EVALUATION OF *COLIA1* GENE RS1107946 POLYMORPHISM IN RELATION TO BONE MINERAL DENSITY AND FRACTURE RISK IN SLOVAK POSTMENOPAUSAL WOMEN

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SUMMARY

Objectives: The aim of the study was the evaluation of the rs1107946 polymorphism of the *COLIA1* gene impact on bone mineral density and fracture risk in Slovak postmenopausal women.

Methods: One hundred and twenty-seven postmenopausal Slovak women with a diagnosis of osteopenia/osteoporosis were genotyped for rs1107946 polymorphism of the *COLIA1* gene. Clinical and anthropometric data were obtained. DNA isolation was performed using a standard protocol. Genetic analyses of the rs1107946 polymorphism of the *COLIA1* gene were performed by the TaqMan SNP genotyping assays.

Results: The study confirmed a statistically significant relationship using an association analysis between the rs1107946 polymorphism of the *COLIA1* gene genotypes and body weight of the Slovak postmenopausal women with osteopenia/osteoporosis ($p = 0.03$). The study revealed a significant association of the risk T allele of the rs1107946 polymorphism of the *COLIA1* gene with osteoporotic fractures ($p = 0.038$). The odds ratio confirmed 2.060 times higher risk of osteoporotic fractures in Slovak postmenopausal women with the presence of risk T allele of the rs1107946 *COLIA1* gene polymorphism (OR = 2.060; 95% CI: 1.024–4.144).

Conclusion: The results of this study revealed an association of T allele of the rs1107946 *COLIA1* gene polymorphism with osteoporotic fractures in Slovak postmenopausal women with osteopenia/osteoporosis and suggest that the rs1107946 polymorphism of the *COLIA1* gene may be a molecular biomarker usable in the management of osteoporosis.

Key words: COLIA1 gene – rs1107946 polymorphism, osteoporosis, postmenopausal women, fracture risk

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INTRODUCTION

Osteoporosis characterized by the loss of bone mass, deterioration of bone microarchitecture and increased risk of fracture is a systemic skeletal disease occurring especially in postmenopausal women (1). Osteoporosis has multifactorial aetiology, the genetic determinants are modulated by hormonal, environmental and nutritional factors (2, 3). In the recent years, the relationship between genetic factors and susceptibility to osteoporosis has been analysed (4). Several candidate genes of osteoporosis have been investigated in relation to bone mineral density (BMD) variations and incidence of fractures (5–11).

Type I collagen is the most abundant protein in bone, gene encoding type I collagen (*COLIA1*) have recently emerged as an important candidate for the genetic regulation of bone mass, mutations affected coding regions give rise to a severe osteoporotic phenotype (12–14). Several studies have investigated the association of polymorphisms within *COLIA1* gene with postmenopausal osteoporosis (15–19). Most of the previous studies have focused on the Sp1 binding site polymorphism (rs1800012) of the *COLIA1* gene. A large-scale study performed by Ralston et al. and meta-analysis of Ji et al. showed that the Sp1 polymorphism of the *COLIA1* gene may be associated with osteoporotic fractures in Caucasian postmenopausal women (15, 16). Several studies suggested that other functional polymorphisms in the *COLIA1* gene interact with the Sp1 polymorphism and regulate the bone tissue (17–21). The single nucleotide polymorphism rs1107946 of the *COLIA1* gene is located in the proximal promoter at a –1997 position in the evolutionary conserved regulatory region. A study by Jin et al. at the haplotype level confirmed the importance of the rs1107946 polymorphism of the *COLIA1* gene in the regulation of *COLIA1* gene expression (25). The present study was aimed at the evaluation of the rs1107946 polymorphism of the *COLIA1* gene in relation to BMD and fracture risk in Slovak postmenopausal women with a diagnosis of osteopenia/osteoporosis.

