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Osteoporosis in Adult Patients with Intellectual and Developmental Disabilities: Special Considerations for Diagnosis, Prevention, and Management

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Abstract: As medical care progresses, patients with intellectual and developmental disabilities are living longer and beginning to experience diseases that commonly afflict the aging population, such as osteoporosis. Osteoporosis and resultant fractures increase disability and threaten the independence of this vulnerable population. In addition, the diagnosis, prevention, and management of osteoporosis present unique challenges in these patients. Critical preventive targets include exercise modification, fall prevention, and monitoring for nutrient deficiencies. Commonly used in diagnosis and treatment monitoring, dual-energy x-ray absorptiometry (DXA) scan of the hip and spine may not be feasible, whereas peripheral DXA or computed tomography may be more accessible for patients with physical disabilities. Pharmacological treatment should be tailored to the individual patient, considering factors such as adherence and comorbidities. Finally, bone turnover markers are a noninvasive, cost-effective option for monitoring treatment response in patients who cannot undergo DXA.

Key Words: cerebral palsy, Down syndrome, intellectual and developmental disabilities, osteoporosis, peripheral dual-energy x-ray absorptiometry

Intellectual and developmental disabilities (IDDs) encompass a broad group of disorders that may negatively affect a person's cognitive, social, emotional, and/or physical development.[1] Initially evident at birth or during childhood, these disorders are typically incurable.[2] As a result of advances in medical care, the life expectancy of most individuals with IDDs approaches that of people without IDDs, and consideration must be taken to prevent and treat diseases commonly afflicting older adults such as diabetes mellitus, cardiovascular disease, dementia, and osteoporosis (OP).[2,3]

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OP is a disease of particular importance, because it may present earlier and with greater severity in patients with IDD.[4] Defined as low mass and structural deterioration of bone, OP leads to skeletal fragility and an increased risk of fracture.[5] OP is especially hazardous in patients with IDD, as fractures increase morbidity and mortality and exacerbate existing disability.[6] Clinical trials to determine safe and effective treatments for OP in this unique population are lacking, and there is a need for educational literature on this topic. This article reviews the etiology of OP in adults with various forms of IDD. It also examines current clinical approaches to diagnosis, prevention, and treatment of OP in adults with IDD.

Etiology of Osteoporosis in Adults with IDD

Although the etiology of OP in adults with IDD differs from that of typical postmenopausal OP, the basic underlying mechanism is the same and involves an imbalance between bone formation and resorption. Normal bone is constantly being remodeled by osteoblasts (bone-forming cells) and osteoclasts (bone-resorbing cells). OP results when osteoclasts break down the bone matrix faster than osteoblasts can rebuild it.[5]

Primary OP results from bone mineral loss during the normal aging process. Although most common in postmenopausal women, estrogen deficiency contributes to primary OP in both men and women. Secondary OP, however, is defined as low bone mineral density (BMD) caused by an underlying disease or medication.[7] Although adults with IDD may develop primary OP as they age, they are predisposed to secondary OP because of their

Key Points

- Certain medications and insufficient bone growth during childhood contribute to the development osteoporosis in adults with intellectual and developmental disabilities
- Diagnosis of osteoporosis in this population requires innovative approaches, as the gold-standard DXA scan may be difficult to perform
- Treatment of osteoporosis in this population involves standard approaches with special consideration given to comorbid conditions and medication adherence

underlying disability, comorbid conditions, malnutrition, immobility, and certain medications. One such medication class is antiepileptic drugs, which are required by many patients with IDD to control seizure disorders. These medications accelerate the degradation of vitamin D into inactive metabolites. As vitamin D is essential for bone mineralization, its deficiency may lead to early-onset OP in patients taking antiepileptic drugs.[8] Another culprit of secondary OP, depot medroxyprogesterone acetate, a progestin-only injection, is a favorable contraceptive option for women with IDD and comorbid epilepsy because it lowers the seizure threshold and has convenient quarterly dosing. The progestin in depot medroxyprogesterone acetate functions by suppressing gonadotropin release, which in turn decreases estrogen release from the ovaries. As estrogen is required for normal bone homeostasis, the resulting deficiency leaves women predisposed to low BMD and OP.[9]

