

Differences in retinal ganglion cell layer and ganglion cell-inner plexiform layer thickness among haemodialysis patients with and without diabetes mellitus

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Abstract

Introduction: This study aimed to compare the thickness of the retinal ganglion cell layer (GCL) and the ganglion cell-inner plexiform layer (GC-IPL) in haemodialysis (HD) patients with and without diabetes mellitus (DM).

Methods: This was a single-centre cross-sectional study conducted in Indonesia. Comprehensive ocular examinations and demographic information were gathered from 110 eyes of 110 HD patients. The sample was divided into DM and non-DM groups. Optical coherence tomography was used to analyse GCL and GC-IPL thickness. The independent t-test or Mann-Whitney test was used to examine the difference between the two groups, and a *p*-value of less than 0.05 was deemed significant.

Results: We analysed 110 eyes of 110 HD patients and divided them into the DM group (27, 24.5%) and non-DM group (83, 75.5%). The average duration of HD in the DM group was lower at 30.8 months than in the non-DM group of 50.6 months

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($p < 0.05$). Hypertension was found in 24 (88.8%) patients in the DM group and 66 (79.5%) in the non-DM group ($p < 0.05$). HD patients with DM group showed significantly thinner GCL in all sectors ($p < 0.05$) and significantly thinner GC-IPL in 4 sectors ($p < 0.05$). In the hypertension cases, GCL and GC-IPL showed significant difference between the two groups ($p < 0.05$).

Conclusion: HD patients with DM demonstrated thinner GCL and GC-IPL. This finding indicates the importance of integrated ophthalmic evaluation in HD patients to prevent further damage of neural retina.

Keywords: biomarker, diabetes mellitus, haemodialysis, retinal ganglion cell, retinal imaging

Perbezaan ketebalan lapisan sel ganglion retina dan sel ganglion-lapisan pleksiform dalam antara pesakit hemodialisis dengan dan tanpa diabetes mellitus

Abstrak

Pengenalan: Kajian ini bertujuan untuk membandingkan ketebalan lapisan sel ganglion retina (ganglion cell layer, GCL) dan lapisan sel ganglion-lapisan pleksiform dalam (ganglion cell-inner plexiform layer, GC-IPL) dalam kalangan pesakit hemodialisis (HD) dengan dan tanpa diabetes mellitus (DM).

Kaedah: Kajian keratan rentas berpusat tunggal ini dijalankan di Indonesia. Pemeriksaan oftalmik menyeluruh dan maklumat demografi diperoleh daripada 110 mata bagi 110 pesakit HD. Sampel dibahagikan kepada kumpulan DM dan kumpulan bukan DM. Tomografi koheren optik digunakan untuk menganalisis ketebalan GCL dan GC-IPL. Ujian-t tidak bersandar atau ujian Mann-Whitney digunakan untuk menilai perbezaan antara kedua-dua kumpulan, dan nilai p kurang daripada 0.05 dianggap signifikan.

Keputusan: Sebanyak 110 mata daripada 110 pesakit HD dianalisis dan dibahagikan kepada kumpulan DM (27 pesakit, 24.5%) dan kumpulan bukan DM (83 pesakit, 75.5%). Purata tempoh HD dalam kumpulan DM adalah lebih pendek, iaitu 30.8 bulan berbanding 50.6 bulan dalam kumpulan bukan DM ($p < 0.05$). Hipertensi didapati dalam 24 pesakit (88.8%) dalam kumpulan DM dan 66 pesakit (79.5%) dalam kumpulan bukan DM ($p < 0.05$). Pesakit HD dengan DM menunjukkan ketebalan GCL yang secara signifikan lebih nipis dalam semua sektor ($p < 0.05$) serta ketebalan GC-IPL yang secara signifikan lebih nipis dalam empat sektor (p

< 0.05). Dalam kes hipertensi, GCL dan GC-IPL menunjukkan perbezaan yang signifikan antara kedua-dua kumpulan ($p < 0.05$).

