and used for statistical analysis. MD is a global index of the age-adjusted average deviation from the mean across all test locations, and PSD is a global index of the uniformity of the deviation compared to age-matched controls. Subjects with reduced retinal function have more depressed MD values (negative) and higher PSD values (positive).

One randomly selected eye was used for the analysis. The nonparametric Mann-Whitney test was used to compare the MD and PSD indices between the study and control groups. To evaluate the relation of visual field indices, duration of diabetes and glycohaemoglobin, the Spearman nonparametric coefficient of correlation was used. For all tests, $p < 0.05$ was considered as statistically significant.

RESULTS

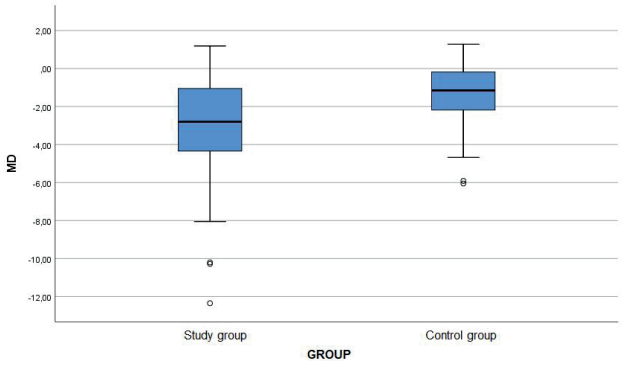
The study group included 22 patients with diabetes type 1 or 2 (10 females and 12 males, mean age 40.95 years (25–58 years). The control group consisted of 21 healthy subjects with mean age 38.24 years (27–53 years). The uncorrected or the best corrected visual acuity was 1.0 in both groups. Patients in the study group suffered from diabetes for 17 ±9.4 years on average (3–35 years). The mean value of glycohaemoglobin in the study group was 60.64 ±16.63 mmol/mol (32–100 mmol/mol), so that the range was quite large.

Mean MD was -3.64 ±3.66 dB (-12.35–1.19) in the study group and 1.48 ±2.12 dB (-6,05–1,28) in the control group. MD values in the study group were significantly decreased ($p < 0.05$) (Graph 1). Mean PSD in the study and control groups was 2.92 ±1.04 dB (1.99–5.61) and 2.23 ±0.33 dB (1.75–2.98) respectively. Again, the difference was statistically significant ($p < 0.05$) (Graph 2).

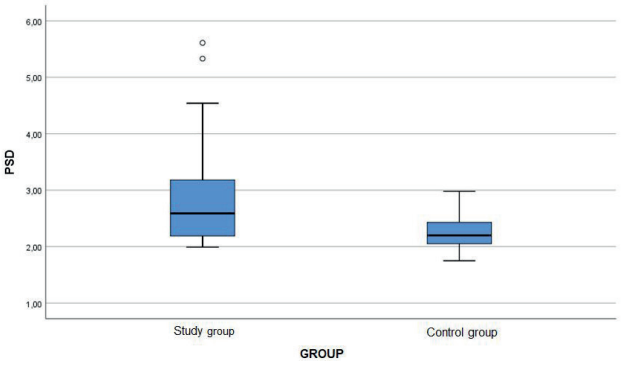
In the diabetic group, no correlation was found between the visual field indices and the duration of diabetes. Statistically significant (negative) correlation was found only for PSD and glycohaemoglobin ($p > 0.05$), meaning that the PSD values decreased with higher glycohaemoglobin. No correlation was found for MD and glycohaemoglobin ($p = 0.17$).

DISCUSSION

Higher blood sugar in diabetic patients leads to vascular changes on the retina, hypoxia, and apoptosis of retinal neurons. In clinical practice, the term "diabetic retinopathy" is reserved for cases where vascular ab-



Graph 1. Comparison of Mean Deviation (MD) between the study and control group. MD was significantly lower in the study group (diabetics) compared to the control group (healthy subjects), $p < 0.05$



Graph 2. Comparison of Pattern Standard Deviation (PSD) between the study and control group. PSD was significantly higher in the study group (diabetics) compared to the control group (healthy subjects), $p < 0.05$

normalities are visible on the retina. However, metabolic changes in the diabetic eye begin much earlier and diabetic retinopathy affects the entire neurovascular unit of the retina. Findings from psychophysical and electrophysiological studies suggest that dysfunction of the neuroretina may precede the characteristic vascular findings [11,12,13]. Hypoxia and disturbance of the metabolism of the photoreceptors and other retinal cell account for a pathological response in electrophysiology and contrast sensitivity tests [12,13]. Similarly, reduction of retinal sensitivity can be detected with perimetry [14].

