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Araştırma Makalesi

Türkiye'deki Postmenopozal Kadınlarda Osteoprotegerin A163G ve T245G gen Polimorfizmleri ile Kemik Mineral Yoğunluğu Arasındaki İlişkinin Analizi

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Ö Z E T

Amaç: Osteoprotegerin (OPG), osteoporoza yatkınlık ile ilgili en önemli aday genlerden biridir. Bu çalışmanın amacı postmenopozal kadınlarda OPG promoter bölgesindeki A163G ve T245G polimorfizmleri ile kemik mineral yoğunluğu (KMY) arasındaki ilişkinin değerlendirilmesidir.

Gereç ve Yöntemler: Çalışmaya primer postmenopozal osteoporozlu 109 gönüllü hasta ve kontrol grubu olarak 85 sağlıklı kadın olacak şekilde toplam 194 kişi dahil edilmiştir. L1, L4, total lomber vertebra (L1-4), boyun, kalça ve total kalça KMY değerleri dual enerji X-ışını absorbsiyometrisi (DEXA) yöntemiyle değerlendirilmiştir. OPG promoter bölgesindeki A163G ve T245G polimorfizmleri polimeraz zincir reaksiyonu (PCR) ve restriksiyon parça uzunluğu polimorfizmi (RFLP) kullanılarak belirlenmiştir.

Bulgular: Postmenopozal kadınlarda genotip frekansları A163G polimorfizmi için AG+GG (%46,8), AA (%53,2); T245G için GG+TG (%36,7), TT (%63,3) olarak kaydedilmiştir. Sağlıklı kadınlara kıyasla, osteoporozlu kadınlar arasında AG+GG (p=0,005) ve GG+TG (p=0,049) genotipleri belirgin şekilde daha yaygın bulunmuştur. Postmenopozal kadınlarda ve kontrollerde sırasıyla T245G ve A163G polimorfizmleri için genotipler ile lomber vertebra KMY değerleri arasında önemli bir ilişki olduğu saptanmıştır (tümü için $p<0.05$). T245G polimorfizmi için GG+TG genotipleri TT genotipine kıyasla daha düşük KMY ile ilişkili bulunmuştur. Benzer şekilde, A163G polimorfizmi için de AG+GG genotipleri AA genotipine kıyasla daha düşük KMY ile ilişkilendirilmiştir.

Sonuç: Bu çalışmada elde edilen bulgular, OPG promoter bölgesindeki T245G ve A163G polimorfizmlerinin KMY'nin genetik düzenlenmesine katkıda bulunabileceğini düşündürmektedir. Bu bulgular, gelecekte yapılacak osteoporoz çalışmalarında OPG geninin rolü araştırılırken yararlı olacaktır.

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Research Article

Association Analysis Between A163G and T245G Gene Polymorphisms of Osteoprotegerin and Bone Mineral Density in Turkish Postmenopausal Women

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ABSTRACT

Aim: Osteoprotegerin (OPG) is one of the most important candidate genes associated with osteoporosis predisposition. The aim of the present study was to evaluate the relationship between bone mineral density (BMD) and two polymorphisms in the OPG promoter, namely A163G and T245G among postmenopausal women.

Material and Methods: A total of 109 women with postmenopausal osteoporosis and 85 healthy controls were included in the study. BMD of L1, L4, total lumbar spine (L1-4), neck, hip and total hip were evaluated by means of dual-energy X-ray absorptiometry. A163G and T245G polymorphisms were determined by PCR and RFLP.

Results: The frequencies of genotypes were as follows: AG+GG (46.8%), AA (53.2%) for A163G and GG+TG (36.7%), TT (63.3%) for T245G. Compared to healthy women, remarkably more women with osteoporosis were found to have AG+GG (p=0.005) and GG+TG (p=0.049). Significant associations were observed between the genotypes and BMD of lumbar spine for the T245G and A163G polymorphisms in postmenopausal women and controls ($p<0.05$ for all). The GG+TG genotypes correlated with lower BMD compared to TT for T245G. Similarly, for A163G, the AG+GG genotypes were associated with lower BMD compared to AA.

Conclusion: Our results suggest that T245G and A163G polymorphisms in the OPG promoter may contribute to the genetic regulation of BMD. These results are expected to be beneficial for further studies investigating the role of OPG in osteoporosis.

