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Pediatric Bone Health Update

Understanding the importance of peak bone mass

Timothy Hereford, MD[1], Alec Kellish, MD[2], Julie Balch Samora, MD, PhD[3], Louise Reid Nichols, FAOA, FAAOS, MD[1,*]

[1] Nemours Children's Health, Wilmington, DE, USA
[2] Thomas Jefferson University, Philadelphia, PA, USA
[3] Nationwide Children's Hospital, Columbus, OH, USA

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ABSTRACT

Bone mass attained early in life is one of the most important determinants of lifelong skeletal health. Bone mineral content increases exponentially during childhood. In fact, 40%-60% of the total adult bone mass is accrued during puberty. By the end of the first 2 decades of life, peak bone mass has been reached. Between ages 20-50, bone mass has plateaued, but it continues to remodel. This is regulated by parathyroid hormone (PTH), vitamin D3, and insulin-like growth factor 1 (IGF-1). After the age of 50, bone mass begins to decrease. The purpose of this paper is to review the importance of maximizing peak bone mass and factors that can modify and maintain peak bone mass.

Key Concepts:

(1) Peak bone mass is attained by the end of the second decade of life.
(2) There are more fractures during peak height velocity in adolescence as the body increases in size but bone mineralization lags behind.
(3) The risk of adult osteoporosis starts in childhood.
(4) There are modifiable and nonmodifiable risk factors that affect peak bone mass.

Level of Evidence: IV

Introduction

Bone mass attained early in life is thought to be the most important modifiable determinant of lifelong skeletal health [1]. Therefore, bone health in an adult (ie, the amount and quality of their bone) is a reflection of everything that has happened to that person from the womb through adolescence [2]. Suboptimal lifestyle factors negatively affect the maximal peak bone mass placing patients at greater risk for low bone mass or osteoporosis (Fig. 1).

When people think about bone health, they often associate it with osteoporosis in the elderly. In reality, bone health, and therefore the risk of osteoporosis, starts in childhood. Bone mineral content increases 40-fold from birth until adulthood and approximately 40%-60% of all adult bone mass is accrued during the adolescent years, particularly during peak height velocity [4,5]. Those who obtain a higher peak bone mass in youth will be better protected against osteoporosis and fractures later in life. After peak bone mass is reached, it remains relatively stable between ages 20-50. During this time, it is important to focus on preventing premature bone loss as bone mass begins to decrease after age 50.

Peak bone mass is defined as the amount of bony tissue at the end of skeletal maturity during the second decade of life. It provides structural strength and can be characterized based on its mass, density, and geometric properties [3]. The National Osteoporosis Foundation further defines peak bone mass according to the individual and population. Individual peak bone mass is the amount of bone mass accrued in young adulthood. It can also refer to the genetic potential for bone strength of the individual [3]. For the population, peak bone mass occurs when age-related changes have plateaued or maximized [6]. Karlsson et al. looked at the effect of physical activity on peak bone mass. They demonstrated that physical activity 1-2 times per week increased bone mineral content (BMC) and bone mineral density (BMD) in children, which can effectively decrease fracture rate [7.]

* Corresponding author: Nemours Children's Hospital Delaware, 1600 Rockland Road, Wilmington, DE 19803, USA.
E-mail address: reid.nichols@nemours.org (L. Reid Nichols).

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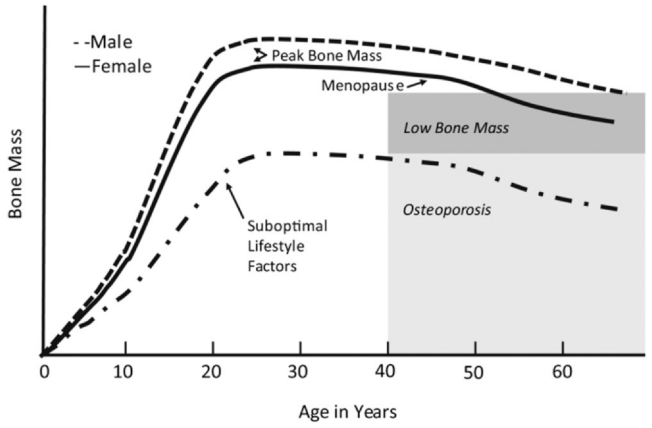

Figure 1. Peak bone mass is achieved with optimal lifestyle factors [3].

