Serum apolipoprotein A1 and B are associated with 6-month persistent and incident diabetic macular oedema in type 2 diabetes

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ABSTRACT

Aims To investigate the associations of baseline apolipoprotein A1 (ApoA1) and B (ApoB) levels with persistent and incident diabetic macular oedema (DMO) after 6 months of follow-up.

Methods This is a prospective cohort study of patients aged ≥30 years with untreated diabetic retinopathy. Examinations, fundus photography and spectral domain optical coherence tomography (SD-OCT) were assessed at baseline, 1, 3 and 6 months. Serum lipids and apolipoproteins were analysed at a pathology laboratory. DMO was confirmed using SD-OCT, classified as (1) incident DMO, (2) persistent DMO and (3) regressed DMO. Eye-specific data were used, controlling for covariates and cluster effect.

Results We recruited 53 patients but only 38 completed the study ([62 eyes), 20 eyes (32.3%) with DMO]. Higher quartile of ApoA1 was associated with lower risk of persistent/incident DMO (p for trend 0.02), while higher ApoB/A1 was associated with higher risk of persistent/incident DMO (p for trend 0.02). Every 10 mg/dL increase in ApoA1 levels was associated with lower risk of persistent/incident DMO (OR 0.69; 95% CI 0.49 to 0.92; p value 0.016), whereas every 0.2 increase in ApoB/A1 was significantly associated with higher risk of persistent/incident DMO (OR 1.4; 95% CI 1.1 to 1.9; p value 0.013) at the end of the study.

Conclusion Individuals with diabetes with higher ApoA1 had lower risk of persistent/incident DMO and those with higher ApoB/A1 had higher risk of persistent/incident DMO at the end of 6 months. These suggest that serum ApoA1 and ApoB/A1 levels may be important risk factors for DMO and could be predictive of persistent/incident DMO despite anti-vascular endothelial growth factor treatment.

INTRODUCTION

Diabetic retinopathy (DR) is the most frequent diabetic microvascular complication causing irreversible visual loss among individuals with diabetes.1 2 Importantly, diabetic macular oedema (DMO) is a common feature of DR responsible for most of visual impairment in persons with diabetes.1,2 While DMO was often considered as presenting in more severe form of DR, recent studies have documented that DMO can also be present solely in less severe DR.3-5 Studies have suggested that DMO was present in nearly 10% of individuals with type 2 diabetes and may develop in 25% of individuals with type 2 diabetes within 10 years of follow-up.6-9

Serum lipids have been considered as one of the major risk factors for DMO, documented in multiple clinical studies.8-9 It has been suggested that in individuals with diabetes, extended dyslipidaemia, along with its complex interactions with other major diabetes risk factors such as long diabetes
duration, poor glycaemic and blood pressure control, may exaggerate diabetes-related retinal microvascular injury and cause breakdown of the blood-retinal barrier (BRB).\textsuperscript{6–7} BRB breakdown may further cause extravascular accumulation of fluid and lipoprotein deposits particularly manifested at the macular region and clinically appeared as DMO.\textsuperscript{6–8}

In addition to standard serum lipid profile, which normally consists of cholesterol, triglycerides, high-density (HDL) and low-density lipoproteins (LDL), there has been an emerging interest in serum apolipoprotein A1 (ApoA1) and B (ApoB). ApoA1 is the main component of HDL and ApoB is found in LDL, intermediate-density (IDL) and very low-density lipoprotein (VLDL).\textsuperscript{7,8} Previous studies have reported cross-sectional associations between serum ApoA1 and B with DR and DMO and further suggested that the roles of ApoA1 and ApoB in the mechanisms of DMO are different than standard lipid profile.\textsuperscript{10,11} ApoA1 is a transporter of lipid particles from peripheral tissue, including retina, to the liver and ApoB sends these particles from liver back to the tissue.\textsuperscript{15} We speculated that dysregulation of apolipoproteins A1 and B therefore may amplify the accumulation of lipid particles in the retinal vasculature, which escalate the magnitude of BRB breakdown and persevering DMO regardless of treatment. However, there is scarcity of prospective data regarding serum apolipoproteins and DMO.\textsuperscript{5,10–12}

In this study, we investigated the associations of serum ApoA1 and ApoB levels measured at baseline and their changes with persistent and incident DMO after 6 months of follow-up in patients with type 2 diabetes.

