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# Multisystem Determinants of Low Bone Mineral Density in Scoliosis: Genetic, Endocrine, Nutritional, and Biomechanical Interactions

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## ABSTRACT

Scoliosis exists as a three-dimensional spinal deformity which develops through the combination of genetic elements, endocrine factors, biomechanical forces, and nutritional components. Research shows that bone mineral density (BMD) reduction exists as a widespread condition throughout adolescent idiopathic scoliosis (AIS), congenital scoliosis, and neuromuscular scoliosis patients. Dual-energy X-ray absorptiometry and high-resolution peripheral quantitative CT scans show that bone density is lower in both cortical and trabecular areas while microarchitectural changes occur which could lead to spinal curve development and growth. The development of skeletal abnormalities results from multiple biological pathways. Research studies using genome-wide and candidate-gene approaches have identified LRP5, VDR, COL1A1, and other essential genes which control osteoblast development and matrix structure. The process of bone formation receives additional influence from epigenetic changes which affect the methylation patterns of osteogenic transcription factors and estrogen-related genes. The specific microRNA patterns found in AIS patients disrupt BMP and SMAD signaling pathways which results in decreased osteogenic potential. The combination of endocrine disorders including estrogen metabolism changes, vitamin D deficiency, and elevated parathyroid hormone levels makes bone defects worse while scientists continue to study melatonin, leptin and growth hormone potential roles. The combination of nutritional deficiencies that affect calcium, magnesium, zinc, and vitamin K2 levels in patients leads to increased metabolic risk. The combination of reduced physical activity, restricted bracing use, and impaired mechanotransduction leads to decreased skeletal loading which prevents adolescents from reaching their peak bone mass. Research evidence supports a complex system model which demonstrates scoliosis and low BMD share common genetic, hormonal, nutritional, and mechanical factors that affect spinal structure and complete skeletal health. The combination of genetic tests with endocrine, nutritional, and biomechanical evaluations will help doctors identify at-risk patients better while developing specific treatments to enhance bone strength and control spinal curve growth.

**Keywords:** Scoliosis, Bone Mineral Density, Osteopenia, Osteoporosis, Genetics, Hormones, Neuromuscular Scoliosis, Idiopathic Scoliosis, Vitamin D, Estrogen

## Introduction

The medical definition of scoliosis describes it as a spinal deformity which creates three-dimensional spinal curvature through lateral bending and vertebral rotation at or above 10 degrees Cobb angle. The different etiologic categories of scoliosis include adolescent idiopathic scoliosis (AIS), congenital scoliosis, and neuromuscular scoliosis, which share common biomechanical and metabolic characteristics but follow different developmental paths. The most common form of scoliosis exists as AIS because it makes up 80-90% of all cases and develops during puberty when fast bone growth meets genetic elements, hormonal changes, and structural factors to create spinal curvature.

Research findings indicate that bone mineral density (BMD) functions as a primary element in scoliosis disease development beyond what scientists initially understood.[1,2] Research based on epidemiologic and imaging data shows scoliosis patients have decreased bone density throughout their bodies along with reduced trabecular, bone density, cortical bone density, abnormal bone structure, and elevated bone turnover indicators.[3-5] The presence of low BMD occurs before doctors can detect spinal curvature through X-rays which indicates that weak bones might act as a risk factor for scoliosis development. The relationship between bone density, scoliosis severity, progression risk, and vertebral loading patterns shows that weak bones increase the mechanical instability of scoliosis.

Multiple factors including genetic elements, epigenetic controls, endocrine system disruptions, insufficient nutrition, defective mechanotransduction, and universal population effects determine the scoliotic bone structure. The review investigates scoliosis-bone density relationships through multiple fields to establish disease mechanisms, enhance patient risk assessment, and develop optimized system-based treatment plans.

## Bone Density and Scoliosis: Epidemiologic and Radiographic Correlations

Multiple studies conducted in different populations have shown that AIS patients develop osteopenia and low bone mineral density at higher rates than the general population. The prevalence of low bone density in AIS girls reaches 20-38%[3,4] and the extent of bone density reduction shows direct correlation with scoliosis curve severity and progression potential. Research has shown that patients with low bone density at their scoliosis diagnosis are more likely to experience significant curve progression exceeding 10 degrees during their adolescent years[6]. The DXA scans reveal that AIS patients have lower trabecular and cortical bone density in their vertebral bodies than their age-related peers[5]. The metabolically active trabecular bone shows more extensive changes than other bone types which leads to vertebral instability and increased deformation risk.

The bone density reduction in AIS patients shows uneven distribution because the scoliotic curve's convex side experiences more bone loss than the concave side due to changes in vertebral column stress distribution[7]. The mechanical environment of Wolff's Law causes bone to adapt through changes in posture and musculature which results in unequal stress distribution across the vertebral column and subsequent osteopenia on the convex side. The microarchitectural changes in AIS patients become evident through HR-pQCT measurements which show decreased trabecular number and thickness and increased trabecular separation[6,7].

