Endocrine and musculoskeletal abnormalities in patients with Down syndrome

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Abstract | Down syndrome has a prevalence of one in 500 to one in 1,000 live births and is the most common cause of mental retardation. Most patients are treated in childhood and adolescence for mental or growth retardation. Studies that evaluate bone mass in Down syndrome are limited, and many are small case series in pediatric and adult populations who live either in the community or in residential institutions. Several environmental and hormonal factors contribute to low bone mineral density in such patients. Muscle hypotonia, low amounts of physical activity, poor calcium and vitamin D intakes, hypogonadism, growth retardation and thyroid dysfunction contribute to substantial impairments in skeletal maturation and bone-mass accrual that predispose these patients to fragility fractures. Here, we review indications and limitations of bone-mass measurements in children, summarize the endocrine and skeletal abnormalities in patients presenting with Down syndrome, and review studies that investigate therapeutic strategies for such patients.

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Introduction

Down syndrome, which is characterized by trisomy of chromosome 21, is the most common chromosomal abnormality that affects live-born infants, with a birth-rate prevalence that varies between 1:500 and 1:1,000.[1] Short stature, typical facial features (epicanthal folds, flat nasal bridge and protruding tongue), cardiac malformations, precocious aging, and Alzheimer disease are prominent characteristics of the disease.[2,3] Mental retardation and an associated delay in gross motor development put these patients at increased risk of atlantoaxial dislocation and spinal-cord compression with hypotonia.[4] Most patients with Down syndrome require treatment during childhood because of mental or growth retardation. Hypotonia, and nutritional and hormonal deficiencies at critical times of bone-mass accretion, namely in infancy and adolescence, have a major role in the impairment of peak bone-mass accrual and correlate with osteoporosis. 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 women with mental retardation in general, and in those with Down syndrome in particular.[5–7] However, studies in pediatric patients are scarce. In this Review, we will outline various endocrine and metabolic factors that could contribute to suboptimal bone health in children and adolescents with Down syndrome, review principles of bone-density measurement in children, then focus on studies that evaluated bone mass in patients with Down syndrome or investigated therapeutic strategies that might help improve bone health in such patients.

Competing interests
The authors declare no competing interests.

Endocrine disorders in Down syndrome

Thyroid dysfunction

Thyroid dysfunction is the most typical endocrine abnormality in patients with Down syndrome, the established risk factors for which are old age and female sex.[8] Hypothyroidism can be either congenital or acquired at any age after birth. The estimated lifetime prevalence rate of thyroid dysfunction in Down syndrome varied widely in different studies (between 3% and 54% in adult patients), owing to variations in population size, age, laboratory assays and definitions of thyroid dysfunction used.[9,10] The New York State Newborn Screening Program reported an incidence of congenital hypothyroidism in babies with Down syndrome of 1:141 live births (12 affected infants of 1,130 live births),[11] compared with an incidence of 1:3,000 to 1:4,000 among healthy newborn babies.[8,12] In a longitudinal study of 85 patients with Down syndrome (age 0–25 years) who did not have congenital hypothyroidism and were followed up for ≤15 years, 30 developed thyroid dysfunction, 28 of whom had hypothyroidism and the other two of whom had hyperthyroidism.[13] Antithyroid autoantibodies were found in 13–34% of adults and older children with Down syndrome who acquired hypothyroidism,[10,11,14] with a gradual increase in the concentration of autoantibodies after 8 years of age.[13] Approximately half of children with Down syndrome may have an elevated TSH level with normal T_3 and T_4 levels, which suggest subclinical hypothyroidism.[15] A delay in maturation of the hypothalamic–pituitary–thyroid axis has been hypothesized as the probable cause, as TSH responses to TSH-releasing hormone tests were more exaggerated in patients with Down syndrome than in controls.[16] Among individuals with Down syndrome, hyperthyroidism occurs much less frequently than