IDDs that have high rates of OP include cerebral palsy (CP), Lennox-Gastaut syndrome, fetal alcohol syndrome, Down syndrome, and spina bifida. The Table details the multifactorial origins of OP in these conditions. Patients with CP have a particularly unique etiology of OP primarily because of insufficient rates of bone growth during childhood rather than bone mineral loss in adulthood. In other words, bones in patients with CP never reach their optimal density in adolescence, so patients with CP present with a more severe, earlier form of OP than their same-age counterparts.[4,10] Regardless of the underlying cause of disability, it is well established that adults with IDD have higher rates of OP than the general population.[16–18]

Diagnosis of Osteoporosis in Adults with IDDs

The gold standard for the diagnosis of OP is a dual-energy X-ray absorptiometry (DXA) scan, which assesses a patient's BMD. The results of a DXA scan are reported as a T score, which is a standard deviation comparing a patient's BMD with that of a healthy 30-year-old of the same sex. A T score <-2.5 is diagnostic for OP, whereas -2.5 to -1.0 indicates osteopenia and a T score of ≥ -1.0 is considered normal.

The *z* score, another measurement reported by DXA, compares a patient's BMD with the average BMD of people of the same age, sex, and ethnicity. A *z* score is used for children, adolescents, premenopausal women, and men younger than 50, and can aid in diagnosing secondary OP in all patients. A *z* score of ≤ -2.0 indicates low BMD. Alternatively, a diagnosis of OP can be made clinically without measuring BMD if a patient suffers a fragility fracture, which is classified as a fall from a standing height or less.[19]

Performing DXA scans on patients with physical and intellectual disabilities poses multiple challenges. Typically performed on the lower spine, hips, and full body, DXA is more involved than conventional x-rays and requires lying flat on a table with the legs situated in specific positions. In patients with CP, for instance, muscle contractures and involuntary movements make it difficult, if not impossible, to properly position the patient. Surgical hardware is another obstacle that may prevent proper patient positioning and obscure bone anatomy because of the radioopaque nature of metal hardware.[20]

In some forms of IDD, measuring the hips, spine, and whole body is simply not feasible; therefore, technologists may prefer to use more accessible sites, where positioning is easier, such as the lateral distal femur.[20] This alternative site for DXA scanning was developed and tested in children with CP who demonstrated difficulty with the classic DXA scanning sites.[21] Although most fractures in adults occur in the hip and spine, peripheral DXA measurements also can be used to predict the risk of central fractures.[20] For this reason, peripheral DXA scanning may prove useful in adults with IDDs who cannot undergo hip, spine, or whole-body DXA.

Although not used as frequently as DXA, peripheral quantitative computed tomography (pQCT) represents another alternative for patients unable to undergo full-body scans. pQCT uses peripheral sites (eg, radius, tibia, femur) with a scan time of roughly 3 minutes per location.[22] Unlike DXA, which measures only BMD, pQCT can measure BMD plus bone geometrical parameters and strength strain index. Despite its many advantages, pQCT has limited longitudinal data for predicting fracture

Table. Pathophysiology of osteoporosis in various intellectual and development disorders

