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Low bone turnover and low bone density in a cohort of adults with Down syndrome

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Abstract

Summary—Increased incidence of osteoporosis in Down syndrome has been reported, but etiology is not established. We report low bone turnover markers and bone mineral density (BMD) in a cohort of people with Down syndrome without consistent clinical risk factors. Our results should guide future studies and treatments for this common problem.

Introduction—To better understand the etiology for osteoporosis in Down syndrome (DS), we measured bone density by dual-energy X-ray absorptiometry (DXA) and circulating biochemical markers of bone formation and resorption in a cohort of 30 community-dwelling DS adults.

Methods—Seventeen males and 13 females followed in the University of Arkansas Down Syndrome Clinic were evaluated by DXA to estimate BMD and underwent phlebotomy to measure serum procollagen type-1 intact N-terminal propeptide (P1NP) to evaluate bone formation, and serum C-terminal peptide of type-I collagen (CTX) to evaluate bone resorption.

Results—Seven of 13 DS females and 12 of 17 DS males had low bone mass at one of measured sites (z -2.0). When data were grouped by age, males had apparent osteopenia earlier than females. The mean P1NP in the normal group was 19.2 ± 5.2 ng/ml vs. 2.2 ± 0.9 ng/ml in the DS group ($P = 0.002$). Serum CTX levels in the normal group were 0.4 ± 0.1 ng/ml vs. 0.3 ± 0.1 ng/ml ($P = 0.369$).

Conclusions—Low BMD in adults with DS is correlated with a significant decrease in bone formation markers, compared to controls without DS, and is independent of gender. These data suggest that diminished osteoblastic bone formation and inadequate accrual of bone mass, with no significant differences in bone resorption, are responsible for the low bone mass in DS. These observations question the use of antiresorptive therapy in this population and focus attention on increasing bone mass by other interventions.

Keywords

Bone density; Bone turnover; Down syndrome; Osteopenia; Osteoporosis; Trisomy 21

Introduction

Down syndrome (DS) occurs in approximately one in every 800 people—400,000 in the USA (National Birth Defects Prevention Network data 1999–2001)—and results from the presence of a third chromosome 21. Despite the high incidence and increasing longevity of people with trisomy 21 [1, 2], relatively little is known regarding the etiology or optimal prevention of common diseases which frequently occur in this group. Diabetes, autoimmune disease, and osteoporosis occur more often in people with DS than in the general population, and DS seems to be an independent risk factor for osteopenia and osteoporosis [3]. As a result, low- or minimal-trauma spine and femur fractures are increasingly important causes for morbidity, but the optimal modality, timing, and duration of osteoporosis therapy remain unknown. Attention to the etiology of low bone mineral density (BMD) in DS may provide new insight into treatment not only for those with DS, but also for the general population where osteoporosis is responsible for more than 1.5 million fractures and \$14 billion in medical care costs annually (US Department of Health and Human Services data 2006).

People with DS now have an average life expectancy of approximately 58 years and are enjoying more active lifestyles [1, 2, 4], but have a higher risk of falls. In addition, health problems often go unnoticed as a result of social inequities and decreased ability to articulate needs [5]. As a result, low- or minimal-trauma spine and femur fractures are increasingly important causes for morbidity: the incidence of fracture in the adult population over 50 has been reported to be as high as 85 % for long bones and vertebral bodies combined [5]. However, the optimal modality, timing, and duration of osteoporosis therapy remain unknown.

Several investigators have reported that children with DS have lower bone mass (volume and area), expressed as BMD, especially in the lumbar spine compared to their peers without mental retardation or with mental retardation but without DS [6–10]. Some studies have even suggested that the bone appears to be produced at an abnormal rate during childhood

[1, 11] and that the low bone density is most exaggerated in young adults [11]. Adults with DS have been found to have lower lumbar spine BMD than controls, and this does not seem to be affected by body weight or soft tissue composition [1, 11].