The bone mineral density of AIS patients shows decreased values in their spine as well as their femoral and radial bones[4,8]. The findings indicate that AIS patients develop a widespread skeletal condition which might result from metabolic or genetic disorders affecting their entire body. The bone metabolism of AIS patients shows abnormal patterns through serum tests which measure osteocalcin and bone-specific alkaline phosphatase and N-terminal

propeptide of type I procollagen (NTX)[9]. The presence of systemic bone metabolism abnormalities indicates that AIS represents a spinal deformity which stems from widespread skeletal dysregulation.

## Genetic and Epigenetic Contributions

Research into the genetic elements which affect bone density and scoliosis development has become more prominent throughout the last few years. Multiple genetic loci which affect bone density have been discovered through genome-wide association studies (GWAS) which include LRP5, VDR, and COL1A1 genes[10-12]. The LRP5 gene functions as a co-receptor in Wnt/β-catenin canonical signaling which drives osteoblast development, as well as cell growth and activity. The LRP5 gene determines bone strength through its dose-dependent mechanism because mutations in this gene result in osteoporosis-pseudoglioma syndrome or high bone mass phenotypes[10,13]. Research has identified two LRP5 SNPs (Ala1330Val and Val667Met) which decrease bone density in AIS patients[14]. The VDR gene contains BsmI polymorphisms which affect bone density and may enhance scoliosis risk when combined with insufficient vitamin D levels[11].The COL1A1 gene which produces the alpha-1 chain of type I collagen maintains essential functions for building strong bone matrices. The Sp1 binding site polymorphism in COL1A1 leads to weaker bones and higher fracture risk and lower BMD which makes AIS patients more susceptible to fast curve progression because of their reduced biomechanical stability[12].

The expression of genes involved in skeletal development receives additional regulation through epigenetic mechanisms. The KAT6B gene shows hypermethylation in scoliosis patient bone tissues which could disrupt essential osteogenic signals needed for proper vertebral development and mineralization[15]. The DNA methylation patterns of estrogen receptor genes and RUNX2 transcription factor which guides osteoblast development have been detected in scoliosis patients and these patterns link to both decreased bone mineral density and spinal curve advancement[16].

The scoliosis disease shows distinct microRNA patterns between patients and controls through specific miRNAs including miR-17-5p, miR-106a-5p, miR-106b-5p, miR-16-5p, miR-93-5p, miR-15a-5p, and miR-181b-5p which play essential roles in AIS development and osteopenia[17]. The abnormal expression of these miRNAs leads to decreased expression of BMP2 and SMAD5 genes which results in decreased bone formation.

Research evidence demonstrates that inherited genetic mutations interact with epigenetic changes to create AIS and its associated bone density problems. The combination of these factors supports a systems biology model which explains scoliosis development through genetic factors, environmental elements, and mechanical forces that produce different clinical outcomes. The research demonstrates that genetic factors together with epigenetic mechanisms play essential roles in scoliosis development and bone density reduction.

## Hormonal Influences and Sexual Dimorphism

Sex hormones play a central role in bone remodeling. Estrogen enhances osteoblast activity and inhibits osteoclast-mediated resorption, contributing to bone accrual during adolescence. Several studies have demonstrated that AIS patients, particularly females, often present with altered estrogen metabolism, and/or delayed menarche[18,19]. These hormonal abnormalities may contribute to both reduced BMD and spinal deformity.

Vitamin D, a steroid hormone with widespread effects on calcium-phosphorus homeostasis, also appears significantly dysregulated in scoliosis. Balioglu et al found that Cobb angle measurements were inversely correlated with serum vitamin D levels[20]. Parathyroid hormone (PTH), which responds to serum calcium levels, may be elevated in vitamin D-deficient AIS patients, exacerbating bone resorption. Other endocrine factors, including leptin, melatonin, and growth hormone, have also been implicated, though further research is needed

to delineate their roles in osteopenia associated with scoliosis.

## Nutritional and Physical Activity Factors

Bone health depends on calcium and vitamin D which work together to control skeletal mineralization and maintain proper calcium levels in the body. The small intestine absorbs calcium through two main mechanisms which include active transcellular transport in the duodenum under 1,25-dihydroxyvitamin D3 regulation and passive paracellular diffusion throughout the jejunum and ileum. The body uses calcium for bone tissue construction or kidney excretion through mechanisms controlled by parathyroid hormone (PTH) and calcitonin. The body increases PTH production when calcium levels become insufficient which leads to bone resorption to maintain blood calcium levels and results in bone density reduction.

The activation of vitamin D requires two sequential hydroxylation steps to produce 1,25-dihydroxyvitamin D [1,25(OH)2D] after starting with 25-hydroxyvitamin D [25(OH)D] in the liver and kidneys. The active form of vitamin D binds to VDR receptors in osteoblasts and intestinal cells to enhance calcium and phosphate uptake and boost osteocalcin production and BMP2 and SMAD5 gene expression[21]. The combination of low 25(OH)D levels in AIS patients leads to decreased BMD and larger Cobb angles which suggests that vitamin D metabolism problems contribute to scoliosis-related osteopenia[20,21].

