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Vitamin D and Calcium Homeostasis in Bone Health Among Individuals with Disorders of Sex Development: A Review

Kasimu Saidu[1*], Bello Lawal Danchadi[1]

[1]*Department of Chemical Pathology and Immunology, Faculty of Basic Clinical Sciences, College of Health Sciences, Usmanu Danfodiyo University, Sokoto, Sokoto State, Nigeria.*

***Corresponding Author:** kasimusaidu@gmail.com* ***Phone:** +234803631 6081*

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ABSTRACT

Background and Purpose: Bone health is critically influenced by hormonal and nutritional factors, particularly vitamin D and calcium. Vitamin D is a naturally occurring bioactive compound that functions as a hormone in the body, regulating calcium absorption and bone metabolism, thereby making it a relevant focus for clinical research within this field. This review aggregates evidence on vitamin D and calcium homeostasis in individuals with DSD, highlighting their roles in bone mineral density, osteoporosis risk, and fracture susceptibility.
Methods: A narrative review of clinical studies, systematic reviews, and guidelines was conducted, with emphasis on common DSD subtypes such as TS, KS, CAH, and AIS.
Results: Hormonal dysregulation, glucocorticoid therapy, and impaired vitamin D metabolism compromise calcium balance and bone mineralization in DSD populations. These alterations significantly contribute to reduced bone mineral density and heightened the risk of osteoporosis. Although hormone replacement therapy and supplementation are beneficial, standardized DSD-specific protocols remain limited.
Conclusion: Individuals with DSD are highly vulnerable to skeletal complications due to vitamin D and calcium disruption. Routine monitoring, early hormone replacement, and nutritional support are essential. Future research should focus on longitudinal studies and evidence-based guidelines tailored to DSD.

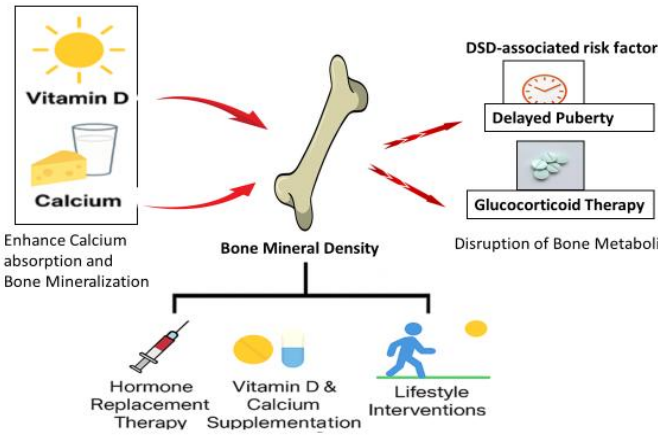

Figure 1: Graphical abstract

INTRODUCTION

Bone health is a fundamental component of overall well-being, governed by a dynamic interplay of hormonal, nutritional, and genetic factors (Rizzoli *et al.,* 2021). Vitamin D and calcium are central to skeletal development and maintenance, facilitating intestinal calcium absorption, modulating parathyroid hormone (PTH) activity, and regulating the activity of osteoblasts and osteoclasts (Weaver *et al.*, 2016). Disruptions in this tightly regulated system can lead to osteopenia, osteoporosis, and reduced bone mineral density (BMD), even among the general population (Bouillon *et al.*, 2019). These risks are markedly amplified in individuals with Disorders of Sex Development (DSD), where persistent hormonal imbalances, delayed puberty, and nutritional deficiencies converge to create a uniquely high susceptibility to skeletal fragility.

DSD represent a diverse group of congenital conditions characterized by atypical chromosomal, gonadal, or anatomical sex development, resulting in a broad spectrum of clinical manifestations and lifelong health concerns (Dar *et al.,* 2018; Hssaini *et al.,* 2024). Historically, clinical management has focused on addressing genital ambiguity and reproductive potential. However, increasing attention is now being directed toward the long-term consequences of chronic sex steroid deficiencies, particularly their impact on bone metabolism. Conditions such as Turner syndrome (45, X), Klinefelter syndrome (47, XXY), congenital adrenal hyperplasia (CAH), and 46, XY gonadal dysgenesis present unique risks to skeletal health. These disorders are often associated with hormonal imbalances arising from gonadal dysfunction or impaired steroidogenesis, and frequently coexist with vitamin D deficiency and disrupted calcium regulation (Gravholt *et al.,* 2017). Beyond the issues of genital development and psychosocial adjustment, individuals with DSD face a heightened risk of metabolic and skeletal complications, notably reduced bone mineral density and osteoporosis (Rangaswamaiah *et al.,* 2020).