METHODS

This was a clinic-based prospective cohort study. We consecutively recruited 53 untreated patients with type 2 diabetes mellitus (DM) and DR, with or without DMO, aged >30 years between March and October 2021 from Jakarta Eye Center (JEC) Primasana Hospital, Jakarta, Indonesia. We excluded eyes with proliferative diabetic retinopathy (PDR) and vitreous bleeding and/or tractional retinal detachment. We also excluded patients who has a history of liver disease, kidney failure, malignancy, myocardial infarction or stroke in the past 3 months; or had any infections in the past 6 weeks. Written informed consent was obtained from each participant.

Clinical assessment and blood chemistry

All participants underwent a standardised clinical and eye examinations at baseline, 1, 3 and 6 months. Clinical examinations were done by trained nurse covering medical history, the use of antihypertensive, lipid lowering and anti-diabetic medications, brief examination of other diabetic complications, assessment of systolic (SBP) and diastolic blood pressure (DBP) using automated digital blood pressure monitor and cuffs, anthropometric and body composition measurements. Hypertension was defined as SBP >140 mm Hg, DBP >90 mm Hg or current use of antihypertensive medications. Height and weight were measured to determine body mass index (BMI).

Height, weight, waist and hip circumference were also measured. Height was measured using a wall-mounted and adjustable tape, and measurement of waist and hip circumferences was made using a 151 cm medical tape. We used a calibrated digital weight scale (Omron Karada Scan Body Composition Scale HBF-375, Omron, Osaka, Japan) to measure weight and other body composition parameters including resting metabolic rate (RMR), total body fat, subcutaneous fat, visceral fat and fat-free mass percentage.\textsuperscript{13} The protocol for this measurement has been used and validated in previous study and documented to have excellent intra-operator (intraclass correlation 0.94) and inter-operator (intraclass correlation 0.95) agreement.\textsuperscript{13}

Fasting (>8-hour) blood samples were obtained from each participant and sent to internationally accredited, local, commercial pathology laboratory for Hba1c, serum lipids (total, HDL, LDL and triglycerides) and apolipoprotein (ApoA1 and ApoB) assessment within 1 week of eye examinations. ApoA1 and ApoB were measured using immunoturbidimetry method. Blood chemistry evaluations were conducted at the beginning of the study and at 6 months’ follow-up.

Eye examination and assessment of DR and DMO

Eye examinations were performed by trained ophthalmic nurse and verified by an ophthalmologist on duty, including visual acuity, intraocular pressure and anterior segment examination. DR and DMO were assessed from fundus photograph (Visucam 224/524, Carl ZEISS Meditec AG, Jena, Germany) and spectral domain optical coherence tomography (SD-OCT) imaging (Cirrus HD-OCT 5000 with AngioPlex, Carl ZEISS Meditec, Dublin, USA). Disc-centred and macula-centred fundus photographs and spectral-domain macular OCT were obtained from each participant. DR was graded as no DR, mild, moderate, severe non-proliferative DR (NPDR) and proliferative DR (PDR), while DMO was categorised as absent and present, following the International Clinical Diabetic Retinopathy Disease Severity Scale.\textsuperscript{14} Mild NPDR is characterised by the presence of only microaneurysm, and moderate NPDR is when there are microaneurysms, retinal haemorrhages (1–3 quadrants), exudates or cotton wool spots without any significant intraretinal microvascular anomalies (IRMA) or venous. Severe NPDR is characterised by severe haemorrhages in all four quadrants, significant venous beading in two or more quadrants, and moderate IRMA in one or more quadrants, and no neovascularisation. PDR is defined by the presence of any neovascularisation (new vessels on the disc or new vessels elsewhere). DMO was determined by the presence of hard exudates, increased macular thickness, loss of foveal depression, and presence of macular fluid from clinical findings, retinal photography and OCT imaging by retinal specialist. We defined incident DMO when DMO was absent at baseline but then
present at 3 or 6 months of follow-up. Persistent DMO was defined as the presence of DMO from baseline to 6-month follow-up regardless of anti-vascular endothelial growth factor (VEGF) injections. Regressed DMO was defined as the absence of DMO at the end of the study in individuals with DMO at baseline.

