Review

Bones and Birth Control in Adolescent Girls

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A B S T R A C T

Peak bone mass acquisition during adolescence is an important determinant of adult bone health. Knowledge about the effects of different contraceptives on peak bone mass acquisition could influence choice of method recommended. This review summarizes normal bone acquisition during adolescence, discusses methods of assessing bone health in this age group, and reviews the effects of different contraceptive options on bone health, both in adults and in adolescents. Based on the evidence, long-acting reversible contraceptives do not appear to affect peak bone mass acquisition or future fracture risk and remain the first-line contraceptive choice for adolescents. Oral contraceptives with doses of ethinyl estradiol greater than 30 μg should be used in preference to lower-dose preparations, and the adverse effects of depo medroxyprogesterone acetate (DMPA) on bone health are reversible on discontinuation of the medication. Concerns about bone health should not prevent use of DMPA in an adolescent who prefers this method.

Key Words: Bone densitometry, DXA, HR-pQCT, Adolescents, Contraception, Low bone mass, Osteoporosis, DMPA, Long-acting reversible contraceptives

Introduction

The adolescent years are critical for peak bone mass acquisition, a major determinant of future bone health. Bone mass attained in early life is the most important modifiable determinant of lifelong skeletal health,[1] and every 10% increase in bone mass during adolescence potentially reduces fracture risk by 50%.[2] Adolescence is also the time of initiation of sexual activity, and improved contraceptive use has contributed to the decline of unintended teen pregnancies.[3] In addition, adolescents are often prescribed contraceptives for their noncontraceptive benefits (eg, menstrual suppression or treatment of dysmenorrhea and acne). Other than the barrier methods, most contraceptives contain hormones, and hormonal status is a major determinant of bone health. This review summarizes normal bone acquisition during adolescence, discusses methods of assessing bone health in this age group, and reviews the effects of different contraceptive options on bone health in adolescents.

Materials and Methods

We performed a PubMed and MEDLINE search for original articles and systematic reviews published between January 1990 and November 2019. Search terms included: “bone health”, “bone mineral density”, “osteoporosis”, “adolescent”, “oral contraceptive”, “depo medroxyprogesterone”, “progestin implants”, “intrauterine devices”, “contraceptive patch,” alone and in combination. Relevant articles were cross-referenced. We limited our search to articles published in English or translated into English.

Normal Bone Acquisition During Adolescence

Bone deposition begins in utero, accelerates during adolescence, and reaches its peak during the second and third decades of life.[4,5] Approximately 40% of adult bone mass is accrued during adolescence, primarily within 2 years of peak height velocity (± 2 years).[1,5] By the age of 19 years, approximately 95% of peak bone mass has been accrued, with limited net gains thereafter.[1,5–7] Age of peak bone mass accrual lags behind age of peak height velocity by approximately 6-12 months.[1,8] This difference in the timing of peak linear growth and peak bone mineral acquisition may confer increased vulnerability to bone fragility and may explain, to some degree, the increased rate of forearm fractures in girls between the ages of 8 and 14 years.[1,9,10] Once peak bone mass is achieved, there is a slow but steady decline in net bone mass until menopause, when the rate of decline increases dramatically, accompanying falling estrogen levels. When a theoretical fracture threshold is reached, a fracture can occur with low-impact trauma.

Bone is metabolically active, comprising a matrix of collagen, hydroxyapatite crystals, and noncollagenous proteins that becomes mineralized by deposition of calcium and phosphate, strengthening the skeleton. The axial and appendicular skeleton contain both cortical and trabecular bone. Cortical bone, comprising 80% of the skeleton, is composed of dense compact layers of lamellar bone and occurs primarily in the shafts of long bones of the extremities, as well as in the cranium. Trabecular bone, comprising approximately 20% of the skeleton, is the spongy bone

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found in the vertebrae and consists of a network of thin plates traversing the marrow cavities of the skeleton. Trabecular bone is more metabolically active than cortical bone, and changes in bone mineral density (BMD) usually become apparent at the spine before other parts of the skeleton because of the higher concentration of trabecular bone in the spine.