One of the often-overlooked challenges in DSD management is the high prevalence of reduced BMD and osteoporosis. These skeletal complications arise from multiple factors, including chronic sex steroid deficiencies, delayed pubertal development, and long-term use of glucocorticoids, particularly in individuals with CAH (Ahmed *et al.,* 2016). Estrogen and testosterone are critical regulators of bone formation and resorption; their deficiency, which is common among hypogonadal individuals with DSD, impairs peak bone mass acquisition and accelerates age-related bone loss (Kawai and Hasegawa, 2022). In addition to hormonal influences, increasing evidence suggests that disturbances in vitamin D and calcium metabolism further exacerbate bone fragility in this population, acting both independently and synergistically with endocrine dysfunction (Charmandari *et al.,* 2014).

Vitamin D plays a pivotal role in calcium absorption and bone mineralization, yet deficiency is commonly observed in individuals with DSD. Contributing factors may include inadequate sun exposure, malabsorption, or genetic predisposition (Gravholt *et al.,* 2017). Similarly, in CAH, chronic glucocorticoid therapy disrupts calcium metabolism by enhancing renal calcium loss and suppressing osteoblast activity (Charmandari *et al.,* 2014). These alterations frequently lead to secondary hyperparathyroidism, which accelerates bone resorption and contributes to diminished BMD (Sobh *et al.,* 2022). Despite these established risks, routine assessment and management of vitamin D and calcium levels in DSD populations remain inconsistent and are not guided by standardized protocols (He *et al.,* 2022). This review provides an aggregate of current knowledge regarding vitamin D and calcium homeostasis in DSD. The primary aim is to consolidate evidence on how these factors influence bone mineral density and skeletal outcomes in affected individuals. The significance of this review lies in addressing the absence of DSD-specific guidelines for bone health, highlighting the mechanisms of bone fragility, and proposing evidence-based strategies for clinical care. By bringing together data from diverse DSD conditions, this review aims to inform both clinical practice and future research on improving skeletal health in this vulnerable population.

