

Konsentrasi Hypoxia-Inducible Factor 1-Alpha, Ekspresi Vascular Endothelial Growth Factor, dan Kepadatan Vaskularisasi Jaringan di Kaki Luka Diabetik yang Menjalani Amputasi dan Non-Amputasi = Hypoxia-Inducible Factor 1-Alpha Concentration, Vascular Endothelial Growth Factor Expression, and Tissue Vascularization Density of Amputated and Non-amputated Diabetic Foot Ulcer

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Abstrak

Luka diabetes merupakan komplikasi mikrovaskular yang sering dikeluhkan oleh pasien diabetes melitus (DM) tipe 2. Vaskularisasi berperan penting dalam penyembuhan luka, yang aktivitasnya diperantarai aktivitas hypoxia-inducible factor 1-alpha (HIF-1) dan vascular endothelial growth factor (VEGF). Belum ada studi klinis yang mengevaluasi aktivitas HIF-1 dan VEGF pada manusia, khususnya pasien DM tipe 2 yang mengalami luka kaki diabetes. Tujuan penelitian adalah untuk mengevaluasi vaskularisasi jaringan, HIF-1, dan VEGF pada luka kaki diabetes yang menjalani amputasi dan non-amputasi.

Studi potong lintang dilakukan di Rumah Sakit Umum Pusat Nasional dr. Cipto Mangunkusumo (RSCM) pada tahun 2020–2021. Subjek penelitian adalah pasien luka kaki diabetik yang dilakukan debridemen/amputasi. Kemudian diambil jaringan viabel tepi luka untuk diperiksa vaskularisasi jaringan (densitas mikrovaskular), ekspresi VEGF, serta area granulasi, di Departemen Patologi Anatomi FKUI-RSCM. Konsentrasi HIF-1 jaringan dikuantifikasi di Departemen Biokimia dan Biologi Molekuler FKUI-RSCM. Data numerik yang diperoleh diuji normalitasnya dengan uji Saphiro-Wilk. Data distribusi normal dianalisis dengan uji t tidak berpasangan. Dilakukan uji regresi logistik bila terdapat > 2 variabel independen dengan nilai $p < 0,25$.

Dari 67 subjek terdapat 30 pasien amputasi dan 34 pasien debridemen yang dianalisis. Proporsi subjek laki-laki pada kelompok amputasi lebih tinggi dibandingkan kelompok debridemen ($p = 0,041$). Tidak terdapat perbedaan bermakna pada status gizi, usia, kejadian hipertensi, gagal ginjal, dan status merokok antar kedua kelompok. Profil glikemik, hematologi rutin, penanda inflamasi, kadar elektrolit, penanda fungsi hati, fungsi ginjal tidak berhubungan dengan tindakan pasien, kecuali kadar albumin. Pada analisis bivariat, kadar albumin lebih tinggi pada kelompok debridemen 2,53/0,49 dibandingkan amputasi 2,94/0,51, $p = 0,002$. Kelompok amputasi memiliki nilai median HIF-1 5,77 (0,55–53,47) pg/mg protein yang jauh lebih rendah dibandingkan kelompok debridemen 26,56 (2,23–211,12) pg/mg protein ($p = 0,001$). Hal serupa juga ditemukan pada nilai VEGF ($p < 0,001$). Pasien dengan HIF-1 $< 8,8065$ pg/mg protein, MVD $< 68,7\%$, VEGF $< 30,443\%$, dan area granulasi $< 33,2802\%$ memiliki aOR 11,116 (IK 95% 1,441–85,752), 10,934 (IK 95% 1,604–74,55), 7,973 (IK 95% 1,301–48,86), 15,589 (IK 95% 1,39–174,867) untuk mengalami amputasi. Kepadatan mikrovaskular, konsentrasi HIF-1, ekspresi VEGF, dan area jaringan granulasi lebih banyak pada pasien non-amputasi. Pasien dengan penurunan jumlah parameter tersebut memiliki risiko lebih tinggi untuk mendapat tindakan amputasi.

.....Diabetic wounds are microvascular complications often complained by people with type 2 diabetes mellitus (DM). Tissue vascularization plays an essential role in wound healing, whose activity is mediated by the activity of hypoxia-inducible factor 1-alpha (HIF-1) and vascular endothelial growth factor (VEGF).

However, no clinical studies evaluate its activity in humans, especially in type 2 diabetes mellitus patients who have diabetic foot ulcers. This study attempts to evaluate whether there are differences in tissue vascularization, HIF-1, and VEGF in diabetic foot wounds that received amputation and non-amputation procedures.

A cross-sectional study was conducted at the Cipto Mangunkusumo National Central General Hospital (RSCM) in 2020–2021. Diabetic foot wound patients who received debridement/amputation were included in this study. Viable tissue at the wound edges was taken. The expression of VEGF, microvascular density, and area of granulated tissue were evaluated in the Department of Pathology and Anatomy, FKUI-RSCM. HIF-1 levels in tissue were quantified at the Department of Biochemistry and Molecular Biology FKUI-RSCM. All numerical data were tested for normality by the Shapiro-Wilk test. Variables with normally distributed data were analyzed by unpaired t-test. A logistic regression test was performed if there were more than two independent variables with a p-value < 0.25.

This study included 67 patients. There were 30 amputees, and 34 debridement patients included in the data analysis. The proportion of male patients in the amputation group was found to be higher than the debridement group ($p = 0.041$). There were no differences in nutritional status, age, the incidence of hypertension, kidney failure, and smoking status between the two groups. The glycemic profile, routine haematological findings, markers of inflammation, electrolyte levels, markers of liver function, and markers of kidney function were not found to be related to the patient's condition, except for albumin levels. In bivariate analysis, albumin levels were found to be higher in the debridement group [2.53 (0.49)] than in the amputee [2.94 (0.51)], $p = 0.002$. The amputee group had a median HIF-1 value of 5,77 (0,55–53,47) pg/mg protein, which was much lower than the debridement group of 26,56 (2,23–211,12) pg/mg protein ($p = 0.001$). Similar condition was also found in the VEGF value ($p < 0.001$). Patients with HIF-1 < 8.8065 pg/mg protein, MVD < 68.7%, VEGF < 30.443%, and granulation area < 33.2802% had risk odds of 11.116 (95% CI 1.441–85.752), 10.934 (95% CI 1.604–74.55), 7,973 (95% CI 1.301–48.86), 15.589 (95% CI 1.39–174.867) for amputation. Microvascular density, HIF-1 levels, VEGF expression, and granulation tissue area were higher in non-amputated patients. Patients with a decrease in these parameters have a higher risk of amputation.