The skeleton continues to remodel itself even after full linear growth has been achieved. During remodeling, bone formation, mediated via osteoblasts, and bone resorption, mediated by osteoclasts, occur concurrently. Remodeling is controlled by circulating hormones including parathyroid hormone, 1-25 dihydroxyvitamin D3, insulin-like growth factor−1 (IGF-1), and calcitonin, and is mediated by local cytokines.[11] In postmenopausal women, low estrogen levels stimulate circulating macrophages to produce osteoclastic cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor−α. These molecules act by the receptor activator of nuclear factor-κB ligand (RANK-L), which activates its receptor RANK and promotes osteoclast activation and bone resorption.[11] Net bone mass depends on the balance between bone resorption and bone formation. During adolescence, bone formation exceeds bone resorption. The converse is true with ageing. Low bone mass during adolescence can therefore be caused by bone loss or by failure to accrue bone.

Genetic factors (eg, a family history of osteoporosis) account for an estimated 60%-80% of the variability in bone mass.[1] Modifiable factors include nutritional status (maintaining a healthy body weight and ensuring adequate dietary intake of calcium and vitamin D), weight-bearing exercise that promotes bone formation, avoidance of smoking, and limiting soda consumption.[4] Sex steroids play a role in optimizing bone mass both though their direct effect on bone but also via sex steroid−induced increases in growth hormone and IGF-1, potent mediators of bone formation. Estrogen is the dominant sex steroid regulating bone metabolism in women[12] and not only reduces bone resorption but also promotes bone formation.

Assessment of Bone Health in Adolescents

Fracture risk, the outcome variable of most relevance, depends on skeletal fragility, but also on age, body weight, and the force of an injury. Skeletal fragility depends on BMD, but also on bone size, geometry, microarchitecture, and bending strength. A bone with a large cross-sectional radius will be less likely to fracture than a smaller bone, even when both bones have the same BMD. BMD accounts for approximately 70% of bone strength, and is a surrogate measure of bone fragility, recognizing that a low BMD does not necessarily translate to increased fracture risk and that it is possible to have increased fracture risk in the presence of normal BMD. The major methods of assessment of bone health are shown in Table 1.

Dual Energy X-Ray Absorptiometry

Dual energy X-ray absorptiometry (DXA) is the preferred method for assessing bone mineral content (BMC) and BMD in children and adolescents.[6,13] The usual sites measured are the lumbar spine (LS), hip, and total body. Advantages of DXA include its availability, speed, precision, low cost, and low dose of radiation (5-6 microSievert, μSv for the LS, hip, and total body), less than the radiation exposure of a transcontinental flight (Table 1).[14] DXA measures BMC by measuring attenuation of X-ray beams as they traverse tissues of varying density. Two-dimensional areal BMD is calculated from BMC by dividing measured BMC by the projected area in the coronal plane of the region scanned. However, bones are 3-dimensional structures and the result, expressed in g/cm^2, underestimates 3-dimensional volumetric BMD in individuals with small bones, including children and adolescents. Robust pediatric and adolescent reference databases for BMD and BMC are included with the DXA software.[7,15,16] Further adjustments can be made to account for size by adjusting for height Z-scores.[1,6,17]

In adults, a 1-standard deviation (SD) decrease in BMD is associated with a 2- to 3-fold increased risk of hip fracture.[18] In adolescents, there is no specific BMD cutoff below which a fracture is more likely to occur, but there is increasing recognition that low BMD in adolescence is associated with fractures both in adulthood and during adolescence.[19–21]

The International Society for Clinical Densitometry (ISCD) provides guidance in interpreting DXA results in children and adolescents. Z-scores (the number of SDs below the age-matched mean) should be used instead of T-scores (the number of SDs below the young adult mean); the term "osteopenia" should no longer be used in DXA reports; and the term "osteoporosis" should not be based on bone densitometry results alone. The ISCD defines low BMD for chronological age as an age-, sex-, and body size−adjusted BMD Z-score of less than −2.[13] The ISCD

Table 1
Methods of Assessment of Bone Health

	DXA	QCT	pQCT	HR − pQCT
Site measured	Lumbar Spine Hip Total Body	Lumbar Spine Hip Distal Radius	Distal Radius Distal Tibia	Distal Radius Distal Tibia
Radiation dose	5−6 μSv	30−7000 μSv	<3 μSv	<3 μSv
BMD	aBMD	vBMD	vBMD	vBMD
Differentiates cortical from trabecular bone	No	Yes	Yes	Yes
Bone geometry	No	Yes	Yes	Yes
Bone microstructure	No	No	No	Yes