All participants received therapy according to indications. Patients with DMO received anti-VEGF (Bevacizumab) injection monthly for three consecutive months. If DMO still persisted after three injections, we continued anti-VEGF injections until 6 months. In addition to anti-VEGF injections, any participants with worse than severe NPDR during the study also underwent pan retinal photocoagulation therapy using PASCAL laser treatment. Participants will get this laser treatment once, but additional laser treatment will be given as clinically indicated.

Statistical analysis
All statistical analyses were performed using Stata Basic Edition (BE) V.17.0 (Statcorp, Texas, USA) as the software for statistical analysis. Baseline characteristics of participants with and without DMO were compared using $\chi^2$ test for proportions and means comparison in tables 1 and 2 was tested using regression, accounting for clustering effect within one individual. The Kolmogorov-Smirnov normality test was carried out to test the normality of the data. Serum lipid and apolipoprotein levels were assessed categorically (in quartiles) and continuously (per SD change). We treated DR and DMO as the dependent variables and level of apolipoproteins and other covariates (age, gender, duration of DM) as independent variables. Because DR and DMO are eye-specific, we used data from both eyes in our analyses and treated each person as one cluster, considering apolipoproteins level was the same at individual level. Generalised estimating equation, multivariable logistic regression was used to assess the association between apolipoprotein parameters and DMO progression, controlling for clustering effect within each individual. This method was proposed by Zeger et al, with the main aim to reduce type 1 error due to correlation between eye-specific within an individual and became commonly used in studies in ophthalmology when the outcomes are eye-specific. We developed two models, unadjusted (model 1) and adjusted for age, gender, duration of DM, SBP and HbA1c (model 2). We assessed the presence of any interaction using likelihood ratio test for interaction. The fitness of the model was tested by examining the normality of the residual and multicollinearity was also checked by looking at the variance influence factor of the model.

RESULTS
There were initially 53 eligible participants (89 eyes) recruited at baseline. However, 10 participants died, and 5 were severely ill due to COVID-19 during the study period, leaving 38 participants (62 eyes) included in the final analyses, 42 eyes (67.7%) with DR without DMO and 20 eyes (32.3%) with DMO at baseline (online supplemental table 1). There were six participants at baseline (15.8%) who had DMO in one eye and none in the other eye. Characteristics of dropped-out participants were presented in online supplemental table 2. Table 1 shows the baseline characteristics of participants/eyes included in the final analysis. Male gender was more common in the DMO group than in the non-DMO group (73.3% vs 39.5%, $p=0.03$). Furthermore, group with DMO had longer diabetes duration (8.2 years vs 5.6 years), worse visual acuity, higher total cholesterol level, lower total body fat and higher resting metabolic rate at baseline than non-DMO group. Other baseline lipid profiles and serum apolipoprotein levels were similar between DMO and non-DMO groups.