Disorder	Definition	Factors contributing to osteoporosis and other conditions increasing fracture risk
Cerebral palsy	Disorder of abnormal central nervous system development leading to impaired coordination, posture, and movement	Insufficient bone growth and mineralization during development[4,10] Structural bone abnormalities (small diameter with thin cortices)[4]
Down syndrome	Genetic disorder caused abnormal cell division that results in an extra full or partial copy of chromosome 21	Growth retardation, hypogonadism, hypothyroidism, muscle hypotonia, precocious aging, small body size[11,12]
Fetal alcohol syndrome	Condition resulting from excessive alcohol exposure during gestation; produces a wide range of physical and neurodevelopmental effects	In utero ethanol exposure → delayed bone ossification, decreased bone length, decreased skeletal maturity, and delayed mean bone age[13]
Lennox-Gestaut syndrome	Severe childhood seizure syndrome with multiple causes, including genetic mutations, perinatal injuries, cortical malformations, infections, and tumors	Unclear whether OP results from the underlying disease, external factors (antiepileptics, immobility, malnutrition), or both[14]
Spina bifida	Congenital disorder caused by incomplete closure of the vertebral column ± meninges during embryogenesis	Decreased bone strength resulting from smaller bones, mineralization defects, and lower bone mass[15]

OP, osteoporosis.

risk.[23] In addition, pQCT and DXA both require that patients remain still throughout the duration of the scan. Finally, pQCT cannot be performed with a standard CT scanner, and many institutions do not have the specific machine required.

Prevention of Osteoporosis and Fractures in Adults with IDDs

In general, the prevention of low BMD is aimed at maximizing peak bone mass and minimizing the rate of bone loss, with the ultimate goals of maintaining bone strength and preventing fractures.[24] Although optimal peak bone mass is usually achieved with lifestyle modifications during adolescence, many of the same strategies can be used to minimize bone loss in adults both with and without IDD. These lifestyle strategies include regular weight-bearing physical activity (at least 2.5 hours/week), adequate nutrition (calcium and vitamin D intake), smoking cessation, limited alcohol intake, and fall prevention.

Physical Activity and Fall Prevention

Regular weight-bearing exercise decreases a patient's fracture risk not only by improving BMD but also by directly preventing falls; however, staying physically active can be challenging for adults with IDDs because of the physical and emotional barriers to exercise that they may face. As such, it is imperative that physicians recommend physical activity options that match the unique abilities of each patient and connect them with appropriate resources. For example, patients who use wheelchairs may require modified seated exercises (eg, leg extensions, shifting body weight) and other patients with decreased mobility may benefit from supported exercises, such as using a chair or a rail to perform exercises. Simply bringing up the topic of exercise is important, as data from the National Health Interview Survey showed that adults with disabilities were 82% more likely to be physically active if their doctor recommended it.[25]

Many patients with IDDs begin working with physical and occupational therapy as children and it is important that they continue to do so throughout adulthood to meet their specific activity needs. For example, physical therapists can help patients who use wheelchairs to perform modified exercises and occupational therapists can help patients with physical disabilities to find ways to successfully navigate their homes without falling. In addition to preventing OP, moderate exercise reduces all-cause mortality and improves quality of life in patients with IDDs.

Vitamin D and Calcium

Calcium and vitamin D are essential nutrients for bone health and maintenance. Obtaining low quantities of vitamin D through inadequate diet or sun exposure can lead to insufficient levels of the vitamin, which can subsequently result in decreased intestinal calcium absorption and low serum calcium levels. To restore serum calcium levels, the body resorbs calcium from existing bone, which can reduce BMD and promote OP.[26]

Although the US Preventive Services Task Force does not recommend calcium and vitamin D supplementation in healthy adults for primary fracture prevention, adults with IDDs have special considerations and may benefit from supplementation. Patients with CP, for instance, may have problems preparing and consuming food, leading to inadequate intake of vitamin D, calcium, and other nutrients. These patients also may be confined to home and have poor sunlight exposure. In addition, approximately half of all patients with CP have epilepsy requiring antiseizure medications, which may contribute to vitamin D deficiency.[27–30] Considering the aforementioned evidence, adults with IDDs may benefit from vitamin D and calcium supplementation to correct deficiencies, promote bone health, and prevent fractures.

