Published in final edited form as:
Curr Osteoporos Rep. 2014 September ; 12(3): 376–382. doi:10.1007/s11914-014-0221-4.

Aneuploidy and Skeletal Health

Archana Kamalakar[1,2], **John R. Harris**[2], **Kent D. McKelvey**[3], and **Larry J. Suva**[1,2,*]

[1]Department of Physiology & Biophysics, University of Arkansas for Medical Sciences, Little Rock, AR

[2]Department of Orthopaedic Surgery, Center for Orthopaedic Research, University of Arkansas for Medical Sciences, Little Rock, AR

[3]Department of Genetics. University of Arkansas for Medical Sciences, Little Rock, AR

Abstract

The normal human chromosome complement consists of 46 chromosomes comprising 22 morphologically different pairs of autosomes and one pair of sex chromosomes. Variations in either chromosome number and/or structure frequently result in significant mental impairment, and/or a variety of other clinical problems, among them, altered bone mass and strength. Chromosomal syndromes associated with specific chromosomal abnormalities are classified as either numerical or structural and may involve more than one chromosome. Aneuploidy refers to the presence of an extra copy of a specific chromosome, or trisomy, as seen in Down's syndrome (trisomy 21), or the absence of a single chromosome, or monosomy, as seen in Turner syndrome (a single X chromosome in females: 45, X). Aneuploidies have diverse phenotypic consequences, ranging from severe mental retardation and developmental abnormalities to increased susceptibility to various neoplasms and premature death. In fact, trisomy 21 is the prototypical aneuploidy in humans, is the most common genetic abnormality associated with longevity and is one of the most widespread genetic causes of intellectual disability. In this review, the impact of trisomy 21 on the bone mass, architecture, skeletal health and quality of life of people with Down syndrome will be discussed.

Keywords

aneuploidy; bone quality; Down Syndrome; bone turnover

Introduction

The discovery in 1956 that the correct chromosome number in humans was 46 ushered in the modern human cytogenetics era[1]. In the ensuing 50+ years, a series of major

*Corresponding Author suvalarryj@uams.edu.

Conflict of Interest
A Kamalakar, JR Harris, and KD McKelvey all declare no conflicts of interest.

Human and Animal Rights and Informed Consent
All studies by KD McKelvey and LJ Suva involving animal and/or human subjects were performed after approval by the appropriate institutional review boards. When required, written informed consent was obtained from all participants.

chromosomal syndromes with altered numbers of chromosomes were reported, e.g. Down syndrome (trisomy 21), Turner syndrome (45, X) and Klinefelter syndrome (47, XXY)[2]. It is now well-established that chromosome abnormalities contribute significantly to genetic disease resulting in reproductive loss, infertility, congenital anomalies, abnormal sexual development, intellectual disability and altered pathogenesis of malignancy, as well as decreases in bone mass and strength. Specific and recurrent chromosome abnormalities have been associated with more than 60 identifiable syndromes and are present in at least 50% of spontaneous abortions, 6% of stillbirths, about 5% of couples with two or more miscarriages and approximately 0.5% of newborns[3]. In women aged 35 or over, chromosomal abnormalities are detected in around 2% of all pregnancies[4,5]. Of particular interest to bone biologists is the decreased bone mass reported in the prototypical human aneuploidy Down syndrome[6–11]. This review is focused on the mechanisms and clinical consequences of low bone mass on the function and quality of life of people with Down syndrome.

Complex phenotypes of Down syndrome

Originally described in 1866[12], Down syndrome is characterized by trisomy of human chromosome 21 (Hsa21). The hundreds of genes on Hsa21 that are at some level of dosage imbalance are presumed to affect a wide-range of developmental pathways and tissues[13]. Trisomy 21 is the most common symptomatic chromosomal abnormality compatible with survival into adulthood and the probability of fetal trisomy 21 is strongly associated with maternal age[14]. Although there appears to be a trend toward increased maternal age in developed countries[15], the trend appears to be offset by the widespread availability of prenatal screening and evolving barriers to elective abortion, ensuring that the incidence of Down syndrome has stabilized at around one in 1000 to one in 800 live births[15,16].

Indeed, the life expectancy of Down syndrome patients born today has increased dramatically from around 9 years in the early part of the twentieth century to greater than 60 years in the second decade of the 21st century[17,18]. The substantial increase in survival is due primarily to improvements in both medical and social care and indicates that the life expectancy of people with Down syndrome is approaching that of the general population[19]. The increased longevity is also now accompanied by a range of significant mid-life health concerns[20]. These findings are of relevance to the US and have considerable implications in terms of the counselling information provided to families at risk of having a child with Down syndrome.