Known secondary causes for low BMD include dietary insufficiency (vitamin D and calcium intake) and endocrine (hypothyroidism, hyperparathyroidism, hypogonadism) and autoimmune (celiac disease) disorders which can lead to inadequate nutrition. Low activity levels, low sunlight exposure, and anticonvulsant use have also been associated with decreased bone mass; however, these are not consistent risk factors in DS patients, leaving the underlying pathophysiology in doubt. For patients having low BMD without identifiable causes, few data exist to guide treatment in premenopausal adults in the general population, and no data exist for treating people with DS.

The majority of bone mass and bone quality are accrued during childhood and adolescence via the process of bone turnover, where bones form and lengthen through the activity of two highly specialized cell types: osteoblasts (which synthesize the bone) and osteoclasts (which remove the bone). The coordinated activity of these cells results in the appropriate length, shape, and quality of the skeleton such that the skeleton is able to support the rigors of daily life. These same cells are then responsible for the maintenance of the skeleton during adulthood and aging [12]. The measurement of bone biochemical markers provides a path to understand the underlying bone physiology, yet such information is scarce in patients with DS [13].

We therefore investigated the etiology of low BMD in people with DS. Based on BMD data in children with DS [1], we hypothesized that inadequate bone accrual in childhood and inadequate bone turnover, and not increased bone resorption in adulthood, may be the leading cause of low bone mass in DS. Therefore, biochemical markers of bone turnover and BMD were measured in adult community-dwelling people with DS.

Methods

Subjects

Thirty DS patients (13 females and 17 males; age range, 19–52 years) attending the University of Arkansas Down Syndrome Clinic were recruited under a UAMS IRB approved protocol. All participants and/or their legal guardians gave informed consent prior to inclusion in the study. Each patient's clinical history was collected, and a team of providers including a MD, APN, dietician, and occupational therapist evaluated the patient. Preventive medical care based on individual assessment and recommended labs for people with DS was obtained [14]. Our control group consisted of a convenience sample of healthy normal volunteers.

Blood was drawn, and biochemical markers of bone turnover were measured in patient serum at the same time using a single lot of reagents. Samples of venous blood were taken from all subjects into serum separator tubes. The blood was allowed to clot for 30 min at room temperature before centrifugation at 2,500×g for 10 min and storage at –20 °C.

Procollagen type-1 intact N-terminal propeptide (P1NP), a marker of bone formation, was measured in patient serum using a competitive RIA according to the manufacturer's protocol (Orion Diagnostica, Espoo, Finland). Intra-assay variation ranged from 3.5 to 5.3 %, and the inter-assay variation was from 3.6 to 5.4 %. The quoted reference ranges are as follows: postmenopausal women, 16–96 ng/ml; premenopausal women, 19–83 ng/ml; and men, 22–87 ng/ml.

The serum C-terminal peptide of type-I collagen (CTx), a marker of bone resorption, was measured in patient serum using an immunoradiometric assay according to the manufacturer's protocol (Immunodiagnostic Systems, Fountain Hills, AZ, USA). Intra-assay variation ranged from 5.2 to 6.8 %, and the inter-assay variation was from 35.6 to 7.4 %. The quoted reference ranges are as follows: postmenopausal women, 0.142–1.351 ng/ml; premenopausal women, 0.112–0.738 ng/ml; and men, 0.115–0.748 ng/ml.

Bone densitometry and biochemical markers

BMD of the posterior–anterior (PA) spine and hip was assessed by dual-energy X-ray absorptiometry (DXA) using a Hologic Discovery A bone densitometer, located in the Bone Densitometry Clinic at the University of Arkansas for Medical Sciences. DXA equipment was calibrated with a lumbar spine phantom and step density phantom following the Hologic guidelines. Measurements were obtained and analyzed using standard manufacturer's protocols. The World Health Organization established criteria were used to classify bone health and osteoporosis. Bone mineral density was measured at the spine, total hip, femoral neck, and distal radius as suggested by the International Society for Clinical densitometry (ISCD). The coefficients of variation of BMD were 1.7 % for the femoral neck, 2.3 % for the lumbar spine, 1.6 % for the upper limbs, and 0.9 % for the lower limbs. The expression BMD / height was calculated to adjust bone mass for whole-body bone size in DS patients as described [1].