MATERIALS AND METHODS

Participants

The study included 100 postmenopausal women diagnosed with osteoporosis – diagnostic criteria: T-score <−2.5 standard deviation (SD), and 27 postmenopausal women with osteopenia

– diagnostic criteria: T-score −1 to −2.5 SD (22). Totally, 127 postmenopausal women with diagnosed osteopenia/osteoporosis (67.2 ± 9.0 years) were divided into groups based on the presence of a fracture. The fracture group included postmenopausal women with at least one osteoporotic fracture (mean age 68.1 ± 8.8 years) and the no fracture group included women without an osteoporotic fracture (mean age 66.4 ± 9.3 years). The women in the study groups were examined clinically by specialists of the National Institute of Endocrinology and Diabetology. The basic anthropological (age, height, weight, body mass index) and clinical data (age of menopause, history of fractures, bone mineral density) were obtained. The study was approved by the Ethics Committee of the University of Prešov. All participants provided a written, informed consent.

BMD Measurements

Dual-energy X-ray absorptiometry (DXA, Hologic, Bedford, MA, USA) was used to measure BMD (g/cm^2) at the lumbar spine (L1–L4) (LS), femoral neck (FN) and total hip (TH), T-score was used to analyse the BMD data.

Genotyping

For the purpose of the study, blood samples were collected from all the women and stored at −20°C. Genomic DNA was isolated and purified from peripheral blood leucocytes by a commercial kit (Promega, Madison, USA) using a standard protocol. SNP genotyping was done using the TaqMan SNP genotyping assays (Custom TaqMan® SNP Genotyping Assays, C_7477171_10; Applied Biosystems, Foster City, CA, USA) with an Applied Biosystems™ 7500 Fast Real-Time PCR System.

Statistical Analyses

The statistics were calculated using the SPSS Statistics software version 20. Considering that the data did not have a normal distribution, non-parametric tests were used for statistical analyses, the chi-square test was used to compare the categorical data, for the comparison of continuous data Mann-Whitney and Kruskal-Wallis tests were used as appropriate. All quantitative data were expressed as mean and standard deviation. The results of the association analyses were expressed as odds ratios (OR) with a 95% confidence interval (CI) and p-value. The analysis of the rs1107946 polymorphism of the *COLIA1* gene in particular genetic models was performed using the SNPStats application (23). P value < 0.05 was considered a statistically significant.

RESULTS

The general characteristics of the basic anthropometric and densitometric parameters of the participating Slovak postmenopausal women with diagnosed osteopenia/osteoporosis are presented in Table 1. Age, height, weight, BMI, age at menopause, lumbar spine L1–L4, femoral neck, and total hip BMD/T-score in the studied groups are shown as mean (SD).

The mean values of lumbar L1–L4 spine, femoral neck and total hip BMD (g/cm^2), and T-score in the group of Slovak postmenopausal women with fractures were lower in comparison with the group of postmenopausal women without fractures; the differences were not statistically significant ($p = 0.19$, $p = 0.14$, $p = 0.18$; $p = 0.23$, $p = 0.06$, $p = 0.06$, respectively).

The distribution of genotypes and alleles of the rs1107946 *COLIA1* gene polymorphism in the studied groups of postmenopausal women using a χ^2 test was analysed. Genotyping data of the rs1107946 *COLIA1* gene polymorphism in the group of Slovak postmenopausal women with osteopenia/osteoporosis and the control group are summarized in Table 2.

The most frequent genotype of the rs1107946 *COLIA1* gene polymorphism was GG (cases 70%, controls 76%) followed by genotype GT (cases 28%, controls 24%). Genotype TT occurred in the group of postmenopausal women with osteopenia/osteoporosis with the frequency of 2%; in the control group the

Table 1. *Descriptive characteristics of studied subjects and comparison of analysed parameters (N = 127)*

