

# Collagen Type I Alpha 1 Gene Polymorphism in Premature Ovarian Failure

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## SUMMARY

**Introduction** Premature ovarian failure (POF) is characterized by amenorrhea, hypergonadotropism and hypoestrogenism in women below 40 years. Osteoporosis is one of the late complications of POF.

**Objective** To correlate collagen type I alpha1 (COLIA1) gene polymorphism with bone mineral density (BMD) in women with POF.

**Methods** We determined the COLIA1 genotypes SS, Ss, ss in 66 women with POF. Single nucleotide polymorphism (G to T substitution) within the Sp1-binding site in the first intron of the COLIA1 gene was assessed by polymerase chain reaction (PCR) followed by single-stranded conformation polymorphism (SSCP) analysis. Bone mineral density (BMD) was measured at the lumbar spine region by dual X-ray absorptiometry. Statistics: Kruskal-Wallis ANOVA, Chi-square test, Spearman correlation test.

**Results** The relative distribution of COLIA1 genotype alleles was SS – 54.4%, Ss – 41.0% and ss – 4.5%. No significant differences were found between genotype groups in body mass index, age, duration of amenorrhea or BMD. A significant positive correlation was observed between BMI and parity.

**Conclusion** The COLIA1 gene is just one of many genes influencing bone characteristics. It may act as a marker for differences in bone quantity and quality, bone fragility and accelerated bone loss in older women. However, in young women with POF, COLIA1 cannot identify those at higher risk for osteoporosis.

**Keywords:** COLIA1; genetic polymorphism; premature ovarian failure; osteoporosis

## INTRODUCTION

Premature ovarian failure (POF) is characterized by the spontaneous cessation of menstruation in post-pubertal women before the age of forty [1]. Women with POF have a hypergonadotropic-hypoestrogenic hormone profile (follicle stimulating hormone >40 IU/L and estradiol <50 pmol/L [2]. Deficiency of estrogen, a critical reproductive hormone for bone acquisition, is associated with an increased bone turnover and accelerated bone loss, leading to the increased susceptibility to osteoporosis and bone fractures. Osteoporosis is a common disabling age-related disease characterized by reduced bone mineral density (BMD), disorganization of skeletal integrity and micro-architecture and increased risk of fragility fractures [3]. Thus, identification of POF subjects with an increased risk for developing osteoporosis is of primary importance.

The inheritance of bone mass is under polygenic control. It accounts for 75-85% of the variance in peak bone mass and plays a role in regulating bone turnover and rate of bone loss [4]. Candidate genes encoding the main regulators of bone metabolism are genes for calcitrophic hormones, bone matrix proteins, steroid hormones and local regulators of bone metabolism. The genes regulating local bone metabolism are: vitamin D receptor, estrogen

receptor, androgen receptor, parathyroid hormone, calcitonin receptor, peroxisome proliferator-activated receptor  $\gamma$ , collagen type I alpha 1 (COLIA1),  $\alpha_2$  HS-glycoprotein, osteocalcin, tissue growth factor  $\beta$ -1, interleukin-6 and 1, apo E, Ca-sensitizing receptor, collagenase and methylenetetrahydrofolate reductase [5].

Grant et al. [6] identified a single nucleotide G→T polymorphism affecting the binding site for the transcription factor Sp1 in the first intron (+1245 G to T) of the COLIA1 gene leading to incorrect triple helix organization in a region important for the regulation of collagen transcription and significantly related to bone mass, higher fragility and osteoporosis. This raised the possibility that genotyping at this site may be of value in identifying women who are at risk for osteoporosis [7]. Transcription factor Sp1 has higher affinity for the “s” than “S” allele, leading to incorrect organization of these chains into triple helix and to the higher fragility.

Some studies provided no evidence for the link between the polymorphism of the COLIA1 Sp1 binding site and osteoporosis [8]. The largest multicentric study performed recently in Europe by the Genetic Markers for Osteoporosis (GENOMOS) consortium revealed a modest association of COLIA1 polymorphism and reduced body mass index [9]. According to the available data there are no studies of COLIA1 genotype and risk for osteoporosis in POF.

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## OBJECTIVE

The aim of this study was to investigate the relationship between COLIA1 gene polymorphism and BMD in Serbian women with POF.