Statistical analysis

All data are presented as mean and standard deviation unless otherwise stated. Data were analyzed by analysis of variance with Bonferroni's post-hoc test and by Student's *t* test where appropriate. A *P* value of <0.05 between groups was considered significant and reported as such.

Results

A total of 30 DS patients (13 female and 17 males) (Table 1) were enrolled along with eight healthy normal volunteers (three males and five females) aged 18–53 years.

The DS cohort's average age was 32 (range, 19–51), and BMI was 31.46. Thirty-seven percent (11/30) had vitamin D, initially, less than 30 ng/l (all were on supplementation of 800 IU/day, along with 1,200 mg/day of calcium) and 57 % (17/30) were treated with synthroid replacement to achieve euthyroid status based on normal TSH (0.34–5.60 uIU/ml). Celiac disease was present in 10 % (3/30) and was treated with gluten-free diet at the time of the study.

DXA scanning revealed that 53.3 % (16/30) of our cohort has low BMD (*z*-scores<−2) at one of multiple sites including the lumbar spine, distal radius, femoral neck, and proximal femur (Table 2).

The mean P1NP in the DS group (2.2±0.9 ng/ml) was significantly lower than the control group (19.2± 5.2 ng/ml) (*P*=0.002; Fig. 1a). In contrast, serum CTx levels were not significantly different with the normal group (0.4±0.1 ng/ml) and the DS group (0.3±0.1 ng/ml) (*P*=0.369; Fig. 1b). Both bone formation and bone resorption in the DS group were suppressed compared with those in normal healthy controls, with bone formation significantly decreased (Fig. 1a), which is indicative of a low bone turnover state.

These data indicate that low bone formation and decreased bone turnover, and not increased bone resorption, are the primary causes of the low bone mass observed in adults with DS.

Discussion

We have investigated the etiology of osteopenia in a cohort of community-dwelling adults with DS. The principal finding of this study is that adult males and females with DS who have no consistent clinical risk factors for osteoporosis have lower bone formation markers compared to controls without DS, and these markers are significantly associated with low BMD.

Previous studies have indicated that increased bone turnover may be responsible for osteopenia. A report of high hydroxyproline-to-creatinine ratio [15] raised the possibility that high bone turnover is a cause for adult osteopenia due to increased bone resorption after puberty. Male adolescents with DS tend to have higher lumbar spine BMD than females [1], but in adulthood, the trend seems to be reversed [10]. This trend was thought to be due to effects of hypogonadism and low serum testosterone or, perhaps, an exaggerated effect of low testosterone over time [1, 16]. However, the data described here suggest the opposite since low testosterone should result in high bone turnover markers. Indeed, our decreased bone turnover and low BMD data are entirely consistent with the histology of the vertebral bone from a patient with DS that revealed absent osteoclasts and reduced osteoblasts [17], not at all consistent with low BMD due to increased bone resorption.

Our data indicate that osteopenia in Down syndrome is due to diminished bone accrual; however, a cause for this is not clear. Multiple signaling pathways have been identified that play essential roles in maintaining bone mass and bone accrual by positively or negatively regulating osteoblasts and/or osteoclasts. The decreased bone formation and bone accrual associated with DS may be associated with altered wnt signaling since wnt signaling pathways have important roles in bone development [18]. Perhaps, most interesting in the context of DS is the modulation of sclerostin expression, which has been shown to be a potent osteocyte-derived endogenous inhibitor of bone formation [19]. Although not measured here, it is tempting to speculate that the levels of circulating SOST maybe increased in this cohort. Such measurements are currently ongoing.

Other factors known to influence the rate and degree of osteopenia in the general population include age, weight, low BMI, alcohol consumption, family history of osteoporosis, smoking, number of pregnancies, vitamin intake, endocrine abnormalities, and physical activity. However, these were not consistently observed in our study. None of our cohort uses tobacco and alcohol or has ever been pregnant, and 28/30 have documented regular physical exercise as part of their day program. In addition, average BMI is well above 25, and this is a negative risk factor for osteoporosis. Despite the above-average incidence of hypothyroidism (17/30 or 57 %), all participants were euthyroid at the time of study. The rate of hypovitaminosis D was similar to that seen in the general population, and all subjects were on vitamin D and calcium supplementation as appropriate. Thus, even in the absence of general population risk factors, BMD was still consistently decreased in DS.

