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Original Article

Lack of Association of *CYP2E1* and *CYP1A1* Polymorphisms with Osteoporosis in Postmenauposal Women

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Osteoporosis is a metabolic bone disease affecting mostly elderly women. As metabolizing enzymes, the roles of few cytochromes have been studied in osteoporosis development. The aim of this study was to assess for the first time the association of *CYP2E1* and *CYP1A1* polymorphisms and osteoporosis in postmenopausal women. 112 postmenopausal women presenting osteoporosis and 93 age and sex matched healthy controls originating from north Iran were enrolled in this study. Rs2031920 and rs3813867 at *CYP2E1* as well as rs4646421 and rs2198843 at *CYP1A1* loci were studied in all subjects using polymerase chain reaction and restriction fragment length polymorphism analysis. Genotype analysis for rs2031920 showed that the CT genotype was present only in osteoporotic patients with a frequency of 4.17%. Similarly GC genotype at rs3813867 locus was present only in osteoporotic patients with a frequency of 3.13%. [G; T] and [C; C] haplotypes for rs3813867- rs2031920 were found with low frequencies only in osteoporotic patients. TT genotype at rs4646421 locus was higher in osteoporotic (8.05%) versus control subjects (3.22%), 14.28% of cases were homozygous for the C allele at rs2198843 locus which is higher than controls (11.84%). The [C; G] haplotype for rs4646421- rs2198843 was predominant in cases (54.47%) and controls (58.6%). GT haplotype was rare in both groups. No significant differences in genotypes or haplotypes frequencies were observed among the osteoporotic and normal subjects. *CYP1A1* and *CYP2E1* loci are not associated to osteoporosis risk in the studied population.

Keywords: Osteoporosis; *CYP1A1*; *CYP2E1*; polymorphism

Osteoporosis is a silent metabolic bone disease characterized by low bone mass and reduction in bone mineral density (BMD) leading to increased susceptibility to fractures (1, 2). Different factors such as environmental, genetic, gender, age, nutrition and hormones are associated with osteoporosis (3-6). Women are more affected than men and according to the World Health Organizati-

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on, 25% of women and 12% of men become affected during their lives (7). Based on, 13% to 18% of women over 50 years have osteoporosis due to minimal ovarian activity that leads to decrease levels of estrogen in postmenopausal women and risk factor for bone loss. Genetic factors including Vitamin D receptor, Estrogen receptor, calcium-sensing receptor and cytochrome P450 genes have been reported as important players in the pathogenesis of osteoporosis (6, 8-10). Estrogen have essential role in bone turnover and establishing balance between bone formation and resorption. Moreover, metabolic pathways related to estrogen are important determinants of bone mineral density (BMD) in postmenopausal women. (11-14).The cytochrome P450 enzymes are a group of heme-containing enzymes placed in the endoplasmic reticulum of hepatocytes. They are required for the removal of carcinogenic compounds from the body (15). They are also essential in the metabolism of many medications, production of numerous agents such as cholesterol, steroids, vitamin D3 and vitamin K as well as metabolism and biosynthesis of estrogen. There are more than 50 CYP450 enzymes but six of them (CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4) metabolize more than 85 percent of drugs and metabolites (16). Cyp1A1, Cyp19, Cyp17, CYP3A4, CYP1A2 and CYP1B1 have been demonstrated to have a role in osteoporosis development (9, 17, 18). Cytochrome P450 2E1 (CYP2E1), a member of the cytochrome P450 superfamily is important for the metabolic activation of many low-molecular-weight toxicants such as N-nitrosamines, aniline, vinyl chloride, urethane and alcohol that is expressed primarily in the liver (19). It has been reported that *CYP2E1* polymorphism is involved in several types of diseases including cancer, hepatitis and tuberculosis (20). Recently, it has been reported that RsaI/PstI polymorphism as well as sex hormones may influence human *CYP2E1* gene expression (21). Also, it has been reported that *CYP1A1* polymorphism may play an important role in estrogen metabolism (22-24). The aim of this study was to investigate for the first time the association between *CYP2E1* and *CYP1A1* polymorphisms with osteoporosis in a population of postmenopausal women originating from north Iran.