## METHODS

The study was performed in a group of 66 women with POF who were referred for clinical evaluation to the Institute of Endocrinology, Clinical Center of Serbia, Belgrade, Serbia. They were ethnically homogenous and of the same socio-economic status and dietary habits. A detailed medical history was obtained from each woman and her dietary calcium intake was assessed using a sequential questionnaire that included food assessment for dietary calcium. Exclusion criteria were BMI over 30 kg/m<sup>2</sup>, bilateral ovariectomy, and use of drugs affecting bone metabolism (glucocorticoids, thyroxine, bisphosphonates, menopause replacement therapy). Women with renal, liver, endocrine diseases, rheumatoid arthritis, malignancy, alcoholism, and long-term immobilization were also excluded. The diagnosis of POF was made according to age (<40 years), the length of amenorrhea (>12 months) and two serum values of follicle stimulating hormone, FSH >40 IU/L and 17 $\beta$  estradiol <20 pmol/L. Osteoporosis was diagnosed by the T-score that was equal to or greater than -2.5 SD using densitometric analysis based on the criteria established by the World Health Organization [10].

The Ethics Committee of the Institute of Endocrinology, Clinical Center of Serbia, Belgrade, approved the study. A written informed consent was obtained from each woman who participated in the study.

Each woman was examined clinically and routine biochemical tests were performed to exclude systemic and metabolic bone disease. Serum hormone measurements, carried out on two consecutive days at 8.00 a.m., following an overnight fast, included FSH, luteinizing hormone (LH), prolactin, estradiol, progesterone and testosterone. Hormone analyses were done by RIA using the standard kit (INEP, Zemun, Serbia).

BMD was measured at the lumbar spine (L2-L4) region by dual energy X ray absorptiometry (DEXA) using a Lunar DPX-L densitometer (Lunar Co, Madison, WI). The coefficient of variation in vitro CV=1.0% as assessed by 300 daily spine phantom measurements. Weight and height were measured just prior to the bone mineral measurement. BMD was presented in g/cm<sup>2</sup>. Calculated T-score was based on the measurements performed in the local population. Z scores were derived from age-matched controls.

Genomic DNA analysis was performed in all women. Genomic DNA was extracted from peripheral blood leukocytes using the standard phenol-chloroform procedure and analyzed by electrophoresis on 1% agarose gel. A rapid PCR/SSCP-based method was used for screening the polymorphism in the promoter of COLIA1. The oligonucleotide primer set was designed to

yield PCR fragment of 160 bp. The upstream primer was 5'-GAGTGGCTTGCGTGGTAGAG-3', and the downstream primer was 5'-ACATTTCAAGTCTTGGGGGG-3'. PCR was performed in a final volume of 25 ml containing 200 ng DNA and 1 U of Stoffel Taq polymerase (Perkin Elmer) on a Techne Genius Thermocycler system. The PCR protocol was 30 cycles of 96°C for 1 minute, and 72°C for 2 minutes and a final performed at 94°C for 2 minutes. PCR products were analyzed by electrophoresis on 2% agarose gel, and resolved on 18% polyacrylamide gel with 5% glycerol. Bands on the gel were visualized by silver staining.

Parameters of various genotype groups were compared by the Kruskal-Wallis ANOVA test. The Chi-square test was used to compare distributions of categorical clinical data. Correlation analyses were performed using the Spearman test. Hardy-Weinberg equilibrium was also tested by the Tools for population, the Genetic analysis program Monte Carlo method with 40,000 random permutations (11). All the calculations were performed with the SPSS statistical package (SPSS Inc. Chicago Illinois, USA). A p-value <0.05 was considered statistically significant.

## RESULTS

The subjects were distributed into three subgroups, according to the COLIA1 gene polymorphism, namely SS, Ss, and ss. Only one woman had the "ss" allele. Baseline characteristics of the groups are shown in Table 1. No significant difference between groups was found for age, age at menarche, duration of amenorrhea, parity, maternal menopausal age, dietary calcium intake (except for a woman in the Ss group who had insufficient calcium intake), smoking habits (45% were smokers), BMI or waist/hip ratio. The hormonal parameters were characterized by elevated FSH (68.3 $\pm$ 8.4 IU/L) and LH (38 $\pm$ 5.6 IU/L) and low levels of estradiol (38.2 $\pm$ 10.7 pmol/L), progesterone (2.1 $\pm$ 0.9 nM/L) and testosterone (1.2 $\pm$ 0.6 nM/L). Prolactin was in normal range (310.6 $\pm$ 68.2 nmol/L).

No significant difference was found between the groups in age, age at menarche, amenorrheic period, delivery, maternal menopause age, body mass index (BMI), waist and hip ratio (W&H) and Z score (Table 1).