DXA, dual energy X-ray absorptiometry; QCT, quantitative computed tomography; pQCT, peripheral computed tomography; HR-pQCT, high-resolution peripheral quantitative computed tomography; aBMD, areal bone mineral density; vBMD, volumetric bone mineral density; μSv, microSievert.

further recommends that in individuals less than 20 years of age, the diagnosis of "osteoporosis" require *both* a low BMD or BMC for age (Z-score less than −2) *plus* a clinically significant fracture, defined as 1 or more of the following: (a) 2 or more long bone fractures by the age of 10 years, or (b) 3 or more long-bone fractures at any age up to age 19 years. The finding of 1 or more vertebral compression fractures is also indicative of osteoporosis.[13]

Quantitative Computed Tomography

In contrast to DXA, quantitative computed tomography (QCT) measures true volumetric BMD, but the dose of radiation is high (30–7000 μSv) (Table 1).[22] Measurements of the spine and hip are obtained using a clinical whole-body scanner equipped with special analysis software. QCT machines are costly and not readily available for clinical use. Peripheral QCT (pQCT) allows for assessment of volumetric BMD of the appendicular skeleton with much lower doses of radiation (<3 μSv). The machines are smaller, are more mobile, and are dedicated to assessment of bone health and not used for other purposes. High-resolution pQCT (HR-pQCT) is a newer modality used primarily for research that also assesses bone microarchitecture and can be used to estimate bone strength.

Bone Health and Contraception

A tiered approach is now recommended for contraceptive counseling of teens, based on demonstrated improved contraceptive effectiveness after eliminating barriers such as cost and medication nonadherence (Table 2).[23] Some contraceptive methods may have an impact on peak bone mass acquisition and could potentially affect future fracture risk. Knowledge about the potential impact of the type of contraception on bone health could influence choice of method.

Combined Oral Contraceptives

Combined oral contraceptives (COC) remain the most popular method of hormonal contraception used by adolescents.[24] COC suppress endogenous estrogen production but also inhibit hepatic synthesis of IGF-1, a potent bone anabolic agent. Healthy young women not on COC have mean serum estradiol levels of 120 pg/mL, with mid-cycle peak levels >200 pg/mL. Women on COC containing 30 μg ethinyl estradiol (EE) have mean estradiol levels of 44 pg/mL and those on COC containing 20 μg EE have mean levels of 41 pg/ml.[25] Lower serum estradiol levels adversely affect BMD.

An early prospective study showed that adolescent girls on COC containing 30 μg EE increased BMD over a period of 1 year, but at a rate lower than healthy controls.[26] In a larger prospective study of 605 women (50% adolescents), Scholes similarly found that adolescents on 30-35 μg EE COC gained LS-BMD but at a lower rate than nonusers (1.33 vs 2.26; 95% CI, −1.89 to −0.13. For adults, there was no such difference between COC users and non\users.[27] Other investigators have similarly found that adolescents on COC accrue less bone than healthy controls.[25,28,29] A meta-analysis of prospective cohort studies limited to adolescents demonstrated that after 1 year, those on COC had a weighted mean LS BMD difference of −0.02 (95% CI, −0.05 to 0.001 g/cm^2) compared to those not exposed to COC (P = .04) and at 2 years, −0.02 (95% CI, −0.03 to −0.01 g/cm^2; P = .0006).[30]

Some investigators have expressed concern about the use of low-dose COC (<30 μg EE) on bone mass acquisition during adolescence.[25,29,31–33] An elegant prospective crossover study examined LS BMD in 56 adolescent girls seeking hormonal contraception and 28 healthy controls. Those seeking contraception were randomized to receive a COC containing either 30 or 15 μg of EE for 9 months, and DXA was obtained at baseline, 9 months, and 18 months. During the initial 9-month period, those assigned to 30 μg EE initially increased spinal BMD by 1%; however, BMD returned to baseline levels after switching to 15 μg EE. In participants initially assigned 15 μg EE, there was minimal increase in spinal BMD in the first 9 months; but after switching to the higher dose, spinal BMD gains paralleled those of controls.[31] At the end of the study, spine BMD increased 2% in the healthy controls, but there was no significant increase in the COC users.