Numerous environmental and hormonal factors have been reported to contribute to low bone mineral density (BMD) in Down syndrome patients[20]. The low BMD in these patients is associated with impairments in skeletal maturation and bone-mass accrual that predispose to fragility fractures, with the likelihood for these fractures increasing with extended life expectancy[21,22]. Several factors have been suggested to contribute to these skeletal impairments and susceptibility to fragility fractures, including muscle hypotonia, low rates of physical activity, endocrine (hypothyroidism, hyperparathyroidism, hypogonadism), and autoimmune disorders (celiac disease) which can lead to inadequate nutrition[20]. Low activity levels, low sunlight exposure and anticonvulsant therapy have also been associated with decreased bone mass but these are not consistent risk factors in Down syndrome,

leaving the underlying pathophysiology unclear[9]. In any case, all Down syndrome patients should be encouraged to maintain adequate calcium levels, sufficient sunlight exposure (Vitamin D) and healthy dietary and exercise habits as can be tolerated (Table 1). It is important that Down syndrome patient and their caregivers and physicians recognize that conditions such as celiac disease or the use of anti-seizure medications adversely affect vitamin D levels, so diligence is required to ensure patients remain vitamin D sufficient.

It is interesting to speculate that the low BMD and low bone turnover may be the result of the presumed low activity levels of Down syndrome children. Although not a consistent risk factor in these individuals, mechanistically an altered set-point for the "mechanostat"[23] would be a plausible explanation for the lower accrual of bone mass. The subsequent low turnover state of Down syndrome adults would maintain such a low bone mass phenotype. The resolution of this intriguing question will require longitudinal studies of activity and/or nutritional levels in children with trisomy Hsa21.

Down syndrome pathologies

Although the underlying genetic cause of Down syndrome, trisomy Hsa21, is the same in all individuals with the disorder, penetrance of the resulting pathologies varies[13]. The majority of Down syndrome patients have learning difficulties, craniofacial alterations and muscle hypotonia. However, the minority have congenital heart malformations, leukemia or gut morphologic abnormalities. The severity of the specific defects is variable and the extent of cognitive impairment varies widely between individuals with trisomy 21, although a majority of pediatric Down syndrome patients will require treatment for intellectual or growth retardation.

Compared with the normal population, individuals with Down syndrome have an 18-fold increased risk of developing leukemia[24]. Specifically, Down syndrome is associated with a 500-fold increased risk of acute megakaryoblastic leukemia. In contrast to blood tumors, individuals with Down syndrome are at a significantly lower risk for developing virtually all types of malignant solid tumors demonstrating that trisomy 21 protects against tumor growth[25].

Growth retardation is a cardinal feature of Down syndrome that has been suggested to be attributable to growth hormone (GH) deficiency, secondary to hypothalamic dysfunction[26]. Thyroid dysfunction is also more common in individuals with Down syndrome than in the general population, and hypothyroidism that is present at birth or develops during childhood or adolescence is the most commonly reported thyroid abnormality in individuals with Down syndrome[27]. Hypothyroidism can be either congenital or acquired at any age after birth, with the primary risk factors being female and old age[27].

Patients with Down syndrome also have a high frequency of abnormalities in sexual development such that infertility, cryptorchidism, small testes and delayed puberty have been reported[28]. Interestingly, Hsiang et al. evaluated gonadal function in noninstitutionalized patients with Down syndrome (53 boys and men and 47 girls and women)[29]. When Down syndrome patients with thyroid dysfunction were excluded, the mean ages of onset and completion of puberty were normal in both sexes, dispelling another

common mistaken belief regarding Down syndrome. In addition, hormone studies of the 23 sexually mature men indicated that serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels were significantly elevated beyond the normal range, but that mean testosterone levels were within the normal range, confirming a diagnosis of partial, primary gonadal dysfunction[29]. These observations have been suggested to predispose individuals with Down syndrome to high bone turnover and bone loss[6,7,30–34]. However, this proposed mechanism regarding the mechanism of low bone mass is one that we and others have recently dispelled in both mice and humans with Down syndrome[8,9,35].

