

Is There a Relation Between Osteoporosis and ABO/Rh Blood Group Antigens?

Balkan Şahin¹, Ali Erhan Kayalar², Mustafa Efendioğlu², Salim Katar³

¹Department of Neurosurgery, University of Health Sciences Turkey, Sisli Hamidiye Etfal Application and Research Center, Istanbul, Turkey

²Department of Neurosurgery, University of Health Sciences Turkey, Haydarpasa Numune Health Application and Research Center, Istanbul, Turkey

³Department of Neurosurgery, Balikesir University, Balikesir, Turkey

Abstract

Introduction: ABO and Rhesus (Rh) blood group antigens play a role in the etiology of many diseases. The aim of this study is to determine their effects (the effects of these antigens) on the development of osteoporosis.

Methods: We retrospectively analyzed all patients, who underwent kyphoplasty for osteoporotic vertebral corpus fractures between May 2014 and October 2019 in Balikesir University Hospital. Age, gender, fracture levels, T-scores, visual analog scale scores, Oswestry disability index scores, and blood groups were taken from the hospital data system and recorded for each patient. The data of blood group distribution among the study patients were compared with the data of healthy individuals in the same region.

Results: ABO blood groups results were not statistically significant in terms of the risk of developing osteoporotic vertebral fractures (OVFs). "Rh positive" blood type is associated with a high incidence of OVFs (91.5%) and the "Rh negative" blood group has the least association with OVFs (8.5%). Comparison of healthy controls with the OVF group revealed that Rh positive patients were at higher risk of OVF development. ($p=0.026$).

Discussion and Conclusion: The findings of this study show that in addition to environmental and genetic factors, Rh blood antigen is also effective in the development of osteoporosis.

Keywords: ABO blood group; osteoporosis; osteoporotic vertebral fracture; Rh blood group.

Osteoporosis is a skeletal disease which presents itself with an increase in bone fragility and possibility of fracture because of decreased bone mass and weakened bone structure. It is asymptomatic until complications such as fracture or vertebral body deformity occur [1]. However, one of the most common complaints of these patients is back pain, which is caused by small fractures due to osteoporosis in the spine. Fractures caused by osteoporosis are mostly seen in

the spine. These spinal fractures, called vertebral compression fractures, occur in approximately 700.000 patients every year [2,3]. Vertebral compression fractures are seen twice as much as other fractures typically associated with osteoporosis such as hip and wrist fractures [4]. Bone mineral density (BMD) is the most important factor that causes the fractures in osteoporosis. However, strength of the bone does not only depend on BMD. Osteoporosis is accepted in the group

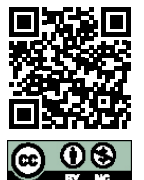
Correspondence (İletişim): Balkan Şahin, M.D. Türkiye Sağlık Bilimleri Üniversitesi Norosirurji Anabilim Dalı, Sisli Hamidiye Etfal Uygulama ve Araştırma Merkezi, İstanbul, Turkey

Phone (Telefon): +90 537 015 58 00 **E-mail (E-posta):** drbalkansahin@gmail.com

Submitted Date (Başvuru Tarihi): 29.04.2021 **Accepted Date (Kabul Tarihi):** 25.05.2021

Copyright 2022 Haydarpasa Numune Medical Journal

OPEN ACCESS This is an open access article under the CC BY-NC license (<http://creativecommons.org/licenses/by-nc/4.0/>).



of multifactorial diseases, in which genetic factors and environmental effects play a role [5,6].

Genetic factors play an important role in the formation of components that provide strength to the bone. Especially, bone-specific alkaline phosphatase and lysine hydroxylase are two important molecules in the formation and durability of the bone. Alkaline phosphatase is a sensitive and specific marker of bone formation and is also an indicator for it. Lysine hydroxylase is a collagen-specific protein. Lysine and hydroxylysine which are found in the collagen, form post-translational cross-links, which stabilizes the collagen and helps increase bone durability [7-9]. These two molecules are synthesized in the Alkaline Phosphatase (ALPL) Gene and Lysine Hydroxylase (PLOD) Gene genetic codons, which are located at the 1p36 locus [10]. Alternations in these genetic codons have been shown to increase the risk of osteoporosis by causing bone mineral loss [11-15].