Other investigators have suggested that low muscle tone and relative immobility are causative for the low BMD, but these would be expected to be associated with increased bone resorption [1, 3, 5, 10, 15]. Muscle tone is certainly reduced in DS, but this should not be confused with an inability to improve muscle strength or endurance in active people with DS as in our cohort. Children and adults with DS who participate in aerobic, balance, and resistance trainings improve in a manner similar to people without DS [20–22], and this should be studied further as it pertains to bone formation.

The finding of low bone formation as a mechanism for low BMD in the adult DS population suggests a new treatment paradigm. Conventional antiresorptive approaches to low bone mass (namely, bisphosphonates) are contraindicated in situations of low bone turnover. In

light of our data suggesting that the basis for low BMD in DS is not elevated bone resorption and does not appear to be associated with hypogonadism, trials of testosterone replacement (or testosterone analogs) in adults may not augment BMD.

At this time, no FDA-approved therapy is available for adults with Down syndrome, and clinicians have few treatment options. Teriparatide (PTH) is a possibility; it is anabolic and increases bone mass when given intermittently. Recently, we reported that the Ts65Dn mouse has a similar bone phenotype as people with Down syndrome and that PTH is anabolic in this animal model (Fowler/McKelvey et al., manuscript submitted for publication). However, this therapy is only approved in humans for the treatment of osteoporosis in men and postmenopausal women who are at high risk for having a fracture, and its use is limited to 2 years. Importantly, it is not known if PTH is anabolic in individuals with Down syndrome, the consequences of ending treatment or what potential side effects may exist after long-term therapy.

Our study contributes to an area that is not well studied or understood, and as such, it cannot be a comprehensive study. In particular, the markers that we measured are not widely used, and as such, there are no well-established normal ranges. In addition, quantitative CT scans may be a better method of measuring bone density than DXA scanning. Finally, we had a small sample of adults with Down syndrome, and these adults—who attend a community Down syndrome clinic—may not be representative of the entire population of people with Down syndrome. In particular, we have not sampled those elderly adults with Down syndrome who have been institutionalized for much of their life.

Additionally, our study focuses on bone health in adults. However, the acquisition of bone mass and the maintenance of bone health are long-term processes which normally begin in childhood, when bone density is rapidly increasing and continues throughout the lifespan [23]. Low bone mass in young adulthood is a strong risk factor for later osteoporosis and fracture; therefore, the accrual of bone mass during childhood and adolescence may reduce osteoporosis risk later in life [24]. Our data suggest that given the low rate of bone accrual in DS, early intervention may be even more critical for this group. Unfortunately, most children and young adults with DS do not receive recommended preventive care [25], further compounding their risk for low BMD and subsequently increased fracture risk. Our cohort and their caregivers receive nutrition counseling, assessments to prevent falls, and scheduled preventive care, but our data indicate that this is not the optimal time to begin intervention. Future studies should therefore focus on the measurement of bone turnover during childhood and may help pinpoint a critical age for intervention, perhaps with vitamins, weight training, or medication.

Further studies are also needed to assess DS-specific factors such as qualitative and quantitative differences in the immune system [26] which have unknown repercussions on bone turnover. Patients with treated hypothyroidism have persistent elevations of autoantibodies [27] which may affect the trabecular bone where bone remodeling is more active [11, 28]. Similarly, people with DS and treated celiac disease continue to have elevations in tissue transglutaminase IgA, with unknown effects on nutrient absorption long term. Finally, the correlation of bone turnover markers with quantitated computed tomography is needed and is the focus of our ongoing studies.