Characteristics	Postmenopausal women			p-value
	All	Fracture group	No fracture group	
	(n = 127)	(n = 65)	(n = 62)	
Age (years), mean (SD)	67.2 (9.0)	68.1 (8.8)	66.4 (9.3)	0.30
Height (cm), mean (SD)	160.6 (7.4)	160.7 (6.8)	160.6 (8.1)	0.97
Weight (kg), mean (SD)	64.9 (11.9)	64.2 (11.8)	65.7 (12.1)	0.49
BMI (kg/m^2), mean (SD)	25.2 (4.2)	25.0 (4.0)	25.5 (4.5)	0.53
Age of menopause (years), mean (SD)	48.9 (5.3)	48.2 (6.2)	49.6 (4.2)	0.37
LS L1–L4 BMD (g/cm^2), mean (SD)	0.791 (0.11)	0.777 (0.08)	0.805 (0.14)	0.19
FN BMD (g/cm^2), mean (SD)	0.603 (0.11)	0.589 (0.12)	0.618 (0.09)	0.14
TH BMD (g/cm^2), mean (SD)	0.733 (0.12)	0.718 (0.11)	0.747 (0.12)	0.18
LS T-score (L1–L4), mean (SD)	−2.67 (1.04)	−2.78 (0.75)	−2.56 (1.27)	0.23
FN T-score, mean (SD)	−2.27 (0.86)	−2.41 (0.90)	−2.12 (0.79)	0.06
TH T-score, mean (SD)	−1.80 (1.00)	−1.96 (0.97)	−1.63 (1.00)	0.06

BMI – body mass index; BMD – bone mineral density; n – number of women; SD – standard deviation; LS – lumbar spine; FN – femoral neck; TH – total hip
Comparison was performed by Mann-Whitney test.

Table 2. *Genotype and allele frequencies of the rs1107946 COLIA1 gene polymorphism in Slovak postmenopausal women*

Genotype and allele frequencies	Cases (n = 127) n (%)	Controls (n = 70) n (%)	OR	95% CI	p-value
GG	89 (70)	53 (76)	1.907	0.013–4.955	0.271
GT	35 (28)	17 (24)			
TT	3 (2)	0 (0)			
G	84%	88%	0.718	0.391–1.318	0.284
T	16%	12%			

n – number of women; GG – homozygous genotype; GT – heterozygous genotype; TT – homozygous genotype; G – guanine; T – thymine; cases – osteopenic and osteoporotic group of postmenopausal women; χ^2 – chi-square test; OR – odds ratio; CI – confidence interval
P-values were calculated by logistic regression analysis.

occurrence of the TT genotype was not confirmed. The genotype distribution of the rs1107946 *COLIA1* gene polymorphism between the studied groups (cases and controls) was not statistically significant (p = 0.271). The frequency of the rs1107946 *COLIA1* gene polymorphism T allele was 16% in the group of Slovak postmenopausal women with osteopenia/osteoporosis and 12% in the control group (p = 2.284).

A higher frequency of the risk T allele of the rs1107946 *COLIA1* gene polymorphism in the fracture group in comparison with the no fracture group of postmenopausal women was found. The association analysis revealed a significant association of the risk T allele of the rs1107946 polymorphism of the *COLIA1* gene with osteoporotic fractures (p = 0.038). The odds ratio confirmed a 2.060 times higher risk of osteoporotic fractures in the Slovak postmenopausal women with the presence of risk T allele of the rs1107946 *COLIA1* gene polymorphism (OR = 2.060; 95% CI: 1.024–4.144) (Table 3). A comparison of the mean values of the analysed parameters between different genotypes of the rs1107946

Table 3. *Association analysis of the rs1107946 COLIA1 gene polymorphism with fracture risk in Slovak women with osteopenia/osteoporosis*

Genotype and allele frequencies	Fracture group (n = 65)	No fracture group (n = 62)	χ^2	OR	95% CI	p-value
GG	63%	77%	3.38	0.122	0.006–2.436	0.087
GT	32%	23%				
TT	5%	0%				
G	79%	89%	4.21	2.060	1.024–4.144	0.038*
T	21%	11%				

n – number of women; GG – homozygous genotype; GT – heterozygous genotype; TT – homozygous genotype; G – guanine; T – thymine; χ^2 – chi-square test; OR – odds ratio; CI – confidence interval
P-values were calculated by logistic regression analysis.

