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Current analysis of skeletal phenotypes in Down syndrome

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Abstract

Purpose: Down syndrome (DS) is caused by trisomy 21 (Ts21) and results in skeletal deficits including shortened stature, low bone mineral density and a predisposition to early onset osteoporosis. Ts21 causes significant alterations in skeletal development, morphology of the appendicular skeleton, bone homeostasis, age-related bone loss, and bone strength. However, the genetic or cellular origins of DS skeletal phenotypes remain unclear.

Recent Findings: New studies reveal a sexual dimorphism in characteristics and onset of skeletal deficits that differ between DS and typically developing individuals. Age-related bone loss occurs earlier in the DS as compared to general population.

Summary: Perturbations of DS skeletal quality arise from alterations in cellular and molecular pathways affected by the overexpression of trisomic genes. Sex-specific alterations occur in critical developmental pathways that disrupt bone accrual, remodeling, and homeostasis and are compounded by aging, resulting in increased risks for osteopenia, osteoporosis and fracture in individuals with DS.

Keywords

Down syndrome; Trisomy 21; bone mineral density; osteoporosis; osteopenia

Introduction

All individuals with Trisomy 21 (Ts21), the most common chromosomal aneuploidy, have skeletal abnormalities and are at risk for osteopenia and osteoporosis [1–3]. Individuals with Down syndrome (DS), affecting ~1/700–1000 live births, exhibit characteristic craniofacial abnormalities, shortened stature, and atlantoaxial subluxation [4–7]. Altered development of skeletal phenotypes in DS begins prenatally and these deficits are manifested throughout life [8, 5]. In the appendicular skeleton, abnormalities include delayed skeletal maturation and development of the secondary centers of ossification, reduced period of epiphyseal closure, early attainment peak bone mass (PBM), and attenuated bone accrual [9, 4, 7, 10, 2, 11, 12]. Likely because of altered developmental processes in the appendicular and vertebral

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Conflict of Interest

The authors declare that they have no conflict of interest.

skeleton, individuals with DS are at increased risk for early onset osteopenia, osteoporosis, and fractures at earlier ages as compared to the normal population [9, 13–15, 3, 16–18]. As the quality of life has improved in individuals with Ts21, the average life expectancy has increased to ~60 years of age [19–21], and older individuals with DS have increased risk for fragility fractures and osteoporosis. Etiological knowledge about DS skeletal phenotypes, including the development of osteoporosis and osteopenia, lags behind our knowledge of other skeletal disorders [22, 23], and essential information about how and when DS bone phenotypes occur is important to understand their potential impact on skeletal health and optimal times for potential treatment of DS skeletal abnormalities.

Characteristics of DS bone deficits

As opposed to age-related osteoporosis in the general population, skeletal defects in DS arise due to dysregulated developmental processes and become apparent during early ages [16]. Growth velocity is severely affected from 6 months to 3 years of age [24]. Around 7 years of age, the skeletal age of children with DS is delayed compared to chronological age [2], and bone growth of the appendicular skeleton during puberty in individuals with DS is stunted [24]. A reduced period of bone growth leads to short stature in individuals with DS, which is reached 3–5 years before maximal height of the general population [24–26, 10, 2]. It has been suggested that individuals with DS have advanced skeletal age compared to humans without DS resulting from early maturation around the age of 15 [2]. Individuals with DS that have a shortened period of bone growth, early attainment of PBM and peak height velocity (PHV), reduced bone mass, and early onset of age-related bone loss [24, 25]. Males and females with DS exhibit distinct differences in bone abnormalities due to sex-specific effects on skeletal growth rates [4, 27, 15, 28, 17]. The reduced PBM in individuals with Ts21 likely leads to increased risk of osteopenia and osteoporosis and may be further compounded by aging [29]. More importantly, it has been observed that adolescent and adults with DS have increased fracture risk from altered skeletal development [16, 30]. There is little knowledge on the causative factors that lead to a reduced stature in DS. Future investigations should focus on how and when Ts21 contributes to impeded bone growth [4].