The genotype frequencies in women with POF were SS - 54.5%, Ss - 41.0%, and ss - 4.5%, whilst allele frequencies in the Hardy-Weinberg equilibrium were SS - 68.4%,

**Table 1.** The baseline characteristics of the study subjects (mean $\pm$ SD)

Genotype	SS group	Ss group
Age (years)	40.8 $\pm$ 4.9	41.7 $\pm$ 3.5
Age at menarche (years)	14.7 $\pm$ 2.1	12.6 $\pm$ 1.2
Amenorrheic period (years)	6.7 $\pm$ 6.2	6.9 $\pm$ 6.6
Delivery (times)	1.0 $\pm$ 0.7	1.8 $\pm$ 1.6
Maternal menopausal age (years)	48.6 $\pm$ 5.9	48.3 $\pm$ 5.8
Body Mass Index (kg/m <sup>2</sup> )	24.4 $\pm$ 3.0	26.1 $\pm$ 5.4
Waist/hip ratio	0.8 $\pm$ 0.1	0.8 $\pm$ 0.1
Z score L <sub>2</sub> -L <sub>4</sub> BMD (g/cm <sup>2</sup> )	-0.9 $\pm$ 1.5	-0.4 $\pm$ 1.6

BMD - bone mineral density

Ss - 35.09%; and ss - 4.4% (Graph 1). This indicated some non-significant excess heterozygosity in POF women. In 120 Serbian women of normal menopausal age, genotype frequencies were SS - 66.6 % homozygotes and Ss - 24.1% heterozygotes [12].

No difference was seen between the groups with respect to lumbar spine BMD (Graph 2). The Ss group had 47% higher Z score than the SS group (-0.44 vs. -0.93). Whilst the SS group showed a negative correlation between BMI and Z score ( $R=-0.16$ ), in the Ss group a positive correlation was present ( $R=0.06$ ), but both were non-significant. Obese women ( $BMI > 25.0 \text{ kg/m}^2$ ) showed a positive correlation between BMI and Z score ( $R=0.25$ ). A significant positive correlation was found for BMI and parity ( $R=0.61, p < 0.05$ ) indicating that women with more than two children were more obese. A non-significant negative correlation was found for the duration of amenorrhoea in years and Z score ( $< 5$  amenorrhoeic years,  $R=-0.4$ ,  $> 5$  years,  $R=-0.34$ ) (Graphs 3 and 4). Also, a non-significant negative correlation was found for age and Z score ( $R=-0.17$ ) and age at menarche and Z score ( $R=-0.37$ ).

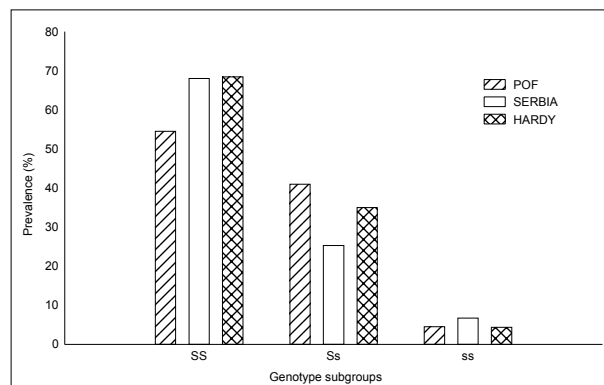
## DISCUSSION

The essential task of BMD measurements is to identify women with POF at increased risk for osteoporosis, thereby enabling appropriate treatment. This is the first study to investigate COL1A1 gene polymorphism in women with POF.

Type I collagen, a major protein of bone, is a heterodimer with two collagen chains encoded by the genes COL1A1 and 2 [13]. A single nucleotide G→T polymorphism is associated with increased binding affinity for the Sp1 protein in the COL1A1 gene, increased allele specific transcription of COL1A1, increased production of collagen protein and difference in bone strength [5]. Ss heterozygotes seem to have lower BMD and higher risk for osteoporosis and fractures.

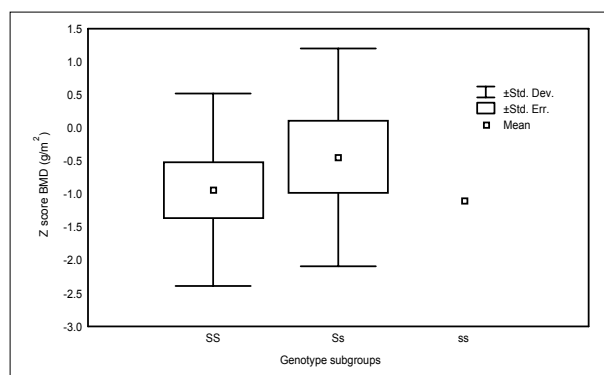
A meta analysis of data from sixteen published studies including a total 4965 individuals showed a significant association between carriage of the COL1A1 "s" allele and low BMD [14, 15]. Bone tissue cores obtained from Ss genotype women had reduced inorganic content and increased organic content, when compared with cores obtained from SS genotype women, possibly reflecting abnormalities in mineralization in Ss genotypes. Individuals with the "ss" genotype had an altered ratio between the amounts of COL1A1 and 2 which could lead to reduced peak bone mass or a higher risk of trabecular perforation during age or menopause-related high bone turnover. It seems that the major defect in osteoporosis is not in the "osteoblast" per se, but in the mechanism for ensuring that a significant number of osteoblasts are assembled in the right place at the right time.