Table 4. *Comparison of anthropometric and densitometric parameters between different genotypes of the rs1107946 COLIA1 gene polymorphism*

Characteristics/genotypes	GG	GT	TT	p-value
	(n = 89)	(n = 35)	(n = 3)	
Age (years), mean (SD)	67.6 (9.3)	66.4 (8.36)	66.7 (12.5)	0.80
Height (cm), mean (SD)	160.6 (7.1)	161.1 (8.0)	152.5 (10.6)	0.28
Weight (kg), mean (SD)	65.2 (11.3)	65.8 (12.9)	47.0 (7.0)	0.03*
BMI (kg/m^2), mean (SD)	25.3 (4.3)	25.3 (4.1)	21.7 (0.9)	0.50
Age of menopause (years), mean (SD)	48.7 (4.7)	49.6 (6.6)	45.7 (4.2)	0.41
LS BMD (L1–L4) (g/cm^2), mean (SD)	0.802 (0.13)	0.772 (0.08)	0.720 (0.10)	0.27
FN BMD (g/cm^2), mean (SD)	0.607 (0.11)	0.600 (0.08)	0.565 (0.11)	0.77
TH BMD (g/cm^2), mean (SD)	0.738 (0.12)	0.731 (0.11)	0.640 (0.15)	0.36
LS L1–L4 T-score, mean (SD)	−2.61 (1.14)	−2.79 (0.75)	−3.30 (0.89)	0.40
FN T-score, mean (SD)	−2.26 (0.88)	−2.28 (0.82)	−2.53 (1.04)	0.85
TH T-score, mean (SD)	−1.79 (1.02)	−1.77 (0.94)	−2.47 (1.19)	0.51

n – number of women; SD – standard deviation; BMI – body mass index; LS – lumbar spine; FN – femoral neck; TH – total hip; GG – homozygous genotype; GT – heterozygous genotype; TT – homozygous genotype
P-values were calculated using Kruskal-Wallis test.

COLIA1 gene polymorphism in the group of Slovak postmenopausal women with osteopenia/osteoporosis is presented in Table 4.

The association analyses revealed a significant association of the rs1107946 *COLIA1* gene polymorphism with the body weight in the Slovak postmenopausal women with osteopenia/osteoporosis ($p = 0.03$). A comparison of the analysed parameters according to the rs1107946 *COLIA1* gene genotypes with BMD and a risk of osteoporotic fractures by a recessive genetic model is shown in Table 5.

The analyses of the BMD mean values according to the rs1107946 *COLIA1* gene genotypes in a recessive genetic model revealed lower BMD values (g/cm^2) in GT+TT genotypes (LS L1–L4 BMD: 0.768 ± 0.08, FN BMD: 0.600 ± 0.08, TH BMD: 0.723 ± 0.11) in comparison with GG genotype (LS L1–L4 BMD: 0.802 ± 0.13, FN BMD: 0.607 ± 0.14, TH BMD: 0.738 ± 0.12), statistically significant differences were not found ($p = 0.15$, $p = 0.63$, $p = 0.54$).

DISCUSSION

The genetic background plays an important role in the development of postmenopausal osteoporosis. A number of studies have demonstrated an association between SNPs in a number of genes and osteoporosis including the rs1107946 polymorphism in the *COLIA1* gene. Based on the published data many polymorphisms of the *COLIA1* gene affect the susceptibility to osteoporosis and development of osteoporotic fractures (15, 16, 18, 24). At first, the association of the rs1107946 polymorphism of the *COLIA1* gene was analysed by Garcia-Giralt et al., the study confirmed the modifying effect of the *COLIA1* gene on transcriptional activity (17). Regarding the rs1107946 of the *COLIA1* gene polymorphism, the previously published results are conflicting. The association of the rs1107946polymorphism of the *COLIA1* gene with bone mineral density in postmenopausal women was confirmed in many studies (16, 19, 25). The study of Husted et al. (27) revealed an association of the T allele of the rs1107946 polymorphism of the *COLIA1* gene with vertebral fractures in Danish osteoporotic postmenopausal women, but no effect of this polymorphism was found in relation to bone mineral density. A study of British postmenopausal women found a higher frequency of the T allele of the rs110794 polymorphism 6 of the *COLIA1* gene in the hip fracture group (25). Haplotype analyses detected a high frequency of the haplotype with the T allele of the rs1107946 polymorphism of the *COLIA1* gene (haplotype: rs1107946 - rs2412298 - rs1800012): T-del-T, T-del-G, T-ins-T in the hip fracture group (24). In Mexican postmenopausal women a higher frequency of the T allele of the rs1107946 polymorphism of the *COLIA1* gene was detected in the fracture group (0.48), the study confirmed a 2.9 times higher risk of a distal radius fracture in postmenopausal women (20). In a study of Polish women with osteopenia/osteoporosis the genotype with the risk T alleles (TT) was associated with low bone mineral density (26).