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Key points

- Down syndrome is associated with multiple endocrine disorders that affect bone integrity
- Growth retardation, hypogonadism, poor calcium and vitamin D intakes, and muscle hypotonia are recognized risk factors for low bone density in general, and in Down syndrome in particular
- Dual X-ray absorptiometry (DXA) of the anteroposterior spine and total body (less head) is the recommended modality for measuring BMD in children
- Adjustment of DXA-derived BMD values for height age, bone age, or lean body mass is useful in situations of growth retardation and maturation delay
- Compared with age-matched, healthy children, those with Down syndrome have lower BMD measurements at the spine, with mean decrements of 1 SD
- Early, planned physical activity, adequate nutrition, and calcium and vitamin D replacement therapy are recommended to maintain bone health in children with Down syndrome

hypothyroidism: in the longitudinal study described above, only two of the 85 patients—both young girls—developed hyperthyroidism.[13] This rate exceeds the incidence of thyrotoxicosis in the general pediatric population, which varies from around 0.1:100,000 in childhood to 3:100,000 in adolescence.[17] In summary, thyroid dysfunction is more common in individuals with Down syndrome than in the general population, and hypothyroidism that is present at birth or manifests during childhood or adolescence is the most commonly reported thyroid abnormality in individuals with this syndrome.

Gonadal malfunction

Patients with Down syndrome have a high incidence of abnormalities in sexual development,[18,19] and delayed puberty is reported in both sexes. The reported abnormalities in girls include hypogonadism, with a delay in either menarche or adrenarche. In boys, described defects vary from ambiguous genitalia, cryptorchidism, micropenis, small testes and low sperm count to scant development of axillary hair and beard.[18,20] Hsiang *et al.*[18] evaluated gonadal function in 100 noninstitutionalized patients with Down syndrome, including 53 boys and men and 47 girls and women and excluding those with thyroid dysfunction. The mean ages of onset and completion of puberty were normal in both sexes. Among the 23 sexually mature men, the mean levels of serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were markedly elevated (18.7 mIU/ml and 16.9 mIU/ml, respectively), but mean testosterone levels were normal, which suggests a diagnosis of partial primary gonadal dysfunction.[18] Similar hormone levels were found in six of the 14 sexually mature women.[18] Interestingly, prepubertal children (six of the 12 boys and seven of the 13 girls) also had elevated serum FSH and LH levels that were more than 2 SD above the mean, with low–normal serum testosterone levels in boys; these findings also reflect primary gonadal failure. Infertility in men with Down syndrome has been attributed to defective spermatogenesis. However, in view of the developmental delay and social obstacles to procreation associated with this syndrome, fertility may be difficult to asses; to date, three reports described men with Down syndrome who became fathers.[21–23] In conclusion, primary gonadal deficiency and abnormal sexual development are common in both men and women with Down syndrome, with few reported cases of fertility in men.

Growth retardation

Growth retardation and short stature are cardinal signs of Down syndrome. Growth velocity is markedly reduced during the normal periods of accelerated growth, namely between the ages of 6 months and 3 years and during adolescence.[24,25] Growth retardation may be attributable to growth hormone (GH) deficiency secondary to hypothalamic dysfunction. This hypothesis is supported by lack of hypothalamic response to levodopa and clonidine challenge tests, but adequate pituitary responses to GH-releasing hormone (GHRH) that were observed in 14 children with Down syndrome (aged 10 months to 5 years) who were compared with 25 control children.[26] All patients had growth retardation with height SD scores (SDS) varying between –1.3 and –4.9, microcephaly with head circumference SDS varying between –5.0 and –0.3, and a delayed bone age. In addition, morphometric studies of the hypothalamic nuclei of patients with Down syndrome showed a diminished number of neurons in the arcuate and ventromedial nuclei responsible for GHRH neurosecretory function.[27] Whether the cause is primary GH deficiency or inadequate insulin-like growth factor (IGF) I response, growth retardation in these patients results in remarkable skeletal maturation delay and short stature.

