Efek fenofibrat oral pada ketebalan retina dan volume makula: Kajian terhadap disfungsi endotel vaskular retina, inflamasi dan angiogenesis pada retinopati diabetik dengan dislipidemia = Effects of oral fenofibrate on retinal thickness and macular volume: Assessments on retinal endothelial vascular dysfunction, inflammation, and angiogenesis in diabetic retinopathy with dyslipidemia.

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Abstrak

Retinopati diabetik (DR) merupakan komplikasi mikrovaskular diabetes melitus (DM). Fenofibrat oral dapat mencegah progresivitas DR dengan mekanisme pengaturan kadar lipid lipid-related dan mekanisme lain nonlipid-related, antara lain dengan mencegah disfungsi endotel, mengurangi inflamasi, dan angiogenesis. Penelitian ini bertujuan mengetahui efek fenofibrat oral terhadap ketebalan makula sentral (CMT) dan volume makula, serta pengaruhnya pada kadar penanda biologis serum disfungsi endotel eNOS, inflamasi (VCAM-1), dan angiogenesis (VEGF) pada penyandang DR dengan dislipidemia.
Penelitian prospektif ini menggunakan disain uji klinis acak tersamar ganda dengan membagi subjek menjadi kelompok intervensi simvastatin dan fenofibrat dan kontrol simvastatin dan plasebo. Penelitian berlangsung sejak Nopember 2016 hingga Oktober 2017, di Klinik Vitreo-retina, Departemen Medik Mata ndash;RSCM Kirana, melibatkan 60 mata dari 30 pasien penyandang DR non-proliferatif NPDR dengan dislipidemia. Penelitian pada tiap subjek dilakukan selama tiga bulan dengan evaluasi klinis, foto fundus, dan spectral domain optical coherence tomography (SD-OCT) makula tiap bulan. Pengukuran kadar eNOS, VCAM-1, dan VEGF, serta HbA1c dan profil lipid dilakukan sebelum dan setelah tiga bulan pengobatan.Sebelum intervensi, pada kedua kelompok tidak didapatkan perbedaan karakteristik demografik, klinik, dan penanda biologis serum. Tidak didapatkan perbedaan bermakna pada CMT kelompok simvastatin fenofibrat 248,0 40,4 m dibandingkan kelompok simvastatin plasebo 265,8 40,8 m, namun CMT lebih rendah secara bermakna pada bulan ke-1 pada kelompok simvastatin fenofibrat. Pada subjek dengan edema makula diabetik DME pemberian simvastatin fenofibrat setelah tiga bulan menunjukkan CMT lebih rendah secara bermakna. Volume makula setelah tiga bulan pemberian obat 10086 886,4 m3 pada kelompok simvastatin fenofibrat dan 10307 1058,6 m3 pada simvastatin plasebo. Perbedaan tersebut tidak bermakna, namun pada subjek dengan regulasi glukosa darah yang baik HbA1c 7 didapatkan volume makula lebih rendah pada bulan ke-2. Kadar penanda biologis serum setelah tiga bulan pemberian obat menunjukkan rerata kadar eNOS dan median VEGF sebesar 3878,8 873,33 pg/mL dan 242,8 86 - 1123,3 pg/mL pada kelompok simvastatin fenofibrat, dibandingkan 4031,2 742,56 pg/mL dan 370 134,8 - 810,6 pg/mL pada kelompok simvastatin plasebo, yang tidak berbeda bermakna, namun penurunan kadar VCAM-1 serum lebih besar secara bermakna pada kelompok simvastatin fenofibrat 50,7 pg/mL, 32,5 - 223,4 pg/mL vs. 40,4 pg/mL, 27,9 - 94,2 pg/mL . Pada subjek dengan kontrol glukosa darah ketat HbA1c 6,5 kadar VEGF 128,7 114,5 - 145,2 pg/mL, lebih rendah secara bermakna dibandingkan 423 86 - 1233,3 pg/mL pada subjek dengan HbA1c > 6,5 .Disimpulkan pemberian simvastatin fenofibrat selama tiga bulan pada subjek DR dengan dislipidemia secara umum tidak menurunkan CMT dan volume makula, namun menurunkan CMT khusus pada subjek DR dengan DME. Pemberian simvastatin fenofibrat pada subjek DR tidak mencegah