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Introduction

Osteoporosis is a complicated disorder in which environmental factors such as exercise, dieting and smoking are involved as well as genetic factors (1-4). Genetic factors have been found to be responsible for 40-75% of the interindividual variation among osteoporotic cases (5, 6). To date, different candidate genes have been analyzed to identify those associated with low BMD and the etiology of osteoporosis. These include genes such as osteoprotegerin (OPG), estrogen receptor alpha, vitamin D receptor, transforming growth factor b1, and collagen type 1a1. Among the genes in question, OPG is one of the most significant candidate genes for osteoporosis and BMD (7, 8). OPG, a key regulator of bone remodeling, is considered as a new member of the tumor necrosis factor (TNF) receptor superfamily discovered in 1997 (3, 9). The OPG gene is located on chromosome 8 and represents a single-copy gene which consists of 5 exons spanning 29 kb of the human genome (10). OPG is synthesized by cardiac myocytes, osteoblasts, cells found in the kidneys, lungs, arterial and venous walls, intestines, endothelium, hemopoietic cells and cells of the immune system. OPG protects the bones from excessive resorption by blocking the terminal stages of osteoclastogenesis, by inhibiting the activation of mature osteoclasts and also by stimulating apoptosis in these cells (11). Growing evidence suggest that OPG is among the most important candidate genes associated with the pathogenesis of osteoporosis (5, 12). To date, several single nucleotide polymorphisms (SNPs) in OPG have been identified, including A163G, T245G, T950C and G1181C, which have been evaluated in terms of their relationship with osteoporosis and BMD (5, 7, 8, 13-15). Several genes among these have been assumed to influence BMD determination; however, the magnitude of impact and the exact role of these genes remain unclear.

The aim of our study was to investigate nucleotide substitutions and the A163G and T245G polymorphisms of OPG in a group of postmenopausal women and to also analyze the possible contribution of these polymorphisms to osteoporosis by assessing their association with BMD.

Material and Methods

In this study, 109 women (mean age, 57.8±6.6 years) with primary postmenopausal osteoporosis and 85 healthy age-matched women (mean age, 56.1±6.7 years) were referred to the outpatient clinic of Physical Therapy and Rehabilitation Department. Individuals who had a history of hip fracture or recent lower back pain complaint with acute onset were excluded from the study. All subjects included in the study underwent clinical examination and routine biochemical tests were performed to exclude any disease (primary hyperparathyroidism, hyperthyroidism, cirrhosis, kidney failure, Cushing syndrome) or drugs (antiepileptics, glucocorticoids) known to affect bone metabolism. None of the subjects had received previous antiresorptive treatment (calcitonin or bisphosphonates) and none had been treated with hormone replacement therapy. Height and weight were measured for each subject, and body mass index (BMI) was calculated (weight divided by squared height; expressed in kg/m2).

Measurement of bone mineral density

BMD at the lumbar spine (L1, L4, L1-4) and femoral neck were assessed by means of dual-energy X-ray absorptiometry (DEXA) on a Hologic, Inc. 1000 device (Hologic Europe, Zaventum, Belgium). Bone mineral content (g) and bone area (cm2) were used to calculate BMD, which was expressed in g/cm2. BMD was also evaluated as the T-score, which represents the number of standard deviations from the mean BMD value calculated based on a control population in the age groups of 20 to 40 years. A T-score lower than –2.5 was considered as the diagnostic threshold for osteoporosis.

The study was approved by the local ethics committee, and all of the subjects who participated in the study completed written informed consent forms.

DNA analysis

DNA was isolated from patient and control peripheral blood samples by high-pure PCR template preparation kit (Roche, USA). The purity and amount of DNA was determined according to absorbance values at 260 nm and 280 nm in

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spectrophotometer. DNAs were examined under Ultraviolet light (UV) after operating in 0.8% agarose gel electrophoresis and staining with ethidium bromide (EtBr). The A163G and T245G gene polymorphisms of the OPG gene were identified by means of the polymerase chain reaction (PCR) technique and restriction fragment length polymorphism (RFLP) assay (16, 17). Primers with the sequences reported by Jorgenson al. and Langdahl et al. (5, 9) were used for A163T and T245G gene polymorphisms, respectively. PCR conditions were 94ºC for 5 minutes, 35 cycles; 94ºC for 1 minute, 55ºC for 1 minute, and 72ºC for 1 minute, and finally 72ºC for 7 minutes.