Women with POF have a insignificantly higher heterozygosity compared with allele frequencies in the Serbian women with normal menopause and Hardy-Weinberg equilibrium. We have not found published data of allele frequencies in women with POF in other countries.

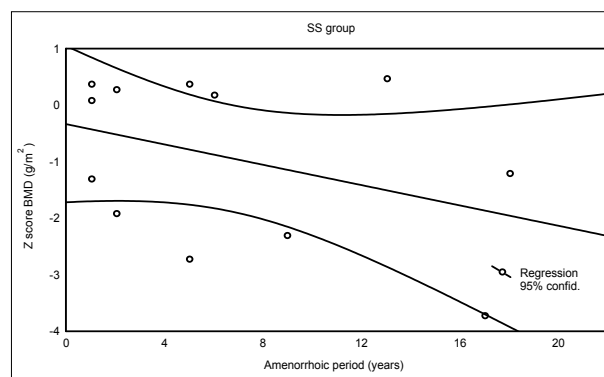


**Graph 1.** Prevalence of genotype subgroups

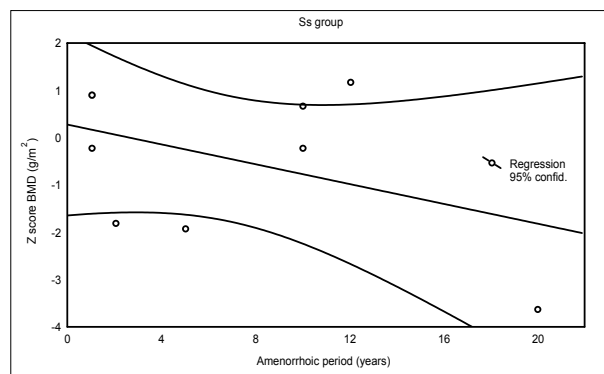
POF – premature ovarian failure; SERBIA – normal postmenopausal women in Serbia; HARDY – Hardy-Weinberg equilibrium



**Graph 2.** Z score in genotype subgroups



**Graph 3.** Correlation of BMD-Z score and amenorrhoeic period (in years) in SS group



**Graph 4.** Correlation of BMD-Z score and amenorrhoeic period (in years) in Ss group

Our findings are in agreement with Liden et al. [16] who found no significant differences between genotype groups with regard to lumbar spine BMD, although this probably reflects the small number of subjects with the "ss" homozygous genotype. This is not surprising, considering that the estimated incidence of POF is only 0.9-3% of the population [17].

The correlation between the age and BMD is one of the most important in most studies of osteoporosis. BMD declines with age and genetic effects on bone density could be mediated by differences in the age-related rate of bone loss as well as by differences in peak bone density. Bone mass at any time point after 35 years of age is a function of the peak bone mass attained at a younger age and of the annual rate of bone loss. Women with POF are younger than women participating in most postmenopausal studies, thus their age-related bone loss rate is unknown. When the subjects in the study of Uitterlinden et al. [15] were divided into five-year categories, the differences in BMD between genotype groups were smaller in younger menopausal women (55-65 years), but became higher with increasing age. They concluded that the genetic effect on BMD associated with the COLIA1 locus is stronger in postmenopausal than in premenopausal women. In a group of postmenopausal women, Langdahl et al. [7] also found that individuals with the ss genotype had significantly lower BMD, but they were older than Ss group. Most studies have found a marked decrease of bone mass between age 40 and 60 years. Thus, our finding of COLIA1 gene polymorphism not being associated with reduced bone density in a heterozygote group of young women with POF is not unexpected. We did not find significant correlation between BMD and aging, which probably reflected both a small number of subjects studied and their relatively narrow age span. It would be very interesting to follow BMD changes in our patients over the next 10-20 years, as this would reflect the effect of aging on bones.

