Visual sensitivity loss in the central 30° of visual field is associated with diabetic peripheral neuropathy

G. P. Sampson · A. M. Shahidi · D. Vagenas ·
N. Pritchard · K. Edwards · A. W. Russell ·
R. A. Malik · N. Efron

Received: 1 November 2011 / Accepted: 20 December 2011 / Published online: 19 January 2012
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Abstract

Aims/hypothesis Impaired central vision has been shown to predict diabetic peripheral neuropathy (DPN). Several studies have demonstrated diffuse retinal neurodegenerative changes in diabetic patients prior to retinopathy development, raising the prospect that non-central vision may also be compromised by primary neural damage. We hypothesise that type 2 diabetic patients with DPN exhibit visual sensitivity loss in a distinctive pattern across the visual field, compared with a control group of type 2 diabetic patients without DPN.

Methods Increment light sensitivity was measured by standard perimetry in the central 30° of visual field for two age-matched groups of type 2 diabetic patients, with and without neuropathy ($n=40/30$). Neuropathy status was assigned using the neuropathy disability score.

Mean visual sensitivity values were calculated globally, for each quadrant and for three eccentricities (0–10°, 11–20° and 21–30°). Data were analysed using a generalised additive mixed model (GAMM).

Results Global and quadrant between-group visual sensitivity mean differences were marginally but consistently lower (by about 1 dB) in the neuropathy cohort compared with controls. Between-group mean differences increased from 0.36 to 1.81 dB with increasing eccentricity. GAMM analysis, after adjustment for age, showed these differences to be significant beyond 15° eccentricity and monotonically increasing. Retinopathy levels and disease duration were not significant factors within the model ($p=0.90$).

Conclusions/interpretation Visual sensitivity reduces disproportionately with increasing eccentricity in type 2 diabetic patients with peripheral neuropathy. This sensitivity reduction within the central 30° of visual field may be indicative of more consequential loss in the far periphery.

G. P. Sampson · A. M. Shahidi · D. Vagenas · N. Pritchard ·
K. Edwards · N. Efron (✉)
School of Optometry and Vision Science and Institute of Health
and Biomedical Innovation, Queensland University of Technology,
60 Musk Avenue,
Kelvin Grove 4059 QLD, Australia
e-mail: n.efron@qut.edu.au

A. W. Russell
School of Medicine, University of Queensland,
Brisbane, QLD, Australia

A. W. Russell
Princess Alexandra Hospital,
Woolloongabba, QLD, Australia

R. A. Malik
Division of Cardiovascular Medicine, University of Manchester,
Manchester, UK

R. A. Malik
Central Manchester Foundation Trust,
Manchester, UK

Keywords Diabetes mellitus · Perimetry · Peripheral neuropathy · Type 2 diabetes · Visual field · Visual sensitivity

Abbreviations

DPN	Diabetic peripheral neuropathy
GAMM	Generalised additive mixed model
LRT	Likelihood ratio test
NDS	Neuropathy disability score
OCT	Optical coherence tomography
PAH	Princess Alexandra Hospital

Introduction

Poor central vision has been identified as an independent risk factor for foot ulceration and lower-extremity amputation in

diabetic peripheral neuropathy (DPN) [1, 2]. This association may simply represent reduced visual acuity interfering with the ability of a patient to detect early foot lesions. However, the relationship could alternatively imply a common underlying neuropathological mechanism for reduction in vision and DPN-related ulceration. If this were the case, peripheral vision quality may also be compromised, and this could potentially impair mobility and balance [3–5]. The relationship between peripheral vision and DPN is currently unknown.

The unique anatomy of the eye, with its transparent media, allows direct and non-invasive optical imaging of nerve structures, especially the cornea and retina. Corneal nerve morphology [6] and corneal sensitivity [7] have both recently demonstrated promising relationships with established clinical measures of DPN. Optical coherence tomography (OCT) has enabled high resolution, non-invasive imaging of the complex neural networks within the retina. Several OCT studies have suggested that diffuse neurodegenerative changes may precede the development of clinically visible vascular complications in the retinas of those with diabetes [8–12], and a link between thinning of the retinal nerve fibre layer and DPN has recently been demonstrated [13]. Evidence of retinal structural abnormality reinforces the prospect that visual function may be affected by neurodegenerative changes in diabetes—separate from the better-characterised visual dysfunction attributable to retinopathy [14].