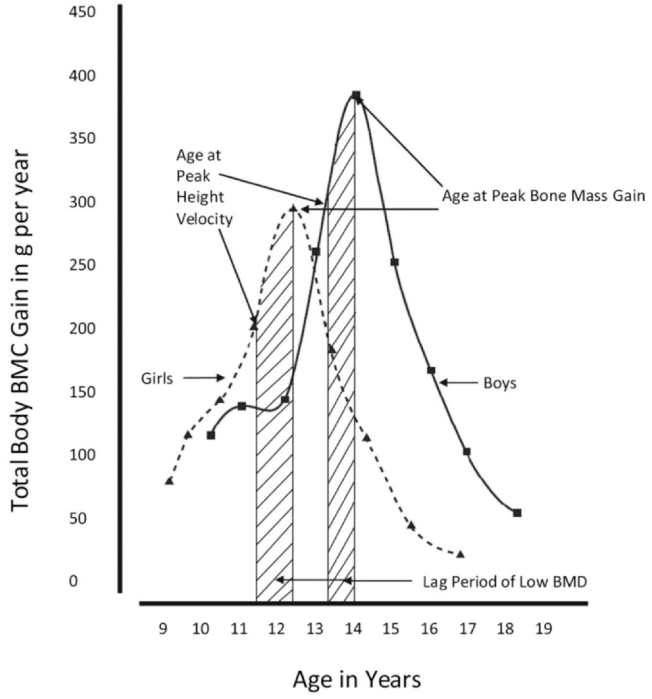

Figure 2. Bone mass accretion accelerates with onset of puberty, and peaks after peak height gain [3]. BMC, bone mineral content.

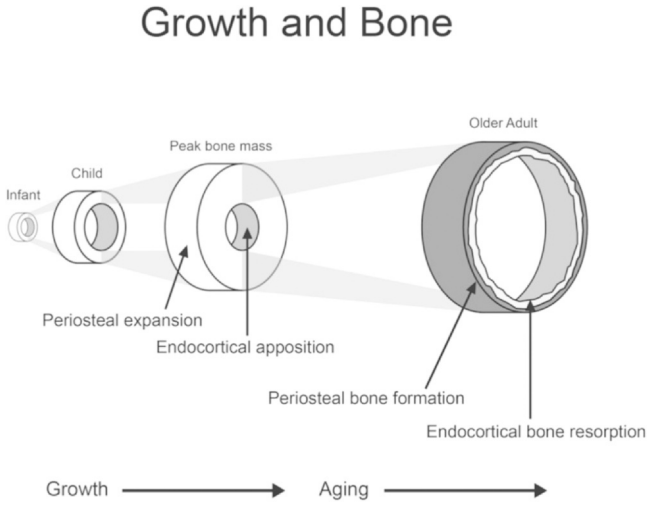

Figure 3. Changes in bone structure with age progression [3].

Table 1
Modifiable and nonmodifiable factors which affect bone health.

Modifiable	Nonmodifiable
Nutrition/diet	Genetic conditions
Body weight	Gender
Exercise	Ethnicity
Medications	
Hormonal status	

Age of peak bone mass accrual lags behind peak height velocity (Fig. 2). At peak height velocity adolescents have reached 90% of their adult stature but have obtained only 57% of their total body bone mineral content [8]. As a result, there is an increased rate of fractures (eg, forearm fractures) during this period. Physical activity often increases during the time of peak height velocity, during which there is also a transient deficiency of cortical bone mass as the calcium demand for skeletal growth is maximized [9]. After linear growth has finished, bone continues to remodel at a rate as high as 50% per year [10]. This remodeling is regulated by parathyroid hormone (PTH), vitamin D3 (1,25-dihydroxyvitamin D), insulin-like growth factor 1 (IGF-1), and calcitonin. Net bone mass depends on the balance between resorption and formation. Over time, bone will change in composition and size (Fig. 3).