Musculoskeletal abnormalities

Reduced muscle strength

Bone mass and bone geometry are influenced by muscle growth and force, which in turn are influenced by biochemical factors (for example, hormones or chronic illnesses).[19] The 'mechanostat hypothesis' explains the relationship between muscle force and bulk to bone mass and geometry in the developing skeleton.[28] According to this theory, bone mass and bone geometry are influenced by growth and muscle development in children and adolescents. The process is further modified by hormonal signals, such as estrogen and androgens.[19] Motor function in individuals with Down syndrome is characterized by hypotonia and hyperflexibility, which results in an increased risk of joint dislocation and retarded motor skills, but little work has been done to quantify this characteristic in this group of patients.[29] Children with nonspastic cerebral palsy also have reduced bone mass secondary to disuse and hypotonicity and are at increased risk of fracture.[30] A similar pathology and physiology could contribute to low bone mass in patients with Down syndrome.

Vitamin D deficiency

Increasing evidence supports a deleterious effect of vitamin D insufficiency on musculoskeletal health in children and adolescents during the critical time of bone-mass accrual.[31] In patients with Down syndrome, risk factors, such as inadequate exposure to sun, inadequate vitamin D intake and malabsorption or increased breakdown of vitamin D that accompanies anticonvulsant therapy, contribute to vitamin D insufficiency.[32] Malabsorption and vitamin deficiencies due to celiac disease have been reported in patients with Down syndrome with a wide prevalence range that varies geographically. Indeed, the frequency of celiac disease in children with Down syndrome in the Netherlands was 7% compared with 0.05% of live births in healthy Dutch children,[33] while in the southeastern US, this condition was present in one of 14 patients with Down syndrome (aged 10 months–30 years, mean age 5 years 3 months).[34] In 1999, the health-care guidelines published by the US-based Down Syndrome Medical Interest Group (DSMIG)[4] recommended an initial screening of patients with Down syndrome for celiac disease at 2 years of age with IgA tissue transglutaminase and total IgA antibodies, and repeated testing thereafter if necessary.

Bone mass

Bone mass acquired during childhood is a key determinant of adult bone health, and a low peak skeletal mass is considered an important risk factor for osteoporosis in adult life.[35] Dual-energy X-ray absorptiometry (DXA), which is most commonly used in children and adults to assess fracture risk, is an efficient, precise and safe method that has a relatively low cost and widespread availability.[36,37] However, BMD measurement using DXA has several limitations in general, and in children in particular. One of these limitations is the intraosseous and extraosseous 'soft tissue effect', whereby the presence of adipose tissue, lean soft tissue, and bone marrow in the scan region of interest can affect the accuracy of the BMD reading, either by increasing or decreasing it. For example, weight loss can result in a decrease in BMD on serial measurements, which can in part be explained by changes in soft-tissue thickness.[38] Other limitations include the effect of bone size on DXA-derived bone measures, as detailed below.

Clinicians must decide whether bone-density measurements in children with chronic illnesses need to be obtained on the basis of the severity and duration of their illness and the presence of fragility fractures.[37] In 2007, the International Society of Clinical Densitometry (ISCD) issued an official position statement on bone-mass measurements in children (Box 1).[30] Their recommendations include measurement of bone mass in children with primary bone diseases (such as osteogenesis imperfecta) or with secondary bone diseases (caused by chronic inflammation, chronic immobilization, endocrine disturbances, childhood cancer, or prior nonrenal organ transplantation) and in children with thalassemia major. The sites recommended as most appropriate and reproducible for densitometry measurements are the posterior–anterior lumbar spine and total body (less head) bone-mineral content (BMC) and areal BMD measurements.[39] The hip (including total and proximal femur) is not a reliable site for measurement in growing children, owing to remarkable variability in skeletal development and lack of good delineation of regions of interest. The recommendations for DXA measurements in children at risk of fracture differ according to the type of bone disease: in children with either primary or secondary bone disease, measurement is recommended at clinical presentation, in those with chronic immobilization, measurement is undertaken at the time of first fracture, and in patients with thalassemia major, DXA measurement is performed either at fracture presentation or at 10 years of age.[30]