To detect the nucleotide substitution A163G, 5 µL of the PCR products were digested with 0.5 mL of the Fast-Digest restriction enzyme MfeI; an enzyme that cuts DNA at specific recognition nucleotide sequences (5' C↓AATTG 3'), in 1X Fast Digest green buffer for 1 hour at 37°C. (Fermentas Life Sciences USA). This digestion yields the following fragments with the indicated size (in bp): AA, 253; AG, 253, 232, 21; GG, 232, 21 (9).

To detect the nucleotide substitution T245G, 5 µL of the PCR products were digested with 0.5 mL of the Fast-Digest restriction enzyme HifI; an enzyme which cuts DNA at specific recognition nucleotide sequences (5' G↓ANTC 3'), in 1X Fast Digest green buffer for 1 hour at 37°C. (Fermentas Life Sciences, USA).

The fragments were then resolved by electrophoresis on a 3% agarose gel, which were stained with 0.1% ethidium bromide and finally analyzed under UV.

Statistical Analyses

After testing the distribution of continuous variables, comparisons of continuous variables were made using independent sample t test, if the distribution is normal. If not, we use Mann Whitney U test for the differences between two groups. The categorical results were expressed as number and percentage. The expected genotype frequencies were analyzed by Hardy-Weinberg method. The $\chi 2$ and Fisher's exact tests were used to evaluate the relationship between the genotypes and osteoporosis. The differences with a p-value below 0.05 were considered as statistically significant. Variables that could be risk factors for osteoporosis were assessed by stepwise logistic regression analysis. Confidence intervals (CIs) were calculated for odds ratios. All of the analyses was conducted by using IBM SPSS Statistics Version 22.

Results

Characteristics of the study group are presented in Table 1. There were no significant differences in the age, height, age of menopause between the group of patients with osteoporosis and the control group. BMD values of all measured sites were significantly lower in patients with osteoporosis compared to the control group ($p < 0.001$ for all comparisons).

Table 1 .Characteristics of women with osteoporosis and controls.

	Osteoporosis (n=109)	**Control (n=85)**	**p**
Age (years)	57.8±6.6	56.1±6.7	0.077
Weight (kg)	65.8±9.4	72.4±12.7	<0.05
Height (cm)	154.0±4.7	155.4±6.0	0.085
BMI	27.8±4.2	29.9±5.0	<0.05
Age at menopause (years)	46.2±11.6	45.7±5.6	0.732
Duration of menapause (years)	12.8±7.9	10.7±8.1	0.095
L1 BMD (g/cm^2)	0.6±0.0	0.7±0.1	<0.001
L4 BMD (g/cm^2)	0.8±0.1	0.9±0.12	<0.001
Total Spine BMD (g/cm^2)	0.7±0.6	0.9±0.1	<0.001
T score (Lomber spine)	-2.6±1.1	-1.2±0.9	<0.001
Total Femur BMD (g/cm^2)	0.7±0.1	0.8±0.1	<0.001
T Score (femur)	-1.4±0.6	-0.6±0.8	<0.001

BMI; body mass index, **BMD**; Bone mineral density. Differences between groups were tested with Student t-test. Result were given as mean±SD.

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In the current study, we performed an analysis of A163G and T245G in polymorphisms in the OPG gene. The A163G and T245G genotypes did not deviate significantly from the Hardy-Weinberg equilibrium (p>0.05 for both). For A163G, the frequency of the A allele was 73.4% and that of G was 26.6%. For T245G, the frequency of the T allele was 78.9% and that of G was 21.1%. The allele distribution of the A163G genotypes were patients with osteoporosis (GG+AG, 46.8%; AA, 53.2%) and control (GG+AG, 27.1%; AA, 72.9%) (X2=7.88, p=0.005). İn addition, the distribution of the T245G genotypes were patients with osteoporosis (GG+TG, 36.7%; TT, 63.3%) and control (GG+TG, 23.5%; AA, 75.5%) (X2=3.88, p=0.049) (Table 2).