Although the entire human population shares similar ABO and Rhesus (Rh) blood groups (types), the frequency and distribution vary between countries and races. ABO and RHD antigens are polymorphic, antigenic and genetic substances that are found mostly on the surface of red blood cells [16]. Hereditary polymorphic traits transferred between humans are found in blood group antigens and are a useful and valuable resource, due to not being affected by environmental factors. The ABO blood group system consists of four basic groups (A, B, O, AB), depending on the presence of A and B antigens, and the genetic localization of ABO blood group antigens is in region 9q34.2 [17]. The Rh blood group system antigens are encoded by two pairs of allele genes which are RHD and RHCCeE. The main antigen of this group is RHD and the group is classified as RH (+) or RH (-) depending on the presence of the RHD antigen. RH blood group antigens are located in the 1p36 gene localization [18].

After being defined in the early 1900s, ABO and RH blood groups have been shown to be associated with various diseases such as cancer, infections, hip fractures, rheumatoid arthritis, cardiovascular, and cerebrovascular diseases [19,20]. In recent studies, it has been shown that enzymes that originate from the same gene loci with the antigenic structures of ABO and RH groups play an important role in folate metabolism, which increases the risk of myelomeningocele formation [21].

It has been shown that alkaline phosphatase and lysine hydroxylase enzymes which cause osteoporosis in their deficiency, and RH blood group antigens originate from the same gene locus (Table 1).

Table 1. Gene localization

	Genetic Loci
Rh protein family	
RhD gene	1p36
RhCcEe gene	1p36
Matrix-related enzymes	
ALPL gene	1p36
PLOD gene	1p36

ALPL: Alkaline phosphatase; PLOD: Lysine hydroxylase.

Our aim in this study is to evaluate the relationship between the distribution of ABO and/or RH blood group antigens and the risk of developing osteoporosis in the Turkish population.

Materials and Methods

This study has been approved by Balıkesir University Ethics Committee (Approval date: 08.04.2020/53). We retrospectively analyzed all patients, who underwent kyphoplasty for osteoporotic vertebral corpus fractures between May 2014 and October 2019 in Balıkesir University Hospital. Age, gender, fracture levels, T-scores, visual analog scale scores, Oswestry disability index scores, and blood groups were taken from the hospital data system and recorded for each patient. T-scores and blood groups were taken from the hospital data system and recorded for each patient. T-score measurements were performed using the Dual Energy X-Ray Absorptiometry method. Patients with osteoporotic vertebral fractures (OVFs) due to use of steroids were excluded from the study. The blood group distribution data among our patients were compared with the most comprehensive data collected from 123,900 healthy individuals from the same region [22].

Results

Three hundred seven patients who were diagnosed with OVF and operated on were retrospectively evaluated. Two hundred twenty seven (73.9%) of the patients included in the study were female and 80 (26.1%) were male. The mean age was 69±4.3 (range 60–79). The most common osteoporotic compression fracture was observed in the vertebral corpus of L1 (n=117), while the least number of fractures were observed in the L3 (n=15) vertebral corpus. The main characteristics of the study population are summarized in Table 2. The distribution of blood group antigens in patients with OVF between national blood group frequencies was different. The distribution of blood groups in patients are as