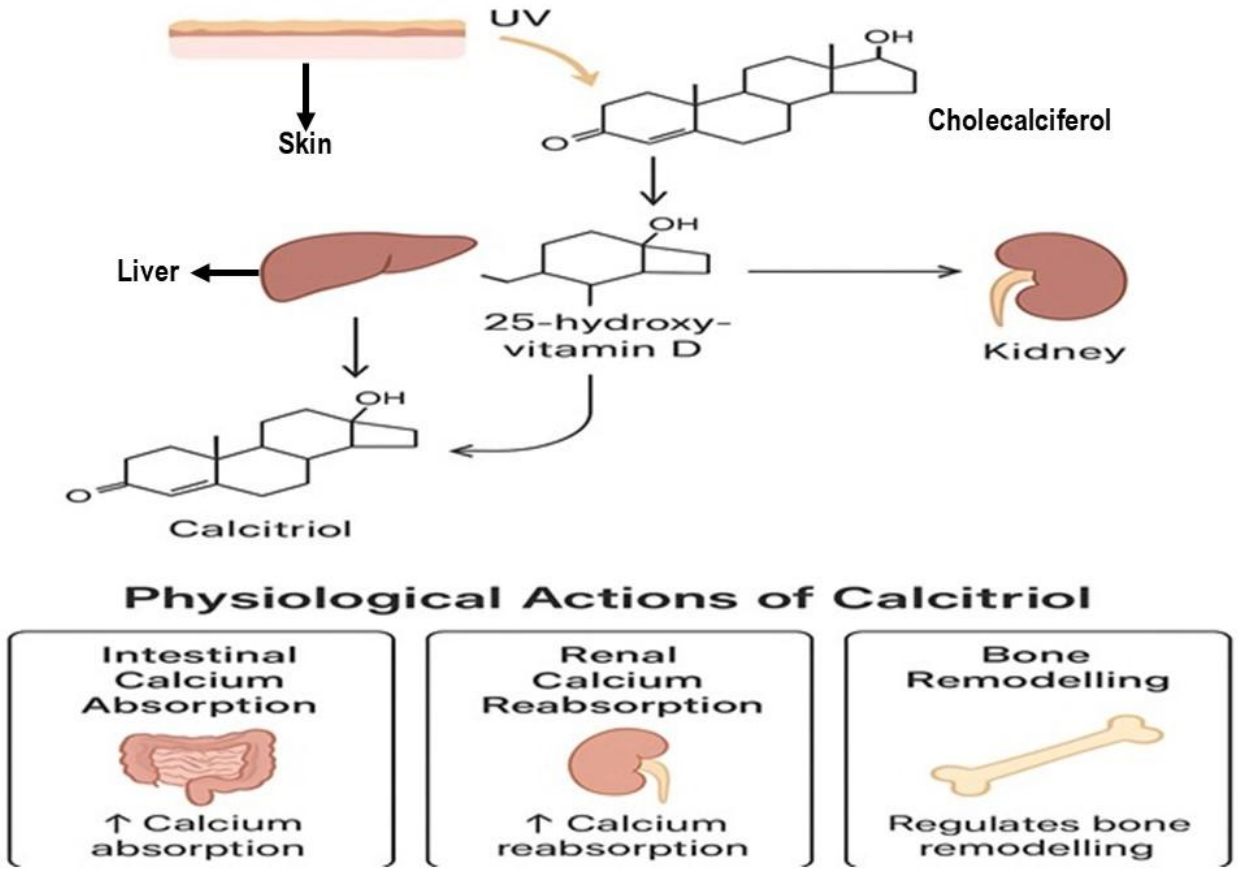

Figure 2: Biochemical Pathway of Vitamin D Synthesis and Activation. This schematic diagram illustrates the endogenous synthesis and activation of vitamin D and its physiological actions. Ultraviolet (UV) radiation converts 7-dehydrocholesterol in the skin into cholecalciferol (vitamin D_3), which is transported to the liver and hydroxylated to form 25-hydroxyvitamin D [25(OH)D], the primary circulating marker of vitamin D status. In the kidneys, 25(OH)D is further hydroxylated by 1α-hydroxylase (CYP27B1) to produce the biologically active form, 1,25-dihydroxyvitamin D (calcitriol). Calcitriol binds to the vitamin D receptor (VDR) and exerts its effects on target tissues, resulting in: (i) increased intestinal calcium absorption, (ii) increased renal calcium reabsorption, and (iii) regulation of bone remodeling via coordinated osteoblast and osteoclast activity.

OVERVIEW OF DISORDERS OF SEX DEVELOPMENT (DSD)

DSD comprise a diverse group of congenital conditions characterized by atypical development of chromosomal, gonadal, or anatomical sex (Hssaini *et al.,* 2024). These anomalies arise from disruptions in the highly regulated processes of sex determination and differentiation, which depend on coordinated genetic, hormonal, and molecular pathways (Hssaini *et al.,* 2024). The term "DSD" was formally introduced in the 2006 Consensus Statement as a more clinically precise and less stigmatizing alternative to earlier terms such as "intersex" (Arboleda *et al.,* 2014; Hssaini *et al.,* 2024). This redefinition has facilitated improved diagnostic clarity and promoted multidisciplinary care approaches in both pediatric and adult populations.

Clinically, DSDs are broadly categorized based on karyotype into three main groups: 46, XX DSD, 46, XY DSD, and sex chromosome DSD (Hssaini *et al.,* 2024). Each category encompasses distinct conditions with variable pathophysiology, hormonal profiles, and clinical outcomes.