Identification of the underlying pathophysiologies of skeletal deficits remains unclear in individuals with DS. Although not the ultimate cause of Ts21 bone abnormalities, which are most likely related to inheritance of three copies of human chromosome 21 (*Homo sapiens* 21 or Hsa21) genes, low BMD associated with Ts21 may be compounded by secondary causes such as nutritional deficiencies, endocrine and autoimmune disorders, sedentary lifestyle, and low sunlight exposure; these factors are not consistent in individuals with DS [12]. Skeletal deficits in individuals with DS may be exacerbated by thyroid disease, hyperparathyroidism, hypotonia, and low muscle mass and strength [31, 23, 32, 33]. Furthermore, low estrogen levels, late menarche and early menopause in females as well as hypogonadism in males may also have considerable effect on skeletal development and BMD. Frequent use of drugs that affect bone metabolism including anticonvulsants, antidepressants, and psychotropic drugs may also negatively affect bone development and homeostasis [14]. Thus, the etiology of all aspects of DS skeletal deficits is likely complex and influenced by genetic and environmental factors.

Mouse models of DS exhibit skeletal abnormalities

The most direct cause of skeletal phenotypes associated with DS is likely the result of specific genes or collections of genes on Hsa21 that are overexpressed and lead to dysregulation of developmental pathways. Mouse models recapitulate the genetic (trisomy) and phenotypic (DS-associated traits) features attributed to Ts21 and have been used to examine the genetic, cellular and developmental bases for skeletal abnormalities associated with DS [34]. Mouse orthologs of Hsa21 genes are found on mouse chromosome 16 (Mmu16), Mmu17, and Mmu10. In the Ts65Dn DS mouse model (most commonly studied DS model; trisomy for ~104 genes and 13 Mb found on Mmu16 orthologous to Hsa21; [35–37]), males are usually infertile and used for experiments because female Ts65Dn mice are generally reserved for colony maintenance.Ts65Dn contain three copies of about half the gene orthologues found on Hsa21, starting from *Mrpl39* to the end of Mmu16 [34]. Ts65Dn mice are also trisomic for ~30 protein coding genes that are not homologous to Hsa21. Male Ts65Dn mice have observable appendicular skeletal deficiencies at 6, 12 and 16 weeks [38, 37, 39]. Ts1Rhr mice are trisomic for 33 genes (4.2Mb), between *Cbr3* and *Mx2*, a genetic region once thought to be necessary for all DS phenotypes, but this theory that has been disproven many times [40, 41]. The trisomic region in Ts1Rhr mice is also trisomic in Ts65Dn mice. No differences in BMD were seen at 3 or 16 weeks in male or female Ts1Rhr DS model compared with control mice, likely due to the ages sampled or the methodology used, including just examining BMD in these animals [42, 43]. The Dp1Tyb DS mouse model (three copies of 148 genes and 23 Mb, including all genes on Mmu16 homologous to Hsa21 from *Lipi* to *Zbtb21)*, a segment that includes trisomic genes found in both Ts65Dn and Ts1Rhr mouse models [44, 43]. Dp1Tyb animals showed distinct differences in bone formation and homeostasis between Dp1Tyb and control mice at 6 weeks (time of bone formation around sexual maturity similar to humans under the age of 20) and at 16 weeks (time of skeletal maturity in mice similar to humans greater than 20 years of age). In addition, the studies with Dp1Tyb mice showed distinct differences in skeletal deficits between male and female mice with increased gene dosage [43].

Measurements of and sexual dimorphism in DS bone abnormalities

There is almost unanimous agreement in the literature that DS predisposes individuals to low bone mass and increased fracture risk, and that factors besides aging cause bone deficits in DS. In the few studies that report no higher prevalence of bone abnormalities in individuals with DS, methodological differences related to BMD measurements and the altered age, stature, and bone size associated with Ts21 may account for some of these findings. Because individuals with Ts21 are usually shorter than normally developing individuals, this leads to smaller bone length and size, a factor that is not taken into account with areal BMD (aBMD) measurements acquired by dual-energy X-ray absorptiometry (DEXA) [9]. Because of these differences, the aBMD DEXA measurement would be lower in a smaller bones and greater in a larger bones [14, 45].