The areal BMD *Z*-score, in which bone density is standardized according to the patient's age, is currently the main parameter used to interpret DXA results. *T*-scores should not be used, because peak bone mass has not yet been achieved in children, and *T*-scores are not generated in the most recent versions of densitometry software. The ISCD recommends that adjustments must be made to DXA readings in situations of chronic

Box 1 | Indications for DXA measurements in children[a]

Primary bone disorders
- Idiopathic juvenile osteoporosis
- Osteogenesis imperfecta

Inflammatory diseases
- Inflammatory bowel disease
- Juvenile idiopathic arthritis
- Cystic fibrosis

Disorders associated with chronic immobilization
- Cerebral palsy
- Myopathic disease
- Epidermolysis bullosa

Endocrine disturbances
- Turner syndrome
- Anorexia nervosa

Cancer and therapies with adverse effects on bone health
- Acute lymphocytic leukemia
- Chemotherapy for cancer in childhood
- Transplant bone disease

Hematological disorders
- Thalassemia

[a]Outlined in the 2007 ISCD pediatric official positions.[30]
Abbreviation: DXA, dual-energy X-ray absorptiometry. Permission obtained from Elsevier Ltd © Bishop, N. *et al.* Dual-energy X-ray aborptiometry assessment in children and adolescents with diseases that may affect the skeleton: the 2007 ISCD pediatric official positions. *J. Clin. Densitom.* **11**, 29–42 (2008).[30]

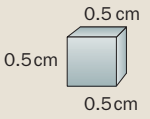
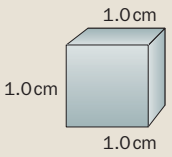
Example	Small vertebral body	Large vertebral body
		
Volumetric density (g/cm^3)	1	1
BMC (g)	0.125	1.0
Area (cm^2)	0.25	1.0
Areal BMD (BMC/area, g/cm^2)	0.5	1.0

Figure 1 | Effect of bone size on dual-energy X-ray absorptiometry-derived BMD. This figure illustrates how two vertebral bodies with identical volumetric densities, but different sizes, have differing areal BMDs. Abbreviation: BMC, bone-mineral content. Permission obtained from the International Society of Clinical Densitometry, (ISCD) ISCD Bone Densitometry Course for Clinicians, Version 7.0, West Hartford, CT, USA.

illnesses that cause growth retardation and maturational delay, such as in patients with Down syndrome. Various other factors also have to be considered, including age, sex, ethnicity, weight, body composition and pubertal development.[30] The most appropriate adjustment to bone densitometry results in growing children will vary, according to the specific clinical profile of the child.[39–41] Special attention must be given to body size, which may affect DXA-derived BMD values, because they are a two-dimensional rather than a true three-dimensional measure. DXA measurement, therefore, underestimates bone mass in children because they have smaller bones than do adults, even in instances where true volumetric density may be the same as that of large bones (as illustrated in Figure 1). No single bone-density measurement can predict risk of fracture in children. Goulding and colleagues[42] were among the first groups to demonstrate the ability of total-body BMD and spine bone-mineral apparent density (BMAD), which is calculated as the mean BMC from L2–L4 divided by the average area of bone from L2–L4 [$BMC_{(L2–L4)}/area_{(L2–L4)}^{3/2}$] to predict fractures. In a prospective cohort of 6,213 children (mean age 9.9 years) who were monitored for up to 24 months, a weak inverse relationship was present between BMD and fracture risk; however, fracture risk showed a closer correlation with BMC than with BMD when adjusted for bone area, height and weight.[43] Similarly, in a prospective evaluation of a cohort of 183 children who were followed up for 8 years, total body BMC, spine BMC, total body BMAD and spine BMD (all adjusted for height, weight and age) predicted upper-limb fractures.[44] According to the latest ISCD recommendation, no single adjustment paradigm offers the best predictions of fracture risk in children; therefore, the optimum estimate is yet to be established; thus "...in children with linear growth or maturational delay, spine and TBLH BMC and areal BMD results should be adjusted for absolute height or height age, or compared to pediatric reference data that provide age, gender and height-specific Z-scores".[39]