Table 2 shows the baseline characteristics of participants who had persistent/incident DMO, regressive DMO and without DMO at 6 months of follow-up. Individuals with

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<tr>
<th>Table 1</th>
<th>Subjects’ characteristics at baseline</th>
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<tr>
<td></td>
<td>Without DMO</td>
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<td></td>
<td>(n=42 eyes)</td>
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<tr>
<td>Clinical characteristics</td>
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<tr>
<td>Age, years</td>
<td>57.5±8.7</td>
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<tr>
<td>Male, n (%)</td>
<td>15 (39.5)</td>
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<tr>
<td>Duration of DM, years</td>
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<td>Systolic blood pressure, mmHg</td>
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<td>Visual acuity, decimal</td>
<td>0.95±0.5</td>
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<tr>
<td>Anthropometry</td>
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<tr>
<td>Weight, kg</td>
<td>61.8±10.6</td>
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<tr>
<td>BMI, kg/m²</td>
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<tr>
<td>Normal, n (%)</td>
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<tr>
<td>Overweight, n (%)</td>
<td>9 (23.7)</td>
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<td>Obese, n (%)</td>
<td>11 (28.9)</td>
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<tr>
<td>Total fat, %</td>
<td>28.0±6.6</td>
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<tr>
<td>Visceral fat, %</td>
<td>8.80±4.3</td>
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<td>RMR, kcal</td>
<td>1373±230.2</td>
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<td>Blood chemistry characteristics</td>
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<td>Lipid profile, mg/dL</td>
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<td>Total cholesterol</td>
<td>214.9±63.4</td>
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<tr>
<td>HDL</td>
<td>46.6±12.6</td>
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<td>LDL</td>
<td>153.1±55.9</td>
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<tr>
<td>Triglycerides</td>
<td>140.6±75.2</td>
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<td>Apolipoprotein, mg/dL</td>
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<tr>
<td>ApoA1</td>
<td>143.4±31.5</td>
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<tr>
<td>ApoB</td>
<td>116.6±35.4</td>
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<tr>
<td>ApoB/A1 ratio</td>
<td>0.86±0.3</td>
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</table>
| ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; BMI, body mass index; DMO, diabetic macular oedema; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RMR, resting metabolic rate.
persistent/incident DMO had significantly higher baseline ApoB levels compared with those with regressed or no DMO at 6 months (165±26.9 mg/dL in persistent/incident DMO vs 128±23.6 mg/dL in regressed DMO vs 110±26.7 mg/dL in no DMO; p<0.01). Similar finding was also observed for ApoB/A1 (1.38±0.3 in persistent/incident DMO vs 0.91±0.1 in regressed DMO vs 0.70±0.2 in no DMO; p=0.01). No significance differences were observed for all the other parameters.

Table 3 shows the associations between lipids and apolipoproteins with persistent/incident DMO at 6 months. After adjusting for baseline age, gender, duration of diabetes and SBP, higher quartile of ApoA1 (1.38±0.3 in persistent/incident DMO vs 0.91±0.1 in regressed DMO vs 0.70±0.2 in no DMO; p=0.01). No significance differences were observed for all the other parameters.

Table 4 shows the associations between 6-month changes in apolipoprotein levels with persistent/incident DMO at the end of the study. Every 10 mg/dL increase in ApoA1 levels was related to lower risk of persistent/incident DMO (OR 0.69; 95% CI 0.49 to 0.92; p value 0.016), while every 0.2 increase in ApoB/A1 was significantly associated with higher risk of persistent/incident DMO (OR 1.99; 95% CI 1.03 to 1.9; p value 0.013) at the end of the study. These associations remained significant after controlling for baseline age, gender, duration of diabetes and SBP.