- **46, XX DSD** refers to individuals with a typical female chromosomal complement who exhibit varying degrees of virilization due to excess androgen exposure. The most prevalent cause is CAH, especially due to steroid 21-alpha hydroxylase (CYP21A2) deficiency. This enzymatic defect impairs cortisol synthesis, leading to compensatory overproduction of adrenocorticotropic hormone (ACTH) and subsequent adrenal androgen excess (Alkhzouz *et al.,* 2021). The resulting hyperandrogenism can

cause masculinization of the external genitalia, while internal female reproductive structures are typically preserved.

- **46, XY DSD** includes individuals with a typical male karyotype who exhibit under-virilized or ambiguous genitalia resulting from impaired androgen synthesis, metabolism, or receptor function. Key conditions in this category include complete and partial androgen insensitivity syndrome (CAIS/PAIS), 5α-reductase deficiency, and various forms of gonadal dysgenesis (Hssaini *et al.,* 2024). Depending on the severity and nature of the defect, affected individuals may present with female, ambiguous, or under virilized male external genitalia, often with undescended testes and absent Müllerian structures.
- **Sex Chromosome DSD** encompasses conditions resulting from abnormalities in the number or structure of sex chromosomes. Common examples include Turner syndrome (45, X) and Klinefelter syndrome (47, XXY). Turner syndrome is characterized by complete or partial monosomy X, leading to streak gonads, short stature, delayed puberty, and infertility due to ovarian insufficiency (Gravholt *et al.,* 2018). In contrast, Klinefelter syndrome arises from the presence of an extra X chromosome in phenotypic males, resulting in small testes, low testosterone levels, gynecomastia, and impaired spermatogenesis (Shiraishi and Matsuyama, 2019).

Hormonal dysregulation is a unifying feature across many DSDs, contributing not only to impaired sexual development but also to broader complications such as infertility, metabolic disturbances, reduced bone mineral density, and psychosocial distress (Dar *et al.,* 2018). CAIS, caused by mutations in the androgen receptor gene, renders tissues unresponsive to circulating androgens. Affected individuals typically present with female external genitalia, undescended testes, and lack internal female reproductive organs such as the uterus and fallopian tubes, often with a short or blind-ending vagina, despite normal or elevated testosterone (Bertelloni *et al.,* 2010; Lanciotti *et al.,* 2019).

The management of DSD is inherently multidisciplinary, requiring collaboration among endocrinologists, geneticists, surgeons, psychologists, and patient advocates. Accurate diagnosis—based on karyotype analysis, hormonal profiling, and imaging—is critical for guiding clinical decisions. While debates continue regarding early surgical interventions, current best practices emphasize individualized care, psychological support, and shared decision-making between healthcare providers, patients, and families (Kreukels *et al.,* 2019).

Bone Health in Individuals with DSD

Bone health is increasingly recognized as a critical yet underappreciated concern in individuals with Disorders of Sex Development (DSD), historically overshadowed by issues related to genital ambiguity and reproductive function (Bertelloni *et al.,* 2010; Lee *et al.,* 2016). A range of DSD conditions—including Complete and Partial Androgen Insensitivity Syndromes (CAIS and PAIS), 5α-reductase deficiency, Klinefelter syndrome (KS), Turner syndrome (TS), and CAH—have been associated with decreased BMD, heightened risk of osteopenia and osteoporosis, and, in some cases, increased fracture susceptibility (Bertelloni *et al.,* 2010; Brommage and Ohlsson, 2018). These skeletal complications are multifactorial, often arising from chronic hormonal imbalances (e.g., hypoestrogenism in TS, androgen excess or deficiency in CAH and AIS), inadequate pubertal progression, delayed or absent hormone replacement therapy (HRT), and nutritional deficits such as vitamin D or calcium insufficiency (Bertelloni *et al.,* 2010). Sex steroids—particularly estrogens and androgens—are vital regulators of bone growth and mineralization, exerting their effects through receptors expressed in osteoblasts, osteoclasts, and chondrocytes (King *et al.,* 2017) (Table 1).

In individuals with CAH, bone health is further compromised by long-term glucocorticoid therapy, which suppresses adrenal androgen production but also impairs osteoblast function and promotes bone resorption (Riehl *et al.,* 2020). Findings from the dsd-LIFE study, as reported by Riehl *et al.* (2020) and Falhammar *et al.* (2022), indicate that higher cumulative doses of glucocorticoids—particularly prednisolone—are associated with significantly lower bone mineral density (BMD), especially in women with the simple-virilizing form of CAH. These studies further demonstrated a dose-dependent inverse relationship between glucocorticoid exposure and BMD, underscoring the need for cautious, individualized dosing strategies.