Musculoskeletal

Patients with Down syndrome experience a number of different musculoskeletal abnormalities and frequently endure osteoarthritic degeneration of the spine as well as low bone mass with resultant fractures of the long bones or vertebral bodies[36]. In addition, people with Down syndrome are hypotonic and often have nutritional and hormonal deficiencies at critical times of bone-mass accretion, namely in infancy and adolescence[37]. These nutritional inadequacies have been suggested to play a major role in the impairment of peak bone-mass accrual and to even correlate with the occurrence of osteoporosis[38]. Several cross-sectional and case–control studies, that included small numbers of patients, have found an increased prevalence of low bone mass and osteoporosis in men and women with mental retardation in general, and in those with Down syndrome in particular[6,7,30,39]. The majority of these studies were making inappropriate comparisons between institutionalized patients with schizophrenia and ambulatory community dwelling individuals with Down syndrome.

As a result, many of these studies missed the low bone turnover phenotype of Down syndrome. Many investigators have hypothesized that hypogonadism and endocrine dysfunction drove the increased bone resorption, leading to the low bone mass observed in Down syndrome patients. More recent studies have used larger Down syndrome patient cohorts, in comparison with non-institutionalized normal controls, rather than institutionalized individuals with mental disorders. These Down syndrome patients with normalized thyroid hormone, Vitamin D levels, adequate exercise and nutrition[9] as well as murine Down's syndrome models[8,35,39] have unequivocally demonstrated that low bone mass is indeed common in males and females with Down syndrome. However, the mechanism is not one of increased bone resorption, but of low bone turnover that is present despite profound hypogonadism[8,35].

In addition to the well-recognized low bone mass phenotype and increased risk of fracture characteristic of Down syndrome, trisomy Hsa21 is also associated with a number of other musculoskeletal abnormalities. Spinal conditions include upper cervical spinal instability, in particular at the atlanto-axial or occipital-cervical joints with a reported incidence of around 10–15% and scoliosis estimated to occur in around 7% of individuals[40–42]. In select patients, spinal fusions are sometimes necessary to improve mobility and alleviate these problems. Extremity abnormalities including patellofemoral instability, a variety of foot conditions and several hip disorders are also common[40,43]. Patellofemoral instability is one of the more common musculoskeletal issues for these patients with an estimated incidence of 10–

20%[40,43]. Treatment usually consists of non-operative modalities but can require soft tissue and bony procedures in persistently symptomatic or recurrent cases[43]. Foot pathology includes pes planus or flatfoot, which is reported at rates close to 2–6% and first ray disorders including metatarsus primus varus and hallux valgus (bunions)[40,44]. The management of these problems almost always begins with non-operative management, such as orthotics or shoe ware modification and only progresses to surgical options when necessary.[44,45].

The hip disorders affecting Down syndrome patients include slipped capital femoral epiphysis (SCFE), Perthes disease and hip instability[16]. SCFE appears to occur in approximately 1.3% of individuals[46]. While the management of this entity, i.e. *in situ* pinning, does not differ from non Down syndrome children, there is an increased complication rate with osteonecrosis being particularly worrisome[47]. The etiology of this is interesting and has been suggested to be the result of the higher incidence of endocrine abnormalities present in Down syndrome[45]. Perthe's disease occurs with an incidence similar to SCFE, around 2%[48] while hip instability occurs in around 2–5% of Down syndrome patients. The etiology appears to be multi-factorial with both bony differences and more importantly soft tissue laxity and hypermobility contributing to the development of this problem[16]. Interestingly, the instability and dysplasia in trisomy Hsa21 differs drastically from typical childhood developmental hip dysplasia in that they are generally asymptomatic in early childhood (<2 yo) with subsequent subluxation/dislocations and dysplasia developing later[44,46,49]. In particular, Bennett and colleagues[49] detailed the natural history of hip dislocations in Down syndrome patients and suggested four specific phases; initial, dislocation, subluxation and fixed phases. These investigators' noted that dysplasia, including posterior acetabular deficiency, occurs during the subluxation phase and that it is the repeated subluxation/dislocations that result in damage to the femoral head[49]. The treatment of this issue usually begins with immobilization in the subluxing/dislocation patient without bony changes and progresses to bony procedures including femoral and acetabular osteotomies to address the bony pathology with capsular placations or tightening as needed[45,46,49,50]. With the increased life expectancy, orthopaedic surgeons may expect to see an ever increasing number of Down syndrome patients with end-stage arthritis of the hip[51]. However, complications with orthopaedic surgery in the Down syndrome population are more common, thus early intervention to avoid surgery is preferred[50]. By providing physicians and surgeons with an awareness of the unique aspects of musculoskeletal disease in the Down syndrome patient population, thoughtful patient care decisions, involvement of family and caregivers, as well as good pre-operative planning, and the appropriate implant choice for total hip arthroplasty will provide reliable pain relief and significantly improved function[16].