The accrual of bone mass during childhood is a key determinant of bone health in adulthood, and a low peak skeletal mass is considered an important risk factor for osteoporosis in adult life.[35] A number of studies have demonstrated an increased frequency of low bone mass in the general population of patients with mental retardation, regardless of whether they live in the local community[5,7,45] or in residential institutions.[46] Eight noninstitutionalized adult patients with Down syndrome were compared with eight adult men with mental retardation. The groups were matched for age, IQ, Tanner stage of sexual development and motor activity, and both groups of patients were compared with 10 students who had a sedentary lifestyle and were within the same age range (25.9 ± 2.9 years).[47] BMD values in the lumbar spine at L2 and L4 were markedly lower (*T*-score −2.66 ± 0.4) in young men with Down syndrome than in age-matched healthy adults, and were markedly lower than those of patients with mental retardation.[47]

In another study, young adults with Down syndrome who lived at home with their families had lower areal BMD and volumetric BMD (vBMD) at all examined regions (hip, spine, total body) than healthy age-matched controls did. In this study, the absolute difference in BMD between the groups at all sites varied between 0.6 and 1.5 SDS. After adjusting for bone size, spine vBMD was markedly lower (by 0.6 SD) in both male and female individuals with Down syndrome than it was in controls.[48] The lumbar spine vBMD was also 5% lower in a group of female and male patients with Down syndrome (age range 14–40 years) who lived in the community than were corresponding values in individuals with mental retardation but without Down syndrome.[45] As for gonadal function and bone mass, 11 sexually mature men with Down syndrome were compared with age-matched, healthy men;[19] BMD in the patients with Down syndrome was 2.55 SD lower than normal values (P <0.001), and these patients were 20 cm shorter than their age-matched controls. Patients had elevated bone-turnover markers (hydroxyproline:creatinine ratio), and higher LH, but not FSH, levels than controls (7.79 ± 3.34 versus 3.95 ± 1.74 mIU/ml, P <0.01; 8.58 ± 4.01mIU/ml versus 7.68 ± 3.44, P = not significant, respectively). Patients also had normal levels of serum testosterone. These findings again support the diagnosis of partial primary hypogonadism, a deficiency that might contribute to the skeletal abnormalities described above.[19]

Multivariate analysis showed that Down syndrome, male sex, low physical activity and little sun exposure were all associated with low spine vBMD, whereas low fat mass and low sun exposure were associated with low femoral neck vBMD.[48] Low muscle strength and low peak BMD are also probable predisposing factors for low BMD in patients with Down syndrome.[49,50] Some experts hypothesize that the extra copy of chromosome 21 could be responsible for the short stature, skeletal abnormalities and early aging that are seen in patients with Down syndrome.[51] BMD data in pediatric

patients with Down syndrome is scarce. In a small Chinese study that included 10 children with Down syndrome (aged 10–16 years) who were compared with 85 healthy Chinese children of the same age, lumbar spine BMD was 8.47 ± 2.69% (mean ± 1 SEM) lower in Down syndrome patients than in controls, with a delay of 2.3 ± 0.5 years (mean ± 1 SEM) on the distribution curve.[52] Fracture rate in adults with mental retardation who lived in institutions is three to 10 times higher than that of the healthy population.[53] Increased age, anticonvulsant use and postmenopausal status all increase the prevalence of fracture at a young age in females with Down syndrome.[54]

Replacement therapies

Thyroid hormone replacement

Thyroid hormone replacement in children with Down syndrome and hypothyroidism or subclinical hypothyroidism improves, but does not normalize, development and cognitive function.[3,9] Antithyroid drugs, such as carbimazole or propylthiouracil and/or radioactive iodine (and, rarely, surgical intervention with partial thyroidectomy) are options for the treatment of hyperthyroidism. We are not aware of any studies that investigated the effect of treatment of thyroid dysfunction on bone metabolism in patients with Down syndrome.