Kesimpulan: Pesakit HD dengan DM menunjukkan GCL dan GC-IPL yang lebih nipis. Dapatan ini menunjukkan kepentingan penilaian oftalmik bersepadu dalam kalangan pesakit HD bagi mencegah kerosakan lanjut pada retina neural.

Kata kunci: biomarker, diabetes mellitus, hemodialisis, sel ganglion retina, pengimejan retina

Introduction

End-stage renal disease (ESRD), also referred to as stage 5 renal failure, is characterized by a glomerular filtration rate of less than 15 ml/min/1.73 m².¹ The primary cause of the illness is diabetes mellitus (DM), which is followed by polycystic kidney disease, glomerulonephritis, and hypertension (HT).^{2,3} The United States Renal Data System recorded 124,411 new ESRD diagnoses in 2015. The disease's annual prevalence was approximately 20,000 cases.⁴ Because ESRD results in irreversible loss of renal function, patients require dialysis or a kidney transplant as part of their renal replacement therapy in order to avoid uraemia. Lowered tear production, band keratopathy, lenticular opacities, conjunctival calcifications, variations in intraocular pressure (IOP), uremic optic neuropathy, and alterations in retinal microvasculature are a few of the many ocular findings.⁵⁻⁷ The thickness of the ganglion cell-inner plexiform layer (GC-IPL) and retinal nerve fibre layer (RNFL) in ESRD patients was also significantly reduced in certain cases, measured by to optical coherence tomography (OCT).^{8,9}

Over the past few decades, OCT has gained widespread usage as a diagnostic technique that can accurately depict retinal architecture. For instance, in individuals with glaucoma, diabetic retinopathy, age-related macular degeneration, and optic neuropathy, it can be used to measure the thickness of the retinal layer.¹⁰⁻¹³ By measuring the thickness of each retinal layer, OCT has also emerged as a useful method for evaluating neurodegenerative diseases, which can be identified far sooner than with funduscopy.^{14,15} Numerous theories demonstrated that ESRD treatments involving dialysis could alter the retinal microvasculature. Retinal ganglion cells may sustain damage from ischemia and elevated neurotoxic substances. The retinal ganglion cell layer (GCL), IPL, and RNFL are among the thinner retinal layers that result from it. Subsequently, this might have an impact on visual function, such as colour perception, visual acuity, and visual fields.

To our knowledge, there isn't much thorough documentation about the changes in GCL and GC-IPL in ESRD patients with and without comorbid conditions, including DM and HT. Thus, using spectral domain (SD)-OCT, the study assessed neuronal retinal profiles and differences, particularly between GCL and GC-IPL

thickness, in haemodialysis (HD) patients with and without DM. We expected that HD patients with and without DM would have different GCL and GC-IPL thicknesses, further emphasizing the value of comprehensive and routine ocular examinations in these patients.

Methods

Study design

The Ophthalmology Department and the Division of Nephrology, Internal Medicine Department, Dr. Soetomo General Academic Hospital, Surabaya, collaborated on this cross-sectional, single-centre study in May and June 2019. Participants were directly recruited from the HD unit is ESRD patients. Written informed consent was obtained from patients who fulfilled the study's inclusion and exclusion requirements. The principles of good clinical practice standards and the Declaration of Helsinki's tenets were followed when conducting the investigations. The Dr. Soetomo General Academic Hospital Surabaya's Institutional Review Board approved the study protocol (Komisi Etik Peneliti Kesehatan Rumah Sakit Dr. Soetomo No.1155/KEPK/V/2019).

Study population

Inclusion criteria were subjects with ESRD who underwent regular maintenance HD twice a week in our centre and in stable clinical condition to undergo eye examination related to the parameters studied. Exclusion criteria were subjects who did not consent, did not complete the required examinations, minors under 18 years of age, spherical equivalent refractive error based on Autorefracto Keratometer (ARK) below 6.00 D, and poor image score on SD-OCT (< 45).

Demographic, clinical characteristics, and laboratory data

The patients' demographic information was collected, including their age, sex, length of HD, intraocular pressure (IOP), spherical equivalent on ARK, best-corrected visual acuity (BCVA), and history of DM and HT. Following five minutes of rest, blood pressure (BP) was taken while seated using a validated equipment in the customary manner.