A large multicenter RCT compared LS BMD accrual in 1361 adolescents randomized as follows: (a) 91-day levonorgestrel (LNG) extended regimen comprising 84 days of LNG 150 μg, 30 μg EE with 7 days of 10 μg EE); (b) 28 days of LNG 100 μg with 20 μg EE followed by 7 days of placebo; or c) healthy controls. Mean change in LS BMD over 12 months was 2.26% in the LNG/30 μg EE extended regimen, similar to the 2.5% increase seen in healthy controls. Bone accrual was significantly lower than healthy controls for those on the 28-day regimen of LNG 100 μg/20 μg EE.[34] Taken together, there is some evidence that COC may be associated with impaired bone accrual during adolescence and that the effect is greatest when using lower-dose (<30 μg EE) preparations.

Impaired peak bone mass accrual does not necessarily translate to increased fracture risk, and whether the above changes in BMD affect fracture risk is not known. A Cochrane review of case-control and cohort studies in adults found that COC use was not associated with

Table 2
Tiered Approach to Contraceptive Counseling

Tier	Method	Typical Use Failure Rate*
Tier 1 (<1 pregnancy per 100 women-years)	LNG implant	0.01%
	LNG IUD	0.1%–0.4%
	Copper IUD	0.8%
Tier 2 (6–12 pregnancies per 100 women in a year)	DMPA	6%
	COC	7%
	Contraceptive patch	7%
	Vaginal ring	7%
Tier 3 (18 or more pregnancies per 100 women in a year)	Male condom	13%
	Female condom	21%
	Withdrawal	22%
	Fertility awareness based methods	24%

LNG, levonorgestrel; IUD, intrauterine device; DMPA, depo medroxyprogesterone acetate; COC, combined oral contraceptives.
* Source: Centers for Disease Control; available at: http://www.cdc.gov/reproductivehealth/UnintendedPregnancy/Contraception.htm.

increased fracture risk.[35] Fracture risk in adolescents on COC is not known, but the consensus is that low dose COC (<30 μg EE) are insufficient to support peak bone mass acquisition.[36]

Depo Medroxyprogesterone Acetate

Depo medroxyprogesterone acetate (DMPA) is a very effective injectable contraceptive administered every 12 weeks. It is particularly appealing to adolescents because it can be given in private and does not rely on patient adherence to a daily regimen. DMPA also suppresses the hypothalamic-pituitary-ovarian axis, resulting in profound hypoestrogenemia. Several cross-sectional and longitudinal observational studies in adolescents reported an association between prolonged DMPA use and decreased BMD.[26,37–39] In response to these findings, the Food and Drug Administration issued a "black box warning" advising practitioners about the negative effects of DMPA on bone health in adolescents who may not yet have achieved peak bone mass. Initial concerns were attenuated by subsequent studies that revealed partial or complete recovery of BMD with discontinuation of DMPA.[27,32,40]

Whether or not DMPA is associated with fractures remains controversial. One large, population-based case-control study of adult women found that current or past DMPA use was associated with increased fracture risk (adjusted odds ratio [OR], 1.49; 95% CI, 0.96-2.33).[41] Another retrospective study of 312,395 adult women compared fracture risk in DMPA users to nonusers and found that before DMPA was started, DMPA users had higher fracture risk than nonusers but that the risk did not increase after starting DMPA, suggesting that factors other than DMPA contributed to the increased fracture risk.[42] A more recent study of 308,876 women aged 12-45 years found that women with recent DMPA use (within 2 years or less) and those with more than 2 years cumulative DMPA use had higher fracture risk than non-users (adjusted HR 1.15, 95% CI 1.01-1.31. Fracture risk was not increased in those with past DMPA use. The investigators concluded that the absolute fracture risk was small and reversible, and that providers should consider DMPA a safe method of contraception.[43]

For most adolescents, the risk of fracture is low, and the benefits of using DMPA to prevent pregnancy outweigh the risks. The Society for Adolescent Health and Medicine recommends continuing to prescribe DMPA to adolescent girls but also suggests discussing the risks and benefits with the patient.[44] The American College of Obstetricians and Gynecologists states that given the importance of prevention of unwanted pregnancy, concerns regarding the effect of DMPA on BMD should neither prevent providers from prescribing DMPA nor limit its use to 2 consecutive years. However, the risks and benefits should be discussed with the patient and clinical judgment be used to assess the appropriateness of use. Routine DXA assessments are not recommended for adolescents on DMPA, but they should be counseled about other contraceptive options that do not affect BMD.[45]