In a small sized sample comparison of individuals with DS and controls, when males and females were analyzed together, total body, spine, femoral neck, and hip BMD were all significantly reduced [45]. Spine but not femoral neck vBMD was significantly lower in

individuals with DS. Although both males and females had reduced BMD in lumbar spine and femoral neck when analyzed separately, only lumbar spine vBMD was significant in males with DS. In a larger cohort of individuals with DS analyzed with a reference control population, lumbar spine aBMD and bone mineral apparent density (BMAD) (taking into account the smaller size of the bone), as well as femoral neck BMD were significantly lower from measurements in a control cohort with and without age and sex adjustments. However, femoral neck BMAD was not significantly different unless age and sex adjustments were made in this cohort [46]. A large cohort of individuals with DS compared to age and sex matched controls recorded significant differences in lumbar spine, femoral neck and total hip areal BMD [47]. When these measurements were adjusted for bone volume, neither lumbar spine nor femoral neck vBMD were significantly different in individuals with DS as compared to controls, and this resulted in a conclusion that most people with DS had "healthy bones" [47]. Analysis of the same population (males and females together) using 3-dimensional (3D)-DEXA modeling methods to measure vBMD found that individuals with DS as compared to controls showed reduced cortical thickness and cortical vBMD, and no differences in integral and trabecular vBMD between the two populations. When adjustments for age and BMI were factored in, males and females with DS analyzed together exhibited lower cortical, integral and trabecular vBMD as compared to control individuals. When males and females with DS were analyzed separately with adjustments for age and BMI, all vBMD parameters were significantly lowered in males with DS, but only cortical vBMD parameters were significantly lower in females with DS as compared to control individuals [48]. These analyses demonstrate the importance of taking bone size and age into consideration when analyzing bone health of individuals with Ts21.

In adolescents, both males and females with DS showed reduced overall BMD as compared to normal controls [28]. Females with DS also exhibited significantly reduced lumbar spine BMD. When these areal measurements were adjusted for bone volume or height (BMDH), only females with DS as compared to typically developing controls had significantly lower BMAD and BMDH. Overall BMAD and BMDH in adolescent males with DS and vBMD in lumbar spine and femoral neck in young males and females with DS were not significantly different from control individuals [28]. When examining individuals with DS as compared to controls under the age of 20, there were also no differences in lumbar spine vBMD or femoral neck strength, while there were differences in these measurements when adolescent and adult men or women with or without DS were compared [9]. In a small study of age 7–10 year old males with DS as compared to controls, total body and pelvic BMD were smaller in individuals with DS, but BMD and two different ways of measuring vBMD in the lumbar spine were not significantly different [49]. Taken together these studies suggest that the inability to detect differences in BMD in adolescents with DS may reflect still developing skeletal differences at these ages. Some skeletal areas may have less BMD earlier in life, and significant BMD differences may not develop until after adolescence in individual with DS. Additionally, the correct utilization of different assessment methodology, taking into account differences in bone size, may be critical in defining potential deficits in adolescents with DS.

From skeletal analyses done on individuals with DS, it is important to have a sex- and age-matched control or reference populations to compare and utilize appropriate T or Z scores

[16]. T scores assess BMD in individuals compared to a young normal reference mean, while Z-scores assess BMD compared to individuals in the general population of the same age and sex possibly highlighting the effects of trisomy on BMD. Individuals with DS have a smaller stature, and have lower BMC and BMD compared to controls; it is imperative to account for differences in skeletal sizes between individuals with Ts21, as aBMD and vBMD analyses may yield different results. There are also different ways to account for the smaller size of DS bones, and these methodological differences should be noted when analyzing the skeleton from individuals with DS.