Our data indicated that the A163G had a significant relationship with BMD and osteoporosis, and subjects with the AA genotype had higher BMD values than those with the AG+ GG genotype (p<0.05, Table 3). BMD in osteoporotic patients with different genotypes of polymorphism T245G differed significantly at the lumbar 1 spine (TT 0.67 ± 0.07 g/cm2 versus TG+GG 0.63 ± 0.09 g/cm2, p<0.05), at the lumbar 4 spine (TT 0.82 ± 0.07 g/cm2 versus TG+GG 0.78 ± 0.09 g/cm2, p<0.05), and at the total lumbar spine (TT 0.76 ± 0.06 g/cm2 versus TG+GG 0.73 ± 0.07 g/cm2, p<0.05) (Table 3).

In the logistic regression analysis, having AG+GG alleles were found to increase the risk of osteoporosis by 2.342-fold compared to having AA alleles (Table 4).

Table 2. Distribution of A163-G, T245-G genotypes in patients with osteoporosis and controls.

Gene Polymorphism	Osteoporosis (n=109,%)	Control (n=85, %)	p
A163G			
AA	58 (53.2)	62 (72.9)	0.005
AG+GG	51 (46.8)	23 (27.1)	
T245G			
TT	69 (63.3)	65 (75.5)	0.049
TG+GG	40 (36.7)	20 (23.5)	

Table 3. BMD of the L1, L4, total spine and total femur in patients with osteoporosis and controls with different genotypes.

Gene Polymorphism	Osteoporosis (n=109)				Control (n=85)			
	L1 BMD (g/cm^2)	L4 BMD (g/cm^2)	Total spine BMD (g/cm^2)	Total femur BMD (g/cm^2)	L1 BMD (g/cm^2)	L4 BMD (g/cm^2)	Total spine BMD (g/cm^2)	Total femur BMD (g/cm^2)
A163G								
AA	0.67±0.07	0.81±0.07	0.76±0.06	0.76±0.11	0.79±0.11	0.94±0.18	0.92±0.11	0.86±0.10
AG+GG	0.63±0.08	0.79±0.09	0.73±0.07	0.79±0.08	0.78±0.12	0.97±0.14	0.90±0.01	0.86±0.09
P	0.093	0.175	**<0.05**	0.321	0.672	0.706	0.493	0.943
T245G								
TT	0.67±0.07	0.82±0.07	0.76±0.06	0.77±0.11	0.78±0.10	0.96±0.14	0.91±0.11	0.87±0.10
TG+GG	0.63±0.09	0.78±0.09	0.73±0.07	0.78±0.08	0.83±0.14	0.91±0.25	0.92±0.10	0.88±0.09
P	**<0.05**	**<0.05**	**<0.05**	0.721	0.248	0.966	0.763	0.790

Bone mineral density (BMD) of all sites among different polymorhiphism groups. BMD is given as mean±SD. Differences between two groups were compared using the Mann-WhitneyUtest.

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Table 4. Risk factors for osteoporosis.

		OR	CI (95%)	p
Costant		16.875		0.008
A163 G	**AA (Reference)**	1		
	AG+GG	2.342	1.212 – 4.524	0.011
BMI		0.903	0.841 – 0.970	0.005

Discussion

In the present study, we evaluated the relationship between bone mineral density and the A163G and T245G polymorphisms of OPG, one of the most important genes linked with osteoporosis predisposition. A significant correlation has been found between the genotypes and BMD values of lumbar vertebra for the A163G and T245G polymorphisms in postmenopausal women as well as the controls. For the T245G polymorphism, GG+TG genotypes were associated with lower BMD compared to the TT genotype. Similarly, AG+GG genotypes correlated with lower BMD values compared to those observed with the AA genotype for the A163G polymorphism.

In view of the importance of OPG variants and the high prevalence of osteoporosis among postmenopausal women, a number of studies have analyzed the association between gene polymorphisms and low BMD (7, 13, 18, 19). The objective of this study was to evaluate the association between BMD and the A163G and T245G polymorphisms of the OPG promoter in Turkish postmenopausal women.

Arko et al. investigated sequence variations in the OPG promoter and analyzed their relationship with BMD in 103 women with postmenopausal osteoporosis. The analysis of single-strand conformation polymorphism, followed by subsequent DNA sequencing, revealed the presence of four nucleotide substitutions, i.e. 209 G>A, 245 T>G, 889 C>T, and 950 T>C. The authors suggested that 209 G>A and 245 T>G polymorphisms found in the OPG promoter could make a contribution to the genetic regulation of BMD (14). In another study by Arko et al., eight polymorphisms were identified in OPG. In these studies, polymorphism 1181G>C was associated with BMD and was likely to be considered as a contributing factor to genetic predisposition with regards to osteoporosis (3). In the present study, we evaluated the A163G and T245G polymorphisms in the OPG promoter.