Sex hormone replacement

The benefit of sex hormone replacement therapy on pubertal development and bone-mass accretion has been well described in disorders of hypogonadism, such as hypopituitarism, and in women with Turner syndrome.[55] In a randomized study that included 16 girls with Turner syndrome, low-dose, systemic estradiol therapy for 6 months (100 ng/kg ethinyl estradiol daily) initiated between the ages of 5 years and 15 years promoted growth and breast budding.[56] Low-dose estrogen therapy is recommended for the management of Turner syndrome;[57] however, we are unaware of studies that examined the efficacy of testosterone or estrogen replacement to improve bone mass in hypogonadal men and women with Down syndrome.

Growth hormone replacement

In one study, GH replacement in patients with Down syndrome (aged 6–9 months) normalized growth velocity, but did not affect head circumference, mental status or gross motor development.[58] In this study, children were divided into a control group and a treatment group. The latter received daily injections of recombinant human GH 0.1 U/kg body weight for 3 years. Serum levels of IGF-I and IGF binding protein 3 normalized during treatment with GH, and an increase from –1.8 to –0.8 SDS in mean height was noted in the treated group, whereas mean height of the control group fell from –1.7 to –2.2 SD. Growth velocity declined after treatment stopped.[58] Similarly, 13 children with Down syndrome, growth retardation and microcephaly were treated with subcutaneous GH at doses of 0.1 mg/kg daily 3 days per week for 1 year, and experienced substantial increments in annual growth rates and head circumference after 1 year of therapy.[59]

None of the above-mentioned studies have to date examined the benefit of GH replacement on BMD measurements in patients with Down syndrome. At present, this therapy is not included in the standard care of children with Down syndrome.

Table 1 | Adequate intake and tolerable upper limit of vitamin D intake[70]

Group of patients	Adequate daily intake[a] in IU (μg)	Upper limit[b] of daily intake in IU (μg)
Infants aged 0–6 months	200 (5)	1,000 (25)
Infants aged 6 months to 1 year	200 (5)	1,000 (25)
Children and adolescents aged 1–18 years	200 (5)	2,000 (50)
Adults aged 19–50 years	200 (5)	2,000 (50)
Adults aged 51–70 years	400 (10)	2,000 (50)
Adults aged >71 years	600 (15)	2,000 (50)
Pregnant women	200 (5)	2,000 (50)
Lactating women	200 (5)	2,000 (50)

[a]Adequate intake is a value based on experimentally derived intake levels or approximation of observed mean nutrient intakes by a group or groups of healthy people. This value is used when the recommended dietary allowance cannot be determined, owing to lack of sufficient scientific evidence. [b]Tolerable upper limit is the highest level of daily intake that is likely to have no adverse health effects in almost all individuals in the specified age-group.

Calcium and vitamin D replacement

The combination of calcium and vitamin D supplementation is effective in the reduction of fracture risk in elderly patients,[60,61] but data on this approach in the pediatric age-group is scarce. Two randomized control trials demonstrated a beneficial effect of vitamin D on bone mass in apparently healthy adolescents.[62,63] Although vitamin D deficiency might be common in mentally handicapped patients, including those with Down syndrome,[64–66] limitations of these studies include the small number and heterogeneity of the patients studied, and their inclusion of institutionalized patients, which made it difficult to draw general conclusions; moreover, few intervention studies are available. In one study, 23 institutionalized adults with Down syndrome were randomly assigned to receive 1 g elemental calcium and 800 IU of vitamin D_3 once daily or placebo for 1 year.[66] Vitamin D_3 supplementation increased mean levels of serum 25-hydroxy-vitamin D from 39 nmol/ml (16 ng/ml) to 76 nmol/ml (30 ng/ml), and normalized the levels of bone-turnover markers and parathyroid hormone levels, thus, these results underscore the crucial role of adequate calcium and vitamin D replacement in maintenance of skeletal integrity. The current dietary recommendation (that is, the 'adequate intake' values) published by the Food and Nutrition Board of the Institute of Medicine in relation to vitamin D across age-groups is presented in Table 1. The adequate intake value is based on experimentally derived intake levels or approximations of observed mean nutrient intakes by a

