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Systematic Review

A Study of COL1A1 Genotype and Bone Marrow Density (BMD) in Osteoporosis in Indian Women- A Systematic Review

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ABSTRACT
Osteoporosis, characterized by increased fracture risk and reduced bone mass, is often linked to genetic factors such as mutations in the COL1A1 gene, which encodes the α1(I) chain of type I collagen, a key bone protein. This systematic review investigates the relationship between COL1A1 polymorphisms and bone mineral density (BMD) in Indian women. Key polymorphisms of interest include the Sp1 binding sites -1997 G>T (rs1107946), 1663in/delT, and +1245 G>T (rs1800012). A comprehensive literature search was conducted in Google Scholar, PubMed, and Scopus, focusing on BMD and COL1A1 genetic data in this demographic. The review addresses ongoing debates about the strength of the link between COL1A1 polymorphisms and low BMD or increased fracture risk. Despite variations in study designs, the findings underscore COL1A1's role in osteoporosis susceptibility in Indian women and highlight the need for more research on genetic markers for targeted osteoporosis interventions.

INTRODUCTION
Studies conducted on a limited scale in India indicate that women over 50 have a significant frequency of osteoporosis. An estimated 46 million out of the 230 million women in this age group who are expected to exist in 2015 or 20% of the total may have osteoporotic bone. The symptoms of osteoporosis, which are believed to have a hereditary basis, include decreasing bone mass, deterioration of the microstructure of the bone, and an elevated risk of fragility fractures (Bernad et al., 2002).[1] The genes that control bone quality, bone geometry, and bone mineral density (BMD) are most crucial in determining the susceptibility to osteoporosis (Karasik et al., 2016).[2] The primary structural protein in bone, type I collagen α1(I) protein chain, is encoded by COL1A1, a major candidate gene for osteoporosis risk (Navarro et al., 2007). The COLIA1 gene has a mapping location 17q21.31–q22 in humans (Qin et al., 2005).[3] Osteoporotic phenotype in osteogenesis imperfecta has also been linked to mutations in this gene (Palagano et al., 2018). Results of GWAS studies have identified hundreds of

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variations influencing bone mineral density, a key factor in osteoporosis and fracture risk (Zhu et al., 2021).[4]

Garcia-Giralt et al. (2002)[5] explored the promoter region of COL1A1 gene that has gene controlling activity. Two new variations (1663indelT and 1997 G/T) were found in the COL1A1 promoter. In postmenopausal women, the -1997 G/T variation is found to be linked to higher bone mineral density (BMD) in the lower spine. Another variation (1663indelT) did not directly affect BMD but interacted with both -1997 G/T and a known intron 1 variation, with those carrying a specific combination showing the highest BMD. These promoter variations may influence bone density by interacting with proteins in bone-forming cells (Garcia-Giralt et al., 2002).[5] The first intron of the Sp1 binding site contains a G→T alteration (rs1800012), which is known as the Sp1 binding site polymorphism. This variation is important because it is linked to low bone properties during early puberty and may have an effect on bone turnover and collagen metabolism physiologically (Suuriniemi et al., 2006).[6] This single nucleotide polymorphism (SNP) modifies the binding affinity of the Sp1 transcription factor, which in turn impacts the expression of the COL1A1 gene (Kurt-Sirin et al., 2014).[7] Numerous studies have consistently linked the Sp1 binding site polymorphism to decreased bone mineral density (BMD) and an increased risk of osteoporotic fractures, underscoring its importance in the etiology of osteoporosis (Gug et al., 2020; Heegaard et al., 2000).[8,9] For example, a study conducted in Turkey examined the effects of Sp1 polymorphism variations in the COL1A1 gene on bone mineral density and their correlation with osteoporosis risk factors in postmenopausal women. The researchers employed PCR-RFLP techniques to detect the polymorphism and DXA scans to measure BMD in 254 participants. Subjects with the "ss" genotype had a tendency towards decreased BMD at the lumbar spine, femoral neck, and total hip, even if the changes were not statistically significant (Kurt-Sirin et al., 2014).[7]

METHOD

We conducted an organized and extensive literature search in electronic databases using keywords such as COL1A1, genotype, bone mineral density, osteoporosis, and Indian women. PubMed, Scopus, and Google Scholar were all searched for research articles up to February 2024. The studies that met our inclusion criteria were those that reported genotype frequencies and BMD measurements, looked at the relationship between COL1A1 polymorphisms and BMD in Indian women, and were published in peer-reviewed publications. Study design, sample size, participant demographics, COL1A1 genotypes, BMD measures, and key findings were all included in the data extraction process.

Using the terms COL1A1, women, and bone mineral density from 2010 to 2024, the search turned up 63 relevant papers on PubMed; 70 studies from the same time included the keywords COL1A, women, and osteoporosis, and 106 studies included the keywords COL1A1, genotype, and osteoporosis. A Google Scholar search for COL1A1 gene influence bone mineral density (2010–2024) yielded 2,600 items; Scopus yielded 802 publications with same keywords (no year filter), and a further search for COL1A1 genotype and bone mineral density, women, osteoporosis generated 3,840 results. We filtered out 280 papers from google scholar, 125 from Pubmed and 400 from Scopus that aligned with your criteria and found that 3 papers belong to Indian women population.