Perimetry describes the psychophysical measurement of increment light sensitivity across the visual field, and this technique is commonly used in ophthalmic practice to investigate central (within 10°) and mid-peripheral (10–30°) visual function in a range of neuropathologies. Perimetry outcomes represent both retinal and post-retinal visual pathway function. Several studies have demonstrated visual sensitivity reduction in the central 30° of visual field in diabetes prior to the development of clinically evident retinopathy [15–18]. This supports the prospect of a subset of visual function changes that are primarily related to neurodegeneration rather than to vascular dysfunction, although these neurodegenerative changes could, themselves, be a result of microangiopathy [19].

To our knowledge, no previous study has investigated the link between perimetry outcomes and DPN. We hypothesise that patients with type 2 diabetes and DPN will exhibit relative losses of visual sensitivity in a distinctive pattern across the visual field compared with a control group with diabetes but without DPN.

Methods

Participants Two age- and disease-duration-matched groups of patients with type 2 diabetes were recruited, consisting of a

cohort with DPN (Neuropathy Disability Score [NDS] ≥ 3 , $n=40$) and a control group without DPN (NDS < 3 , $n=30$). Study participants were recruited from the Department of Diabetes and Endocrinology at the Princess Alexandra Hospital (PAH), Woolloongabba, QLD, Australia. Those with any medical condition (other than diabetes) known to be independently associated with neuropathy, or with current foot ulceration or infection, were excluded.

All participants underwent assessment of visual acuity, slit lamp biomicroscopy, retinal photography, OCT and tonometry. All had best-corrected visual acuity of at least 6/9.5, no history of retinal laser photocoagulation, no diagnosis or reasonable suspicion of glaucoma or ocular hypertension and no evidence of corneal (or any ocular media) compromise, cataract or maculopathy. Any history of neuro-visual pathology or medication use known to independently affect visual fields was also an exclusion criterion. Fundus photography (Visucam Pro NM; Carl Zeiss Meditec, Jena, Germany) was used to grade retinopathy status (two observers) with reference to the Australian National Health and Medical Research Council grading scale [20]. Potential participants with retinopathy classed as moderate, severe or proliferative were excluded from analysis. Applying all of these criteria, a total of 24 potential participants were excluded from the study.

The cohort with DPN consisted of 16 patients with no evidence of retinopathy and 24 with ‘minimal’ to ‘mild’ classification [20]. The control group had 19 patients with no retinopathy and 11 with minimal to mild retinopathy. The study was approved by separate institutional ethics committees at the Queensland University of Technology and at PAH. All aspects of the study conformed to the Declaration of Helsinki and all participants provided written informed consent prior to involvement.

Neuropathy disability score The modified NDS was determined for each participant. This involved assessment of pin prick, vibration- and temperature-sensation sensitivity, and Achilles tendon reflex response, and provided a score between 0 and 10. An NDS ≥ 3 defined the presence of neuropathy [21].

Visual field assessment All participants underwent perimetry for one eye (selection based on better visual acuity), with the central 30° of visual field being assessed—the most commonly used format in clinical ophthalmic practice. A Medmont M700 Automated Perimeter (Medmont International P/L, Vermont, VIC, Australia) was used for all visual field assessments. This is a well-validated [22] automated static perimeter, which quantifies visual sensitivity at fixed points across the visual field by measuring increment light detection thresholds against a uniform background luminance at each point. The M700 uses a dedicated test bowl with in-built light-emitting diodes; a custom-designed software program controls

stimulus presentation. The spatial pattern of stimuli for this study employed 106 test points and used a continuously modified staircase algorithm to determine a threshold for each point—the level at which a flash of light can just be detected against the background.