Table 2. Characteristics of the patients

	n (%)
Gender	
Females	227 (73.9)
Males	80 (26.1)
Age	
Females	68.9±4.31
Males	69.1±4.25
Lesion level	
T11	47 (15.3)
T12	38 (12.4)
L1	117 (38.1)
L2	42 (13.6)
L3	15 (4.9)
L4	31 (10.7)
L5	17 (5.5)
Blood groups	
A	127 (41.3)
B	57 (18.6)
O	93 (30.3)
AB	30 (9.8)
Rh+	281 (91.5)
Rh-	26 (8.5)

following: A: 127 (41.3%), B: 57 (18.6%), O: 93 (30.3%), AB: 30 (9.8%), Rh+: 281 (91.5%), Rh-: 26 (8.5%) (Table 3). When the patients are compared with the healthy control group; while the ratio of groups A and O decreased, it was observed that the ratio of groups B and AB increased. However, these results were not statistically significant in terms of the risk of developing OVF (Table 3). "Rh positive" blood type is associated with high incidence of OVF (91.5%) and "Rh negative" blood group has least association with OVF (8.5%). Comparison of healthy controls with the OVF group revealed that Rh-positive patients were at higher risk of OVF development ($p=0.026$). Patients with Rh-positive blood group showed significantly higher probability of developing OVF when compared with Rh-negative patients (OR=1.57).

Table 3. Comparison of osteoporotic patients and control groups

Antigens	Patients (n=307)	Control Group (n=123.900)	P
A	127 (41.3%)	43.81%	0.387
B	57 (18.6%)	15.21%	0.163
O	93 (30.3%)	33.79%	0.194
AB	30 (9.8%)	7.16%	0.077
Rh+	281 (91.5%)	87.31%	0.026
Rh-	26 (8.5%)	12.69%	0.026

Discussion

In this study, we have evaluated the relationship between the most common blood group antigens and osteoporosis. To the best of our knowledge, it is the first general study to evaluate ABO and Rh with osteoporosis. We have not observed a significantly higher risk for osteoporosis between blood groups, OVF cases and controls from large cohort studies in the same regions, between A, B, O and AB blood groups, as risk factors for the development of osteoporosis. However, we have found that Rh positivity was significantly higher in relation to the development of osteoporosis.

Considering the complex biology of the skeletal structure, bone mass is under the control of many genes. Various epidemiological and clinical findings in the past years underline the importance of genetics in the pathogenesis of osteoporosis [23,24]. BMD, used in the diagnosis of osteoporosis, is a complex feature that does not show dominant-recessive features in a single gene locus, which does not fit the classical mendelian inheritance patterns [10]. Although there are many environmental factors affecting BMD, recent studies have focused on the impact of genetic structure on the pathogenesis of osteoporosis, and the existence of many candidate genes that have an effect on bone mass has been reported [25,26]. In addition, epidemiological studies show that positive family history is a risk factor for OVF formation in osteoporosis. It has been shown that OVF increases the mortality risk by approximately 60% [27]. The most important reason for the conflicting data has been shown to be the study of different ethnic character groups, which means that genetic studies on osteoporosis should be performed between patient groups of the same region or groups of the same origin. In recent years, studies involving various candidate genes have identified some regions and genes involved in osteoporotic fracture pathogenesis and bone mass regulation. In the single Nucleotide Polymorphism studies, a link with BMD in the 1p36 region has been identified [28]. In bone formation mechanism, the ALPL gene, which is one of the most important matrix-related enzymes, and PLOD gene and RH blood group antigens (RHD, RHCCeE) are located in the chromosome 1p36.

Bone tissue consists of 30% organic matrix and 70% inorganic matrix. The extracellular organic matrix, which is named as osteoid and contains a large amount of osteoblasts, is transformed into bone when it is mineralized. Organic matrix provides the flexibility of the bone. Ninety percent of the organic matrix consists of type 1 collagen [29]. The lysine and hydroxyline in the collagen make posttranslational cross-links, and hydroxylation of the lysine residues