Behavioral Health Considerations

In the general population, it is well established that tobacco smoking is associated with reduced BMD and increased fracture risk.[31,32] As such, for patients who smoke, clinicians should provide tobacco cessation counseling, paying particular attention to the patient's cognitive capacities and tailoring the counseling appropriately. Heavy alcohol consumption (>2 drinks per day) decreases BMD and increases fracture risk; however, the effects of moderate alcohol use are unclear and have been associated with decreased fracture risk in some studies.[33,34] Although moderate alcohol use may improve bone health slightly, patients with IDDs should not be encouraged to start drinking simply for this purpose, because alcohol may interfere with medications or exacerbate medical and psychologic comorbidities. Patients with IDDs also should be screened and treated if necessary, for major depressive disorder, as major depressive disorder can exacerbate factors that contribute to OP, such as inactivity, poor nutrition, and medication noncompliance.

Treatment of OP in Adults with IDD

Bisphosphonates

First investigated for use in bone disorders in the 1960s, bisphosphonates (eg, alendronate, risedronate) remain the first-line treatment for OP in the general population.[35] With a chemical structure similar to pyrophosphate, bisphosphonates function by preferentially attaching to hydroxyapatite in bone with high turnover. Osteoclasts then bind and become stuck to bisphosphonates, preventing them from adhering to and breaking down more bone. Both oral and intravenous (IV) bisphosphonates have been well studied, and multiple randomized controlled trials highlight their efficacy in preventing fractures and reducing bone loss in postmenopausal women and other populations with OP.[36–39]

Although bisphosphonates are a highly effective, relatively safe therapy for OP, their use must be tailored to the unique needs of adults with IDDs. Traditional oral bisphosphonate use is associated with upper gastrointestinal adverse effects and may increase the risk of reflux esophagitis in bedbound patients who cannot remain upright after taking oral medications. As

such, physicians may wish to treat bedridden patients with IV bisphosphates, which do not carry the same risk of upper gastrointestinal adverse effects as their oral counterparts. Although little research exists on the topic, a 2017 study by Kaga et al examined IV alendronate use in 62 hospitalized adults with severe motor and intellectual disabilities. Participants in the bisphosphonate treatment group had significantly improved BMD and bone metabolism markers, and fewer fractures than controls at 6 months, 1 year, and 2 years after starting treatment.[40]

Medication compliance is another consideration that may prompt physicians to select an IV over an oral bisphosphonate when treating adults with IDD. IDDs and related social factors (eg, socioeconomic status, living/care arrangements) can hinder oral medication adherence.[41] In contrast with the daily, weekly, or monthly dose required for oral bisphosphates, IV formulations are typically given as a supervised infusion once per year, bypassing any issues with compliance.

As approximately 15% of older adults with intellectual disability have chronic kidney disease (CKD), prescribers should be mindful of the impact of bisphosphonate therapy on the kidneys.[42] Because bisphosphonates are renally cleared, lower doses and slower infusion rates are generally used in patients with CKD.

Parathyroid Hormone Analogs

Endogenous parathyroid hormone (PTH) regulates serum calcium concentration through its effects on the kidneys, bone, and intestines. Normally, when serum calcium levels are low, PTH stimulates osteoblasts to activate osteoclasts, which resorb bone and release calcium into the bloodstream. As such, persistently elevated PTH levels result in bone mineral loss; however, low, pulsatile doses of PTH stimulate osteoblasts more than osteoclasts. Once-daily injections of PTH analogues (eg, teriparatide, abaloparatide) capitalize on this principle and work to increase BMD. PTH analogs are unique among pharmacological OP therapies because they are the only anabolic agents (ie, drugs that increase bone formation). Other therapies (bisphosphonates, selective estrogen receptor modulators [SERMs], denosumab) slow bone resorption, but do not increase new bone formation.