DISCUSSION
This prospective study demonstrated that individuals with diabetes with higher ApoA1 at baseline had lower risk of persistent/incident DMO and those with higher ApoB/A1 had higher risk of persistent/incident DMO after 6 months of follow-up. Increasing ApoA1 level was also significantly associated with lower risk of persistent/incident DMO, while increasing ApoB/A1 ratio was associated with higher risk of persistent/incident DMO at 6 months despite any treatment, independent of baseline age, gender, duration of diabetes and SBP.
<table>
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<tr>
<th>Variables</th>
<th>Model 1</th>
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<th>P value</th>
<th>Model 2</th>
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<td>OR (95% CI)</td>
<td>P value</td>
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<td>Adjusted OR (95% CI)</td>
<td>P value</td>
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<td>0.50 (0.09 to 2.65)</td>
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<tr>
<td>3rd quartile (142–152)</td>
<td>0.38 (0.81 to 1.78)</td>
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<td>0.30 (0.08 to 1.78)</td>
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<tr>
<td>4th quartile (155–208)</td>
<td>0.08 (0.01 to 0.74)</td>
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<td>0.04 (0.00 to 0.85)</td>
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<tr>
<td>Per 1 SD increase</td>
<td>0.74 (0.34 to 1.61)</td>
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<td></td>
<td>0.58 (0.25 to 1.27)</td>
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<td>Apolipoprotein B, mg/dL</td>
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<td>1st quartile (63–95) Reference</td>
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<td>6.72 (0.76 to 59.8)</td>
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<td>3rd quartile (114–124)</td>
<td>1.61 (0.23 to 11.1)</td>
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<td>1.72 (0.13 to 10.9)</td>
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<td>4th quartile (132–221)</td>
<td>10.0 (1.62 to 61.5)</td>
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<td>Per 1 SD increase</td>
<td>1.71 (0.95 to 3.06)</td>
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<td>0.99 (0.12 to 7.92)</td>
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<td>Per 1 SD increase</td>
<td>1.31 (0.77 to 2.21)</td>
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<td>0.89 (0.09 to 9.15)</td>
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<td>2.50 (0.39 to 15.9)</td>
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<td>0.86 (0.09 to 8.06)</td>
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<td>Per 1 SD increase</td>
<td>0.84 (0.47 to 1.51)</td>
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<td>1.16 (0.53 to 2.60)</td>
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<td>Triglyceride, mg/dL</td>
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<td>0.23 (0.03 to 1.76)</td>
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<td>4th quartile (216–412)</td>
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<td>0.47 (0.07 to 3.12)</td>
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<td>Per 1 SD increase</td>
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<td>0.75 (0.37 to 1.55)</td>
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Continued
There is scarcity of data regarding serum apolipoproteins and DMO.5–12 Previous studies have mostly reported only cross-sectional associations of serum apolipoproteins with presence of DR.5 10 11 18 19 ApoA1 was inversely associated with presence and severity of DR, while ApoB and ApoB/A1 have shown their positive relationships with both presence and severity of DR.10 20 21 In this study, we did not find significant associations between serum apolipoproteins and presence of DR at baseline because we only included patients with DR. Nevertheless, our study findings provide additional knowledge in the existing literature that serum apolipoproteins were prospectively associated with DMO.

Associations of ApoA1 and ApoB/A1 with persistent/incident DMO after 6 months fitted well with pathophysiological process of DMO. The central mechanism in the pathophysiology of DMO is breakdown of blood-retinal barrier (BRB).6 7 18 BRB is a biological unit mainly formed by tight junction of retinal vascular endothelial (RVE) cells, network of glial cells and retinal pigment epithelium, which preserve low permeability milieu at the retina.6 7 In diabetes, there is evidence of RVE cells loss resulted in the disruption of BRB, increased permeability and movement of fluids across BRB, and finally fluid accumulation in the inner retina.6 7

The mechanism of BRB breakdown is complex and highly influenced by long diabetes duration, poor glycaemic control and other systemic profiles including dyslipidaemia.6 7 Serum apolipoproteins, which are closely related to lipids circulation, are speculated to play important role in the retinal vascular damage.10 Apolipoproteins bind lipid particles to form lipoprotein and transport these lipoproteins in the blood and cerebrospinal fluid, and are key in lipid uptake and clearance in peripheral tissue.22 23 ApoA1, which is the main component of HDL, is important in transporting lipids from tissue to the liver for degradation process.24 25 Moreover, ApoA1 is also associated with decreased production of some important proinflammatory cytokines (ie, tumour necrosis factor, interleukin 1β and interleukin 6) and may downregulate vascular endothelial growth factor, hence showing vasoprotective effects in small vessels.10 24 25 Meanwhile, ApoB is the main apolipoprotein in chylomicrons, VLDL, LDL and IDL which transport cholesterol from the liver to tissues. ApoB is also known to be responsible for inflammatory and atherosclerotic process.26 These explain that higher ApoA1 level in some individuals may link to less atherogenic process at the retinal vasculature, less severe RVE cells loss and less BRB damage than those who had lower ApoA1, manifested as lower risk of persistent/incident DMO.10 27