occurs by the effect of lysyl hydroxylase. These help stabilize the collagen. The second important topic is bone mineralization; ALP plays a role in initiating extracellular matrix mineralization by breaking down PPI, a strong inhibitor of mineralization [30]. In addition, ALP reduces the mineralization-inhibiting effect of osteopontin by dephosphorylating it [31]. In the recent ALPL gene mutation studies on 1q36 chromosome, In Japan, c.1559delT mutation is seen in 40.9% of the cases and p.Phe327Leu mutation is seen in 13.6% of the cases [32,33]. In Canada, the p.Gly334Asp mutation is more common in the Mennonite community [34]. In Europeans, p.Glu191Lys mutation is seen at 7–14%, this rate is 21.3–27.6% in patients with the moderate clinical form of HPP [35,36]. P.Asp378Val is a missense mutation, which is the most common mutation in America (15.6%). It was found that these mutations cause problems in ALP enzyme activity, which makes osteoporosis more severe in patients. About 370 mutations (missense, nonsense, frame shift mutation, insertion) have been identified in ALPL and PLOD genes localized in the 1q36 chromosome.

ABO blood group antigens are encoded on chromosome 9q34 and encode RHD gene D antigen and RHCE gene CcEe antigen on chromosome 1q36 [16,17]. There is an interesting hypothesis about the pathophysiological connection between colorectal cancer, gastric cancer, glioblastoma multiforme and astrocytomas of the central nervous system cancers, and the ABO and Rh blood groups [37,38]. The relationship between ABO and Rh antigens and tumor necrosis factor- α , E-selectin, P-selectin and intercellular adhesion molecule-1 has been shown that ABO and Rh alleles affect the formation and spread of malignancy [38]. In addition, the relationship between ABO and Rh blood groups and hip fractures, rheumatoid arthritis, Alzheimer's disease and Behçet's disease have been revealed [19,39]. In this presented study, we conducted a retrospective analysis of patients with OPV to investigate the effect of ABO and Rh blood groups on OP development. There was no significant difference between the ABO blood group and the possibility of developing OP, but in the presence of Rh antigen, OP development was statistically significant. In a recent study involving only postmenopausal women in South Korea, only ABO blood groups were evaluated, it was seen that osteoporosis prevalence was higher in patients with AB blood group [40]. In our study, although the A, B and AB groups were seen at a higher rate than the normal population, they were not found statistically significant (Table 2). In addition, although it was not evaluated, all patients were reported to be RH+, in the same study conducted in South Korea. When evaluated from this point of view, we

think that it is in parallel with our study. Due to the close similarity between the genetic positions of important enzymes in bone metabolism and Rh antigens, allele variants in Rh genes on the 1p36 chromosome might be important for OP hereditary susceptibility.

Conclusion

As a result, we found differences in the distribution pattern of ABO blood groups in patients with OP compared with the general healthy population and we found that the distribution of the ABO blood group was not a risk factor for OP development. Individuals with Rh antigen had a higher risk of developing OP. Based on the findings of this study, we think that the presence of Rh antigen has an effect on the development of OP under the influence of genetic factors.

Ethics Committee Approval: This study has been approved by Balikesir University Ethics Committee (Approval date: 08.04.2020/53).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: B.Ş., S.K.; Design: B.Ş., S.K.; Data Collection or Processing: S.K.; Analysis or Interpretation: B.Ş., S.K., A.E.K.; Literature Search: B.Ş., A.E.K., M.E.; Writing: B.Ş., S.K.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study received no financial support.

References

- Ling X, Cummings SR, Mingwei Q, Xihe Z, Xiaoashu C, Nevitt M, et al. Vertebral fractures in Beijing, China: The Beijing Osteoporosis Project. *J Bone Miner Res* 2000;15:2019–25.
- Wong CC, McGirt MJ. Vertebral compression fractures: A review of current management and multimodal therapy. *J Multidiscip Healthc* 2013;6:205–14.
- Ensrud KE, Schousboe JT. Clinical practice. Vertebral fractures. *N Engl J Med* 2011;364:1634–42.
- Fink HA, Milavetz DL, Palermo L, Nevitt MC, Cauley JA, Genant HK, et al. What proportion of incident radiographic vertebral deformities is clinically diagnosed and vice versa? *J Bone Miner Res* 2005;20:1216–22.
- Zajickova K, Zofkova I. Osteoporosis: genetic analysis of multifactorial disease. *Endocr Regul* 2003;37:31–44.
- Lee HJ, Kim SY, Kim GS, Hwang JY, Kim YJ, Jeong B, et al. Fracture, bone mineral density, and the effects of calcitonin receptor gene in postmenopausal Koreans. *Osteoporos Int* 2010;21:1351–60.
- Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan J. The use of biochemical markers of bone turnover in osteoporosis. Committee of scientific advisors of the international osteoporosis foundation. *Osteoporos Int* 2000;11:S2–17.
- Durmaz B., Biyokimyasal Göstergeler, Osteoporozda Kemik