In summary, our data have demonstrated new insight into the pathogenesis of osteoporosis in Down syndrome. Future interventions will need to rethink osteoporosis prevention strategies and focus on improving low bone formation and bone turnover as pathways to prevent fracture in people with DS. In addition to improving the health and longevity of people with Down syndrome, these new insights may also help to understand possible

mechanisms of osteoporosis in the general population, providing insights into additional treatments for this critical public health concern.

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Fig. 1.

Serum marker of bone formation is decreased in DS. Serum measurement of bone formation and bone resorption markers in control and DS subjects. **a** Mean level of P1NP is significantly decreased and lower in DS than that in the control. **b** Mean CTx is lower in DS compared with that in the control. Asterisk denotes $P < 0.05$ vs. control

Table 1

Baseline clinical characteristics of male and female participants

Age (years)	BMI	TSH (reference, 0.34–5.600)	Calcium (reference, 8.6–10.2)	Creatinine (reference, 0.9–1.3)
Males				
19	24.07	2.31	9.40	1.20
22	30.6	2.66	9.60	1.00
23	39.45	2.31	8.80	0.90
24	29.3	1.37	9.10	0.90
24	29.3	1.46	9.20	ND
27	32.65	1.7	9.30	1.10
27	23.77	1.59	9.20	0.80
28	43.9	1.49	9.20	0.80
28	27.5	2.32	9.90	1.00
29	30.18	4.54	9.20	1.20
29	26.8	1.97	9.90	1.00
30	38.3	4.66	8.90	1.30
34	42.91	3.82	9.40	1.12
34	36.99	2.49	9.10	1.20
34	35.33	2.33	9.10	1.40
36	34.76	4.74	8.90	1.20
42	24.25	2.78	9.40	0.80
49	28.36	1.73	8.80	1.00
Average	32.13	2.57	9.24	1.05
Females				
21	25.31	0.52	9.1	1.2
22	26.75	2.08	9.5	0.5
25	44.34	4.41	9.4	0.8
25	42.75	1.76	9	0.8
27	44.3	2.74	9.6	0.7
30	27.95	1.64	8.6	1.1
32	40.16	1.24	9.4	1.3
36	27.7	3.09	9.2	0.8
40	24.87	4.31	9.5	0.9
43	38.1	1.15	9	0.8
44	20.06	2.47	8.8	1
51	28.38	6.21	8.9	1.2
Average	32.56	2.64	9.17	0.93

ND no data available

Table 2

BMD z-scores at different bone sites of male and female participants

Age (years)	Distal radius z-score	Lumbar PA z-score	Femoral neck z-score	Femoral trochanter z-score
Males				
19	-2	-2.5	-1.8	-1.9
22	-1.9	-2.0	-0.1	-0.6
23	-0.7	-1.9	-1.3	-0.7
24	-1.6	-2.2	-1.7	-1
24	-1.1	-1.9	-0.9	-1.2
27	-1.1	-2.6	-2.3	-2.3
27	-1.7	-2.1	-0.8	-0.6
28	-3.1	-2.0	-1.8	-1.9
28	-2.3	-1.5	-3.1	-2.3
29	-1.1	-1.4	-1.5	-1
31	-2.3	-1.7	-1.7	-1
34	-1.5	-1.0	-1.1	-1
34	-2	-0.7	-0.5	-1
34	-0.9	-2.2	-2	-1.7
36	-2.1	-1.9	-0.2	-1.1
42	-0.9	-1.9	-1.9	-1.4
49	2.1	-2.1	-2.1	-1.1
Females				
21	-0.9	0.7	-1.2	0
22	-2.3	0.1	-0.3	0.6
25	-1.1	-0.5	-0.4	0.6
25	-0.3	-0.2	-0.1	1.4
27	-0.8	-0.5	-0.8	0.2
30	0.2	-1.5	-1.5	-0.6
32	-2.5	-1.8	-1.6	-1.9
36	0	0.0	-0.1	0.6
40	-0.2	0.4	-0.9	0.2
43	-1.4	-3.4	-2	-1.3
44	-0.5	-1.5	-3.3	-1.8
51	-2.9	-2.5	-1.9	-2

Italicized values indicate individual patients with a z-score of -2.0 at any bone site