In the present study, the genetic contribution of the rs1107946 polymorphism of the *COLIA1* gene to bone mineral density and a fracture risk in Slovak postmenopausal women was analysed. Our study revealed a frequency of the risk T allele of the rs1107946 polymorphism of the *COLIA1* gene in the Slovak postmenopausal women with osteopenia/osteoporosis (0.16) similar to frequencies detected in British (0.17) and Danish (0.17) postmenopausal women with fractures (25, 27).

The present study revealed an association of T allele of the rs1107946 *COLIA1* gene polymorphism with osteoporotic fractures in the Slovak postmenopausal women with osteopenia/osteoporosis ($p = 0.038$). No significant associations of the rs1107946 polymorphism of the *COLIA1* gene with BMD at lumbar spine (L1–L4), femoral neck and total hip were detected. The results of our study confirmed previous reports demonstrating the rs1107946 polymorphism of the *COLIA1* gene as a risk factor of osteoporotic fractures (25, 27). The detected allele frequencies of the rs1107946 polymorphism of the *COLIA1* gene are consistent with the hypothesis that the T allele of the rs1107946 *COLIA1* gene polymorphism increases the risk of osteoporotic fractures (15, 20, 25, 26).

Table 5. *Comparison of analysed parameters between genotypes of the rs1107946 COLIA1 gene polymorphism by recessive genetic model*

Characteristics/genotype	GG (n = 89)	GT + TT (n = 38)	p-value
Age (years), mean (SD)	67.6 (9.3)	66.4 (8.5)	0.50
Height (cm), mean (SD)	160.6 (7.1)	160.7 (8.2)	0.99
Weight (kg), mean (SD)	65.2 (11.3)	64.3 (13.5)	0.71
BMI (kg/m^2), mean (SD)	25.3 (4.3)	25.1 (4.1)	0.79
Age of menopause (years), mean (SD)	48.7 (4.7)	49.3 (6.5)	0.59
LS L1–L4 BMD (g/cm^2), mean (SD)	0.802 (0.13)	0.768 (0.08)	0.15
FN BMD (g/cm^2), mean (SD)	0.607 (0.14)	0.600 (0.08)	0.63
TH BMD (g/cm^2), mean (SD)	0.738 (0.12)	0.723 (0.11)	0.54
LS T-score (L1–L4), mean (SD)	−2.61 (1.13)	−2.83 (0.76)	0.28
FN T-score, mean (SD)	−2.56 (0.88)	−2.30 (0.82)	0.77
TH T-score, mean (SD)	−1.79 (1.02)	−1.82 (0.97)	0.88

n – number of women; SD – standard deviation; BMI – body mass index; LS – lumbar spine; FN – femoral neck; TH – total hip; GG – homozygous genotype; GT – heterozygous genotype; TT – homozygous genotype
P-values were calculated using Mann-Whitney test.

The results of our study indicate that the rs1107946 polymorphism of the *COLIA1* gene may affect susceptibility to osteoporotic fractures in Slovak postmenopausal women with osteopenia/osteoporosis. More studies are needed to clarify the contribution of the rs1107946 polymorphism of the *COLIA1* gene to the development of osteoporosis.

CONCLUSION

The results of this study revealed an association of the risk T allele of the rs1107946 *COLIA1* gene polymorphism with osteoporotic fractures independently of BMD in the Slovak postmenopausal women with osteopenia/osteoporosis. The study confirmed the role of the rs1107946 *COLIA1* gene polymorphism in the risk of osteoporotic fractures and suggested that the rs1107946 *COLIA1* gene polymorphism may be a molecular biomarker usable in the management of osteoporosis in Slovak postmenopausal women.

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Conflict of Interests

None declared

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