- Kalitesi, Ed: Kutsal Y.G., 1. Baskı, Güneş Tıp Kitabevi. Ankara. 2004;s:175-192.
9. Tanakol R. Primer ve sekonder laboratuvar tetkikleri osteoporoz tanısında ve biyokimyasal kemik döngü göstergeleri. In: Domaniç Ü, Göksan S, editors. Osteoporoz. Ankara: Ortopedi ve Travmatoloji Yayın Evi; 2000. p.28–33.
 10. Tural Ş, Kara N, Alaylı G. Genetics of Osteoporosis. *Turk J Osteoporosis* 2011;17:100–9.
 11. Mornet E, Simon-Bouy B. Génétique de l'hypophosphatasie [Genetics of hypophosphatasia]. *Arch Pediatr* 2004;11:444–8. [Article in French]
 12. Eyre D, Shao P, Weis MA, Steinmann B. The kyphoscoliotic type of Ehlers-Danlos syndrome (type VI): Differential effects on the hydroxylation of lysine in collagens I and II revealed by analysis of cross-linked telopeptides from urine. *Mol Genet Metab* 2002;76:211–6.
 13. Heikkinen J, Toppinen T, Yeowell H, Krieg T, Steinmann B, Kivirikko KI, et al. Duplication of seven exons in the lysyl hydroxylase gene is associated with longer forms of a repetitive sequence within the gene and is a common cause for the type VI variant of Ehlers-Danlos syndrome. *Am J Hum Genet* 1997;60:48–56.
 14. Giunta C, Randolph A, Steinmann B. Mutation analysis of the PLOD1 gene: An efficient multistep approach to the molecular diagnosis of the kyphoscoliotic type of Ehlers-Danlos syndrome (EDS VIA). *Mol Genet Metab* 2005;86:269–76.
 15. Michigami T, Uchihashi T, Suzuki A, Tachikawa K, Nakajima S, Ozono K. Common mutations F310L and T1559del in the tissue-nonspecific alkaline phosphatase gene are related to distinct phenotypes in Japanese patients with hypophosphatasia. *Eur J Pediatr* 2005;164:277–82.
 16. Avent ND, Reid ME. The Rh blood group system: A review. *Blood* 2000;95:375–87.
 17. Reid ME, Mohandas N. Red blood cell blood group antigens: Structure and function. *Semin Hematol* 2004;41:93–117.
 18. Avent ND, Reid ME. The Rh blood group system: A review. *Blood* 2000;95:375–87.
 19. Kuru T, Olcar HA. Relationship between the ABO blood system and proximal femoral fracture Patterns in the Turkish population. *Biomed Res Int* 2020;2020:1834525.
 20. Anstee DJ. The relationship between blood groups and disease. *Blood* 2010;115:4635–43.
 21. Isik S, Cevik S, Turhan AH, Baygul A, Hanimoglu H. ABO and Rh blood groups and risk of myelomeningocele. *Turk Neurosurg* 2020;30:449–53.
 22. Eren C. Analysis of distribution of ABO and Rh blood groups in İstanbul Province. *Dicle Med J* 2019;46:241–6.
 23. Gennari L, Becherini L, Falchetti A, Masi L, Massart F, Brandi ML. Genetics of osteoporosis: Role of steroid hormone receptor gene polymorphisms. *J Steroid Biochem Mol Biol* 2002;81:1–24.
 24. Gennari L, Merlotti D, De Paola V, Calabrò A, Becherini L, Martini G, et al. Estrogen receptor gene polymorphisms and the genetics of osteoporosis: A HuGE review. *Am J Epidemiol* 2005;161:307–20.