Although research on the use of PTH analogs in adults with IDD is limited, we believe that these agents may be particularly effective in patients with a distinct pathophysiology of OP—for example, patients with CP, in whom OP results from an inadequate rate of bone growth during childhood rather than bone mineral loss. Considering this distinct pathophysiology, the anabolic PTH analogs could provide a unique benefit to patients with CP by promoting the formation of bone that was never optimally mineralized in the first place.

Another benefit of PTH analogs is that they are generally well tolerated, with few serious adverse effects. Hypercalcemia and hypercalciuria are two common adverse effects that typically can be managed with a dose reduction, decreased calcium supplementation, or temporary vitamin D cessation.[43] In addition, it should be noted that the alarming association of PTH therapy with osteogenic sarcoma (OS) is minimal and the two may not even be correlated. In the United States, a patient registry that began in 2009 has reported no cases of OS to date among its 63,270 registered patients.[44] Out of an abundance of caution, however, PTH therapy should be avoided in patients with an increased baseline risk for OS (eg, children and adolescents with incomplete epiphyseal fusion, patients with previous radiation therapy involving the skeleton).

Other Pharmacological Therapies

Other therapies for the treatment of OP include denosumab, SERMs, and calcitonin. Denosumab is a human monoclonal antibody that functions by inhibiting the receptor activator of nuclear factor-κB-ligand, which in turn prevents the development of osteoclasts. It is not typically used as initial therapy for OP because of the greater availability, low cost, and proven efficacy of oral bisphosphonates. There is controversy surrounding denosumab versus bisphosphonate therapy, however, with some studies showing a larger improvement in BMD with denosumab.[45–47] In addition, its infrequent dosing (subcutaneous injection once every 6 months) may prove valuable in adults with IDD who have difficulty adhering to daily oral bisphosphonates. Finally, it is not really cleared like bisphosphonates, making it useful in IDD patients with comorbid CKD.

The SERMs are synthetic molecules that bind estrogen receptors throughout the body and function as agonists or antagonists, depending on the target tissue and the specific medication. Because many disease pathologies involve estrogen, SERMs are used to treat a wide variety conditions, including breast cancer, infertility, and OP.[48] Raloxifene is a SERM that has high estrogen activity in bone and therefore increases BMD and prevents fractures in patients with OP. An estrogen antagonist in breast tissue, raloxifene also reduces the risk of breast cancer.[49] Because of their greater efficacy, bisphosphonates are typically prescribed over raloxifene for the treatment of OP; however, raloxifene is a reasonable option for the prevention and treatment of OP, especially in postmenopausal women looking to decrease their risk of breast cancer.[50] In adults with IDD, it should also be noted that SERMs are oral medications taken once daily, which may pose a challenge with adherence.

Calcitonin is a naturally occurring peptide that binds to osteoclasts and inhibits bone resorption. It is not used as a first-line therapy because it is less effective than other agents; however, it provides acute pain relief in patients with vertebral fractures. Nasal calcitonin preparations have a higher bioavailability than intramuscular preparations, but daily nasal administration may be challenging in patients with IDD. In addition, calcitonin may be associated with adverse events such as hypersensitivity reactions, hypocalcemia, and potential increased cancer risk.[51,52]

Monitoring Treatment Response

Monitoring response to OP therapy is essential for evaluating drug efficacy and identifying patients who may benefit from a

change in medication or dose. Although there are several published guidelines, the recommendations for the frequency of monitoring and the ideal site to monitor vary. Most societies recommend follow-up BMD testing 1 to 2 years after initiating treatment. The monitoring interval thereafter varies among societies, with many advocating less frequent monitoring if stable BMD is achieved.[53–55] Most guidelines recommend follow-up scans of the hip and spine, which may be difficult to perform on adults with IDDs. An alternative option for these patients is serial DXA measurements of peripheral body sites (eg, radius, tibia, femur). Although fewer data exist on peripheral DXA, it may be the only DXA option that is feasible for patients with severe physical disabilities.