Materials & Methods

Subjects

This case-control study contained 112 postmenopausal women presenting osteoporosis and 93 age and sex matched healthy controls that were referred to Valiasr Hospital in Ghaemshar, Mazandaran, Iran. All subjects consented to participate to this study and demographic data were collected upon personal interview. Also, the study was approved by the scientific and ethics committees of north research center of Pasteur institute, Amol, Iran.

DNA extraction

Genomic DNA was extracted from whole blood using salting out method. Briefly, 5ml whole blood was digested with proteinase K followed by 6 M sodium acetate treatment. The DNA was collected after alcohol precipitation, and then dissolved in 10 mM Tris (pH 8.0) and 0.1 mM EDTA.

Analysis of *CYP2E1* gene polymorphisms

Two single-nucleotide polymorphisms of *CYP2E1* (rs3813867 and rs2031920) were studied by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. The cycling conditions consisted of an initial denaturation at 94 °C for 5 min followed by 35 cyc--les, each consisting of denaturation at 94 °C for 45 seconds, annealing at 59°C for 1 min, extension at 72 °C for 60 seconds and one final cycle of extension at 72°C for 7 min. The PCR products were

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Table 1. PCR and RFLP conditions for the CYP1A1 and CYP2E1 genotyping

Gene	SNP	Primer sequence	PCR product (bp)	Enzyme	RFLP product (bp)	Reference or source
CYP1A1	rs4646421	F: 5'-GCTCAATCTAGCTGG TCTCCA -3' R: 5'-GAGTCCTACCCACCA CACTTAG -3'	417	NspI	231, 138	This study
CYP1A1	rs2198843	F: 5'-GTCCCTCAGAGAACA AGGCAG -3' R: 5'- CTCCTCTCAGCTTC ACAGGCA -3'	404	PstI	299, 105	This study
CYP2E1	rs2031920 rs3813867	F: 5'-CCA GTC GAG TCT ACA TTG TCA-3' R: 5'-TTC ATT CTG TCT TCT AAC TGG-3'	413 413	RsaI PstI	354, 59 299, 114	(25)

digested overnight with either RsaI (rs2031920) or PstI (rs3813867) restriction enzymes at 37°C. The evaluation of the digestion patterns was achieved by electrophoresis on a 3% agarose gel followed by ethidium bromide staining. The expected sizes of the products after digestion with RasI were as follows: 413 bp for the T allele (no cutting), 354 bp and 59 bp for the C allele. The expected sizes after digestion with PstI are 299 bp and 114 bp for the C allele, while the G allele remains uncut with 413 bp size.

Analysis of *CYP1A1* gene polymorphisms

We developed specific PCR–restriction fragment length polymorphism tests for two single-nucleotide polymorphisms of *CYP1A1* (rs4646421 and rs2198843). PCRs for both SNPs were performed under following conditions, after initial denaturation at 95 °C for 5 minutes 35 cycles each consisting of denaturation at 94 °C for 45 seconds, annealing at 60 °C for 45 seconds, extension at 72 °C for 45 seconds and a final elongation step at 72 °C for 7 minutes were performed. The PCR products were digested overnight with either NspI (rs4646421) or PstI (rs2198843) restriction enzyme at 37°C and the presence of restriction sites was identified by agarose gel electrophoresis. The information about sequence of primer pairs, size of PCR products and digested products with restriction enzymes is listed in Table 1.

Statistical analyzes

The χ^2 test was used to evaluate differences in the distributions of genotypes and allele frequencies between cases and controls. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were used to describe the strength of associations. An adjusted two-tailed P value less than 0.05 at 95% CI was considered as statistically significant.

Results

Age and BMD analysis

In this study, we examined 112 postmenopausal cases with osteoporosis aged 59.35± 7.76 years and 93 normal subjects aged 57.37± 5.56 years. The BMD analyzes showed that BMD was significantly lower in osteoporosis patients (0.817± 0.074) than normal subjects (1.231± 0.104) (P< 0.0001).