 25. Peacock M, Turner CH, Econs MJ, Foroud T. Genetics of osteoporosis. *Endocr Rev* 2002;23:303–26.
 26. Uitterlinden AG, van Meurs JB, Rivadeneira F, Pols HA. Identifying genetic risk factors for osteoporosis. *J Musculoskeletal Neuronal Interact* 2006;6:16–26.
 27. Senturk T. Erkeklerde Osteoporoz. *J Immunol Rheumatol* 2002;2:132–8.
 28. Ferrari S. Human genetics of osteoporosis. *Best Pract Res Clin Endocrinol Metab* 2008;22:723–35.
 29. Feng X: Chemical and Biochemical Basis of Cell-Bone Matrix Interaction in Health and Disease. *Curr Chem Biol* 3: 189–196, 2009.
 30. Yadav MC, Simão AM, Narisawa S, Huesa C, McKee MD, Farquharson C, et al. Loss of skeletal mineralization by the simultaneous ablation of PHOSPHO1 and alkaline phosphatase function: A unified model of the mechanisms of initiation of skeletal calcification. *J Bone Miner Res* 2011;26:286–97.
 31. Narisawa S, Yadav MC, Millán JL. In vivo overexpression of tissue-nonspecific alkaline phosphatase increases skeletal mineralization and affects the phosphorylation status of osteopontin. *J Bone Miner Res* 2013;28:1587–98.
 32. Michigami T, Uchihashi T, Suzuki A, Tachikawa K, Nakajima S, Ozono K. Common mutations F310L and T1559del in the tissue-nonspecific alkaline phosphatase gene are related to distinct phenotypes in Japanese patients with hypophosphatasia. *Eur J Pediatr* 2005;164:277–82.
 33. Orimo H, Goseki-Sone M, Inoue M, Tsubakio Y, Sakiyama T, Shimada T. Importance of deletion of T at nucleotide 1559 in the tissue-nonspecific alkaline phosphatase gene in Japanese patients with hypophosphatasia. *J Bone Miner Metab* 2002;20:28–33.
 34. Greenberg CR, Taylor CL, Haworth JC, Seargeant LE, Philipps S, Triggs-Raine B, et al. A homoallelic Gly317→Asp mutation in ALPL causes the perinatal (lethal) form of hypophosphatasia in Canadian mennonites. *Genomics* 1993;17:215–7.
 35. Whyte MP. Hypophosphatasia - aetiology, nosology, pathogenesis, diagnosis and treatment. *Nat Rev Endocrinol* 2016;12:233–46.
 36. Hérasse M, Spentchian M, Taillandier A, Mornet E. Evidence of a founder effect for the tissue-nonspecific alkaline phosphatase (TNSALP) gene E174K mutation in hypophosphatasia patients. *Eur J Hum Genet* 2002;10:666–8.
 37. Allouh MZ, Al Barbarawi MM, Hiasat MY, Al-Qaralleh MA, Ababneh EI. Glioblastoma and ABO blood groups: Further evidence of an association between the distribution of blood group antigens and brain tumours. *Blood Transfus* 2017;15:543–7.
 38. Kahramanca S, Anuk T, Yildirim AC, Kaya O. Blood group characteristics in colorectal cancers. *Turk J Colorectal Dis* 2018;28:76–9.
 39. Renvoize EB. ABO and Rhesus blood groups in Alzheimer's disease. *Age Ageing* 1985;14:43–5.
 40. Choi JW, Pai SH. Associations between ABO blood groups and osteoporosis in postmenopausal women. *Ann Clin Lab Sci* 2004;34:150–3.