Non-invasive handheld electroretinography and early retinal dysfunction in pre-diabetes

Varo Kirthi*, Kate Reed, Benjamin Zuckerman, Timothy L. Jackson

Department of Ophthalmology, Faculty of Life Sciences and Medicine, King's College London, United Kingdom *v.kirthi@nhs.net

INTRODUCTION

- Handheld electroretinography (HERG) is a novel, non-invasive device for assessing retinal function. A full-field flicker ERG can be obtained in under five minutes using sensor strips placed on the cheek.
- HERG can predict the onset of future vision-threatening diabetic retinopathy (VTDR). [1]
- HERG can differentiate between sight-threatening and non-sight threatening diabetic retinopathy:

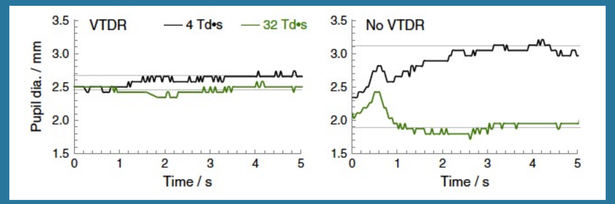


Figure 1. Pupillary responses. *Performed in dim (4 Td·S) and bright light (32 Td·S) comparing a patient with VTDR (left) to a patient without VTDR (right).*

- The potential for HERG to detect early retinal dysfunction in pre-diabetes remains unexplored.

METHODS

- Participants were recruited into study groups defined by HbA1c parameters:

a) Normal glucose tolerance (NGT): <39 mmol/mol
b) Pre-diabetes (PD): 39-47 mmol/mol
c) Type 2 diabetes (T2DM): >47 mmol/mol

Inclusion criteria	Exclusion criteria
≥18 years of age Either NGT, diagnosed PD or T2DM Able to with all study procedures and provide informed consent	Inability to obtain clear fundus imaging Presence of maculopathy or retinopathy of non-diabetic aetiology History of: - Intravitreal treatment or surgery to either eye within last 3 months - Any ocular trauma - Known glaucoma, uveitis or corneal disease

- Each participant underwent HbA1c testing and undilated HERG in each eye.
- Outcomes measures were peak amplitude and implicit time at two flash intensities obtained in each eye and grading of retinopathy using dilated two-field fundus photography.

Baseline characteristic	Normal glucose tolerance (n = 20)		Pre-diabetes (n = 29)		Type 2 diabetes (n = 26)	
	Mean	***(SD)***	***Mean***	***(SD)***	***Mean***	***(SD)***
Male sex, n (%)	9	(45·0)	16	(55·2)	15	(57·7)
Age in years	55·3	(11·1)	61·0	(9·4)	60·7	(10·4)
Time since diagnosis of pre-diabetes or diabetes, n	-		<1 year: 6 1-5 years: 7 >5 years: 3 Unknown: 13		<1 year: 5 1-5 years: 10 >5 years: 9 Unknown: 2	
HbA1c %	5·4	(0·2)	6·0	(0·2)	7·3	(0·9)
Body mass index in kg/m²	27.3	(5.9)	86.0	(10.8)	88.6	(8.6)
Retinopathy on fundus imaging, n (%)	0	-	0	-	9	(34.6)

Table 1. Baseline characteristics by study group.

HERG parameter	Normal glucose tolerance (n = 20)		Pre-diabetes (n = 29)		Type 2 diabetes (n = 26)	
	Mean	***(SD)***	***Mean***	***(SD)***	***Mean***	***(SD)***
Peak amplitude at 16 Td·S in µV	**19.4** †	(5.6)	**15.4** †	(5.9)	15.9	(5.6)
Peak amplitude at 32 Td·S in µV	**22.2** *†	(6.4)	**17.0** †	(6.4)	**16.7** *	(6.1)
Implicit time at 16 Td·S in msec	30.9	(2.4)	**30.3** ‡	(2.4)	**32.2** ‡	(2.6)
Implicit time at 32 Td·S in msec	**29.2** *	(2.0)	**28.9** ‡	(2.1)	**31.1** *‡	(2.4)
Pupil area ratio (unitless)	1.80	(0.10)	1.75	(0.08)	1.72	(0.07)

Table 2. HERG parameters by study group. *Participants divided by study group. Values presented are means with standard deviations (SD) in brackets, unless otherwise stated. Numbers in bold show statistically significant differences between groups. P<0.05 on two-tailed t-tests or Mann-Whitney tests shown by * (NGT vs T2DM), † (NGT vs PD) and ‡ (PD vs T2DM).*

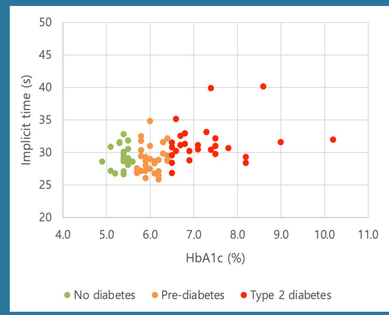


Figure 2. Age-corrected implicit time in worse eye with bright illuminance (32 Td·S)

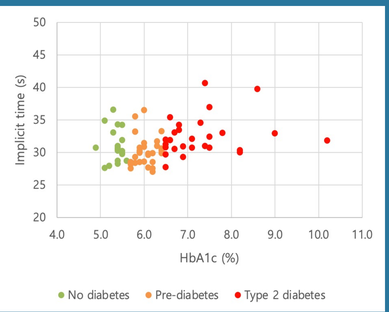


Figure 3. Age-corrected implicit time in worse eye with dim illuminance (16 Td·S)

RESULTS

- Baseline characteristics for the 75 participants recruited are shown in Table 1 and HERG parameters in Table 2.
- HERG identified reductions in peak amplitude of retinal responses in PD compared to NGT.
- Implicit times in the worse eye showed a positive correlation with HbA1c at high (r = 0.46) and low (r = 0.33) flash intensities (Figures 2 and 3).
- Peak amplitude had a weak negative correlation with HbA1c at high (r = -0.22) and low (r = -0.17) flash intensities.
- No significant association was noted between HbA1c and pupillary light response (r=-0.03).
- All participants were graded R0M0 in both eyes, except six with type 2 diabetes, who were graded no worse than R1M1 in either eye.

CONCLUSIONS

- These changes may represent early retinal neurodegeneration occurring before visible retinopathy.
- This is in keeping with multifocal ERG abnormalities reported in up to 60% of individuals with type 2 diabetes and no visible retinopathy. [2]
- The association between implicit time and HbA1c suggests that retinal dysfunction may precede visible and gradable retinopathy changes.
- HERG may have potential in screening for early retinal disease, particularly in pre-diabetes.

ACKNOWLEDGEMENTS

We thank LKC Technologies Inc for their technical support and for providing a RETeval-DR device for the purposes of our study. We also thank King's College Hospital R&I for funding the purchase of disposable electrode kits.

REFERENCES

1. Maa AY, Feuer WJ, Davis CQ, *et al.* A novel device for accurate and efficient testing for vision-threatening diabetic retinopathy. *J Diabetes Complicat* 2016;30:524–32.
2. Santos AR, Ribeiro L, Bandello F *et al.* Functional and structural findings of neurodegeneration in early stages of diabetic retinopathy: cross-sectional analyses of baseline data of the EUROCONDOR project. *Diabetes* 2017;66(9):2503-10.