The essential mineral magnesium functions as a cofactor for more than 300 enzymatic reactions which include multiple ATP-dependent processes in osteoblasts. The mineral helps maintain bone structure through its ability to stabilize hydroxyapatite crystals and control PTH hormone release. The absence of magnesium leads to reduced bone formation and increased osteoclastic bone breakdown which results in decreased bone mineral density. The essential mineral zinc supports osteoblast development and collagen production in bone cells. The enzyme alkaline phosphatase requires zinc as a structural element to perform its function of depositing hydroxyapatite during bone formation. The absence of zinc during adolescence leads to delayed bone development and reduced peak bone density according to research[22,23]. The carboxylation process of osteocalcin requires Vitamin K2 (menaquinone) to function because osteocalcin needs this modification to bind hydroxyapatite for bone mineralization. The post-translational modification of osteocalcin becomes essential for its ability to bind hydroxyapatite because it enables effective bone mineralization. Research shows that insufficient vitamin K2 levels in the body lead to higher fracture risks and damaged bone structure. The body absorbs Vitamin K2 through the ileum through passive diffusion of micelles which then transport the vitamin to bone and liver tissues through chylomicrons in the lymphatic system. The combination of vitamin K2 and vitamin D3 supplementation leads to substantial increases in bone mineral density[24].

Research on AIS patients has shown that their consumption of essential micronutrients remains insufficient which could make their existing genetic and hormonal conditions worse[21]. The scoliosis patient population of adolescents shows lower consumption of calcium, magnesium, and vitamin D compared to their peers who do not have scoliosis. The insufficient nutrient supply becomes worse because patients with gastrointestinal disorders experience malabsorption and changes in their gut microbiota which reduces their ability to absorb nutrients.

Physical exercise which includes weight-bearing activities and resistance training serves as a vital factor for bone remodeling and skeletal loading. The integrin-FAK-ERK cascade functions as a mechanotransduction pathway which osteocytes use to generate signals from mechanical stress that results in increased osteoblast activity and new bone matrix formation[22]. The physical activity levels of AIS patients remain lower than average because they experience discomfort, self-esteem issues, their

brace usage is restricting and their motor skills are impaired. The decreased mechanical forces on bones result in slower bone formation rates which makes BMD worse. Research shows that exercise programs which focus on postural control and axial loading can help improve spinal stability and reduce osteopenia in AIS patients[22].

The research demonstrates that bone health depends on the complex interaction between dietary micronutrients, endocrine regulators, and biomechanical loading. The management of scoliosis in growing adolescents requires both improved nutrient intake and regular physical activity as essential components. The reduced mechanical stress on bones prevents normal bone development which results in decreased BMD.

## Congenital and Neuromuscular Scoliosis

The presence of vertebral anomalies in congenital scoliosis leads to abnormal spinal mechanics which disrupts normal bone development and skeletal loading patterns. Research on BMD in congenital scoliosis patients shows that early vertebral malformations create conditions for developing osteopenia in specific areas or throughout the entire body[23]. Neuromuscular scoliosis occurs with cerebral palsy and Duchenne muscular dystrophy to produce severe osteoporosis in patients. The combination of non-ambulatory status, chronic corticosteroid use, poor nutrition, and endocrine dysfunction leads to osteoporosis in these patients. The DXA scans of these patients reveal BMD levels that fall below critical thresholds and their vertebrae frequently experience compression fractures.

## Demographics and Ethnic Variation

Demographic variables further modulate the way BMD changes in scoliosis patients. The prevalence of scoliosis and its associated osteopenia levels vary between different ethnic groups. The BMD levels of Caucasian AIS patients are lower than those of African-American and Asian patients who have the same condition[25]. The BMD levels of male AIS patients who have scoliosis are significantly lower than those of female patients with the same condition[26].

The treatment plans for patients need to consider their geographic location, sun exposure, their socioeconomic status, and dietary preferences, because these factors create treatment differences between patients.

## Clinical Implications and Future Research Directions

The established link between scoliosis and low BMD requires healthcare providers to perform DXA tests and bone metabolism serum marker assessments on new patients during their initial diagnosis and during their growth spurts. The identification of osteopenia in patients enables healthcare providers to start early interventions which combine nutritional support with hormonal treatment and biomechanical therapy to control scoliosis curve progression.

The treatment of scoliosis may include three new approaches which combine specific nutrient supplements with exercise plans and new pharmaceuticals that boost bone density. The combination of genetic and epigenetic testing enables healthcare providers to create personalized treatment plans for their patients. Future research needs to conduct extensive longitudinal investigations which study the direct links between BMD and scoliosis development. The combination of omics data with endocrine biomarkers and mechanobiological models will create predictive models that show how scoliosis curves progress and respond to treatment.

## Conflicts of Interest:

The author declares no conflict of interest.

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