CYP2E1 genotyping

The frequencies of C and T alleles for rs2031920 as well as genotype distribution among studied subjects are shown in Table 2. The C allele was present in all normal subjects while its frequency was 0.982 among osteoporotic subjects. The wild type homozygous genotype (CC) was the most frequent in osteoporotic subjects (96.42%) as well as in normal subjects (100%). None of the analyzed subjects showed TT genotype. RsaI polymorphism genotype distributions were in Hardy-Weinberg equilibrium (P= 0.847). Figure 1A

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Table 2. Distribution of *CYP2E1* and *CYP1A1* genotype and allele frequencies in osteoporotic cases compared to controls for rs2031920, rs3813867, rs4646421 and rs2198843

			wild type homozygous	Heterozygous	Mutant homozygous	OR (95% CI)
rs2031920 polymorphism	**C allele**	**T allele**	**CC**	**CT**	**TT**	
Osteoporosis (n=112)	0.982	0.018	108(96.42)	4(3.58)	0	1.00
Normal (n=93)	1	0	93(100)	0	0	7.75(0.41-145)
rs3813867 polymorphism	**G allele**	**C allele**	**GG**	**GC**	**CC**	
Osteoporosis (n=112)	0.986	0.014	109(97.32)	3(2.68)	0	1.00
Normal (n=93)	1	0	93(100)	0	0	5.9772 (0.30-117)
rs4646421 polymorphism	**C allele**	**T allele**	**CC**	**CT**	**TT**	**1.00**
Osteoporosis (n=112)	0.767	0.233	69(61.6%)	34(30.35 %)	9(8.05%)	1.1498(0.62-2.11)
Normal (n=93)	0.822	0.178	63(67.6%)	27(29.09%)	3(3.22%)	2.7391(0.70-10.57)
rs2198843 polymorphism	**G allele**	**C allele**	**GG**	**GC**	**CC**	**1.00**
Osteoporosis (n=112)	0.674	0.326	55(49.10 %)	41(36.62%)	16(14.28 %)	1.1069(0.60-2.01)
Normal (n=93)	0.704	0.296	49(52.68 %)	33(35.48 %)	11(11.84%)	1.2959(0.54-3.05)

represents the electrophoresis pattern after digestion of PCR products with RsaI.

The distributions of the genotypes and frequencies of C and G alleles for rs3813867 of the studied subjects are summarized in Table 2. The allele frequency for the G allele among osteoporotic population was 0.986, while all control subjects had the G allele. The wild type homozygous genotype (GG) was the most frequent in both groups. None of the analyzed subjects showed CC genotype. PstI polymorphism genotype distributions were in Hardy-Weinberg equilibrium (P= 0.885). Figure 1A is a representative of PstI genotyping analysis on PCR products of *CYP2E1* gene.

CYP1A1 genotyping

The frequencies of the C and T alleles and genotype distribution of rs4646421 are summarized in Table 2. The C and T allele frequencies were found to be 0.822 and 0.178 among the control subjects, and 0.767 and 0.233 among osteoporotic subjects, respectively. The distribution of CC and CT genotypes in osteoporotic cases were 61.6% and 30.35%, respectively compared to 67.6% and29.09% in healthy controls. TT genotype was higher in osteoporotic subjects (8.05%) versus control subjects (3.22%), but the difference was not significant. Observed genotypes were in Hardy-Weinberg equilibrium (P= 0.1401). Figure 1B sho

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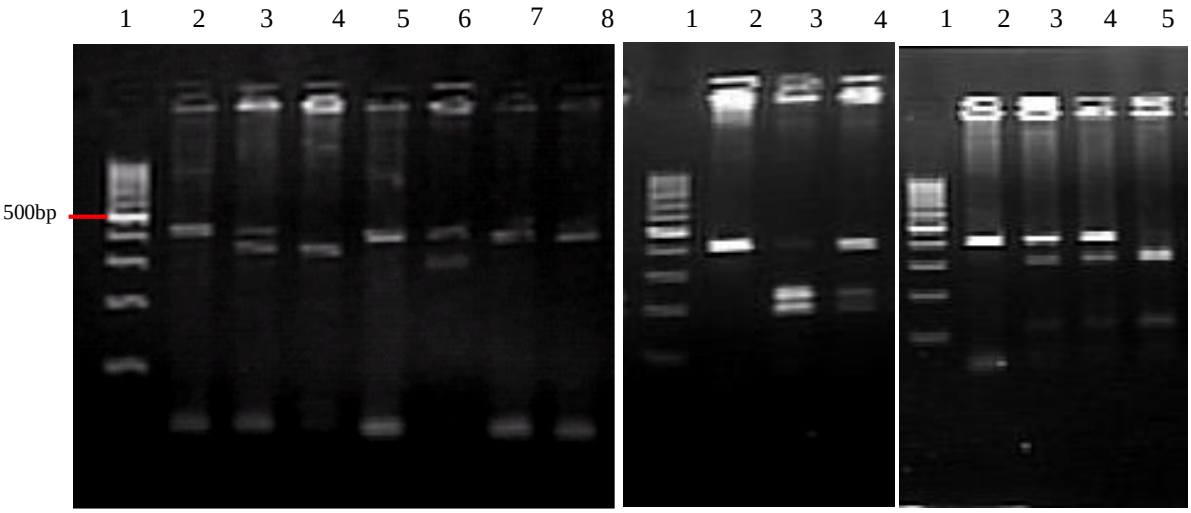