Modifiable and nonmodifiable factors

Bone health factors can be both modifiable and nonmodifiable (Table 1) [4]. Modifiable factors include nutrition/diet, body weight, exercise, medications, and hormonal status. It is important for Orthopaedic surgeons to discuss these topics with their patients and provide the appropriate information, resources, and/or referrals to optimize these factors. Nonmodifiable factors include genetic conditions, gender, and ethnicity. Generally, men have greater bone mass than females. Higher bone mass is also observed in Black/African American individuals compared to White, non-Hispanic, or those individuals of Asian descent [8,11]. Although specific genes that influence bone mass have not yet been identified, genetics may account for up to 70% of variance in bone mass [8,12.]

Table 2
Conditions associated with reduced bone mass in children and adolescents.

Genetic conditions	**Medications**
Osteogenesis imperfecta	Glucorticoids
Idiopathic juvenile osteoporosis	Anticonvulsants
Turner	Chemotherapy
	Leuprolide acetate
Chronic illness	Protein pump inhibitors
Cystic fibrosis	Selective serotonin receptor inhibitors
Cushing syndrome	Depot medroxyprogesterone acetate
Hypogonadonism	
Hypothyroidism	**Endocrine conditions**
Hypoparathyroidism	Cushing syndrom
GH deficiency	Hypogonadism
Connective tissue disorders	Hyperthyroidism
Inflammatory bowel disease, celiac disease	Hyperparathyroidism
Childhood cancer	Growth hormone deficiency
Cerebral palsy	Diabetes mellitus
Chronic immobilizations	
Eating disorders	
Anorexia nervosa	
Bulemia nervosa	
Female athlete triad	
Obesity	

Table 3
Common prescription medications and effect on bone health with recommendations for screening and management [19].

Drug class	Mechanism of action	Reversibility on medication discontinuation	Screening recommendation	Management recommendation	Alternate medication
Glucocorticoids (GC)	Decreased bone formation and increased bone resorption	Fracture risk decreases to baseline within 2 years	Fracture risk analysis with DXA or FRAX Monitor vitamin D and calcium levels	Calcium and vitamin D supplementation Bisphosphonate or teriparatide according to fracture risk DXA scan every 2 years	Limit dose and duration of GC Use alternative immunosuppressive agents according to underling disease condition
Proton pump inhibitors (PPIs)	Unknown but maybe due to decreased intestinal absorption of calcium	Fracture risk reverses within 1 year	No recommendation	Calcium and vitamin D supplementation If possible, avoid PPI use with bisphosphonates	H_2 blockers
Antiepileptic drugs (AEDS)	Uncertain but may include inactivation of vitamin D	Unknown	Fracture risk analysis with DXA or FRAX Monitor vitamin D and calcium levels every 6–12 months	Calcium and increased vitamin D supplementation: non-enzyme-inducing AEDs give 1000–1200 IU vitamin D and for enzyme-inducing AEDs give 2000-4000 IU vitamin D daily Bisphosphonates in postmenopausal women and men $>$ 50 years	Newer agents like levetiracetam
Medroxyprogesterone acetate (MPA)	Reduced estrogen level leading to increased bone resorption	Partial to full recovery of bone loss at spine and hip	DXA scan controversial in this premenopausal population Monitor vitamin D and calcium levels	Calcium and vitamin D supplementation Limit therapy to 2–3 years No data on bisphosphonates prophylaxis and is currently not recommended	Oral hormonal contraceptives, low-dose estrogen replacement with depot MPA, other birth control methods
Aromatase Inhibitors	Reduced estrogen production leading to increased bone resorption	Unknown	Fracture risk analysis with DXA or FRAX Monitor vitamin D and calcium levels	Calcium and vitamin D supplementation Bisphosphonates for moderate- to high-risk patients Denosumab as alternative DXA scan every 2 years while on treatment	Not applicable
GnRH agonists	Prevent the production of LH and FSH thereby decreasing testosterone and estradiol leading to increased bone resorption	May be reversed in 2 years depending on dose and duration of therapy	Fracture risk analysis with DXA or FRAX Monitor vitamin D and calcium levels	Bisphosphonates, denosumab, raloxifene, or toremifene for moderate- to high-risk patents DXA scan every 2 years while on treatment	Second line: androgen receptor blockers in men without bone metastasis
Serotonin selective reuptake inhibitors	Uncertain	Probable	Fracture risk analysis with DXA or FRAX for patients with other osteoporosis risk factors Monitor vitamin D and calcium levels	Calcium and vitamin D supplementation	Alternative classes of antidepressants
Thiazolidinediones	Decreased bone formation	Unknown	Fracture risk analysis with DXA or FRAX for patients with other osteoporosis risk factors Monitor vitamin D and calcium levels	Avoid in established osteoporosis No data for prevention	Metformin, sulfonylureas, insulin
Calcineurininhibitors	Excessive osteoclasts and bone resorption with glucocorticoids	Unknown	DXA/FRAX analysis prior to kidney transplant Monitor vitamin D and calcium levels	Calcium and vitamin D supplementation DXA prior to and every 2 years post organ transplant Bisphosphonates for T score $<$ -2.0	
Heparin	Osteoblast inhibition with decreased bone formation; increased bone resorption	Near complete reversal of BMD	No published recommendations	No published recommendations	Fondaparinux if applicable
Warfarin	Decreases bone mineralization	Unknown	No published recommendations	No published recommendations	