Ophthalmic examination

All participants had a thorough ocular examination on enrolment day conducted by the same team of skilled ophthalmologists. Using ARK, we measured BCVA, IOP, contrast sensitivity, anterior segment examination, posterior segment measurement in low light without pupillary dilation, and refractive parameters for both eyes. Additionally, fundus photos in colour were obtained.

SD-OCT measurement

One or two drops of tropicamide eye drop were previously injected into each eye before retinal layer measurements were performed to assess each sector's GCL and GC-IPL thickness SD-OCT. Our system has an optical resolution of 8 μ m and an A-scan velocity of 100,000 A-scans/second. It measures the macula and optic disc over a 6 x 6-mm area. The superior (S), superonasal (SN), inferonasal (IN), inferior (I), inferotemporal (IT), and superotemporal (ST) sectors are the six divisions of the retinal layer used for macular measurements. GCL thickness is denoted by GCL+, and GC-IPL layer thickness is denoted by GCL++. The generated images were then charted in circle diagrams in three distinct colours (green: within the normal range, yellow: marginal, and red: outside the normal range) after being examined and compared to a normative database.

Statistical analysis

SPSS statistical software for Windows, version 26.0 (SPSS, Chicago, Illinois, USA), was used for all statistical analyses. Only the right eye was examined. The demographic and clinical features of the research population were summarised into mean/median and percentages displayed in tabular form. Data normality was evaluated using Kolmogorov-Smirnov. This study compared the GCL and GC-IPL thickness of HD patients with ESRD according to their DM status using a comparison test. To ascertain whether these differences occurred between the two groups, the Mann-Whitney Test was employed if the data were not normally distributed, and the independent T-test was employed if they were. A statistical result was considered significant if p was less than 0.05.

Results

Patient characteristics

Only 110 eyes of 110 enrolled patients who satisfied the inclusion and exclusion criteria were analysed out of 218 willing participants. Table 1 displays the baseline characteristics of the study population. Two groups of participants were formed: ESRD patients with DM ($27 \pm 24.5\%$) and ESRD patients without DM ($83 \pm 75.5\%$). The duration of HD was 30.8 months for the DM group and 50.6 months for the non-DM group. When comparing the two groups, no significant differences were found in any of the variables.

Table 1. Clinical characteristics of the study population. Data are given as mean \pm SD.

Variables	Total patients (N = 110)	DM group (n = 27)	Non-DM group (n = 83)	P
Age (years)	46 \pm 10.9	48.2 \pm 6.6	50.3 \pm 11.2	0.009
Gender, n (%)				
Female	49 (44.5 %)	12	37	0.882
Male	61 (55.5 %)	15	46	0.720
Duration of HD (months)	38.8	30.8	50.6	0.021
IOP (mmHg)	13.0 \pm 2.1	12.5 \pm 1.6	11 \pm 2.2	0.276
SE	1.63 \pm 1.4	2.06 \pm 1.6	1.44 \pm 1.4	0.007
BCVA	0.3 \pm 0.4	0.4 \pm 0.6	0.2 \pm 0.2	0.008
History of HT+	90	24	66	0.019

DM: diabetes mellitus; IOP: intraocular pressure; SE: spherical equivalent; BCVA: best-corrected visual acuity; HT: hypertension
 Bold: Statistically significant, $p < 0.05$