Figure 1. Representative electrophoresis patterns for *CYP3E1* and *CYP1A1* genotyping. A, RFLPs of the PCR products of *CYP2E1* gene digested with Rsa I and Pst I. Lane 1: Molecular Weight Marker (100 bp ladder); lanes 2 and 8: undigested; lanes 3 and 6 heterozygous; lanes 4 and 7: homozygous wild-type; lane 5: mutant homozygous. **B**, RFLPs of the PCR products of *CPY 1A1* rs4646421 digested with NspI. Lane 1: Molecular Weight Marker (100 bp ladder); lane 2: mutant homozygous; lane3: homozygous wild-type; lane 4: heterozygous. **C**, RFLPs of the PCR products of *CPY 1A1* rs2198843 digested with PstI. Lane 1: Molecular Weight Marker (100 bp ladder); lane 2: mutant homozygous; lanes 3 and 4: homozygous wild-type; lane 5: heterozygous.

-ws the electrophoresis pattern after digestion of PCR products with NspI.

The frequencies of the C and G alleles as well as genotype distribution in controls and patients for rs2198843 are shown in Table 2. Allelic frequencies for G and C allele were 0.674 and 0.326 among osteoporotic subjects versus 0.704 and 0.296 in control subjects, respectively. The distribution of GG and GC genotypes in osteoporotic cases was 49.1% and 36.62% compared to 52.68% and 35.48% in healthy controls, respectively. As shown in Table 1, 14.28% of osteoporotic cases were homozygous for the C allele which is higher than controls (11.84%) but the difference is not significant**.** Genotype distributions of rs2198843 was in Hardy-Weinberg equilibrium (P= 0.1401)**.** The electrophoresis pattern after digestion of PCR products with stI is shown in figure 1C.

Haplotypes analyzes

Haplotype data for rs2031920 and rs3813867 at *CYP2E1* locus are provided in Table 3. Our study revealed that the osteoporotic population has three haplotypes, while healthy controls have only one haplotype. But no significant difference in distribution of the common haplotype was observed in patients with osteoporosis and healthy controls. The predominant haplotype in this study was [G; C] Table 3.

Haplotype data for rs4646421 and rs2198843 at *CYP 1A1* locus are shown in Table 4. Four haplotypes were identified in osteoporotic as well as normal subjects. The haplotype [C; G] was predominant in osteoporotic (54.47%) and control subjects (58.6%). In this study, [G; T] haplotype was rare in both osteoporotic and normal subjects.

Table 3 Associations between [rs3813867; rs2031920] haplotypes of *CYP2E1* and osteoporosis

	Osteoporosis n (%)*	Normal n (%)	OR (95% CI)	P value
[G; C]	218 (97.32)	186 (100)	1.00 (reference)	
[G; T]	1(0.446)	0	2.5606(0.10-63.23)	0.56
[C; C]	1(0.446)	0	2.5606(0.10-63.23)	0.56`

*For 1.8% of the analyzed subjects haplotype assignment was not possible due to heterozygocity in both loci.

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Table 4. Associations between [rs3813867; rs2031920] haplotypes of *CYP1A1* and osteoporosis

	Osteoporosis no. (%)*	Normal no. (%)*	OR (95% CI)	P value
[C; G]	122(54.47%)	109(58.6%)	1.00	
[C; C]	26(11.6%)	24(12.9%)	1.0332(0.56-1.90)	0.91
[T; G]	5(2.24%)	3(1.62%)	1.4891(0.34-6.37)	0.59
[T; C]	23(10.27%)	10(5.38%)	2.0549(0.93-4.51)	0.07

*For 21.42 % of the analyzed osteoporotic subjects and 21.5% of normal subjects haplotype assignment was not possible due to heterozygo-city in both loci.