In CAIS, resistance to androgen signaling leads to compromised bone health despite normal or elevated testosterone levels. Reduced BMD is a frequent finding, particularly among individuals who have undergone gonadectomy without prompt initiation or consistent adherence to estrogen replacement therapy (King *et al.,* 2017). In a retrospective study of 113 women with CAIS, King and colleagues reported reduced BMD at both the spine and hip, regardless of the age at gonadectomy. Interestingly, even participants with intact gonads often exhibited suboptimal BMD, suggesting that androgen resistance alone may significantly impair bone homeostasis. By contrast, individuals with PAIS or 5α-reductase deficiency generally show more favorable bone outcomes, especially when gonads are retained or when hormone therapy is effectively managed (King *et al.,* 2017).

Table 1: Osteoporosis risk and contributing factors in major DSD subtypes.

DSD Condition	Relative Osteoporosis Risk	Key Contributing Factors	References
Turner syndrome	3-5× higher than control	Estrogen deficiency, *SHOX* gene mutation, Vitamin D deficiency.	(Kawai & Hasegawa, 2022; Lichiardopol and Moţa, 2007).
Complete AIS	~4× higher	Androgen resistance, Late gonadectomy (>20 years)	(King *et al.,* 2017)
CAH	2-3× higher	Long-term Glucocorticoid use, low androgens	(Charmandari *et al.,* 2014; Claahsen - van der Grinten *et al.,* 2022)

Risk estimates are relative to age- and sex-matched control populations. AIS = Androgen Insensitivity Syndrome; CAH = Congenital Adrenal Hyperplasia

In KS (47, XXY), the most common chromosomal cause of male hypogonadism, is strongly associated with reduced bone mineral density and increased osteoporosis risk (Gravholt *et al.,* 2018). Although testosterone deficiency has traditionally been viewed as the primary factor underlying skeletal fragility in KS, emerging evidence points to a critical role for vitamin D deficiency. In a study of 127 men with KS, Ferlin *et al.* (2015) reported that low serum 25-hydroxyvitamin D levels were significantly correlated with reduced BMD at both the lumbar spine and femoral neck—even in those with normal testosterone levels. Notably, testosterone replacement therapy alone did not significantly improve BMD in this cohort. However, vitamin D supplementation using calcifediol resulted in substantial increases in bone density over two years, highlighting the essential role of adequate vitamin D status in bone health maintenance among individuals with KS (Ferlin *et al.,* 2015).

Fracture prevalence in individuals with DSD is an emerging clinical concern. Data from the dsd-LIFE cohort reported 21 fractures among patients with CAH, although no statistically significant differences in fracture rates were observed across CAH subtypes. These findings suggest a generalized vulnerability to skeletal fragility irrespective of disease severity. Broader population-based studies further highlight the role of environmental and nutritional factors in bone health. In a study from Enugu State, Nigeria, urban children demonstrated higher BMD compared to their rural counterparts, with age and body weight identified as significant predictors in the urban group, whereas age alone was predictive in rural children (Nwogu *et al.,* 2019). Similarly, a national survey in Egypt revealed a high prevalence of osteopenia and osteoporosis among adolescents with short stature, particularly in boys—31.1% had relative osteoporosis and 44.7% had relative osteopenia. Among stunted girls, 5.4% exhibited relative osteoporosis and 54.2% had osteopenia (Ibrahim *et al.,* 2011). These findings underscore the need for early screening and preventive strategies, particularly in resource-limited settings.