False-positive and false-negative responses and fixation losses were recorded and analysed by the software incorporated within the instrument, providing three comprehensive indices of individual visual field reliability. All visual fields included in the analysis were classified as reliable by each of the three indices. Participants from both groups were naive with regards to previous perimetry experience. The Medmont M700 provides a range of inherent analysis tools with the aim of quantifying the risk of neurological disorder or disease. One software-inherent summary index ('overall defect'—mean sensitivity loss compared with a normative dataset) is reported for controls, but is not analysed for this study. The M700 software provides a comparison with an age-specific normative database and is able to highlight test points that have a high probability of being atypical thresholds. This method and overall defect were used in the current study to determine whether individual control group (no neuropathy) visual field outcomes were normal or compromised.

Data analysis Raw data represent visual sensitivity levels (inverse of increment light detection thresholds) in logarithmic dB units and these data are used for the primary analysis techniques developed in this study. Differences in visual sensitivity outcomes between neuropathy and control groups were assessed globally (all points in the 30° visual field) and in each quadrant. The quadrant division approach allows comparisons based on commonly applied visual field analysis paradigms for other neuropathologies. A separate method evaluates three concentric rings (0–10°, 11–20° and 21–30°). This concentric analysis was designed for the present study to examine whether relative visual sensitivity changes are occurring with increasing distance from central fixation for the neuropathy group. Previously demonstrated diffuse loss of inner retinal integrity using OCT [11, 12] supports this approach. A single average dB score is used to represent global, quadrant or concentric ring results. In combination, these three analytical techniques provide adequate characterisation of hypothesised visual field changes occurring in association with DPN.

A generalised additive mixed model (GAMM) was used for analysing raw data at an individual level. The GAMM uses a complex modelling approach, essential for these data because of the non-linear outcomes demonstrated for at least one of the groups. It enables data to be analysed with a regression-type method while allowing greater flexibility for defining trends within different groups. This is achieved by using individual cubic splines for modelling data trends between measured values. GAMMs also take into account the correlation between measurements from the same individual

[23]. Neuropathy status and retinopathy levels were included as factors, whereas eccentricity, age and disease duration were fitted as covariates; this enables measurement of the relative effect of each of these variables within the model. Factors and covariates were selected based on variables previously shown to be likely to affect the outcome variable of interest (visual sensitivity). Random effects for eccentricity and individual participants were also fitted to allow for the repeated measures nature of these data. PASW Statistics, version 18 for Macintosh, and R statistical software [24]—specifically, package 'amer' [25]—were used for statistical analyses.

Results

Summary demographic and screening information for participants from both groups is presented in Table 1. There were no significant between-group differences for age ($p=0.11$), disease duration ($p=0.18$) or for HbA_{1c} levels ($p=0.64$).

Results for the global, quadrant and concentric analyses are summarised in Table 2. Global mean visual sensitivity was comparatively reduced by 1.08 dB in diabetic patients with neuropathy. Quadrant results showed that the 1 dB difference was essentially consistent across all four quadrants (Fig. 1). The concentric analysis revealed that the difference between group means amplified with increasing distance from the centre of the visual field (fixation point). This difference was higher by a factor of five for the outermost eccentricity ring (1.81 dB at 21–30°) compared with the innermost ring (0.36 dB at 0–10°).

The GAMM indicated that neuropathy status, as well as its interaction with eccentricity, significantly affected visual sensitivity ($p=0.02$, estimated by likelihood ratio test [LRT]). Age also had an independent effect ($p<0.001$, LRT). Figure 2 shows GAMM-predicted values for visual

Table 1 Study participant demographic and screening information (expressed as mean±SD in rows 2–5) classified by NDS

Characteristic	Type 2 diabetes without neuropathy (control)	Type 2 diabetes with neuropathy
<i>n</i>	30	40
Age (years)	55±9	58±6
Diabetes duration (years)	10±9	13±8
HbA _{1c} (%)	7.8±1.6	7.6±1.5
HbA _{1c} (mmol/mol)	62.1±17.2	60.1±16.4
NDS	0.4±0.7	5.9±2.2
Sex		
Men	12	26
Women	18	14

No neuropathy, NDS <3; neuropathy, NDS ≥3

Table 2 Visual sensitivity in type 2 diabetic patients with and without neuropathy, for global, quadrant and eccentricity analyses