Discussion

Our measurement of bone density and bone biochemical markers in community dwelling Down syndrome patients compared to the normal population[9] was the first to challenge the idea that low bone mass in Down syndrome was not due to increased bone cell activity and lifestyle differences[13,31,33]. In fact, the low bone mass phenotype was observed in a murine Down syndrome model (Ts65Dn)[8,35], and was treatable with intermittent parathyroid

hormone[8]. The decreased bone turnover in Down syndrome is an entirely unexpected result, given the hypogonadism and infertility apparent in both animals and humans with the disorder[52,53]. Although hypogonadism is a consistent finding in men with Down syndrome,[10,28,54] the pathophysiology of the infertility in men with Down syndrome remains unclear.

However, what is clear is that males with Down syndrome are generally infertile and have significant disruption of one or more levels of the hypothalamic-pituitary-gonadal axis resulting in elevated FSH and LH levels and inconsistent testosterone levels, that are frequently in the low-normal range[28,29,52]. Whatever the final cause of the hypogonadism and infertility in males, our current appreciation of the endocrine regulation of bone would favor significantly increased, not decreased bone turnover. It is critical to note additional clinical evidence in support of this surprising observation. In the only pathologic post-mortem examination of bone from a Down syndrome patient[55], bone histology directly confirmed low bone mass and the mechanism of decreased bone turnover, although it was incorrectly diagnosed as osteoporosis[55]. In that study evaluating vertebral sections from a 49-year old Down syndrome female, a complete lack of active osteoclasts and decreased osteoblast number along the bone trabeculae was noted[55].

Given the skeletal consequences of low bone mass and bone strength in Down syndrome, namely increased fracture risk and frequency[21,22], clinical intervention becomes important. In the face of low bone turnover, current anti-catabolic agents (bisphosphonates; Prolia™) are contraindicated. At the moment, no anabolic therapy is approved in this patient population. In fact, the only FDA-approved anabolic agent (intermittent parathyroid hormone; Forteo™) is approved only for the treatment of osteoporosis in men and post-menopausal women, who are at high risk for a fracture. PTH is not approved in the Down syndrome patient population, and pharmacologic intervention in people with trisomy Hsa21 is complicated by social and consenting issues and a reluctance of pharmaceutical companies to treat this underserved population. As such there is an urgent and unmet need for alternative treatments to increase bone mass and strength in Down syndrome.

A number of alternative treatment options that can increase bone mass, so called anabolic agents, exist and/or are currently under development[56]. At this time, the primary bone anabolic pharmaceutical target is the inhibition of the sclerostin pathway. Sclerostin is the product of the *SOST* gene produced mainly by osteocytes, and is a potent negative regulator of bone formation via inhibition of the Wnt signaling pathway[57]. In fact, a human anti-sclersotin antibody is in clinical development, but its use in the Down syndrome populations is likely not a priority. Although a promising therapeutic opportunity that is associated with increased bone mineral density and bone formation with decreased bone resorption in postmenopausal women with low bone mass[58], the efficacy of anti-sclerostin therapy to increase bone mass in patient populations such as Down syndrome is unknown.

As a result, the exploration of other bone anabolic approaches has led us and others to consider nutritional supplements as a unique way to increase bone mass and strength[59,60]. In the Down syndrome population, the utility of a nutritional supplement in the form of an oral additive is a particularly attractive and viable therapeutic option. To provide a direct and

potentially efficacious alternative bone anabolic approach, we have been pursuing the utility of a proven blueberry nutritional intervention. Numerous studies have shown robust skeletal anabolism with blueberry diets in preclinical models[61–63], as well as with other nutritional supplements[59,60,64,65]. As such, these approaches provide an attractive, non-pharmaceutical option in the clinical setting of Down syndrome.

In the Down syndrome population, routine screening for thyroid hormone deficiency and celiac disease are warranted, as is monitoring vitamin D and calcium levels[20]. The musculoskeletal consequences of poorly managed calcium and vitamin D as well as minimal physical activity, is well-documented in the general population[66]. However, these deleterious consequences in Down syndrome, in the face of inherently low bone turnover, maybe exacerbated. As such, increased diligence by physicians, patients and care-givers is required.

Conclusions

In summary, this discussion provides clarification of the mechanisms that contribute to the low bone mass in Down syndrome and more importantly, provide the basis for new directions for the treatment of the osteopenia that impacts this population. In light of the elevated fracture risk and fracture rate in adult Down syndrome patients, studies that carefully assess bone mass accrual during childhood are required, as are evidence-based recommendations for bone density screening and appropriate treatment options. Indeed, we strongly support the need to consider bone anabolic therapies in appropriate healthy adult Down syndrome patients with low BMD.