Because of low sample sizes in DS bone studies, it has been often assumed that males and females with DS have similar skeletal measures, and bone measures for both sexes have been combined, often across wide age ranges. The possibility of sex-related differences in BMD and skeletal development suggested that females with DS might be poorer at acquiring bone mass compared to males [9, 28]. Recent comprehensive studies with large sample sizes of male and female adults with Ts21 measured BMD in both the femoral neck and lumbar spine compared to normal developing populations across various stages of life [46, 50, 18]. Individuals with DS had reduced BMD compared to the normal populations with males beginning in their 20s and females in their 40s [46, 50, 18]. Both males and females with DS reached PBM at younger age, suggesting impairment in bone accrual during adolescence, and experience bone loss sooner and at a higher rate than the general population [46, 50, 18]. Femoral neck BMAD in males with DS declined sharply around 20 years of age whereas females with DS did not experience a sharp decline in femoral neck BMAD until after 40 years of age [46, 50]. These studies show that males with DS begin losing BMD in the femoral neck much earlier than females with DS, suggesting a protective effect of female biological sex in terms of maintaining BMD [46, 32, 50, 18]. These data suggest that males with DS experience bone deficits earlier and are more severe (relatively comparing to normal individuals with the same sex) than females with DS.

To better understand the sexual dimorphism in DS, males and females from the Dp1Tyb DS mouse model were analyzed [43]. Male Dp1Tyb as compared to control mice have trabecular and cortical skeletal deficits at 6 and 16 weeks of age. At 6 weeks of age, female Dp1Tyb and control females have similar (but lower than normal males) trabecular bone properties. At 6 weeks of age, male Dp1Tyb and female Dp1Tyb mice generally have similar bone properties, suggesting there similarities in skeletal development in both male and female trisomic animals. At 16 weeks of age, trabecular and cortical parameters are different between male and female Dp1Tyb mice as compared to littermate controls with Dp1Tyb males displaying trabecular anomalies and more severe abnormalities as compared to their controls than females. Although Dp1Tyb mice have more Hsa21 homologous genes in three copies than Ts65Dn mice, skeletal abnormalities in male Dp1Tyb and Ts65Dn mice are comparable in scope and magnitude in male 6- and 16-week-old male mice [43]. From these results and the data from humans with DS summarized above, we hypothesize that sex-specific effects contribute to the incidence and severity of skeletal abnormalities in humans with Ts21.

Proposed cellular mechanisms for bone abnormalities in DS

The tendency for smaller and weaker bones in individuals with Ts21 is accompanied by altered bone morphology and impaired bone mineralization [9, 51, 13, 3, 30]. Low bone mass acquisition during childhood and adolescence predisposes adverse skeletal health associated with Ts21 [28]. Multiple hypotheses have been posited about how DS skeletal phenotypes are caused at the cellular level, including insufficient bone development, low bone turnover, decreased osteoblast activity, increased osteoclast activity, and a "mechanostat" hypothesis (Table 1) [37, 47, 52, 33, 53]. These hypotheses are not mutually exclusive of each other, but evidence for some of these hypotheses seems to be at odds with others. Cellular quantification in mostly DS mouse models and bone biomarkers in animals and humans with DS has been used to propose and test these hypotheses.

In prenatal Ts65Dn mice, femurs showed altered percent bone volume indicative of abnormal mineralization [54]. Femurs from Ts65Dn male mice at 6 weeks showed decreased osteoblast and increased osteoclast activity during bone development and disruptions in bone homeostasis continued at 16 weeks [37, 38]. In male 12-week-old Ts65Dn mice, tibias and femurs showed significantly decreased osteoblast activity and numbers of osteoclasts as compared to euploid littermates [39]. Additionally, serum propeptide of type 1 procollagen (P1NP—marker for bone formation) and Tartrate-resistant acid phosphatase 5b (TRAP 5b—marker for bone resorption) levels were decreased in 2 year old, but not 12-week-old Ts65Dn as compared to euploid mice. Sclerostin antibody treatment normalized the effects of the low bone turnover seen in male Ts65Dn mice at 12 weeks of age [55]. This treatment increased osteoblast but not osteoclast parameters in both trisomic and euploid mice. Our recent analysis of 16-week-old male and female Dp1Tyb DS model mice indicates that differences in cellular activity are affected by age, sex, and bone location and suggests a much more complicated picture of how trisomic activity affects cells that are important in bone development and homeostasis [43]