As BMI is an important factor for BMD, the differences in BMD have been accompanied by the differences in body weight. Obesity, as reflected by BMI >25 kg/m<sup>2</sup>, appear to influence BMD positively. Whilst Hadjidakis et al. [18] observed a significant positive correlation between vertebral mineral density and BMI in the immediate period following the last menstruation and in all age segments in POF, in our study there was a positive correlation only in the Ss group (R=0.06). This could be explained as the influence of endocrine activity of adipose tissue on bone metabolism. We found a statistically significant correlation between BMI and parity.

Although COLIA1 alleles have been found by some workers to predict fractures after correction for BMD, other investigators have found no association between the COLIA1 genotype and BMD or osteoporotic fractures [16, 19]. Some other factors contribute to the risk of osteoporotic fractures including advancing age, low BMI, previous

fractures, muscle weakness and impaired vision. In our group only one woman with the Ss genotype had multiple fractures. She is now 44 years old, menarche was at 13 years, amenorrheic period was 20 years, previously she had regular cycles, BMI was 24.2 kg/m<sup>2</sup>, and waist/hip ratio was 0.8. However, her calcium intake was insufficient, as she disliked dairy products, and she also smoked. Additionally, she had rheumatoid arthritis and Sicca syndrome. Thus, there were a number of factors other than polymorphism which could have been responsible for her osteoporosis.

There are many gene-gene and gene-environment interactions which determine the skeletal phenotype. Bone mass is under the control of many genes with relatively small effects, rather than few genes with a large effect, as Kobayashi et al. [20] have observed. Our results are consistent with previous findings [21] that different genes seem to act in various combinations, causing individual degrees of susceptibility in given persons.

## CONCLUSION

The COLIA1 gene polymorphism may principally act as a marker of increased bone fragility and accelerated bone loss in older women, rather than a marker of lower peak bone mineral density. It may be a marker of differences in bone quality (bone structure or matrix composition, as well as bone quantity).

Further genetic studies on other candidate genes are required, due to the multifactorial nature of the disease. The aim of the future studies will be to define genes regulating bone mass and bone turnover, their interactions and interactions with environmental factors leading to osteoporosis.

The complex biology of the skeleton with so many factors involved in skeletal growth and development and the universal nature of age-related bone loss make it extremely unlikely that there is a single gene for osteoporosis. This would explain why the genetic markers studied to date account for only a small part of the variance in bone mineral density.

Complex future genetic studies of women with POF may answer the question of their premature aging and faster "biological clock". Pharmacogenomics of drug responsiveness may in future determine the selection of patients with POF for a given effective therapy.

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## Генски полиморфизам колагена тип I алфа 1 у превременој инсуфицијенцији јајника

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### КРАТАК САДРЖАЈ

**Увод** Превремена инсуфицијенција јајника (ПИЈ) се одликује аменорејом, хипергонадотропизмом и хипоестрогенијом код жена млађих од 40 година. Остеопороза је касна компликација овог стања.

**Циља рада** Циљ истраживања је био да се упореде генски полиморфизам колагена тип I алфа 1 (*COL1A1*) са густином коштане масе код жена са ПИЈ.

**Методе рада** Одређиван је *COL1A1* генотип *SS*, *Ss* и *ss* код 66 жена са ПИЈ помоћу есеја за реакцију ланчаног умножавања ДНК (енгл. *polymerase chain reaction – PCR*). Полиморфизам једног нуклеотида (замена *G* у *T*) у оквиру *Sp1* везујућег места у првом интрону гена *COL1A1* одређиван је применом *PCR*, након чега се приступило анализи конформационог полиморфизма. Густина коштане масе је мерена на нивоу лумбалног дела кичме помоћу апсорпциометрије. Хормонске анализе за фоликулостимулишући хормон, лутеинизирајући

хормон, естрадиол, пролактин, прогестерон и тестостерон урађене су применом метода *RIA*. При статистичкој обради података коришћени су: Краскал–Волисов (*Kruskal–Wallis*) *ANOVA* тест,  $\chi^2$ -тест и Спирманов (*Spearman*) тест корелације. **Резултати** Релативна дистрибуција алела *COL1A1* генотипа била је: *SS* 54,4%, *Ss* 41,0% и *ss* 4,5%. Није утврђена значајна разлика између група према генотипу за гуштину коштане масе, старост испитаница, период аменореје или индекс телесне масе жена. Значајна позитивна корелација је уочена за индекс телесне масе и паритет.

**Закључак** *COL1A1* је само један од многих гена који утичу на карактеристике кости. Код жена старије животне доби он може бити маркер квалитета, квантитета и осетљивости кости. Код младих жена са ПИЈ *COL1A1* не може да укаже на оне жене код којих постоји већи ризик за настанак остеопорозе.

**Кључне речи:** *COL1A1*; генски полиморфизам; превремена инсуфицијенција јајника; остеопороза