(*continued on next page*)

Table 3 (*continued*)

Drug class	Mechanism of action	Reversibility on medication discontinuation	Screening recommendation	Management recommendation	Alternate medication

BMD, bone mineral density; DXA, dual energy x-ray absorptiometry; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone agonist; LH, luteinizing hormone; PPI, proton pump inhibitors; FRAX, Fracture Risk Assessment Tool.

Inherited conditions that affect peak bone mass

Certain genetic conditions such as Turner's syndrome, osteogenesis imperfecta, and juvenile idiopathic osteoporosis are at greater risk for reduced bone mass. Turner's syndrome causes low BMD and osteoporosis secondary to ovarian failure. This affects women with Turner's syndrome 2 to 3 decades earlier than postmenopausal women. They are twice as likely to fracture the metacarpal bones, femoral neck, lower spine, and forearm [13]. Osteogenesis imperfecta is caused by mutations in the COL1A1 or COL1A2 gene. There is modification of collagen molecules, thinner collagen fibers, hyper mineralization of bone tissue at a bone matrix level leading to decreased trabecular number, connectivity, thickness, volumetric bone mass and decreased cortical thickness [14.]

Bone mass can be influenced by chronic illnesses such as cystic fibrosis, connective tissue disorders, juvenile idiopathic arthritis, lupus, irritable bowel syndrome, celiac disease, chronic renal failure, cancer, cerebral palsy, and eating disorders. In addition, young women who experience amenorrhea secondary to excessive exercise can cause bone loss due to loss of estrogen. Endocrinopathies such as Cushing syndrome, hypogonadism, hypothyroidism, hyperparathyroidism, and growth hormone deficiency also impact bone mass (Table 2) [1,3.]

Medications that affect peak bone mass

Commonly prescribed medications can have harmful effects on bone homeostasis leading to decreases in bone mineral density and increases in fracture frequency through a variety of mechanisms. Prescribed medications such as glucocorticoids, anticonvulsants, chemotherapy agents, leuprolide acetate, proton pump inhibitors (PPI), selective serotonin reuptake inhibitors, and depot-medroxyprogesterone acetate (DMPA) can also impact bone health. Many physicians are not aware of the deleterious effect of these medications on BMD. The effects of these medications on BMD can be significant. Approximately 30%-40% of patients treated with glucocorticoids (GC), even at low doses, develop fractures [15]. The direct effect of GCs is to reduce recruitment of osteoblast precursors which ultimately results in decreased bone formation. Indirectly, GCs decrease calcium resorption, suppress growth hormone, and interfere with parathyroid pulsatility [15]. PPIs may increase fracture risk, although the mechanism is not clear. One theory is that they may interfere with intestinal absorption of calcium [16]. Antiepileptic drugs such as phenytoin can accelerate inactivation of Vitamin D resulting in decreased calcium uptake, secondary hyperparathyroidism, and acceleration of bone loss [17]. DMPA inhibits gonadotropin secretion which reduces estrogen and leads to a decrease in BMD [18]. Table 3 reviews some common medications and their harmful effects on bone health and homeostasis [19.]