Acknowledgments

This work was supported by the Carl L. Nelson Chair of Orthopaedic Creativity (LJS), the Rockefeller Chair in Clinical Genetics (KDM) and a grant from the UAMS Translational Research Institute (TRI) UL1RR029884. The authors would like to thank Dr. MR Forwood of Griffith University (Australia) for his review of the manuscript.

LJ Suva has received research support from the NIH.

References

Papers of particular interest, published recently, have been highlighted as:

•• Of major importance

• Of importance

1. Tijo J-H, Levan A. The chromosome number of man. Hereditas. 1956; 42:1–6. **Original elucidation of the number of human chromosomes
2. Wallerstein R, Yu MT, Neu RL, et al. Common trisomy mosaicism diagnosed in amniocytes involving chromosomes 13, 18, 20 and 21: karyotype-phenotype correlations. Prenatal diagnosis. 2000 Feb; 20(2):103–122. [PubMed: 10694683]
3. Luthardt, FW.; Keitges, E. eLS. John Wiley & Sons, Ltd; 2001. Chromosomal Syndromes and Genetic Disease.
4. Hassold GN, Dreitlein JF, Beale PD, Scott JF. Dynamics of the two-dimensional axial third-nearest-neighbor Ising model: Entrainment and diffusivity. Physical review. B, Condensed matter. 1986 Mar 1; 33(5):3581–3584.

5. Schreinemachers DM, Cross PK, Hook EB. Rates of trisomies 21, 18, 13 and other chromosome abnormalities in about 20 000 prenatal studies compared with estimated rates in live births. Human genetics. 1982; 61(4):318–324. [PubMed: 6891368]
6. Angelopoulou N, Souftas V, Sakadamis A, Mandroukas K. Bone mineral density in adults with Down's syndrome. European radiology. 1999; 9(4):648–651. [PubMed: 10354878]
7. Baptista F, Varela A, Sardinha LB. Bone mineral mass in males and females with and without Down syndrome. Osteoporos Int. 2005 Apr; 16(4):380–388. [PubMed: 15365695]
8. Fowler TW, McKelvey KD, Akel NS, et al. Low bone turnover and low BMD in Down syndrome: effect of intermittent PTH treatment. PloS one. 2012; 7(8):e42967. [PubMed: 22916188] ** Identifies efficacy of anabolic therapy to increase Bone mass in Down syndrome
9. McKelvey KD, Fowler TW, Akel NS, et al. Low bone turnover and low bone density in a cohort of adults with Down syndrome. Osteoporos Int. 2012 Apr; 24(4):1333–1338. [PubMed: 22903293] * Demonstrates low bone mass and turnover in Down syndrome males and femals compared with normal controls
10. Sakadamis A, Angelopoulou N, Matziari C, Papameletiou V, Souftas V. Bone mass, gonadal function and biochemical assessment in young men with trisomy 21. European journal of obstetrics, gynecology, and reproductive biology. 2002 Jan 10; 100(2):208–212.
11. Zubillaga P, Garrido A, Mugica I, Ansa J, Zabalza R, Emparanza JI. Effect of vitamin D and calcium supplementation on bone turnover in institutionalized adults with Down's Syndrome. European journal of clinical nutrition. 2006 May; 60(5):605–609. [PubMed: 16391575]
12. Down JLH. Observations on an ethnic classification of idiots. Clinical Lecture Reports, London Hospital. 1866; 3:259–262. * Original description of Down syndrome
13. Antonarakis SE, Lyle R, Dermitzakis ET, Reymond A, Deutsch S. Chromosome 21 and down syndrome: from genomics to pathophysiology. Nat Rev Genet. 2004 Oct; 5(10):725–738. [PubMed: 15510164]
14. Huether CA, Ivanovich J, Goodwin BS, et al. Maternal age specific risk rate estimates for Down syndrome among live births in whites and other races from Ohio and metropolitan Atlanta, 1970–1989. Journal of medical genetics. 1998 Jun; 35(6):482–490. [PubMed: 9643290]
15. Cocchi G, Gualdi S, Bower C, et al. International trends of Down syndrome 1993–2004: Births in relation to maternal age and terminations of pregnancies. Birth defects research. Part A, Clinical and molecular teratology. 2010 Jun; 88(6):474–479.
16. Zywiel MG, Mont MA, Callaghan JJ, et al. Surgical challenges and clinical outcomes of total hip replacement in patients with Down's syndrome. The bone & joint journal. 2013 Nov; 95-B(11 Suppl A):41–45. [PubMed: 24187350]
17. Coppus AM, Evenhuis HM, Verberne GJ, et al. Survival in elderly persons with Down syndrome. Journal of the American Geriatrics Society. 2008 Dec; 56(12):2311–2316. [PubMed: 19093931]
18. Glasson EJ, Sullivan SG, Hussain R, Petterson BA, Montgomery PD, Bittles AH. The changing survival profile of people with Down's syndrome: implications for genetic counselling. Clinical genetics. 2002 Nov; 62(5):390–393. [PubMed: 12431254]
19. Zigman WB. Atypical aging in Down syndrome. Developmental disabilities research reviews. 2013 Aug; 18(1):51–67. [PubMed: 23949829]
20. Hawli Y, Nasrallah M, El-Hajj Fuleihan G. Endocrine and musculoskeletal abnormalities in patients with Down syndrome. Nature reviews. 2009 Jun; 5(6):327–334.
21. Lohiya GS, Crinella FM, Tan-Figueroa L, Caires S, Lohiya S. Fracture epidemiology and control in a developmental center. The Western journal of medicine. 1999 Apr; 170(4):203–209. [PubMed: 10344173]
22. Schrager S, Kloss C, Ju AW. Prevalence of fractures in women with intellectual disabilities: a chart review. J Intellect Disabil Res. 2007 Apr; 51(Pt 4):253–259. [PubMed: 17326806]
23. Suva LJ, Gaddy D, Perrien DS, Thomas RL, Findlay DM. Regulation of bone mass by mechanical loading: microarchitecture and genetics. Current osteoporosis reports. 2005 Jun; 3(2):46–51. [PubMed: 16036101]
24. Hasle H, Clemmensen IH, Mikkelsen M. Risks of leukaemia and solid tumours in individuals with Down's syndrome. Lancet. 2000 Jan 15; 355(9199):165–169. [PubMed: 10675114]