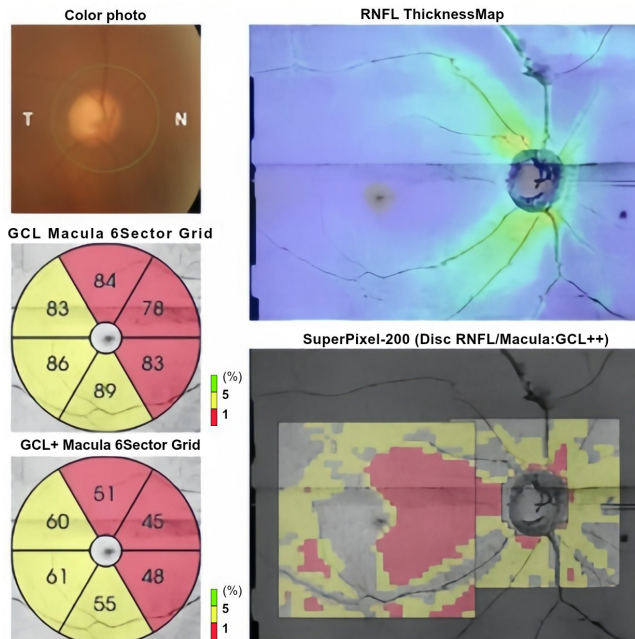


Fig. 1. GCL and GC-IPL thickness in haemodialysis ESRD patients with diabetes mellitus.

Table 2. Differences of ganglion cell layer thickness in haemodialysis patients based on diabetes mellitus status

Average GCL thickness (mm) per sector	Total patients (n = 110)	DM group (n = 27)	Non-DM group (n = 83)	P
Superior	69.4 ± 10.7	65.8 ± 15.2	70.7 ± 8.7	0.014
Superonasal	66.5 ± 11.4	60.8 ± 17.1	68.4 ± 8.7	0.005
Inferonasal	61.5 ± 11.5	54.8 ± 18.7	63.7 ± 7.0	0.047
Inferior	64.6 ± 10.3	58.5 ± 15.4	66.7 ± 6.8	0.007
Inferotemporal	65.4 ± 13.9	62.4 ± 21.2	66.4 ± 9.9	0.004
Supertemporal	104.5 ± 11.2	102.0 ± 16.1	105.3 ± 9.0	0.009

DM: diabetes mellitus; GCL: ganglion cell layer; DM: diabetes mellitus

Bold: Statistically significant, $p < 0.05$

Differences of GCL thickness in haemodialysis patients based on diabetes mellitus status

Figure 1 shows the six sectors that comprise the retinal layer: superior (S), superonasal (SN), inferonasal (IN), inferior (I), inferotemporal (IT), and superotemporal (ST). The inferonasal quadrant measured $54.8 \pm 18.7 \mu\text{m}$ in the DM group and $63.7 \pm 7.0 \mu\text{m}$ in the non-DM group had the lowest average sectoral thickness values of GCL ($p = 0.047$). In contrast, the DM group's superotemporal sector had the highest average sectoral thickness values of $102.0 \pm 16.1 \mu\text{m}$, while the non-DM group was $105.3 \pm 9.0 \mu\text{m}$ ($p = 0.009$). Table 2 shows the sectoral macular GCL thickness values in the DM and non-DM groups.

Differences of ganglion cell layer-inner plexiform layer thickness in haemodialysis patients based on diabetes mellitus status

The results of sectoral measurements of GCL thickness in both eyes between the two groups are displayed in Table 3. The inferotemporal sector measured $88.2 \pm 31.5 \mu\text{m}$ for the DM group and $91.4 \pm 12.1 \mu\text{m}$ for the non-DM group; the inferotemporal sector has the lowest average sectoral thickness values of GC-IPL ($p = 0.011$). The DM group had a maximum average sectoral thickness value of $107.2 \pm 21.2 \mu\text{m}$, while the non-DM group was $115.8 \pm 12.7 \mu\text{m}$ ($p = 0.137$). Significant variations were identified in the superonasal, inferonasal, inferotemporal, and superotemporal sectors ($p < 0.05$). There was no significant difference based on DM status ($p > 0.05$) in GC-IPL thickness in the superior and inferior sectors.