For patients in whom DXA measurements are impossible or unreliable, monitoring bone turnover markers (BTMs) is an additional, cost-effective option for assessing treatment response. Although not routinely done in practice, measuring BTMs can be particularly useful in certain individuals, such as patients with impaired drug absorption, malnutrition, or suspected compliance issues.[56] In these patients, a common approach involves measuring BTMs before and 3 to 6 months after beginning bisphosphonate therapy.[57] Although there are many BTMs available, serum carboxy-terminal collagen crosslinks and fasting urinary N-telopeptide have been investigated in a multinational randomized controlled trial of postmenopausal women on oral risedronate. The study by Eastell et al demonstrated that participants with a significant decrease in BTMs had a decreased fracture risk.[58] The optimal cutoff for a decrease in these markers is not universally accepted, however, and the utility of BTMs has not been studied in the specific population of adults with IDDs. In addition, BTMs are only useful in patients taking antiresorptive therapy, not in patients taking anabolic agents (eg, PTH analogs), as they cause BTMs to increase because of their bone-building nature.

Conclusions

As medical care continues to improve, patients with IDD are living longer and facing many of the same diseases that affect the general aging population. OP is one such disease that frequently presents earlier in adults with IDDs than in those without IDDs. Because fractures from OP increase rates of disability and mortality, effectively diagnosing, preventing, treating, and monitoring OP is critical. Unique challenges arise in diagnosing and monitoring patients with IDDs because of difficulty performing DXA at the traditional sites of the hip and spine. For these patients, peripheral DXA and BTM measurements may provide innovative solutions. In adults with IDDs, treatment decisions should be individualized based on factors such as comorbid conditions, fracture risk, compliance, cost, and patient preference.