Sector	Visual sensitivity (dB)		
	Type 2 diabetes without neuropathy (control)	Type 2 diabetes with neuropathy	Between-group difference
Global	22.15	21.07	1.08
Quadrant			
Superior temporal	22.83	21.74	1.09
Superior nasal	22.22	20.93	1.29
Inferior nasal	21.81	20.85	0.96
Inferior temporal	21.78	20.80	0.98
Eccentricity			
0–10°	24.27	23.91	0.36
11–20°	22.49	21.57	0.92
21–30°	19.80	17.99	1.81

sensitivity as a function of eccentricity for control (no neuropathy) and neuropathy groups after adjustment for the effect of age. This figure demonstrates that the pattern of predicted values differs between the two groups. For smaller degrees of eccentricity (i.e. closer to central fixation) there is no significant difference. Visual sensitivity decreases in both groups; however, it does so in an almost linear fashion for controls, whereas the rate of decrease steepens for the neuropathy group after approximately 7° eccentricity. After 15°, outcomes for the two groups are distinct (95% CI for these predictions no longer overlap).

Retinopathy and disease duration were not significantly related to visual sensitivity ($p>0.90$, LRT, when both factors were removed compared with the full model). Retinopathy levels were marginally higher in the cohort with peripheral neuropathy; this is difficult to avoid given that both are related to duration of disease. Disease duration was marginally (but not significantly) higher in the DPN group. The GAMM analysis

allows these differences, but measures the relative effect of each factor. Neither retinopathy status nor disease duration significantly explained the results of this study, in contrast to neuropathy status and its interaction with visual field eccentricity.

Control group mean ‘overall defect’ was +2.53 dB (range −1.75 to +5.41). This positive summary index value indicates that global results for the group as a whole compared favourably with healthy age-matched normative data. In addition, 28 of 30 diabetic non-neuropathic visual fields were classified as uncompromised using a separate (glaucoma-related) criterion of not more than three adjacent points flagged at the 5% or lower probability levels of being abnormal values [26]. Although these frequently employed clinical field loss benchmarks necessarily differ from the newly developed analytical techniques used in the current study, together they indicate that the control group performed comparably with a healthy normal sample.

Fig. 1 Mean visual sensitivity by quadrant for diabetic patients with neuropathy and without neuropathy. The diabetic patients with neuropathy have no meaningful selective regional loss within individual quadrants. Black diamonds, with neuropathy; white diamonds, without neuropathy **Fig. 2** GAMM-predicted values for visual sensitivity as a function of eccentricity (adjusted for the effect of age) for diabetic patients with neuropathy and without neuropathy, with their corresponding 95% CIs. The diabetic patients with neuropathy have a steeper visual sensitivity change with eccentricity compared with diabetic patients without neuropathy (controls). The CIs separate beyond 15°. Black/grey solid lines, with neuropathy/corresponding 95% CIs; black/grey dashed lines, without neuropathy/corresponding 95% CIs

Discussion

Principal findings In his influential 1927 text, ophthalmologist Harry Traquair described the visual field as ‘a hill of vision surrounded by a sea of blindness’ [27]. It is a useful analogy that allows visual sensitivity across the entire visual field to be imaged as though it were a topographic map of an island mountain—with foveal vision as the summit and a gradual drop in elevation on all sides into the non-seeing ocean. In the current study, it has been demonstrated that the shape of the ‘hill of vision’ alters in association with DPN in patients with type 2 diabetes.

There is evidence in the DPN cohort of a concentrically focused loss of visual sensitivity that increases with eccentricity. In comparison with diabetic patients without neuropathy, this group had a central hill of vision that was characterised by a consistent increase in steepness on all sides. This is best demonstrated by the differing GAMM patterns and separation of 95% CIs beyond 15° eccentricity. The mean values (darker central lines) in Fig. 2 can be considered as two-dimensional sections through the hill of vision for each group. These data show (after age adjustment) virtually no difference in profile within the central 7°; beyond this, the neuropathy group has a manifestly steeper slope as it extends into the mid-periphery. Quadrant analysis indicated no predilection for localised loss in the manner that may be expected with early glaucoma or with vascular or compressive lesions of the visual pathways. In other words, the hill of vision does not appear to be eroded selectively on any particular side—an observation that may be of clinical significance in respect of differentially diagnosing these various pathologies.