### Table 3

Continued

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<td>Adjusted OR (95% CI)</td>
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<td>Model 1: Univariate.</td>
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<tr>
<td>Model 2: Multivariate adjusted for age, sex, duration of DM, baseline SBP and HbA1c.</td>
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### Table 4

Associations between 6-month changes in apolipoprotein levels with persistent/incident DMO at the end of the study

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<th>Model 2</th>
<th>P value</th>
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</thead>
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<td>Adjusted OR (95% CI)</td>
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<td>Apolipoprotein A1</td>
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<tr>
<td>Per 10 mg/dL increase</td>
<td>0.69 (0.49 to 0.92)</td>
<td>0.016</td>
<td>0.65 (0.46 to 0.92)</td>
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<td>Apolipoprotein B</td>
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<tr>
<td>Per 10 mg/dL increase</td>
<td>1.11 (0.89 to 1.39)</td>
<td>0.35</td>
<td>1.06 (0.81 to 1.37)</td>
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<tr>
<td>Apolipoprotein B/A1 ratio</td>
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<tr>
<td>Per 0.2 increase</td>
<td>1.41 (1.08 to 1.86)</td>
<td>0.013</td>
<td>1.45 (1.07 to 1.97)</td>
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Model 1: Univariate.
Model 2: Multivariate adjusted for age, sex, duration of DM, baseline SBP and HbA1c. DM, diabetes mellitus; SBP, systolic blood pressure.
There are strong implications of this study findings. Our data showed no associations of standard lipid profile with DMO. This was in line with previous study showing stronger associations of serum apolipoproteins with DR than standard lipid profile, strengthen the notion that serum apolipoproteins were possibly more important measures than standard lipid profile in the context of DR/DMO. In addition, our study also demonstrated that changes in ApoA1 were associated with lower risk of DMO and changes in ApoB/A1 were associated with higher risk of DMO at the end of study, despite anti-VEGF treatment. Importantly, individuals with higher ApoA1 at baseline were likely to have their DMO regressed at the end of the study (online supplemental table 3). These suggest that serum apolipoprotein measures might be used for clinical marker to identify those who will likely have successful outcomes of anti-VEGF treatment and that improvement of serum apolipoprotein level may be necessary to yield good treatment outcome.

The strengths of this study include its prospective design, assessment of DMO using SD-OCT verified by retinal specialist and repeated measurement of serum apolipoproteins at baseline and at the end of study. However, some limitations were also present. First, the proportion of patient who did not return for follow-up was considerably high due to COVID-19 morbidity and mortality (28.4%). Our analyses showed that proportion of DMO in group with completed follow-up and dropped out was not significantly different. Individuals who failed to complete the follow-up had significantly higher SBP, lipid profiles and serum ApoA1 and ApoB levels compared with those who completed the follow-up (online supplemental table 2). While this may have induced bias, this difference is less likely to diminish the associations or change the direction of associations. In fact, because dropped-out participants had higher serum lipids and apolipoproteins, if they were included in the final analysis, the associations between serum apolipoproteins with DMO could have been stronger. We have attempted to contact the patient and offer home pick-up; however, COVID-19 restriction had become significant disadvantage for further effort. Second, due to small number of participants, we were unable to split individuals with DMO progression in the separate analysis and we were also unable to estimate DMO risk measures for those with better apolipoprotein profiles at the end of the study. Lastly, the overall follow-up time might be less sufficient to observe the long-term effect of apolipoprotein levels on clinical DMO. Also, there was some information bias because we did not know exactly the history of DMO before our baseline or how long has the DMO been present before the baseline examination. Chronic DMO may respond less optimally to treatment. Further cohort study with larger sample size and longer follow-up period is needed to eliminate this information bias as well as to conclude the predictive value of apolipoproteins in patients with DR/DMO.