penurunan kadar eNOS, peningkatan kadar VCAM-1 dan VEGF, namun pengendalian gula darah yang baik dapat mencegah peningkatan kadar VEGF. Simvastatin fenofibrat dapat dipertimbangkan sebagai terapi ajuvan pada penyandang DR dengan DME yang disertai dislipidemia. Pengontrolan glukosa yang baik merupakan manajemen utama pada DR.
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Diabetic retinopathy (DR) is a microvascular complication of diabetes mellitus (DM) due to structural and biochemical changes. Previous studies showed that oral fenofibrate prevents DR progression through lipid-regulating and nonlipid-related mechanisms, including preventing endothelial dysfunction, reducing inflammation and angiogenesis. This study aims to investigate the effects of oral fenofibrate on central macular thickness CMT and macular volume, and on specific biomarkers of endothelial dysfunction eNOS, inflammation VCAM-1 , and angiogenesis VEGF in DR individuals with dyslipidemia.
This is a prospective, double-blind randomized clinical trial, with subjects divided into intervention group simvastatin fenofibrate and control group simvastatin placebo. This study was conducted from November 2016 to October 2017 at the Vitreo-retina Clinic, Department of Ophthalmology ndash; RSCM Kirana, involving 60 eyes from 30 non-proliferative DR patients NPDR with dyslipidemia that met inclusion criteria. Each subject was observed for three months, with monthly clinical evaluation, fundus photo, and macular spectral domain optical coherence tomography SD-OCT . Serum eNOS, VCAM-1, and VEGF biomarkers, as well as HbA1c and lipid profile, were examined before and after intervention.Before intervention, there were no differences in demographic and clinical characteristics, and serum biomarker levels between two groups. After three months of treatment, there was no significant difference between CMT in the intervention group and the control group 248 40.4 ? m vs. 265.8 40.8 ? m , but a significantly lower CMT was observed in the intervention group at the first month. There was also a significantly lower CMT compared to the control group 294 39,2 vs 263 24,4, p=0,045 in eyes with diabetic macular edema DME . Macular volume after three-month treatment was 10086 886.4 ? m3 in the intervention group and 10307 1058.6 ? m3 in the control group, this difference was not significant. However, in all subjects with good blood glucose regulation HbA1c 7 , macular volume in the second month was significantly lower compared to subjects with HbA1c > 7 . Serum biologic marker levels after three-month treatment showed no significant difference between control and intervention group, respectively, in mean eNOS 3878.8 873.33 pg/mL vs 4031.2 742.56 pg/mL and median VEGF levels 242.8 86 - 1123.3 pg/mL vs 370 134.8 - 810.6 pg/mL . Nonetheless, the decrease in VCAM-1 level was significantly higher in the intervention group 50.7 pg/mL, 32.5 - 223.4 pg/mL vs. 40.4 pg/mL, 27.9 - 94.2 pg/mL . In subjects with tighter blood glucose control HbA1c 6.5 , serum VEGF level was 128.7 114.5 - 145.2 pg/mL, which was significantly lower compared to 423 86 - 1233.3 pg/mL in subjects with HbA1c > 6.5 .In conclusion, three-month treatment with simvastatin fenofibrate does not reduce CMT and macular volume in overall DR subjects with dyslipidemia, but it reduces CMT in subjects with DME. Simvastatin fenofibrate treatment in DR subjects does not prevent lowering of serum eNOS levels, elevation of VCAM-1 levels, and elevation of VEGF levels, but tight blood sugar control prevents elevation of serum VEGF. Although good glucose control remains the most essential in the management of DR, simvastatin fenofibrate may be considered as adjuvant therapy for DR with dyslipidemia and DME.