Contraceptive Patch and Vaginal Ring

In adults, a combined contraceptive vaginal ring (NuvaRing) that releases 15 μg EE and 120 μg etonorgestrel/day used for 2 years did not change LS BMD in healthy premenopausal women. However, in the control group, BMD did increase slightly, resulting in a statistically significant difference in BMD between the groups at 2 years.[46] A study in adults comparing the vaginal ring with a contraceptive patch delivering 150 μg of norelgestromin and 20 μg EE weekly for 3 weeks did not find any significant change in LS BMD in either group over a period of 12 months.[47] A small study of 5 adolescents and 5 aged-matched controls found that at 1 year, whole-body BMC increased 3.9% in healthy controls but that there were no significant changes in those on the patch, suggesting that the patch attenuates bone mass acquisition.[48] Physiologic doses of transdermal estrogen (100 μg of 17β-EE applied 3 times per week) have been shown to increase BMD both in adolescents with anorexia nervosa[49] and in normal weight oligo- and amenorrheic athletes[50]; however, the estrogen patch is not a contraceptive. These studies suggest that the contraceptive patch and vaginal ring do not adversely affect bone health in adult women, but data in adolescents are limited.

Long-Acting Reversible Contraceptives (LARC)

Contraceptive Implants

In adults, both cross-sectional[51] and prospective[52–54] studies suggest that the contraceptive implant does not adversely affect bone mass, although one study found lower BMD of the distal radius and ulna in the implant group but no significant difference in BMD of the spine or femoral neck,[51] and another found reduced BMD at the ulna but not at the distal radius.[53] Data are limited on the effect of the LNG implant use during adolescence. One study of 7 adolescents found a significant increase in BMD over 12 months.[26] It has been proposed that the LNG implant may not have such a deleterious effect on BMD as DMPA because estrogen levels are not suppressed to the same degree.[36]

Levonorgestrel IUD

Both cross-sectional and prospective studies have shown that the LNG-IUD does not adversely affect bone mass in adult women.[55,56] The LNG-IUD releases LNG directly into the endometrial cavity at an initial rate of 20 μg/day with only small amounts of hormone absorbed into the systemic circulation. Mean serum levels of estradiol in the LNG-IUD group were 98.2 ± 12.7 pg/mL, similar to those found during the follicular phase of the menstrual cycle.[55] The LNG-IUD does not suppress endogenous estrogen production to the same degree as DMPA and the amenorrhea frequently observed in LNG-IUD users is secondary to the direct antiproliferative effect of LNG on the endometrium[55] and not a result of hypothalamic suppression. Furthermore, LNG releases 19 nor-progestogen, which has a beneficial effect on bone.[57]

Copper IUD

The copper IUD releases copper ions, causing an increase in uterine and tubal fluids containing enzymes, macrophages, and prostaglandins that act to impair sperm function and fertilization. It does not suppress endogenous estrogen production. In a study of 80,833 women with IUDs, there was no increased fracture risk.[43] However, users of the copper IUD were not differentiated from users of the LNG IUD.

Summary

Optimal peak bone mass accrual during adolescence is an important predictor of future bone health. When prescribing contraception for an adolescent, prevention of unplanned pregnancy remains the priority, but knowledge about the different contraceptive options can inform choice of method. Irrespective of the method selected, general measures to optimize bone health are recommended: maintaining a healthy body weight, dietary intake of at least 1300 mg/day of calcium, 600 IU/day of vitamin D, limiting soda consumption, promoting weight-bearing exercise, and avoiding smoking and alcohol use.[4] In adolescents, COC preparations with doses of EE $\geq$30 μg should be used in preference to low-dose ($<$30 μg) EE preparations. DMPA negatively affects BMD during adolescence, but the effects are reversible on discontinuation of the medication, and concerns about bone health should not preclude its use in an adolescent who prefers this method. Although prospective data on the use of LARC in adolescents are limited, LARC does not appear to affect peak bone mass acquisition or future fracture risk, and remains the first-line contraceptive choice for adolescents.

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