In our study, MD was significantly lower in the study group, compared to the control group and PSD was, on the contrary, significantly higher. With the same good level of visual acuity in both groups, this finding can be interpreted as a sign of early retinal dysfunction in diabetic patients. Therefore, our results support the theory that diabetic retinopathy is initially rather a retinal neurodegeneration than a vascular abnormality and blue-on-yellow perimetry can help to reveal this neuronal dysfunction in an early phase. Two mechanisms are probably responsible for this feature.

Firstly, SWAP selectively tests the koniocellular pathway. Standard (white-on-white) perimetry uses a white stimulus that tests two major groups of retinal ganglion cells – magnocellular and parvocellular. However, there is a considerable overlap of retinal receptive fields and so a non-selective stimulus may not detect an incipient loss of retinal ganglion cells. By using special stimuli, as in SWAP, changes of retinal sensitivity can be detected earlier than with standard perimetry [14,15].

Secondly, it has been documented that patients suffering from diabetes or glaucoma exhibit colour vision deficits, predominantly of the short wavelengths of the spectrum. The loss occurs at an early stage of the disease, even before structural changes' alterations are visible, and is considered as a sign of early neurodegeneration in diabetic retina. The presence of tritan deficit in glaucoma patients can also be regarded as a sign of neurodegeneration, although of a different origin. For example, in the study by Kurtenbach et al., the colour contrast threshold was the most sensitive method to distinguish between normal, diabetic and glaucoma patients. The tritan deficit had the highest area under curve (AUC) in diabetics [13].

Neuroretinal dysfunction in diabetes affects inner retinal layers, so that methods that selectively test inner retinal function can detect damage earlier than others. Apart from SWAP, we may mention FDT perimetry (Frequency Doubling Perimetry, Carl Zeiss), Pattern Electroretinography (PERG), colour vision or contrast sensitivity tests. The use of these methods in screening and monitoring of the disease, or in assessing the effect of new treatment modalities for diabetes could be interesting.

In our study, we found no relation between the visual field indices and the duration or compensation of diabetes. Similarly, in the 2014 study by Hellgren et al. that evaluated the progression of retinal dysfunction in diabetic patients by means of standard automated perimetry, visual acuity and fundus photography, no correlation between visual field deterioration and the duration of diabetes or the level of HbA1c was found [16]. Additionally, Verrotti et al. did not find any relationship between standard perimetry and metabolic control of diabetes [17]. Nitta et al. in their study evaluated the influence of clinical factors in diabetic patients without retinopathy on blue-on-yellow perimetry. They did not find any difference in MD or PSD between diabetic patients and healthy subjects. Nevertheless, in the diabetic group, a longer duration of diabetes and inferior compensation were associated with a significantly lower MD value on blue-on-yellow perimetry [18].

The absence of any relationship between the visual field indices and the compensation of diabetes could be interpreted by the influence of current metabolic parameters on the result of psychophysical methods of measuring visual functions, including perimetry. For example,

contrast sensitivity normalises in hyperoxia [19], hyperglycaemia increases the score of contrast sensitivity [20] and hypoglycaemia has a negative impact on contrast sensitivity [21].

A limitation of our study is the small number of patients and subjects in both groups, caused by the only limited time of our study and by strict inclusion criteria, especially the absence of any lens opacity. However, despite these limitations, our results seem to correlate with other studies on this topic.

CONCLUSION

Decreased retinal sensitivity in the study group can be interpreted as a sign of neuroretinal dysfunction in the early stages of diabetic retinopathy. Thus, our results suggest that perimetry testing with SWAP can provide additional information to conventional visual acuity testing and photographic documentation, when monitoring patients with diabetes or evaluating the effect of novel therapeutic approaches.

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