

Short Wavelength Automated Perimetry and Peripapillary Retinal Nerve Fiber Layer in Early Diabetes

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ABSTRACT

Objective: To investigate the significance of short wavelength automated perimetry (SWAP) in detecting retinal functional impairment in early diabetic patients without retinopathy and with mild non-proliferative diabetic retinopathy (NPDR).

Materials and Methods: This is a prospective, cross-sectional study of 37 eyes of early diabetics which were divided into 2 groups: no DR with 18 subjects and mild NPDR with 19. All subjects underwent HBA1C, SWAP, peripapillary RNFL thickness measurement and fundus photo. Visual field indices: MD and PSD as well as average RNFL thickness were compared among the 2 groups. Correlation of MD with RNFL thickness and HBA1C were also analyzed.

Results: There was no statistically significant difference in the MD (-4.46 ± 3.03 vs -2.94 ± 2.21 ; $p=0.09$), PSD (3.08 ± 1.28 vs 2.69 ± 0.47 ; $p=0.23$) and average peripapillary RNFL thickness (98.47 ± 6.89 vs 98.72 ± 11.01 ; $p=0.93$) among early diabetics with mild NPDR and no signs of DR. There is no correlation between MD and RNFL thickness in the no DR group ($R^2=0.017$) and the mild DR group ($R^2=0.000$). There was a weak correlation between MD and HBA1C in the no DR group ($R^2=0.137$), while no correlation was seen in the mild NPDR group ($R^2=0.000$).

Conclusion: SWAP does not appear to be a sensitive measure of worsening retinopathy in older individuals with early diabetes. The usefulness of SWAP and peripapillary RNFL thickness in the early stages of retinopathy are inconclusive.

Keywords: SWAP, perimetry, RNFL, diabetes, retinopathy, sensitivity

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Diabetic retinopathy (DR) remains a major cause of morbidity in diabetic patients and is one of the leading causes of preventable blindness in developing countries.¹ It carries a significant socioeconomic cost for healthcare systems worldwide.² Since diabetes is expected to increase from 366 million in 2011 to 552 million in 2030, DR will become a serious problem in the future.³ The global public health burden of DR highlights the significance of early detection and searching for new approaches beyond current standards of diabetes care.

DR is considered to be a microvascular complication caused by the imbalance in the metabolic pathways secondary to hyperglycemia. The clinically demonstrable changes in the retinal vasculature in diabetes have led to the general assumption that the retinopathy is solely a microvascular disease. However, the retina is not mainly a vascular tissue; rather, it is a neurovascular unit interconnected to form functional molecular interactions.⁴

A diagnosis of DR is given once microangiopathic signs such as microaneurysms, the first visible fundus manifestations are detected in the retina. Emerging evidence shows that the increase in oxidative stress due to diabetes leads to retinal ganglion cell (RGC) apoptosis and glial cell impairment and loss even before microangiopathic signs are seen.⁵⁻⁷ Indeed, RGC apoptosis has been noted in animal models as early as 14 weeks, while a manifest vasculopathy was not observed until approximately 6 months after the induction of diabetes.⁸ This may imply that neuronal dysfunction can occur prior to clinically detectable signs of vasculopathy.

This neurodegeneration corresponds with previous functional studies showing neuroretinal deficits including electroretinogram (ERG) abnormalities, loss of dark adaptation, color disturbances and decrease in contrast sensitivity in patients with diabetes without clinically detectable retinopathy.⁹⁻¹³ However, visual field defects occurring in early diabetes have received comparatively little attention. Majority of studies on visual fields in diabetic retinopathy used Standard Automated Perimetry (SAP) which resulted in reduction of retinal sensitivity in diabetic subjects without retinopathy as well as those with more severe retinopathy.^{4, 14-16}

In this investigation, sensitivity was assessed using short wavelength automated perimetry (SWAP), a more selective perimetry designed to expose blue

stimuli on an intense yellow background and is established in detecting pre-perimetric glaucoma. The principle of this method is selectively testing the short wavelength sensitive (SWS) cone mechanisms which are less redundant and are reported to be more susceptible to damage in diabetes.^{11, 17} Previous studies have reported earlier functional deficits in diabetic patients with minimal to no retinopathy using the SWAP technique compared to SAP.¹⁸⁻²¹