Vitamin D Metabolism and Calcium Regulation in DSD

Vitamin D and calcium are essential for skeletal integrity, operating through a finely coordinated physiological system involving the skin, liver, kidneys, gastrointestinal tract, and bone (Dominguez *et al.,* 2021). Endogenous vitamin D synthesis begins in the skin, where ultraviolet (UV) radiation converts 7-dehydrocholesterol into cholecalciferol (vitamin D_3). This precursor is hydroxylated in the liver to form 25-hydroxyvitamin D [25(OH)D], the primary circulating marker of vitamin D status (Dominguez *et al.,* 2021). In the kidneys, 25(OH)D undergoes a second hydroxylation by 1α-hydroxylase (CYP27B1) forming the biologically active metabolite 1,25-dihydroxyvitamin D [$1,25(OH)_2D$ or calcitriol] (Veldurthy *et al.,* 2016). A schematic diagram illustrating the biochemical conversion and chemical structures of vitamin D synthesis and activation is presented in Figure 1 for improved clarity and scientific inclusiveness. Calcitriol binds to vitamin D receptor (VDR), regulating calcium and phosphate homeostasis by enhancing intestinal absorption, increasing renal reabsorption, and modulating bone remodeling through osteoblast and osteoclast activity (Christakos *et al.,* 2015) as shown in Figure 2.

In individuals with DSD, vitamin D and calcium homeostasis are frequently disrupted due to a combination of endocrine abnormalities, gonadal insufficiency, and long-term medical therapies. Hypogonadism—common in DSD subtypes such as CAIS, Turner syndrome, and Klinefelter syndrome—plays a central role in this disruption. Sex steroids like estrogen and testosterone are known to enhance the expression of vitamin D receptors

(VDR) in intestinal and bone tissues (Bertelloni *et al.,* 2010; Christakos *et al.,* 2015). Consequently, deficiency of these hormones diminishes vitamin D responsiveness and calcium absorption, impairing bone mineralisation and increasing the risk of osteopenia and osteoporosis (Bertelloni *et al.,* 2010; Ferlin *et al.,* 2015).

Additionally, impaired vitamin D activation has been documented in individuals with Klinefelter syndrome. Ferlin *et al.* (2015) demonstrated that men with KS had significantly lower serum 25(OH)D levels, independent of testosterone status, suggesting intrinsic defects in vitamin D synthesis or metabolism. These low vitamin D levels were strongly correlated with reduced BMD at the lumbar spine and femoral neck. Importantly, vitamin D supplementation using calcitriol improved BMD significantly, whereas testosterone therapy alone yielded limited skeletal benefits.

In individuals with CAH, bone health is adversely affected by both chronic androgen excess and long-term glucocorticoid therapy. Glucocorticoids, while necessary to control adrenal hyperactivity , inhibit the renal enzyme CYP27B1, thereby reducing the conversion of 25(OH)D to its active form, calcitriol. Simultaneously, they upregulate CYP24A1, an enzyme that promotes vitamin D catabolism, further depleting active vitamin D levels (Riehl *et al.,* 2020). These disruptions impair calcium absorption and contribute to mineral imbalance. Additionally, glucocorticoids suppress osteoblast differentiation, enhance osteoclast activity, and promote urinary calcium excretion cumulatively leading to reduced bone formation and lower BMD (Riehl *et al.,* 2020; Veldurthy *et al.,* 2016). Clinical data from Riehl *et al.* (2020) showed that many adults with CAH had elevated parathyroid hormone (PTH) levels and insufficient 25(OH)D, indicating compromised calcitriol activity and secondary hyperparathyroidism. To mitigate these effects, vitamin D sufficiency — typically defined as serum 25(OH)D ≥30 ng/mL (75 nmol/L) — should be maintained through dietary or pharmacologic means (Holick, 2007). In addition, daily calcium intake should meet recommended thresholds (1,000–1,200 mg/day) to support adequate bone remodeling (Medicine, 2011) (Table 2).

Table 2: Disruptions in Vitamin D-Calcium Homeostasis in DSD and Clinical Implications.