In conclusion, findings from our study demonstrated that persons with diabetes with higher ApoA1 at baseline had lower risk of persistent/incident DMO than those with lower ApoA1. Meanwhile, individuals with diabetes with higher ApoB/A1 showed higher risk of persistent/ incident DMO after 6 months of follow-up than those who had lower ApoB/A1. Increasing ApoA1 level was associated with lower risk of persistent/incident DMO, while increasing ApoB/A1 ratio was associated with higher risk of persistent/incident DMO at 6 months despite anti-VEGF. While larger prospective study is needed to confirm, our data provide initial evidence that serum ApoA1 and ApoB/A1 levels may be important risk factors for DMO and that changes in ApoA1 and ApoB/A1 might also be predictors of persistent/incident DMO despite anti-VEGF treatment.

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Contributors SS planned the study, led the data collection, interpreted the findings, wrote initial draft of the manuscript and revised the manuscript. MJ supervised, performed data quality checking and data interpretation, critically reviewed and edited the manuscript. TDG supervised, critically reviewed and edited the manuscript. ADJP performed partial data collection, data quality checking and critically reviewed the manuscript. KHK performed partial data collection, data quality checking and critically reviewed the manuscript. MBS supervised, conceptualised the study, performed partial data analysis and interpretation, critically reviewed and edited the manuscript. SS and MBS are the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study followed the tenets of the Declaration of Helsinki. Ethical clearance was granted by the Medical and Research Ethics Committee, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada (KE/FK/0353/EC/2021). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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Muhammad Bayu Sasonoko http://orcid.org/0000-0002-0366-8335
REFERENCES


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**Supplementary table 2. Included vs. Dropped-out subjects’ characteristic**

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<td>Male, n (%)</td>
<td>21 (55.3)</td>
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<td>139.2 ± 22.4</td>
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<td>DME, n (%)</td>
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<tr>
<td>Triglycerides</td>
<td>142.5 ± 65.1</td>
<td>223.5 ± 92.3</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Apolipoprotein, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apo A1</td>
<td>143.6 ± 31.6</td>
<td>161.8 ± 30.5</td>
<td>0.02*</td>
</tr>
<tr>
<td>Apo B</td>
<td>119.6 ± 29.1</td>
<td>144.8 ± 44.6</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Apo B/A1 ratio</td>
<td>0.87 ± 0.3</td>
<td>0.93 ± 0.3</td>
<td>0.44</td>
</tr>
</tbody>
</table>

DME: diabetic macular edema, HDL: high-density lipoprotein, BMI: body mass index, LDL: low-density lipoprotein, RMR: resting metabolic rate.

* Significant p value
**Supplementary table 3.** Serum apolipoprotein levels and regressed DMO at the end of study

<table>
<thead>
<tr>
<th>Variables</th>
<th>Persistent DMO (%)</th>
<th>Regressed DMO (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apolipoprotein A1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 135</td>
<td>11 (68,8)</td>
<td>0 (0)</td>
<td>0.013</td>
</tr>
<tr>
<td>&gt; 135</td>
<td>5 (31,2)</td>
<td>4 (100)</td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 122.5</td>
<td>7 (43,8)</td>
<td>2 (50)</td>
<td>0.82</td>
</tr>
<tr>
<td>&gt; 122.5</td>
<td>9 (56,3)</td>
<td>2 (50)</td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein B/A1 Ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 0.85</td>
<td>5 (31,2)</td>
<td>4 (100)</td>
<td>0.013</td>
</tr>
<tr>
<td>&gt; 0.85</td>
<td>11 (68,8)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>