This study aims to determine the significance of SWAP in detecting changes in retinal sensitivity in early diabetic patients without retinopathy and with mild NPDR and to correlate these findings with the peripapillary RNFL thickness as well as glycemic control (HBA1C). To our knowledge, this is the first study correlating functional changes using SWAP and morphologic changes in peripapillary RNFL thickness using SD-OCT in early diabetics.

This study may aid in early functional monitoring of diabetics even before clinically detectable vascular manifestations are evident. SWAP and peripapillary RNFL thickness may serve as functional biomarkers of visual dysfunction in early diabetics. From the clinical point of view, the early identification of neurodegeneration will be crucial for implementing an early treatment based on drugs with a neuroprotective effect.

MATERIALS AND METHODOLOGY

This is a prospective, cross-sectional study. The study population consisted of 40 eyes of 40 patients with type 2 diabetes of less than 5 years duration, at least 18 years of age without signs of diabetic retinopathy and with mild non-proliferative diabetic retinopathy (NPDR) from private clinics and social service department (Ophthalmology, Internal Medicine and Endocrinology) of St. Luke's Medical Center, Quezon City from November 2015-June 2016. This study protocol was reviewed and approved by the Institutional and Ethics Review Board of St. Luke's Medical Center. The study adhered to the tenets of the Declaration of Helsinki. All subjects provided signed informed consents.

Exclusion criteria were the following: history of glaucoma or ocular hypertension, media opacity, best corrected visual acuity (BCVA) worse than 20/40 (logMAR 0.3), refractive error of more than $\pm 6D$, astigmatism of more than $\pm 3D$, diabetic

macular edema or other causes of macular edema or pathology, prior laser therapy or ocular surgery, ocular diseases such as cataract worse than nuclear sclerosis (NS) 2 by Lens Opacity Classification Study (LOCS) III, vision-threatening retinal diseases, uveitis or neurologic problem and unreliable visual field results.

Procedures

After securing the informed consent, all subjects underwent routine history taking focusing on age, diabetes duration and treatment. Complete eye examination was performed which consisted of BCVA, refraction, intraocular pressure (IOP), slitlamp anterior segment examination and dilated fundus examination using indirect ophthalmoscopy. Patients were then stratified into no DR group and mild DR group. Patients were then scheduled for the examination proper. Blood samples were then collected for glycosylated hemoglobin (HBA1C) (Variant II Haemoglobin A1C program, Bio-Rad, Hercules, CA, USA).

Visual fields were first tested using the Humphrey visual field analyzer (model 750; Humphrey-Zeiss, San Leandro, CA) with size V stimulus, blue in yellow background and SITA-SWAP strategy. Two SWAP tests were performed to rule out learning curve 1 week apart. Results were considered reliable if there were less than 20% fixation losses, less than 33% false negatives and less than 33% false positives.

Pupils were then dilated using Sanmyd-P eye drops (Tropicamide 0.5%, Phenylephrine HCl 0.5%) every 15 minutes for 2 doses. Cirrus HD-OCT (Carl Zeiss Meditec, Inc. Dublin, CA) optic disc cube program was used to measure the average peripapillary RNFL thickness. Zeiss Visupac FF450 plus IR (Carl Zeiss Meditech AG, Germany) was used to take the ETDRS Modified 7-field stereoscopic photos.

Outcome Measures

The primary outcome measure was mean deviation (MD) among diabetic patients with no DR and mild NPDR.

Secondary outcome measures were pattern standard deviation (PSD), average peripapillary RNFL thickness, correlation of MD with average RNFL thickness and correlation of MD with HBA1C among diabetic patients with no DR and mild NPDR.