RESULTS

Seven studies met the inclusion criteria, out of which 3 studies precisely included the examination of influence of COL1A1 gene polymorphisms in altering the susceptibility of a lowered BMD and osteoporosis, encompassing a total of 499 Indian women. The studies

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varied in sample size, ranging from 150 to 350 along with control participants. The mean age of participants was between 35 and 65 years.

COL1A1 polymorphisms and BMD

Numerous studies have looked at the connection between bone health and COL1A1 gene polymorphisms. Three polymorphisms have been identified in the 5' regulatory region of the COL1A1 gene: -1997 G > T (rs1107946), -1663 (rs2412298), and +1245G/T (rs1800012) (Jin et al., 2011).[10] In 1044 elderly Swedish women, the COL1A1 gene's Sp1 polymorphism was found to be associated with lower femoral neck bone mineral density (BMD) and an increased risk of wrist fractures (Gerdhem et al., 2004). Interestingly, it seems that the's' allele had a greater impact on fracture risk (Gerdhem et al., 2004). Zhang et al. (2015) discovered a connection between hip BMD and the -1997 G/T polymorphism in the COL1A1 regulatory area in a different study involving Chinese families (Zhang et al., 2015) .

The first meta-analysis by Mann and Ralston (2003)[11] comprising 26 inclusive studies corresponding to 7849 individuals, strengthened the link between COL1A1 Sp1 polymorphism and fracture risk in the population. The association with fracture appears independent of bone mineral density (BMD) effects, suggesting the polymorphism may influence fracture risk through additional mechanisms (Mann & Ralston, 2003).[11]

Moreover, an year later, research study by Liu et al 2004[12] linked COL1A1 gene variations PCOL2 (-1997 G/T) in the promoter, Sp1 (1546 G/T) to BMD in elderly Caucasian women. Notably, the interaction of these SNPs had a stronger association with BMD (p=0.001-0.003) compared to their individual effects. The GG haplotype showed a 2.7% higher average BMD (p=0.006-0.026), suggesting a potential protective effect against osteoporosis (Liu et al., 2004).

The COL1A1 gene is important for bone health, as demonstrated by a different meta-analysis. This relevance is reinforced by the correlation found in the gene between osteoporosis risk and the -1997 G > T (rs1107946) variation. A meta-analysis comprising 32 research with a total of 24,511 people examined the correlation between bone health and COL1A1 gene polymorphisms (-1997G/T, -1663indelT, Sp1). The TT genotype, or Sp1 variation, is associated with a notably reduced bone mineral density (BMD) in the hip and spine as well as an increased risk of fractures. Associations with BMD were also observed for the other polymorphisms, but publication bias cannot be entirely ruled out. Further investigation is warranted to elucidate the roles of -1663in/delT and -1997G/T polymorphisms in affecting BMD linking to osteoporosis and to further determine their potential interactions with other Sp1 polymorphisms in osteoporosis susceptibility (Jin et al., 2011).[10] Interestingly a meta-analysis in 2015, investigated the relationship between bone health in osteoporosis and two genetic polymorphisms (rs1107946 and rs2412298) of the COL1A1 gene focusing on fracture risk and bone mineral density (BMD). Although there were no obvious trends in the population as a whole, several subgroups showed some intriguing results. The ‘T’ allele of the polymorphism rs1107946 has been linked to increased BMD in the lumbar spine, or lower back among Caucasians. Furthermore, GG genotype was linked to increased total hip BMD, especially in those who were approaching or past menopause. Both of these SNPs, nevertheless, did not clearly correlate with fracture risk (Xie et al., 2015).

The meta-analysis study by Wu et al. (2017)[13] offers compelling evidence. It assessed the relationship between a polymorphism in the COL1A1 gene, +1245G/T, and the risk of osteoporosis in postmenopausal women in a total of 1557 participants (including osteoporosis, osteopenia, and healthy controls from 5 studies). The GG genotype of the polymorphism is significantly correlated with an increased risk of osteoporosis, but only in the context of a co-dominant genetic model. There is no discernible correlation with the risk

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of osteopenia. These findings suggest a potential link between the GG genotype and elevated osteoporosis risk in this population, however further research is warranted for confirmation (Wu et al., 2017).

A recent study by Saito et al 2022[14] investigated how the COL1A1 gene polymorphisms influence bone mineral density (BMD) in Caucasian individuals. Researchers analyzed four specific variations (SNPs) within this gene in over 600 people (313 Caucasian males and 308 Caucasian females). PCOL2 mutation showed a clear link to BMD in elderly Caucasian women. Another variation (Sp1) had a suggestive association. Interestingly, the combined effect of these two variations was even stronger than their individual effects on BMD. Individuals carrying the GG haplotype at the PCOL2 and Sp1 loci exhibited significantly higher BMD (Moradifard et al., 2020),[15] suggesting a potential epistatic effect on BMD regulation and potentially influencing susceptibility to osteoporosis in elderly Caucasian females (Saito et al., 2022).[14] While past studies linked COL1A1 gene variations to bone mineral density (BMD), other studies also investigated their impact on bone's mechanical properties. Their analysis revealed that specific variations in the COL1A1 regulatory region were associated with weaker bone and lower quality, independent of BMD. This suggests these variations might influence bone health through mechanisms beyond just mineral density.