Mechanism/ Pathway	Disruption in DSD	Affected Conditions	Clinical Consequences	Recommended Interventions	References
↓ Vitamin D activation (↓CYP27B1)	Glucocorticoids inhibit 1α-hydroxylase, reducing calcitriol synthesis	CAH	Impaired calcium absorption, low active vitamin D	Monitor 25(OH)D; consider calcifediol supplementation	(Riehl *et al.*, 2020)
↓ Serum 25(OH)D	Reduced vitamin D despite normal testosterone	Klinefelter syndrome	Decreased BMD, especially in the spine and femoral neck	Vitamin D supplementation; monitor levels	(Ferlin *et al.,* 2015)·
Glucocorticoid-induced bone loss	Long-term therapy impairs osteoblasts and promotes resorption	CAH	Increased fracture risk, osteopenia/ osteoporosis	Minimise dose; regular DEXA scans	(Riehl *et al.,* 2020)
BMD unresponsive to testosterone alone	Vitamin D deficiency limits the therapeutic effect of androgens	Klinefelter syndrome	Persistent low BMD despite TRT	Combine TRT with vitamin D Supplemen-tation if deficient	(Ferlin *et al.,* 2015)
↓ Intestinal calcium absorption	Due to calcitriol deficiency and steroid effects	CAH, hypogonadal DSDs	Risk of secondary hyperparathyroidis m and bone loss	Ensure calcium intake; monitor PTH	(Christakos *et al.,* 2015; Holick, 2007)
Estrogen/testoster one deficiency	Decreased VDR expression, impaired bone accrual	CAIS, TS, KS	Reduced calcium absorption, low peak bone mass	Early HRT initiation and monitoring	(Bertelloni *et al*., 2010; Gravholt *et al*., 2018)

Disruptions in Vitamin D-Calcium Homeostasis in DSD and Clinical Implications: ↓ = decrease in; CAH = Congenital Adrenal Hyperplasia; CAIS = Complete Androgen Insensitivity Syndrome; TS = Turner Syndrome; KS = Klinefelter Syndrome; VDR = Vitamin D Receptor; TRT = Testosterone Replacement Therapy; DEXA = Dual-Energy X-ray Absorptiometry; 25(OH)D = 25-hydroxyvitamin D, an indicator of vitamin D status; Calcitriol = Active vitamin D [$1,25(OH)_2D$]

CONCLUSION

Bone health in individuals with DSD is shaped by a multifaceted interaction of hormonal dysregulation, nutritional deficiencies, and long-term therapeutic exposures. Disruptions in vitamin D and calcium metabolism—whether due to hypogonadism, chronic glucocorticoid use, or impaired absorption—significantly contribute to reduced BMD and increased fracture risk. Clinical evidence consistently supports the need for proactive monitoring of vitamin D status, calcium intake, and BMD, especially in high-risk groups such as those with CAH, TS, KS and CAIS. Early and sustained implementation of hormone replacement therapy, along with targeted nutritional supplementation and lifestyle modifications, offers a promising strategy to preserve skeletal health. However, the absence of standardized, DSD-specific guidelines and the scarcity of long-term outcome data underscore the need for personalized, multidisciplinary approaches. Future research should prioritize longitudinal studies to refine clinical protocols and improve bone health outcomes in this vulnerable population.

Future Directions

Although awareness of bone health concerns in individuals with Disorders of Sex Development (DSD) is increasing, substantial research gaps persist. Most available data are derived from cross-sectional studies, such as the dsd-LIFE project, which offer limited insight into long-term skeletal outcomes. There is a clear need for well-designed longitudinal studies to evaluate the lifelong effects of hormone replacement therapy, glucocorticoid exposure, and vitamin D and calcium supplementation on bone mineral density and fracture risk. In addition, standardized clinical guidelines specific to DSD are lacking. Current bone health recommendations are often extrapolated from the general population, despite the distinct pathophysiological and treatment-related differences in DSD. Tailoring protocols based on factors such as chromosomal pattern, gonadal function, age at diagnosis, and surgical history is essential to improving care.

Finally, advancing toward individualized, multidisciplinary care models is critical. The heterogeneity of DSD demands integrated approaches that consider not only genetic and hormonal variables but also nutritional status, psychosocial support, and patient preferences. Such strategies will be key to optimizing skeletal outcomes and overall quality of life in this underserved population.

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AUTHORS' CONTRIBUTION

KS and BLD conceptualized and designed the study. BLD wrote the original draft. KS reviewed and edited the manuscript. All the authors read and approved the final manuscript for publication.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this review article.

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AUTHORS' DECLARATION

The authors declare that this work is original and that any liability for claims relating to the content of this article will be borne by them.

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