Table 3. Differences of ganglion cell layer-inner plexiform layer thickness in haemodialysis patients based on diabetes mellitus status

Average GC-IPL thickness (mm) per sector	Total patients (n = 110)	DM group (n = 27)	Non-DM group (n = 83)	P
Superior	113.7 ± 15.2	107.2 ± 21.2	115.8 ± 12.7	0.137
Superonasal	111.9 ± 15.9	102.3 ± 22.7	115.1 ± 12.5	0.016
Inferonasal	102.7 ± 17.8	96.4 ± 27.8	104.7 ± 11.7	0.028
Inferior	91.7 ± 19.3	86.6 ± 31.9	93.4 ± 12.4	0.194
Inferotemporal	90.6 ± 18.8	88.2 ± 31.5	91.4 ± 12.1	0.011
Supertemporal	105.3 ± 14.1	103.0 ± 21.8	108.4 ± 10.4	0.016

GC-IPL: ganglion cell-inner plexiform layer DM: diabetes mellitus

Sub-analysis on hypertension as confounding factor

One of the confounding factors is HT, which has been shown in earlier research to also reduce the thickness of the GCL and GCL-IPL. To examine the differences between groups with and without HT and DM, a sub-analysis was conducted. There was no discernible difference in the thickness of GCL and GC-IPL between the non-DM group with and without HT ($p = 0.30$). There was a significant difference in the thickness of GCL and GC-IPL between the DM(-) HT(+) and DM(+) HT(+) groups ($p = 0.006$).

Discussion

According to earlier research, ocular abnormalities are frequently observed in individuals with ESRD, particularly in those who also have concomitant conditions, including DM and HT. According to research by Widjaja *et al.*, hyperglycaemia and elevated diastolic blood pressure are the main predictors of cataracts and conjunctival and corneal calcification, which are the most common visual abnormalities in HD patients.¹⁶ The GCL was assessed in our current study by comparing and analysing changes in GCL and GC-IPL thickness in ESRD patients with DM to ESRD patients without DM. In ESRD patients with DM, we found some notable reductions

in the GCL in every sector of the GCL circular scans. In contrast, we only observed a significant decrease in the superonasal, inferonasal, inferotemporal, and superotemporal sectors of the eye in the GCL-IPL circular scans, despite the fact that thinning was present in nearly every sector of the DM group. Additionally, this study demonstrates that samples with concomitant HT alone did not exhibit a reduction in GCL and GC-IPL thickness. In contrast to the sample with comorbid HT alone, the group with comorbid DM and HT displayed a considerable reduction in thickness.

As far as we are aware, there aren't many studies that compare the thickness of GCL and GCL-IPL in ESRD patients with and without DM. Few studies also demonstrate that ESRD patients have thinner IPL and GCL than healthy controls. However, there is notable thinning reported in a number of articles about RNFL assessment in ESRD patients. Gadelha *et al.* examined RNFL in the eyes of 22 ESRD patients in comparison to a healthy control group. Significant thinning was observed in the ESRD superior, nasal, and inferior sector RNFL.¹⁷ Other studies also show the processes of retinal neurodegenerative indication in ESRD patients. In comparison to 38 healthy controls, Jung *et al.* assessed retinal alterations in 32 ESRD patients. With the exception of patients with DM, it showed a notable decrease in RNFL and GC-IPL thickness in ESRD patients.⁹ Our results were comparable to those of Pekel *et al.*, who compared the average macular GCL-IPL thickness of healthy controls and patients with type 2 DM and found a statistically significant difference in the superonasal macular GCL-IPL thickness between the DM and control groups. Because GCL-IPL thickness was decreased in DM patients without retinopathy, the author also came to the conclusion that neuroretinal changes can occur before microvascular problems in DM.¹⁸⁻²⁰ Similar findings were reported by other researchers, who found that patients with and without diabetic retinopathy had variations in the thickness of the macular retina and each individual layer.²¹⁻²⁵ The RNFL may also narrow as a result of axonal loss.²⁶

Our study, which found decreased macular GCL-IPL thickness in many sectors in both DM and ESRD patients, was consistent with all of these investigations. GCL was considerably lower in ESRD patients with DM in this study. Other studies have also observed similar changes. Van Dijk *et al.* assessed GCL thickness in type 1 DM patients with mild diabetic retinopathy and found GCL weakening in the pericentral region.²⁴ GCL and RNFL in type 2 DM patients did not significantly decline, according to another study. Reduced thickness of the inner retinal layer, including GCL and GC-IPL, is caused by the activation of metabolic pathways, such the polyol and hexosamine pathways, which are driven by hyperglycaemia and result in the production of free radicals and advanced glycation end products. Retinal microangiopathy and retinal neurodegeneration are the results of neural retina disorders brought on by the activation of these pathways.²⁷⁻²⁹