References

1. Eunice Kennedy Shiver National Institute of Child Health and Human Developoment. Intellectual and developmental disabilities (IDDs): condition information. National Institutes of Health. https://www.nichd.nih.gov/health/topics/idds/conditioninfo/default. Published 2016. Accessed July 9, 2020.
2. Kripke C. Adults with developmental disabilities: a comprehensive approach to medical care. *Am Fam Physician* 2018;97:649–656.
3. Coppus AMW. People with intellectual disability: what do we know about adulthood and life expectancy? *Dev Disabil Res Rev* 2013;18:6–16.
4. Henderson RC, Kairalla JA, Barrington JW, et al. Longitudinal changes in bone density in children and adolescents with moderate to severe cerebral palsy. *J Pediatr* 2005;146:769–775.
5. Lane NE. Epidemiology, etiology, and diagnosis of osteoporosis. *Am J Obstet Gynecol* 2006;194(2 suppl):S3–S11.
6. Jasien J, Daimon CM, Maudsley S, et al. Aging and bone health in individuals with developmental disabilities. *Int J Endocrinol* 2012;2012:469235.
7. Mirza F, Canalis E. Management of endocrine disease: secondary osteoporosis: pathophysiology and management. *Eur J Endocrinol* 2015;173:R131–R151.
8. Beerhorst K, Huvers F, Renier W. Severe early onset osteopenia and osteoporosis caused by antiepileptic drugs. *Neth J Med* 2005;63:222–226.
9. Kyvernitakis I, Kostev K, Nassour T, et al. The impact of depot medroxyprogesterone acetate on fracture risk: a case-control study from the UK. *Osteoporos Int* 2017;28:291–297.
10. Paksu MS, Vurucu S, Karaoglu A, et al. Osteopenia in children with cerebral palsy can be treated with oral alendronate. *Childs Nervous System* 2012;28:283–286.
11. Tang JYM, Luo H, Wong GHY, et al. Bone mineral density from early to middle adulthood in persons with Down syndrome. *J Intellect Disabil Res* 2019;63:936–946.
12. García-Hoyos M, Riancho JA, Valero C. Salud ósea en el síndrome de Down. *Med Clín* 2017;149:78–82.
13. Snow ME, Keiver K. Prenatal ethanol exposure disrupts the histological stages of fetal bone development. *Bone* 2007;41:181–187.
14. *Beyond Seizures: Comorbid Clinical Features and Multidisciplinary Management of Lennox-Gastaut Syndrome and Dravet Syndrome*. Carlsbad, CA: Greenwich Biosciences; 2018.
15. Marreiros H. Update on bone fragility in spina bifida. *J Pediatr Rehabil Med* 2018;11:265–281.
16. Zylstra RG, Porter LL, Shapiro JL, et al. Prevalence of osteoporosis in community-dwelling individuals with intellectual and/or developmental disabilities. *J Am Med Dir Assoc* 2008;9:109–113.
17. Lohiya GS, Crinella FM, Tan-Figueroa L, et al. Fracture epidemiology and control in a developmental center. *West J Med* 1999;170:203–209.
18. Glick NR, Fischer MH, Heisey DM, et al. Epidemiology of fractures in people with severe and profound developmental disabilities. *Osteoporos Int* 2005;16:389–396.
19. Jeremiah MP, Unwin BK, Greenawald MH, et al. Diagnosis and management of osteoporosis. *Am Fam Physician* 2015;92:261–268.
20. Sheridan KJ. Osteoporosis in adults with cerebral palsy. *Dev Med Child Neurol* 2009;51(suppl 4):38–51.
21. Harcke HT, Taylor A, Bachrach S, et al. Lateral femoral scan: an alternative method for assessing bone mineral density in children with cerebral palsy. *Pediatr Radiol* 1998;28:241–246.
22. Link TM. Osteoporosis imaging: state of the art and advanced imaging. *Radiology* 2012;263:3–17.
23. Stagi S, Cavalli L, Cavalli T, et al. Peripheral quantitative computed tomography (pQCT) for the assessment of bone strength in most of bone affecting conditions in developmental age: a review. *Ital J Pediatr* 2016;42:88–88.
24. Lewiecki EM, Silverman SL. Redefining osteoporosis treatment: who to treat and how long to treat. *Arq Bras Endocrinol Metabol* 2006;50:694–704.
25. Carroll DD, Courtney-Long EA, Stevens AC, et al. Vital signs: disability and physical activity—United States, 2009-2012. *MMWR Morb Mortal Wkly Rep* 2014;63:407–413.
26. Nair R, Maseeh A. Vitamin D: the "sunshine" vitamin. *J Pharmacol Pharmacother* 2012;3:118–126.
27. Shaikh AS, Guo X, Li Y, et al. The impact of antiepileptic drugs on vitamin levels in epileptic patients. *Curr Pharm Biotechnol* 2018;19:674–681.