In a study by Yu et al., g.18861A>G and g.25548C>T SNPs were identified and the data obtained in their study suggested that there were significant differences in terms of BMD values of the femoral neck hip, spine and total hip among women with the different g.18861A>G genotype. Postmenopausal women who had the AA genotype had remarkably higher BMD than those with the AG and GG genotypes. A significant association was not found between the g.25548C>T variant and BMD values of femoral neck hip, spine and total hip. Their findings suggested that OPG variants were associated with BMD and osteoporosis in Chinese postmenopausal women (20). In our study, we detected the role of OPG in the pathogenesis of osteoporosis through association analyses. Our data indicated that A163G had a significant correlation with BMD and osteoporosis, and subjects with the AA genotype had higher BMD values than those with the AG+ GG genotype. In addition, T245G was also associated with BMD and osteoporosis, and subjects with the AA genotype had higher BMD values compared to those with the TG+ GG genotype.

Shen et al. identified the g.18910G>A and g.27406C>T genotypes. Their data indicated that important differences were found in terms of neck hip BMD, spine BMD and total hip BMD among different g.27406C>T genotype; subjects with genotype CC had considerably higher values than those with genotype CT and TT. Results from the aforementioned study show that OPG variants were associated with BMD in Chinese postmenopausal women (8). In our study, we initially evaluated the genetic effects of the A163G and T245G polymorphisms on BMD and osteoporosis in postmenopausal women by means of association analysis. Results from this study indicated significant differences in genotypic frequencies between postmenopausal patients with primary osteoporosis and healthy controls. New association studies in different populations are warranted in order to explain the possible roles of these polymorphisms. In a study carried out with postmenopausal Danish women, an important negative association was demonstrated between S-OPG and peripheral measures of bone mass, and higher odds ratios were noted for fractures. Moreover, the A163G mutation in the OPG promoter had an important effect on bone mass and fracture status regardless of serum osteoprotegerin levels (9). The present study confirms the findings put forward in the study by Jorgensen et al., i.e. a higher prevalence of the G allele of the A163G polymorphism and higher bone mass in individuals

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with the AA genotype compared to those with the GG+AG genotype.

In similar relevant studies, certain genetic polymorphisms such as A163G, T245G, T950C, G1181C, g.18861A>G, and g.27406C> in OPG have been found to play a genetic role in BMD and osteoporosis (7, 12-14, 21). The two other polymorphisms shown to have an effect on BMD and fractures, namely T950C and G1181C, were investigated by Langdahl et al., as well as Wynne et al.; however, these two groups reported conflicting results. The latter study found an opposite result for the G1181C polymorphism and noted no influence with regards to the T950C polymorphism (5, 22). A study by Ueland T et al., also found no significant relationship between variations in G1181C, T950C and A163G and bone mass in elderly Australian women (23). In the present study, an important association of genotypes with BMD at the lumbar spine was observed for the T245G and A163G polymorphisms in the group of postmenopausal women as well as the controls. Differing from previous studies, Wang et al. reported the relationship of OPG g.18873C>T and g.27522G>A genetic polymorphisms with BMD and osteoporosis in postmenopausal women (24). Finally, in a recent study of randomly selected 22 postmenopausal women and 59 women without osteoporosis, there was a trend for A163G polymorphism in terms of a positive correlation with higher bone loss. Furthermore, the results of their study indicated that a significantly greater number of women with osteoporosis had AG polymorphism compared to women without osteoporosis, while no significant difference was found in the prevalence of TT and GG polymorphisms between patients with and without osteoporosis (15). We also found similar results in the present study.

Based on our results, we suggested that the associations between the A163G and T245G polymorphisms and low spine BMD are caused by one of them and merely reflected by the other one because of linkage disequilibrium or by a true effect of both polymorphisms. Unfortunately, due to the limited sample size, this study does not permit a clarification of the interdependency between BMI, bone mass, and A163G when assessed in a logistic regression analysis model with all the parameters included. This interdependency needs to be addressed in larger studies. Better understanding of this mechanism requires further studies that aim to investigate the association between these two SNPs or other genetic variants and osteoporosis in larger populations, and to elucidate the underlying molecular mechanism.

Declaration of conflicting interests

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