Reduced bone formation was also seen in adults with DS, with significant reductions in serum P1NP and no differences in C-terminal telopeptide (CTx—marker of bone resorption) as compared to controls without DS [33]. However, a larger comparison of adults with DS and control individuals showed higher P1NP and alkaline phosphatase (ALP) and similar CTx levels compared to their normal counterparts [47]. A single postmortem histological evaluation of lumbar spine from a 49-year-old male with DS reported that reduced osteoblasts and no osteoclast activity and this case is often cited as evidence for the "low bone turnover" hypothesis in DS [52]. Differences in bone turnover biomarkers in individuals with Ts21 highlight the importance in controlling for age, lifestyle and understanding the penetrance and severity of skeletal phenotypes associated with DS.

The mechanostat hypothesis relates to Wolff's law and suggests that in a healthy individual, increased physical activity places a larger strain on the bone that will adapt. If loading on a specific bone is greater, the bone will undergo formative remodeling to withstand the loading and become stronger [28]. When adolescent males and females with DS were assigned to a physical exercise program for 21 weeks, total and hip bone mineral content (BMC) increased as compared to individuals with DS without the exercise program [56].

Adolescents with DS (males and females combined) with low physical activity also had low BMD [17]. Higher physical activity in females with DS correlated with increased femoral neck BMD but not in males [57]. Whole body vibration training for 20 weeks in adolescents with DS showed improvement in BMC, BMD, and vBMD in appendicular bones and lumbar spine [58]. The effects of physical activity on skeletal improvement in individuals with DS need to be further investigated. Much work remains to be done to understand the cellular mechanisms causing Ts21 skeletal phenotypes. It may be that there are diverse mechanisms playing similar roles in males and females with DS at different ages and different bone locations.

Trisomic genetic influences on bone

Triplication of Hsa21 results in a wide variety of phenotypes associated with DS, likely due to increased dosage of ~200 protein coding genes on Hsa21 influencing both downstream and indirect effects [59]. Two main hypotheses have arisen to explain how Ts21 perturbs normal biological functions: the first proposes the gene dosage effect, overexpression of Hsa21 gene(s) has direct effects or downstream consequences; the second, developmental instability, the presence of an extra chromosome leads to global disruption of gene expression. It has been suggested that phenotypes associated with DS involve both proposed mechanisms, and that typical ~1.5 fold overexpression is caused by a higher fraction of trisomic cells expressing trisomic genes [60].

The gene-phenotype relationship in DS has been investigated for a number of traits associated with Ts21 [34, 61]. It has been hypothesized that *DYRK1A*, a gene found in three copies in humans with DS and many DS mouse models, significantly contributes to many DS phenotypes including cognitive impairment and skeletal malformations [62–64]. DYRK1A is a serine-threonine kinase that regulates many downstream proteins and transcription factors [62, 65–67]. Male and female *Dyrk1a* transgenic mice (increased copy number of just *Dyrk1a*) exhibited significantly reduced bone mass, including percent bone volume, and reduced trabecular skeletal parameters [68]. The osteoporotic phenotype of *Dyrk1a* transgenic mice was characterized by osteoblast deficiencies, resulting in the low bone mass phenotype [68]. Returning *Dyrk1a* to two functional copies from conception in otherwise trisomic Ts65Dn mice (Ts65Dn,*Dyrk1a*+/−) restored trabecular deficits, cortical architecture, decreased osteoclast number and increased osteoblast number and activity in Ts65Dn mice to euploid levels [38]. Trisomic animals with a reduced copy number of *Dyrk1a* also exhibited increased strength in whole bone properties compared to euploid controls. Trisomic *Dyrk1a*, however, does not have a significant role in developing prenatal skeletal abnormalities in Ts65Dn mice [54]. From these results it appears that the timing of DYRK1A overexpression is important to its contribution to DS-associated skeletal deficits [69]. Genetic expression of *Dyrk1a* and other trisomic genes may dynamically fluctuate over time, suggesting that there are critical time points or ages of development that influence overall skeletal health and development, leading to lifelong skeletal deficits.