The prominent studies on Indian women

The first study on Indian population was conducted by Singh et al. (2013)[16] on northwest Indian postmenopausal women. The researchers investigated whether certain genetic variations (SNPs) in the COL1A1 gene are linked to osteoporosis in the population. The study involved 349 women, involving those with osteoporosis (145), those with osteopenia (87), and those with normal bone density or the control group (117). The GT haplotype in two specific SNPs rs1800012 and rs1107946 was found to be associated with an increased risk of osteoporosis in this population group (Singh et al., 2013)

Current research in postmenopausal women indicates that the T allele of the COL1A1 Sp1 polymorphism is associated with reduced bone mineral density (BMD) and an increased risk of osteoporotic fractures. Nevertheless, previous studies, namely those conducted in Asian communities, produced inconclusive results. These contradictions encompassed the absence of a connection between the polymorphism and bone health, or even the nonexistence of the T allele itself in certain investigations. The lack of clarity about the relevance of the COL1A1 Sp1 polymorphism as a genetic risk factor for osteoporosis is emphasised by this uncertainty. Therefore, it is essential to conduct more rigorous research investigations on the COLIA1 gene in other populations in order to get universal confirmation.

While a limited Indian study examined females, the association in Sikkimese men of Northeast India remains unexplored. Thus, the study conducted by Soibam et al. in 2019 [17] aimed to assess the correlation between the Sp1 binding site polymorphism in the COL1A1 gene and low bone mineral density (BMD) in a population comprising both women and men. A total of 150 individuals were examined, consisting of 75 males and 75 females, who had bone conditions such as primary osteopenia and osteoporosis. Additionally, 150 healthy individuals between the ages of 35 and 65 were included as controls. The Sp1 polymorphism was very rare, found in only 2.7% of women and 1.3% of men with bone problems. Statistical analysis showed no association between the low bone density and genetic polymorphism. This suggests the Sp1 polymorphism is unlikely to be a major factor in low bone density for this population (Soibam et al., 2019). However, the investigation in southern parts of India is still lacking.

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A targeted sequencing analysis of COL1A1 and COL1A2 genes was performed in 35 Indian patients and revealed mutations in 25 patients (71%). COL1A1 mutations were found in 14 cases, with six being novel variants (Stephen et al., 2014). Single-stranded conformation polymorphism (SSCP) analysis indicated that BMD values in osteoporotic women are unaffected by the G to T substitution in the COL1A1 gene. Hence, these studies are not sufficiently promising to evaluate the role of SNPs in BMD linked to osteoporosis. However, there are several important research studies among Indian population that reveal a strong relationship between COL1A1 gene polymorphisms with genetic bone disorder Osteogenesis imperfecta but not osteoporosis suggesting their role in bone genetics (Berti et al., 2023; Mehta et al., 2024). [18,19]

CONCLUSION

Research on the association between polymorphisms in the COL1A1 gene and osteoporosis susceptibility is inconclusive. Even after taking bone mineral density (BMD) into account, some continue to exhibit correlations with fracture risk, while others continue to show no correlation. The polymorphism COL1A1 Sp1 is linked to a slight decrease in bone mineral density and a higher risk of fracture; nevertheless, it is possible that publication bias played a role in the results. Hence, it is safe to conclude although the Sp1 polymorphism in COL1A1 is found at a known locus that can affect gene regulation, it is yet unknown how exactly this polymorphism affects the synthesis of collagen. The available studies are based on functional investigations that analyse the possible correlation between osteoporotic fractures and changes in COL1A1 gene. Further studies are needed to definitively understand the role of the 1663in/delT and -1997G/T polymorphisms in osteoporosis susceptibility. This systematic review suggests that more conclusive and extensive researchers should be conducted at the mRNA and protein levels, DNA-protein binding, allele-specific gene expression, and the biomechanical characteristics of bone in connection to COL1A1 genotypes.

FUTURE PERSPECTIVES

Osteoporosis treatment currently faces limitations, highlighting the need for innovative approaches. In addition to COL1A1 and COL1A2 genes, many other specific genes with newly discovered polymorphisms like PON1, PON2, CYP 17, DRD4, COMT, CCR2, MMP-1, IRAK1, and MMP-9, and their interaction can be known to identify biomarkers of low BMD and osteoporosis. The success of miRNA-based therapies in orthodontics direct the researchers to explore the potential of functional genomics along with utilising DNA microarrays and proteomic analysis to gain a deeper understanding of bone formation and osteoporosis development. By targeting specific miRNAs that regulate bone formation and breakdown, this approach could offer new avenues for promoting bone growth, inhibiting bone loss, and ultimately combating the debilitating effects of osteoporosis. This exciting development holds promise for a future where osteoporosis treatment is more effective and less reliant on medications with limitations.

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