Strengths and weaknesses of the study This study is the first to investigate the relationship between visual fields and peripheral neuropathy status. The demonstrated association has dual implications; it identifies a previously unacknowledged source of visual injury in diabetes, and it supports the prospect that this vision loss is attributable to neural rather than clinically measurable vascular damage. Limitations of the study include the inability to rule out a subclinical microvascular cause for the putative neural damage—the answer to this question lies beyond the scope of this study. The association with a range of other microvascular complications—for example, microalbuminuria—has not been exhaustively investigated and may provide a useful starting point for further investigation into the relative roles of vascular and neural factors in diabetic visual compromise.

Strengths and weaknesses in relation to other studies While this study has demonstrated a relative visual loss in a cohort with peripheral neuropathy, the group without neuropathy showed no evidence of visual field loss according to

separate but well-established and commonly employed clinical measures. This raises the prospect that previously reported visual field loss (using these measures) associated with pre-retinopathy diabetes [15–18] may have been attributable to neuropathy status. This factor was not accounted for in any of these earlier studies.

Implications of the study The demonstrated effect sizes are relatively small. At face value, the 2 dB relative sensitivity reduction at 20–30° eccentricity is unlikely to create a visual disability that is of much practical significance for the affected cohort. However, if the change in hill of vision shape remained consistent beyond 30°, extrapolation of the steeper gradient suggests that the peripheral visual field may be conspicuously contracted in people with DPN. Returning to our analogy, the entire island of vision would have a smaller diameter if this were confirmed.

Mobility is known to be impaired with visual field loss [4] and the risk of falls is increased [3, 5, 28]. Given that patients with DPN also have greater likelihood of gait compromise [29] the risk of injury from falls may be further amplified by the twin mechanisms of impaired mobility control and reduced peripheral vision sensitivity. The findings of this study therefore indicate a need for evaluation of the true peripheral visual field in this population—beyond the commonly assessed central 30° to the measurable limits of visual field.

Retinopathy unquestionably remains the most visually ominous entity for those with diabetes. Retinopathy levels, however, failed to explain the findings of this study. Primary neuropathic injury is the most likely explanation and this may constitute a currently unrecognised second, and more peripherally oriented, threat to vision. Several recent reviews have raised the prospect of primary neural injury as the cause of visual loss that has previously been attributed to vasculopathy [30–32]. The association with DPN status is additionally interesting given the relatively non-intuitive relationship between a vision variable mediated through the central nervous system and the distal lower-limb nerve damage of peripheral sensory neuropathy. This provides support for a model of pervasive neural dysfunction that could simultaneously affect elements of the central, peripheral and autonomic nervous systems in patients with type 2 diabetes. The findings of this study may, nevertheless, still be attributable to a primary underlying microvascular neuropathology that is common to all branches of the nervous system [19]. Regardless, it does not diminish the potential importance of the demonstrated visual compromise.

Unanswered questions and future research Further work needs to be undertaken in response to these findings. Studies

on type 1 diabetic cohorts are indicated and longitudinal studies will be important to look at progression over time. The relationship between DPN and other visual function measures, such as contrast adaptation and electroretinography, could also be informative. The association between diabetic visual field loss and a full range of metabolic and vascular factors is also of interest. Most importantly, the putative visual sensitivity loss beyond 30° needs to be confirmed and characterised by detailed large-sample studies of the entire visual field. The current study has revealed a previously unidentified mid-peripheral visual field loss in type 2 diabetic patients with neuropathy. Extrapolation of these findings into the extreme periphery may have genuine consequences for this population.

Acknowledgements The authors would like to express their gratitude towards the patients who participated in this study.

Funding This study was funded by the National Health and Medical Research Council (Australia) and the George Weaber Foundation Trust.

Contribution statement NE devised the original concept for the experiment. GPS, AMS, NP, KE, AR and NE designed the experiment. GPS, AMS, NP and KE conducted the clinical trial. GPS, AMS, DV and NP collated and analysed the data. GPS and DV did the statistical analysis. GPS and AMS drafted the article. All authors contributed to interpretation of the data and critical revision for important intellectual content. All authors approved the final version of the manuscript.

Duality of interest All authors declare that they have no duality of interest associated with this manuscript.

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