group (or groups) of healthy people.[67] Of note, in 2008 the American Academy of Pediatrics issued recommendations for vitamin D intake that exceeded these values: this body recommends that infants, children and adolescents who do not obtain 400 IU per day through vitamin D-fortified milk or foods should receive 400 IU of supplemental vitamin D daily.[68] However, no specific recommendation for vitamin D intake in children with Down syndrome exists.

Physical education

Early, planned physical and educational programs demonstrated marked improvement in motor development, strength and dynamic balance ability in handicapped children and adults, such as those with Down syndrome, but we are unaware of any investigations of such therapeutic interventions on bone mass.[69,70] Infants with Down syndrome start walking about 1 year later than healthy children. In one study of 30 families with infants affected by this disease, the children were randomly assigned to receive traditional physical therapy every other week in addition to practice-stepping on a treadmill for 8 min daily, 5 days per week. These patients were compared with infants who received physical therapy only.[69] The intervention group learned to walk remarkably sooner (in 73.8 days with help and in 101 days without help of their parents) than the control group did.

In another study, 20 adult patients with Down syndrome (mean age 26.8 ± 7.8 years) were randomly allocated to undergo a progressive resistance-training program twice weekly at a community gymnasium that included six exercises using weight machines for upper and lower extremities. These patients were compared with a control group that continued normal activities of daily living with no exercise.[70] After 10 weeks, a remarkable improvement in upper-limb muscle endurance and a trend toward improved upper-limb muscle strength and function were seen in the intervention group compared with the control group. No significant difference between the two groups was detected in lower-limb muscle performance.

Conclusions

Down syndrome is a leading cause of mental retardation in the pediatric population. Patients with Down syndrome are at risk of growth retardation, endocrine abnormalities and nutritional deficiencies that lead to an increased risk of developing osteoporosis. Young patients with Down syndrome have decreased BMD of the spine as well as inferior muscle strength compared with healthy individuals and age-matched patients with mental retardation. Such decrements could be explained by a reduced body size and thus bone size, and muscle hypotonia, which are associated with Down syndrome. Lack of physical exercise, insufficient exposure to the sun, low levels of vitamin D and prolonged use of anticonvulsants are all additional risk factors for low BMD. Hypogonadism, celiac disease, GH deficiency and hypothyroidism are commonly associated with Down syndrome and can contribute to decrements in skeletal maturation, and thus bone-mass accrual.

In patients with Down syndrome, screening for thyroid hormone deficiency at birth and once yearly throughout life is indicated, as is screening for celiac disease at 2 years of age, and periodically thereafter. GH therapy is currently not warranted, and although sex hormone replacement therapy could be a useful option to maintain bone integrity in such patients, this alternative has not been investigated. Adequate intakes of calcium and vitamin D, along with enhanced physical activity, are recommended interventions on the basis of their safety and efficacy in the general population and the (limited) data available in patients with Down syndrome. In this group of patients, studies are needed that carefully assess bone-mass accrual in childhood, changes in bone mass in young adulthood, and the effect of various hormone replacement therapies on bone-mass changes to establish evidence-based recommendations for osteoporosis screening and therapeutic interventions for its prevention.

Review criteria

We searched for articles in EMBASE and PubMed databases that were published between 1990 and 2008 by entering the key words "bone mass", "Down syndrome", "gonadal dysfunction", "growth retardation", "thyroid dysfunction" and "vitamin D", and limited the search to children and adolescents (age 0–18 years). Articles reviewed were in English, and included clinical trials, reviews, research papers and case reports. Papers that discussed genetic studies on fetuses, Down syndrome *in utero* or were not available were excluded. Also included were relevant articles identified from above references, relevant chapters and reviews, and additional related articles suggested by reviewers.

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