Discussion

Many genetic factors were reported as having a significant effect on bone remodeling and bone mass. Therefore, polymorphism in genes controlling drugs and metabolism such as *CYP450* may act as strong candidate loci for increased risk of genetically influenced disorders such as osteoporosis. Several studies show that the genetic polymorphisms in *CYP450* are associated with osteoporosis in postmenopausal women (9, 17, 18, 26, 27). However, there is no information about the impact of *CYP2E1* (RsaI/ PstI) genetic polymorphi-sms on osteoporosis susceptibility. This is the first study evaluating the *CYP2E1* polymorphisms in osteoporotic subjects. In this study, rs2031920 and rs3813867 were studied in 93 healthy subjects and 112 patients with osteoporosis. Genotype analysis for rs2031920 showed that the CT genotype was present only in osteoporotic patients with a frequency of 3.58%. Genotype analysis for rs3813867 showed that the GC genotype was present only in osteoporosis patients with a frequency of 2.68%. There were no significant differences in genotype frequencies among the osteoporotic and normal subjects although the risk for the heterozygous genotype was seven-fold greater than the homozygous wild type CC genotype for rs2031920 (OR= 7.75) in osteoporotic cases. Similarly, the risk for the heterozygous genotype was five-fold greater than the homozygous wild type GG genotype for rs3813867 (OR= 5.9772) in osteoporotic cases. Haplotypes distribution at *CYP2E1* locus was not significantly different between the osteoporotic subjects and control s (P= 0.5), but the risk for the [G; T] and [C; C] haplotype subjects to have osteoporosis is three-fold greater than it is for the [G; C] haplotype (OR= 2.56). Our findings on alleles and genotype frequencies are similar to another study in Iran which analyzed two hundred healthy individuals from the southwest population (28). The comparison of genotype distribution between Iranian and other populations shows that its distribution is similar to Indian, Turkish and some European populations such as German, British and French (21, 29-32) but is different from other Asians, including Japanese and Chinese and also from Italians (33-35). Based on WHO criteria, 11.9% of Native American women, 10% of Asians, 9.8% of Hispanics, 7.2% of Whites, and 4.2% of Blacks were osteoporotic (36). These distribution differences among ethnicities strongly support the genetic contribution to disease occurrence. Cyp17 and CYP 19 enzymes are involved in estrogen biosynthesis while CYP3A4, CYP1A2, CYP1B1 and CYP1A1 contribute to its metabolism (37). Polymorphism in the cytochrome P450 enzymes related to estrogen biosynthesis and metabolism may lead to increased risk of hormone-dependent disorders such as breast cancer (23, 24, 38-41) and osteoporosis (9, 17, 18, 26). It has been reported that *CYP1A1* polymorphism may play an

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important role in estrogen metabolism (9, 22, 24, 42). Genotype analysis for rs4646421 showed that the frequency of TT genotype was higher in patients with osteoporosis than in controls. Although no significant associations were observed between osteoporotic and normal subjects, but osteoporosis risk was three times greater in individuals with TT genotype than individuals with CC and CT genotypes. Genotype analysis for rs2198843 showed that the distribution of genotypes was approximately similar in both groups. There were no significant differences in genotype frequencies among the osteoporotic subjects and normal ones. Haplotypes were neither significantly different between them (P= 0.07), but the risk for the mutant [T; C] haplotype subjects to have osteoporosis was two times greater than it was for the wild haplotype [C; G] (OR= 2.05). In this study, we found [G; T] and [C; C] haplotypes for *CYP2E1* [rs3813867; rs2031920] and [C; T] haplotypes for *CYP1A1* [rs4646421; rs2198843] with low frequencies in osteoporotic patients. However, as osteoporosis is a complex disease and many genetic factors may contribute in the development of this disorder, a single polymorphism may not show a significant association with the disease unless it is strongly associated. Thus, other polymorphisms in candidate genes should be studied in order to find a polymorphism panel for osteoporosis risk evaluation. Correspondingly, it was also recommended to study a larger sample size, as minor alleles with strong impact on disease development may have more chances to be identified. Moreover, other population studies should be performed to replicate our findings.

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Conflict of interest

The authors declared no conflict of interests.

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