25. Yang Q, Rasmussen SA, Friedman JM. Mortality associated with Down's syndrome in the USA from 1983 to 1997: a population-based study. Lancet. 2002 Mar 23; 359(9311):1019–1025. [PubMed: 11937181]
26. Castells S, Beaulieu I, Torrado C, Wisniewski KE, Zarny S, Gelato MC. Hypothalamic versus pituitary dysfunction in Down's syndrome as cause of growth retardation. J Intellect Disabil Res. 1996 Dec; 40(Pt 6):509–517. [PubMed: 9004111]
27. Waller DK, Anderson JL, Lorey F, Cunningham GC. Risk factors for congenital hypothyroidism: an investigation of infant's birth weight, ethnicity, and gender in California, 1990–1998. Teratology. 2000 Jul; 62(1):36–41. [PubMed: 10861631]
28. Suzuki K, Nakajima K, Kamimura S, et al. Eight case reports on sex-hormone profiles in sexually mature male Down syndrome. International journal of urology : official journal of the Japanese Urological Association. 2010 Dec; 17(12):1008–1010. [PubMed: 20973837]
29. Hsiang YH, Berkovitz GD, Bland GL, Migeon CJ, Warren AC. Gonadal function in patients with Down syndrome. American journal of medical genetics. 1987 Jun; 27(2):449–458. [PubMed: 2955699]
30. Angelopoulou N, Matziari C, Tsimaras V, Sakadamis A, Souftas V, Mandroukas K. Bone mineral density and muscle strength in young men with mental retardation (with and without Down syndrome). Calcified tissue international. 2000 Mar; 66(3):176–180. [PubMed: 10666490]
31. da Silva VZ, de Franca Barros J, de Azevedo M, de Godoy JR, Arena R, Cipriano G Jr. Bone mineral density and respiratory muscle strength in male individuals with mental retardation (with and without Down Syndrome). Research in developmental disabilities. 2010 Nov-Dec;31(6): 1585–1589. [PubMed: 20541908]
32. Gonzalez-Aguero A, Vicente-Rodriguez G, Moreno LA, Casajus JA. Bone mass in male and female children and adolescents with Down syndrome. Osteoporos Int. 2011 Oct 22; 22(7):2151–2157. [PubMed: 20967423]
33. Guijarro M, Valero C, Paule B, Gonzalez-Macias J, Riancho JA. Bone mass in young adults with Down syndrome. J Intellect Disabil Res. 2008 Mar; 52(Pt 3):182–189. [PubMed: 18261017]
34. Kao CH, Chen CC, Wang SJ, Yeh SH. Bone mineral density in children with Down's syndrome detected by dual photon absorptiometry. Nuclear medicine communications. 1992 Oct; 13(10): 773–775. [PubMed: 1491844]
35. Blazek JD, Gaddy A, Meyer R, Roper RJ, Li J. Disruption of bone development and homeostasis by trisomy in Ts65Dn Down syndrome mice. Bone. 2011 Feb 1; 48(2):275–280. [PubMed: 20870049] * First low bone mass demonstration in Ts65 DN mice
36. van Allen MI, Fung J, Jurenka SB. Health care concerns and guidelines for adults with Down syndrome. American journal of medical genetics. 1999 Jun 25; 89(2):100–110. [PubMed: 10559765]
37. Clark EM, Ness AR, Bishop NJ, Tobias JH. Association between bone mass and fractures in children: a prospective cohort study. J Bone Miner Res. 2006 Sep; 21(9):1489–1495. [PubMed: 16939408]
38. Tabensky A, Duan Y, Edmonds J, Seeman E. The contribution of reduced peak accrual of bone and age-related bone loss to osteoporosis at the spine and hip: insights from the daughters of women with vertebral or hip fractures. J Bone Miner Res. 2001 Jun; 16(6):1101–1107. [PubMed: 11393787]
39. Olson LE, Mohan S. Bone density phenotypes in mice aneuploid for the Down syndrome critical region. American journal of medical genetics. 2011 Oct; 155(10):2436–2445. [PubMed: 21915988] * Provides first detailed glimpse of low bone mass in Down syndrome animal models
40. Morad M, Kandel I, Merrick-Kenig E, Merrick J. Persons with Down syndrome in residential care in Israel: trends for 1998–2006. International journal of adolescent medicine and health. 2009 Jan-Mar;21(1):131–134. [PubMed: 19526704]
41. Pizzutillo PD, Herman MJ. Cervical spine issues in Down syndrome. Journal of pediatric orthopedics. 2005 Mar-Apr;25(2):253–259. [PubMed: 15718913]
42. Pueschel SM, Scola FH, Tupper TB, Pezzullo JC. Skeletal anomalies of the upper cervical spine in children with Down syndrome. Journal of pediatric orthopedics. 1990 Sep-Oct;10(5):607–611. [PubMed: 2144299]

