Analisis Reseptor Estrogen pada Pasien Endometriosis ditinjau dari Aspek Variasi Genotip, Tingkat Ekspresi mRNA dan Fosforilasi Serin 105. = Analysis of Estrogen Receptor in Endometriosis Patients from the Aspect of Genetic Variation, mRNA Expression and Serin 105 Phosphorylation

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Abstrak

Endometriosis adalah kelainan ginekologis yang dimanifestasikan dengan adanya kelenjar dan sel endometrium yang berkembang di luar uterus. Endometriosis merupakan penyakit multifaktorial dimana faktor genetik dan lingkungan berinteraksi menyebabkan timbulnya penyakit ini. Beberapa penelitian telah melaporkan bahwa endometriosis merupakan penyakit yang terkait dengan hormon estrogen. Mekanisme kerja estrogen ditentukan oleh kuantitas dan aktivitas reseptor estrogen. Namun demikian analisa variasi genetik, ekspresi dan aktivitas estrogen reseptor sampai saat ini belum banyak diketahui. Tujuan Penelitian ini adalah untuk menganalisa variasi genetik, ekspresi mRNA dan aktivasi ER pada jaringan endometriosis. Alel gen reseptor estrogen RE dan RE dari 83 sampel penderita endometriosis dibandingkan dengan 76 kontrol menggunakan metoda PCR RFLP. Pengukuran ekspresi mRNA dari 18 jaringan penderita endometriosis dan 18 kontrol dilakukan dengan menggunakan metoda kuantitatif Real Time PCR (qRT-PCR). Pengukuran kadar estrogen serum (E2) dilakukan dengan metoda ELISA. Deteksi aktivasi ER dilakukan dengan uji fosforilasi reseptor estrogen (serin 105) dengan metoda Western Blot. Hasil uji Chi-square ditemukan bahwa frekuensi alel A (normal) dan alel G (mutan) pada gen RE SNP rs9340799 dalam populasi berbeda bermakna (p=0,012) dan OR 1,772 dan kedua frekuensi alel dari hasil uji keseimbangan menurut Hardy-Weinberg berbeda bermakna (p = 0,003). Frekuensi alel (normal dan mutan) dalam populasi RE SNP rs2234693 tidak menunjukkan perbedaan bermakna dan seimbang dalam populasi. Frekuensi genotip pada SNP RE rs4986938 pada endometriosis dibandingkan kontrol berbeda bermakna (p=0,015) dan OR 0,311 dengan populasi seimbang. Menurut keseimbangan Hardy-Weinberg dan frekuensi alel normal G dan alel mutan A juga berbeda bermakna (p=0,034) dan OR =0,438. Hasil pengukuran ekspresi mRNA menunjukkan terjadi peningkatan ekspresi ER 49,52 kali disbanding kontrol sedangkan RE tidak menunjukkan perbedaan dibandingkan kontrol. Kadar estradiol serum (E2) fase proliferasi tidak menunjukkan perbedaan bermakna dibanding kontrol. Hasil uji Spearman menunjukkan tidak ada korelasi kadar estradiol dengan ekspresi RE dan RE (p>0,05). Fosforilasi ER pada Serin 105 menunjukkan penurunan pada kelompok endometriosis dibandingkan jaringan normal dengan perbandingan nilai intensitas pita yakni 0,1 pada endometriosis dan 4,2 pada kontrol. Sebagai kesimpulan, frekuensi alel A dan G gen RE berbeda bermakna pada SNP rs9340799 dan frekuensi alel di dalam populasi tidak seimbang. Distribusi genotip normal GG dan mutan AA serta frekuensi alel G dan alel A gen RE berbeda bermakna pada SNP rs4986938. Ekspresi (mRNA) RE lebih tinggi secara signifikans pada kelompok endometriosis dibandingkan kontrol. Ekspresi protein Fosforilasi ER pada Serin 105 menunjukkan penurunan pada endometriosis dibandingkan jaringan normal.

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environmental factors interacting to cause this disease. Several studies have reported that endometriosis is a disease associated with the hormone estrogen. The mechanism of action of estrogen depends on the quantity and activity of estrogen receptors. However, genetic variation, expression and estrogen receptor activation in endometriois patients have not been fully characterized. The aim of this study was to analyze genetic variation, ER expression and determine ER activation in endometriosis patients. This study determined the alleles of the estrogen receptor gene RE and RE from 83 blood samples from endometriosis patients compared with 76 controls using the RFLP PCR method. Quatitative Real time PCR was used to analyze mRNA expression of RE genes from 18 tissues with endometriosis and 18 controls. Measurement of serum estrogen (E2) levels was carried out using the ELISA method. Furthermore, the phosphorylation test of estrogen receptor (serin 105) was carried out using the Western Immunobloting method. The results of the Chi-square test found that the frequencies of the A (normal) allele and G (mutant) allele in the RE SNP gene rs9340799 in the population were significantly different ($p=0.012$) and OR 1.772 and the two allele frequencies from the results of the balance test according to Hardy-Weinberg were significantly different. ($p = 0.003$). Allele frequencies (normal and mutant) in the RE SNP population of rs2234693 did not show significant and balanced differences in the population. The genotype frequency of SNP RE rs4986938 in endometriosis compared to control was significantly different ($p=0.015$) and OR 0.311 with a balanced population. According to the Hardy-Weinberg balance, the frequencies of the normal G allele and the mutant A allele were also significantly different ($p=0.034$) and OR=0.438. Er expression showed 49,52 folds increase compared to control ($p=0.00$), whereas ER did not show a significat different compared to control. There was no different in serum estradiol (E2) levels compared to controls. The results of the Spearman test showed that there was no correlation between serum estradiol levels and the expression of RE and RE ($p>0.05$). Phosphorylation Ser105 of ER showed a decrease in the endometriosis group compared to control with a comparison of values of 0.1 and 4 2. As a conclusion, The A and G allele frequencies of the RE gen gene were significantly different in SNP rs9340799 and the allele frequencies in the population were not balanced. The distribution of normal genotypes of GG and AA mutants and the frequency of G allele and A allele of RE gene were significantly different at SNP rs4986938. RE (mRNA) expression was significantly higher in the endometriosis group than the control group. Phosphorylated ER protein expression in Serin 105 showed a decrease in endometriosis compared to normal tissue.