Involvement of *Dyrk1a* in cell signaling pathways related to neurogenesis, transcription factors, cell cycle regulation, and cellular communication has been investigated, although the majority of these studies examined *Dyrk1a's* role in neurodegeneration and cancer [70–77].

Overexpression of *Dyrk1a* has been suggested to disrupt NFAT, a regulator of osteoclastogenesis, leading to a low-bone turnover phenotype [62, 68]. The Wnt signaling pathway also plays a role in bone homeostasis; loss of function of the Wnt pathway in mice caused high bone mass phenotypes, while gain of functions resulted in osteoporotic like phenotypes. It has been suggested that *Dyrk1a* activity can affect Wnt target genes or substrates such as SIRT1, FOXO1, DKK3 and DVL1 and alter bone homeostasis [78–80]. Future investigations should focus on molecular mechanisms responsible for altered expression of Hsa21 dosage-sensitive genes, including *Dyrk1a*, and the influence of overexpressed trisomic genes on non-Hsa21 genes on skeletal development and homeostasis.

Conclusions

Skeletal phenotypes associated with DS have been difficult to elucidate due to small sample sizes, wide range of ages analyzed, combining males and females and the utilization of different protocols to determine DS skeletal phenotypes. Recent studies with larger samples sizes that analyze males and females with DS separately and at similar ages, and take into account the typical small skeletal size of individuals with DS begin to show important sex-specific differences at particular ages. From more recent evaluations of skeletal health in individuals with DS, it appears that males with DS exhibit age-related decline in BMD earlier than females with DS, while females with DS exhibit lower BMD across all ages but a slower decline. Comprehensive studies on adolescents with DS need to be done to understand when and how osteopenia, osteoporosis and susceptibility to fragility fractures begin. Additionally, investigations in cellular function, molecular signaling pathways, and genetic expression are needed to identify how skeletal deficits arise. At present there are significant gaps in knowledge of bone health in adolescents with DS, how bone abnormalities develop in a sex-specific manner across time, and how Ts21 causes genetic, cellular and molecular changes that lead to DS skeletal deficits. It is possible that investigations into these areas could help identify potential molecular targets for therapy to lessen the effects of Ts21 on osteoporosis and skeletal fractures, both in younger and older individuals. Increasing skeletal health screenings in the DS population would also help elucidate relevant ages for sex-specific therapeutic intervention.

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Table 1:

Hypotheses for cellular causes of developing DS skeletal deficits

Hypothesis	Cellular or molecular mechanism	References
Early developmental aberrations	Low percent bone volume in E17.5 Ts65Dn mice.	Blazek et al 2015
	Lower mineralizing surface in 6-week-old male Ts65Dn mice.	Blazek et al 2011
	Lower osteoclast number in 6-week-old Ts65Dn mice.	Blazek et al 2015
Low bone turnover	Low osteoblast and osteoclast numbers in 12-week-old male Ts65Dn mice.	Fowler et al 2012
	Low P1NP and TRAP quantification in 2-year-old male Ts65Dn mice.	Williams et al 2017
Altered bone homeostasis	Low osteoblast and high osteoclast activity in 6-week-old male Ts65Dn mice. 16-week- old male mice continue with altered trabecular and cortical bone.	Blazek et al 2011
		Blazek et al 2015
Sex and age specific changes	Increased osteoblast activity and reduced osteoclast activity in trabecular bone of 16- week-old male Dp1Tyb mice.	Thomas et al 2020
	Decrease in osteoblast activity in trabecular bone of 16-week-old male Dp1Tyb mice.	
Low bone formation	Low serum P1NP and normal CTx in adult males and females (combined) with DS as compared to controls	McKelvey et al 2017
Increased osteoblastogenesis	Higher P1NP and ALP levels in adult males and females (combined) with DS as compared to controls	Garcia Hoyos et al 2017
Adynamic bone	Reduced osteoblasts and no observed osteoclasts in 49-year-old man with DS.	Grimwood et al 2000
Mechanostat	Reduced physical activity correlates with low bone mass. Increasing activity improves bone mass.	Garcia Hoyos et al 2017
		Matute-Llorente 2013
		Matute-Llorente 2017
		Matute-Llorente 2015