43. Mendez AA, Keret D, MacEwen GD. Treatment of patellofemoral instability in Down's syndrome. Clinical orthopaedics and related research. 1988 Sep.(234):148–158. [PubMed: 2970357]
44. Diamond LS, Lynne D, Sigman B. Orthopedic disorders in patients with Down's syndrome. The Orthopedic clinics of North America. 1981 Jan; 12(1):57–71. [PubMed: 6451852]
45. Caird MS, Wills BP, Dormans JP. Down syndrome in children: the role of the orthopaedic surgeon. The Journal of the American Academy of Orthopaedic Surgeons. 2006 Oct; 14(11):610–619. [PubMed: 17030594]
46. Shaw ED, Beals RK. The hip joint in Down's syndrome. A study of its structure and associated disease. Clinical orthopaedics and related research. 1992 May.(278):101–107. [PubMed: 1532929]
47. Bosch P, Johnston CE, Karol L. Slipped capital femoral epiphysis in patients with Down syndrome. Journal of pediatric orthopedics. 2004 May-Jun;24(3):271–277. [PubMed: 15105722]
48. Greene WB. Closed treatment of hip dislocation in Down syndrome. Journal of pediatric orthopedics. 1998 Sep-Oct;18(5):643–647. [PubMed: 9746417]
49. Bennet GC, Rang M, Roye DP, Aprin H. Dislocation of the hip in trisomy 21. The Journal of bone and joint surgery. British volume. 1982; 64(3):289–294. [PubMed: 6212586]
50. Katz DA, Kim YJ, Millis MB. Periacetabular osteotomy in patients with Down's syndrome. The Journal of bone and joint surgery. British volume. 2005 Apr; 87(4):544–547. [PubMed: 15795208]
51. Gill CE, Taylor HM, Lin KT, et al. Difficulty in securing treatment for degenerative hip disease in a patient with Down syndrome: the gap remains open. Journal of the National Medical Association. 2006 Jan; 98(1):93–96. [PubMed: 16532986]
52. Stefanidis K, Belitsos P, Fotinos A, Makris N, Loutradis D, Antsaklis A. Causes of infertility in men with Down syndrome. Andrologia. 2011 Oct; 43(5):353–357. [PubMed: 21806650]
53. Moore CS, Hawkins C, Franca A, et al. Increased male reproductive success in Ts65Dn "Down syndrome" mice. Mammalian genome : official journal of the International Mammalian Genome Society. 2010 Dec; 21(11–12):543–549. [PubMed: 21110029]
54. Pradhan M, Dalal A, Khan F, Agrawal S. Fertility in men with Down syndrome: a case report. Fertility and sterility. 2006 Dec; 86(6):1765, e1761–e1763. [PubMed: 17094988]
55. Grimwood JS, Kumar A, Bickerstaff DR, Suvarna SK. Histological assessment of vertebral bone in a Down's syndrome adult with osteoporosis. Histopathology. 2000 Mar; 36(3):279–280. [PubMed: 10809596] * Only histologic analysis of human bone from a Down syndrome patient
56. Bone H. Future directions in osteoporosis therapeutics. Endocrinology and metabolism clinics of North America. 2012 Sep; 41(3):655–661. [PubMed: 22877435]
57. Spatz JM, Ellman R, Cloutier AM, et al. Sclerostin antibody inhibits skeletal deterioration due to reduced mechanical loading. J Bone Miner Res. 2013 Apr; 28(4):865–874. [PubMed: 23109229]
58. McClung MR, Grauer A, Boonen S, et al. Romosozumab in postmenopausal women with low bone mineral density. The New England journal of medicine. 2014 Jan 30; 370(5):412–420. [PubMed: 24382002]
59. Jesudason D, Clifton P. The interaction between dietary protein and bone health. Journal of bone and mineral metabolism. 2011 Jan; 29(1):1–14. [PubMed: 20972896]
60. New SA, Robins SP, Campbell MK, et al. Dietary influences on bone mass and bone metabolism: further evidence of a positive link between fruit and vegetable consumption and bone health? The American journal of clinical nutrition. 2000 Jan; 71(1):142–151. [PubMed: 10617959]
61. Chen JR, Lazarenko OP, Wu X, et al. Dietary-induced serum phenolic acids promote bone growth via p38 MAPK/beta-catenin canonical Wnt signaling. J Bone Miner Res. 2010 Nov; 25(11):2399–2411. [PubMed: 20499363]
62. Zhang J, Lazarenko OP, Blackburn ML, Badger TM, Ronis MJ, Chen JR. Blueberry consumption prevents loss of collagen in bone matrix and inhibits senescence pathways in osteoblastic cells. Age (Dordrecht, Netherlands). 2012 May 4.
63. Zhang J, Lazarenko OP, Kang J, et al. Feeding blueberry diets to young rats dose-dependently inhibits bone resorption through suppression of RANKL in stromal cells. PloS one. 2013; 8(8):e70438. [PubMed: 23936431]
64. Arjmandi BH, Khalil DA, Lucas EA, et al. Dried plums improve indices of bone formation in postmenopausal women. Journal of women's health & gender-based medicine. 2002 Jan-Feb; 11(1):61–68.