Sample Size Determination

Sample size was calculated based on the study of Zico et al.²¹ wherein the standard deviations of MD of controls versus no signs of DR are 2.02 and 1.12, respectively. Given an alpha error of 0.05, Power of 95%, Type 2 hypothesis, effect size of 2.19, the sample size calculated per group was 18. 18 multiplied by 2 groups are 36 which were the minimum total subjects needed.

Data Analysis

Data were analyzed using the SSPS software version 20 (SSPS Inc., Chicago, IL, USA). T-test was used to analyze the mean difference in MD, PSD and average peripapillary RNFL thickness among the subjects with no signs of DR and mild NPDR. Linear regression was used to correlate the relationship of MD with the average peripapillary RNFL thickness and HBA1C among the population. Significance was attributed when $P < 0.05$.

RESULTS

Demographic Characteristics

Among the 40 subjects, 3 were excluded due to unreliable visual field results. Thus, a total of 37 eyes of 37 patients were included in the study. The eye with the worse diagnosis was considered. If both eyes had similar diagnosis, the study eye was randomly selected.

The subjects had a mean age of 52 ± 8.12 years of age (range 32-68). Mean BCVA was 0.06 ± 0.10 logMAR. The mean HBA1C was 6.7 ± 1.24 (range 5.2-9.6), while the mean duration of diabetes was 2.95 ± 1.47 years. 18 eyes had no signs of DR and 19 had mild NPDR. The demographic characteristics are presented in Table 1.

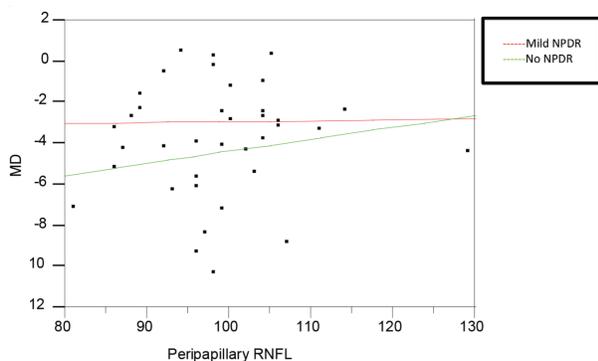
Table 1. Demographics

Characteristics	Mild NPDR = 18	No DR = 19
Age	51.33 \pm 7.203	52.84 \pm 9.032
BCVA	0.033 \pm 0.084	0.079 \pm 0.113
HBA1C	6.223 \pm 0.998	7.232 \pm 1.281
Diabetes duration	2.50 \pm 1.295	3.37 \pm 1.535
Sex (male/female)	6 (33.3%)/12 (66.7%)	3 (15.8%)/16 (84.2%)
Good glycemic control	13 (72.2%)	8 (42.1%)
No Treatment	5 (27.8%)	13 (68.4%)
Oral Hypoglycemic treatment	13 (72.2%)	6 (31.6%)

The mean deviation (MD) in mild NPDR group was -4.46 ± 3.03 dB which was more depressed compared to the no DR group which was -2.94 ± 2.21 dB. However, the difference was not statistically significant ($p=0.09$). The pattern standard deviation (PSD) was also more depressed in those with mild NPDR compared to those with no DR (3.08 ± 1.28 dB vs 2.69 ± 0.47 dB). However, no statistically significant difference was seen ($p=0.23$). No significant difference was seen between the peripapillary RNFL thickness between the mild NPDR group and no DR group (98.47 ± 6.89 vs 98.72 ± 11.01 , $p=0.93$).

Linear regression analysis showed no correlation between MD and peripapillary RNFL thickness in the no DR group ($R^2=0.017$) and mild NPDR group ($R^2=0.000$). A scatter plot of MD vs peripapillary RNFL is shown in Table 2. There was a weak and positive correlation between MD and HBA1C in those with no DR ($R^2=0.137$). However, there was no correlation found between MD and HBA1C in those with mild DR ($R^2=0.000$). A scatter plot of MD vs HBA1C is shown in Table 3.