28. Teagarden DL, Meador KJ, Loring DW. Low vitamin D levels are common in patients with epilepsy. *Epilepsy Res* 2014;108:1352–1356.
29. Chaudhuri JR, Mridula KR, Rathnakishore C, et al. Association of 25-hydroxyvitamin D deficiency in pediatric epileptic patients. *Iran J Child Neurol* 2017;11:48–56.
30. Hadjipanayis A, Hadjichristodoulou C, Youroukos S. Epilepsy in patients with cerebral palsy. *Dev Med Child Neurol* 1997;39:659–663.
31. Ward KD, Klesges RC. A meta-analysis of the effects of cigarette smoking on bone mineral density. *Calcif Tissue Int*. 2001;68:259–270.
32. Kanis JA, Johnell O, Oden A, et al. Smoking and fracture risk: a meta-analysis. *Osteoporos Int* 2005;16:155–162.
33. Felson DT, Zhang Y, Hannan MT, et al. Alcohol intake and bone mineral density in elderly men and women. The Framingham Study. *Am J Epidemiol* 1995;142:485–492.
34. Sampson HW. Alcohol and other factors affecting osteoporosis risk in women. *Alcohol Res Health* 2002;26:292–298.
35. Russell RG. Bisphosphonates: the first 40 years. *Bone* 2011;49:2–19.
36. Delmas PD, Adami S, Strugala C, et al. Intravenous ibandronate injections in postmenopausal women with osteoporosis: one-year results from the dosing intravenous administration study. *Arthritis Rheum* 2006;54:1838–1846.
37. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998;280:2077–2082.
38. Harris ST, Blumentals WA, Miller PD. Ibandronate and the risk of non-vertebral and clinical fractures in women with postmenopausal osteoporosis: results of a meta-analysis of phase III studies. *Curr Med Res Opin* 2008;24:237–245.
39. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356:1809–1822.
40. Kaga Y, Ishii S, Kuroda I, et al. The efficacy of intravenous alendronate for osteoporosis in patients with severe motor intellectual disabilities. *No To Hattatsu* 2017;49:113–119 [in Japanese].
41. Hefti E. Factors affecting adherence in patients with intellectual disabilities. https://www.pharmacytimes.com/contributor/erik-hefti-pharmd-ms/2016/11/factors-affecting-adherence-in-patients-with-intellectual-disabilities. Published November 7, 2016. Accessed February 7, 2021.
42. de Winter CF, Echteld MA, Evenhuis HM. Chronic kidney disease in older people with intellectual disability: results of the HA-ID study. *Res Dev Disabil* 2014;35:726–732.
43. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;344:1434–1441.
44. Gilsenan A, Harding A, Kellier-Steele N, et al. The Forteo Patient Registry linkage to multiple state cancer registries: study design and results from the first 8 years. *Osteoporos Int* 2018;29:2335–2343.
45. Lyu H, Jundi B, Xu C, et al. Comparison of denosumab and bisphosphonates in patients with osteoporosis: a meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab* 2019;104:1753–1765.
46. Brown JP, Prince RL, Deal C, et al. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. *J Bone Miner Res* 2009;24:153–161.
47. Mok CC, Ho LY, Ma KM. Switching of oral bisphosphonates to denosumab in chronic glucocorticoid users: a 12-month randomized controlled trial. *Bone* 2015;75:222–228.
48. Martinkovich S, Shah D, Planey SL, et al. Selective estrogen receptor modulators: tissue specificity and clinical utility. *Clin Interv Aging* 2014;9:1437–1452.
49. Rey JRC, Cervino EV, Rentero ML, et al. Raloxifene: mechanism of action, effects on bone tissue, and applicability in clinical traumatology practice. *Open Orthop J* 2009;3:14–21.
50. D'Amelio P, Isaia GC. The use of raloxifene in osteoporosis treatment. *Expert Opin Pharmacother* 2013;14:949–956.
51. Overman RA, Borse M, Gourlay ML. Salmon calcitonin use and associated cancer risk. *Ann Pharmacother* 2013;47:1675–1684.
52. Muñoz-Torres M, Alonso G, Mezquita Raya P. Calcitonin therapy in osteoporosis. *Treat Endocrinol* 2004;3:117–132.
53. Schousboe JT, Shepherd JA, Bilezikian JP, et al. Executive summary of the 2013 International Society for Clinical Densitometry Position Development Conference on bone densitometry. *J Clin Densitom* 2013;16:455–466.
54. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int* 2014;25:2359–2381.
55. Watts NB, Bilezikian JP, Camacho PM, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of postmenopausal osteoporosis. *Endocr Pract* 2010;16(suppl 3):1–37.
56. Lewiecki EM, Watts NB. Assessing response to osteoporosis therapy. *Osteoporos Int* 2008;19:1363–1368.
57. Wheater G, Elshahaly M, Tuck SP, et al. The clinical utility of bone marker measurements in osteoporosis. *J Transl Med* 2013;11:201.
58. Eastell R, Vrijens B, Cahall DL, et al. Bone turnover markers and bone mineral density response with risedronate therapy: relationship with fracture risk and patient adherence. *J Bone Miner Res* 2011;26:1662–1669.