65. Deyhim F, Stoecker BJ, Brusewitz GH, Devareddy L, Arjmandi BH. Dried plum reverses bone loss in an osteopenic rat model of osteoporosis. Menopause (New York, N.Y. 2005 Nov-Dec; 12(6):755–762.

66. Riggs BL. Role of the vitamin D-endocrine system in the pathophysiology of postmenopausal osteoporosis. Journal of cellular biochemistry. 2003 Feb 1; 88(2):209–215. [PubMed: 12520516]

Table 1

Options for the maintenance of bone health in Down syndrome

DIETARY
Adequate calcium (Indicate normal range)
Age<50 (1,000 mg/day) total dietary and supplemental calcium
Age>50 (1,200 mg/day) total dietary and supplemental calcium
Vitamin D
Age<50 (400–800 international units (IU) daily[*]*)*
Age>50 (800–1,000 international units (IU) daily[*]*)*
Healthy food choices and a well-balanced diet
Dairy products, fish, fruits and vegetables
EXERCISE
Weight-bearing exercise as indicated and tolerated
Support and encourage appropriate activity levels
High-impact weight-bearing exercise e.g.: Hiking, stair-climbing
Low-impact weight-bearing exercise e.g.: Fast walking, low-impact aerobics
Non-Impact exercise as indicated and tolerated
Increase muscle strength to decrease the risk of falls and fracture
Improve balance, posture and daily function
Muscle-strengthening exercise e.g.: Functional movements (standing and rising up on your toes), Using elastic exercise bands.
ENDOCRINE
Endocrine management decisions
Routine Bone Density measurements (annual)
Follow Thyroid hormone levels, (T3, T4, TSH)
Identify Celiac disease

[*]According to the Institute of Medicine (IOM), the safe upper limit of vitamin D is 4,000 IU per day for most adults