Table 2. Scatter plot of MD vs peripapillary RNFL



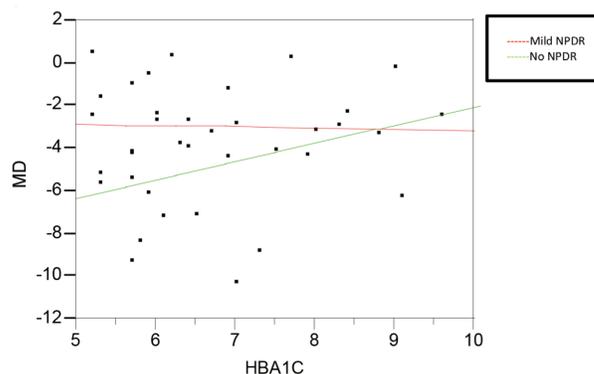
Mild NPDR

Term	coefficient	P value
Intercept	-3.432 (y intercept)	0.502
RNFL	0.005 (slope)	0.922

No DR

Term	coefficient	P value
Intercept	-10.239 (y intercept)	0.339
RNFL	0.059 (slope)	0.586

Table 3. Scatter plot of MD vs HBA1C



Mild NPDR

Term	coefficient	P value
Intercept	-2.577 (y intercept)	0.472
RNFL	-0.058 (slope)	0.918

No DR

Term	coefficient	P value
Intercept	-10.789 (y intercept)	0.013
RNFL	0.882 (slope)	0.119

DISCUSSION

This study compares functional deficits measured by short-wavelength automated perimetry and structural change measured by average peripapillary RNFL thickness in early diabetic patients with no signs of diabetic retinopathy and mild nonproliferative diabetic retinopathy.

Our study did not find a statistically significant difference in the MD and PSD between the mild NPDR group and no DR group. This was in contrary to the study of Zico et al. which showed that SWAP MD was more depressed in the mild NPDR group compared to the no DR group (-5.74 ± 3.11 vs -4.44 ± 2.02 , $p=0.04$) which suggests that generalized reduction in retinal sensitivity was greater in mild NPDR compared to those with no DR. SWAP PSD, a measurement of localized visual field defects, was also found to be more depressed in the mild NPDR group compared to the no DR group (3.02 ± 0.92 vs 2.11 ± 0.98 , $P=0.005$). This implies that localized defects were deeper in those with mild NPDR compared to those with no DR. In comparing between SWAP

and SAP, it was found that the SWAP MD was more depressed than SAP MD in both study groups which confirms the findings that short wavelength sensitivity is affected earlier than achromatic sensitivity in early diabetic retinopathy.²¹ This was also consistent with the study of Afrashi et al. which showed that the diabetic group had a significantly lower MD compared to control group (-5.23 ± 3.67 vs -1.18 ± 2.40 , $p=0.000$). However, no statistically significant difference was found in the PSD between diabetic group and control group (3.17 ± 1.07 vs 3 ± 1.07 , $p= 0.34$).¹⁸

Consistent data have shown that SWAP MD is more reduced in diabetic retinopathy.¹⁸⁻²¹ This is explained by the susceptibility of the short wavelength sensitive cones to ischemic stimuli thus leading to early selective loss of this cell component. Short wavelength sensitive cones are also less redundant leading to early detection of losses.¹⁷

Our study yielded results which were contrary to those published. Possible explanations are the test retest variability of SWAP and the lens absorption properties. The study by Bengtsson et al. showed that MD test retest variability was greater with SWAP compared to SAP ($p= 0.000$) with a median variability of 1.34 dB for SWAP and 0.71dB for SAP.²² Another explanation is the absorption properties of the lens. Cataract absorbs the short wavelength stimulus thus decreasing its transmission which leads to the reduction of the hill of vision. This translates to more depressed visual fields.²³ A study by Lutze et al. also suggests that increase rate of lens density reported in diabetic patients can lead to an apparent reduction in S cone system sensitivity.²⁴

In our study, VA was not found to be a significant confounding factor, since 72.9% have a VA of 0.0 logMAR and both subgroups had almost similar VA (0.033 ± 0.840 in the mild NPDR group vs 0.079 ± 0.113 in the no DR group). However, it was noted that among the 37 subjects, 72.9% were above 50 years of age and those in the no DR group were older and had a larger standard variation compared to the mild NPDR group (52.84 ± 9.032 vs 51.33 ± 7.203). It was also found that the no DR group had a longer duration of diabetes (3.37 ± 1.535 vs 2.50 ± 1.295) and poorer glycemic control (7.232 ± 1.281 vs 6.228 ± 0.998) compared to the mild NPDR group. Therefore in our study, age and diabetes-induced increase in lens density may have had some contribution in the reduction of S cone system sensitivity in these patients.