In contrast, a substantial decrease in GC-IPL thickness was observed in samples with a history of HT for more than 5 years in a previous study that compared 84 hypertensive patients with 117 healthy controls.³⁰ Retinal microcirculation problems

could be the cause of this decrease in retinal thickness. Ischemia in the retinal region is brought on by vasoconstriction and retinal vascular spasm to make up for the rise in systemic blood. Apoptosis can occur in the GCL, which is extremely vulnerable to hypoxic stress.³¹ Another study assessed the thickness of the GC-IPL after splitting the HT group into those with a duration of less than 10 years and those with a duration of more than 10 years. Over a 10-year period, a notable reduction in GC-IPL thickness was observed in the HT group. Therefore, when assessing peripapillary microvasculature, the length of HT should be taken into account.³² Furthermore, some earlier research also suggested a link between the incidence of ocular defects and elevated systolic blood pressure.³³

According to our study, HD patients who have concomitant conditions experience retinal deterioration. As a result, early identification of neurodegenerative alterations as determined by SD-OCT is crucial and may eventually be incorporated into standard diagnostic screening procedures. The findings of this study may also serve as a guide for HD patients regarding the significance of a comprehensive ophthalmology examination. This study's cross-sectional design, limited sample size, and failure to account for certain confounding variables, such as HT, were among its weaknesses. This study did not provide any information on the control of blood flow velocity or quick of dialysate during HD to evaluate the removal of uremic toxins that may impact retinal neurodegenerative diseases. Future research should address each of those constraints.

Conclusion

This study's findings demonstrated a neurodegenerative process in the retinal layer associated with ESRD patients undergoing frequent HD. It may imply the significance of more regular ocular follow-up of ESRD patients with comorbidities, particularly DM and HT, in order to prevent further damage to the neural retina. Therefore, an integrated planned examination between the HD unit and the ophthalmology department must be improved.

Declarations

Ethics approval and informed consent

Written informed consent was obtained from patients who fulfilled the study's inclusion and exclusion requirements. The principles of good clinical practice standards and the Declaration of Helsinki's tenets were followed when conducting the investigations. The Dr. Soetomo General Academic Hospital Surabaya's Institutional Review Board approved the study protocol (Komisi Etik Peneliti Kesehatan Rumah Sakit Dr. Soetomo No.1155/KEPK/V/2019).

Competing interests

None to declare.

Funding

This study was funded by the Universitas Airlangga Research Grant (Grant SK Rektor Unair No.1408/UN3/2019), which had no involvement in the design, conduct, authorship, or publication of this article.

Authors' contributions

SAW and IY conceived and designed the study. Research execution and data collection: DR, IY, ADP, RSD. Data analysis and interpretation include DR, ADP, and MF. DR, SAW, and YP prepared the manuscript and wrote the original text. Critically review and edit for essential intellectual content: SAW, YP, AT, MF, and WS. Final approval for the submitted version: SAW, YP, and AT.

Acknowledgements

The authors would like to thank the DiORSS (Diabetic Ocular Renal Surabaya Study) team and Vitreo-retinal Division of the Department of Ophthalmology Faculty of Medicine Universitas Airlangga/RSUD Dr. Soetomo, as well as Ophthalmology Instrument's Suppliers in Surabaya for their contributions to this study: PT Pancaraya Krisnamandiri (Autorefkeratometer type accuref k-90030, Shinnipon); PT Berjaya Mandiri (Houvitaz NCT, HNT-7000 non-contact tonometer); PT Triastri Meditama (slit-lamp biomicroscopy vision 66 type); PT Topsindo Megah Utama (3D OCT, DRI-OCT Triton, Topcon Incorporation).

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