Respons Makrofag Terhadap LDL Teroksidasi Dari Pasien Diabetes Melitus Tipe 2: Kajian Ekspresi CD36, ABCA1, IL-1² dan IL-10 = Macrophage Response To Oxidized LDL From Type 2 Diabetes Mellitus Patients: A Review On CD36, ABCA1, IL-1² and IL-10 Expressions

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Abstrak

Diabetes melitus banyak dikaitkan dengan risiko tinggi aterosklerosis dan komplikasinya. Makrofag merupakan kunci dalam semua tahap aterosklerosis dan sudah diketahui berperan penting dalam patomekanisme penyakit metabolik dan kardiovaskuler. Makrofag menginternalisasi LDL teroksidasi melalui scavenger receptor seperti CD36. Makrofag juga mempunyai sistem transpor aktif seperti ABCA1 untuk eliminasi kolesterol dari makrofag ke akseptor ekstraseluler. Keterlibatan protein CD36 dan ABCA1 dalam mekanisme masuk dan keluarnya kolesterol pada makrofag diduga berhubungan dengan risiko pembentukan sel busa sehingga diperlukan penelitian pola ekspresi CD36 dan ABCA1 serta ekspresi sitokin pro-inflamasi IL-1b dan anti inflamasi IL-10 makrofag pada subyek non T2DM dan T2DM. Pengamatan dilakukan pada 11 subyek non T2DM dan 13 subyek T2DM. Disain penelitian menggunakan studi obervasional dan intervensi invitro. Monosit distimulasi menjadi makrofag menggunakan M-CSF. Tahap selanjutnya, makrofag dibagi dalam tiga perlakuan yaitu tanpa stimulasi, stimulasi LPS dan stimulasi ox-LDL. Ekspresi makrofag CD36 dan ABCA1 diukur secara flowcytometri menggunakan alat BD FACSCanto II Flow Cytometer sedangkan ekspresi IL-1b dan IL-10 makrofag diukur dengan multiplex immunoassay pada alat LuminexTM 200. Pada penelitian ini ditemukan adanya hubungan negatif rasio Trigliserida/HDL dengan ekspresi makrofag CD36-ABCA1+. Makrofag yang distimulasi ox-LDL menunjukkan perbedaan ekspresi CD36+ABCA1- pada subyek non T2DM dan T2DM yang tidak signifikan (p=0,12) sedangkan ekspresi CD36-ABCA1+ menunjukkan perbedaan yang signifikan (p=0,04). Subyek non T2DM menunjukkan ekspresi CD36-ABCA1+ dominan tinggi (72.7%) sedangkan pada subyek T2DM dominan ekspresi rendah (59.2%). Makrofag yang distimulasi LPS dan ox-LDL menunjukkan perbedaan rasio IL-1b/IL-10 pada subyek non T2DM dan T2DM (p=0.05; p=0.02). Subyek T2DM menunjukkan rasio IL-1b/IL-10 lebih tinggi dibandingkan non T2DM. Analisa hubungan rasio IL-1b/IL-10 dengan ekspresi makrofag CD36-ABCA1+ menunjukkan kecenderungan subyek dengan rasio IL-1b/IL-10 tinggi mempunyai ekspresi makrofag CD36-ABCA1+ rendah. Analisis juga menunjukkan 62% subyek T2DM menunjukkan eskpresi makrofag CD36- & ABCA1+ rendah disertai rasio IL-1b/IL-10 tinggi dan hsCRP diatas nilai median sedangkan subyek non T2DM 91% menunjukkan ekspresi CD36-ABCA1+ tinggi dengan rasio IL-1b/IL-10 rendah dan hsCRP rendah. Pada penelitian ini ditemukan adanya hubungan ekspresi makrofag CD36-ABCA1+ dan rasio IL-1b/IL-10 terhadap hs-CRP yang merupakan penanda risiko penyakit kardiovaskuler.

.....Diabetes mellitus is associated with a high risk of atherosclerosis and its complications. Macrophages are key in all stages of atherosclerosis and are known to play an important role in the pathomechanism of metabolic and cardiovascular disease. Macrophages internalize oxidized LDL via scavenger receptors such as CD36. Macrophages also have active transport systems such as ABCA1 for elimination of cholesterol

from macrophages to extracellular acceptors. The involvement of CD36 and ABCA1 proteins in the mechanism of entry and exit of cholesterol in macrophages is thought to be associated with the risk of foam cell formation, so it is necessary to study the expression patterns of CD36 and ABCA1 as well as the expression of the pro-inflammatory cytokine IL-1b and anti-inflammatory IL-10 in macrophages in non-T2DM subjects and T2DM. Observations were made on 11 non-T2DM subjects and 13 T2DM subjects. The research design used observational studies and in vitro interventions. Monocytes were stimulated to become macrophages using M-CSF. In the next stage, macrophages were divided into three treatments: no stimulation, LPS stimulation and ox-LDL stimulation. The expression of CD36 and ABCA1 macrophages was measured by flowcytometry using the BD FACSCanto II Flow Cytometer while the expression of IL-1b and IL-10 macrophages was measured by multiplex immunoassay on the LuminexTM 200. This study found a negative relationship between triglyceride/HDL ratio and expression of CD36-ABCA1+ macrophages. Ox-LDL stimulated macrophages showed insignificant differences in CD36+ABCA1- expression in non-T2DM and T2DM subjects (p=0.12) while CD36-ABCA1+ expression showed significant differences (p=0.04). Non-T2DM subjects showed high dominant CD36-ABCA1+ expression (72.7%) while T2DM subjects had low dominant expression (59.2%). The LPS and ox-LDL-stimulated macrophages showed different ratios of IL-1b/IL-10 in non-T2DM and T2DM subjects (p=0.05; p=0.02). T2DM subjects showed a higher IL-1b/IL-10 ratio than non-T2DM subjects. Analysis of the relationship between the IL-1b/IL-10 ratio and CD36-ABCA1+ macrophage expression showed a tendency for subjects with a high IL-1b/IL-10 ratio to have low CD36-ABCA1+ macrophage expression. The analysis also showed that 62% of T2DM subjects showed low expression of CD36- ABCA1+ macrophages with high IL-1b/IL-10 ratio and hsCRP above the median value, while 91% of non-T2DM subjects showed high CD36-ABCA1+ expression with IL-1b/IL-10 low and low hsCRP. In this study, it was found that there was a relationship between the expression of CD36-ABCA1+ macrophages and the ratio of IL-1b/IL-10 to hs-CRP which is a marker of cardiovascular disease risk.