The pathophysiology behind the deterioration of test points despite the absence of retinopathy can only be speculated upon. In glaucoma, it has been established that structural damage precedes functional damage.²⁵ In diabetes, recent studies have demonstrated that retinal neurodegeneration is present even before the development of clinically detectable microvascular damage. Oxidative stress leads to retinal ganglion cell (RGC) apoptosis even without overt signs of diabetic retinopathy.^{5-8,16,26} Recent studies have consistently shown that macular RNFL and ganglion cell layer (GCL) are thinner in diabetic patients without signs of retinopathy compared controls.²⁷⁻³⁰ However, there is conflicting data on the occurrence of peripapillary RNFL thinning in diabetic patients without detectable diabetic retinopathy.³¹⁻³²

Our study showed that there is no statistical difference in the peripapillary RNFL of mild NPDR compared to those with no DR. This was similar to the study of Oshitari et al. which showed no significant change in peripapillary RNFL thickness in patients with no DR compared to controls³¹. In contrary, a metaanalysis showed that the average peripapillary RNFL thickness in diabetic patients without diabetic retinopathy was significantly decreased compared to controls ($P = 0.0003$)³².

The discrepancy in our result may be due to the fact that RNFL thickness is known to decrease with increasing age.³³ Since majority of our subjects were above 50 and the subjects in the no DR group were older, the normal aging process might have masked the small differences between the 2 groups.

The study of Ozdek et al. found that there was an evident decrease in the peripapillary RNFL thickness as the retinopathy and glycemic control worsened.³⁴ However, our study revealed no correlation between MD and peripapillary RNFL thickness in mild NPDR and no DR. This may be due to the variability of the SWAP perimetry and age-related attenuation of the RNFL.

In those with mild NPDR, no correlation was found between the MD and HBA1C. This was in contrary to the study of Zico et al, which showed a significant correlation between SWAP MD and HBA1C.²¹ Surprisingly, in the no DR group, there is a weak and positive correlation between HBA1C and MD which suggests that as the HBA1C worsens, there is improvement in the MD. This can be due to the higher HBA1C found in the no DR group compared

to the mild NPDR group and the variability that HBA1C contributes to the visual function. The study of Bengtsson et al. revealed that HBA1C can be a factor for variability at peripheral test points but not at paracentral points of the visual field. A positive correlation was seen with SAP which indicates that an increase in HBA1C fluctuation, increases variability. However, there is a negative correlation with SWAP which suggests that a decrease in HBA1C fluctuation, increases variability²².

Knowledge of the random test retest variability is essential in interpreting perimetric tests. Because of the variability of SWAP, it has been suggested that SAP and FDT are more reliable functional tools for monitoring progression in those without signs of diabetic retinopathy²².

In conclusion, SWAP does not appear to be a sensitive measure of worsening retinopathy in older individuals with early diabetes. The usefulness of SWAP and peripapillary RNFL thickness in the early stages of retinopathy are inconclusive. Whether SWAP can essentially be used for early screening requires further studies. Nevertheless, neurodegenerative changes of retina and corresponding visual functional impairment in diabetics need more attention during evaluation of diabetic retinopathy.

This study has some limitations. First of all, majority of those recruited were above 50. Therefore, age-related lens changes were inevitable. The study characteristics were also not uniform. This could have led to the variability in the SWAP indices. Recommendations for further studies would be to increase the sample size and to recruit young diabetic patients with clear lens and 20/20 vision. By removing the possible confounders, the tests may yield more conclusive results.

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