Bone health ingredients and importance of vitamin D

Bone has collagen and mineral components which are necessary for bone strength. Ingredients for healthy bone include calcium, vitamin D, vitamin C, vitamin K, silicon, boron, and magnesium. Vitamin D produces osteocalcin to aid in bone absorption of calcium. Boron extends the half-life of vitamin D and estrogen. Vitamin K carboxylates osteocalcin to enable calcium binding. Silicon attracts calcium, and magnesium also assists in forming bone [20]. Vitamin C helps form collagen and directly impacts the osteoblast's ability to make bone [21–23.]

One of the key ingredients in this recipe is vitamin D. Understanding the physiology surrounding this vitamin is critical for understanding bone health. Vitamin D can be found as supplements in the form of vitamin D3 or D2. Pre-vitamin D3 can be converted to vitamin D3 on the skin, by UV-B rays from the sun, and is then hydroxylated first in the liver to 25-hydroxyvitamin D, then again in the kidney to become the active form: calcitriol (1,25-dihydroxyvitamin D). Calcitriol promotes absorption of calcium from the intestine. Vitamin D3 has a half-life of 2-3 weeks and reaches steady state by 8-12 weeks [24]. Vitamin D3 that is acquired from animals and fish is better absorbed and lasts longer than vitamin D2 which is from plants [25,26.]

Vitamin D deficiency is a national crisis affecting 70% of US children. Obesity as well as other factors such as insufficient intake contribute to vitamin D deficiency [27–29]

There are few foods in nature which naturally contain vitamin D. Salmon, tuna, mackerel and fish oils are the best natural food sources. Small amounts of vitamin D are found in beef liver, cheese, and egg yolks. Fortified foods have some vitamin D and include certain types of orange juice, milk, yogurt, and cheese [4]. However, it is generally not realistic for most of the population to get adequate vitamin D from food and sun alone; supplementation should be recommended and utilized (Table 4).

It is important to be on the lookout for the "calciopenic diet" because inadequate calcium intake effects the body's ability to reach peak bone mass. These are individuals who may be lactose intolerant or have a milk allergy, decline dairy intake, or opt for beverages rather than milk [32]. Vegan diets are at risk for excluding vitamin D-rich and calcium rich food [33]. Multivitamins alone do not provide sufficient vitamin D or calcium without the proper diet.

There are varying recommendations for adequate serum vitamin D levels and supplementation dosing guidelines. The recommended daily allowance (RDA) based on population statistics from the Institute of Medicine accepts lower values for normal vitamin D than others. They define normal 25(OH)D in adults as greater than 20 ng/mL, vitamin D insufficiency as less than 20 ng/mL, and deficiency as levels less than 12 ng/mL. The Endocrine Society uses these values: less than 20 ng/mL for deficient; 20-29 ng/mL insufficient; and greater than or equal to 30 ng/mL for normal serum levels. Their recommended target levels for 25(OH)D is 40 to 60 ng/mL [29]. There are no guidelines specifically for children, and therefore adult guidelines are used. Children with vitamin D deficiency are 6 times more likely to have a higher severity fracture than those with normal vitamin D levels [34]. Providing children with supplemental vitamin D should decrease risk for low-energy fractures and improve healing in fractures [35,36]. Vitamin D levels can be monitored to help ensure adequate intake. Recommendations for specific amounts are discussed elsewhere in this journal.

Weight-bearing and peak bone mass

Weight-bearing exercises and strength training are critical in helping children reach peak bone mass and maintain overall good

Table 4. Selected food sources of vitamin D [30,31].

Food	IUs per serving*	Percent DV†
Cod liver oil, 1 tablespoon	1,360	340
Salmon (sockeye), cooked, 3 ounces	447	112
Mackerel, cooked, 3 ounces	388	97
Tuna fish, canned in water, drained, 3 ounces	154	39
Orange juice fortified with vitamin D, 1 cup (check product labels, as amount of added vitamin D varies)	137	34
Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 1 cup	115-124	29-31
Yogurt, fortified with 20% of the DV for vitamin D, 6 ounces (more heavily fortified yogurts provide more of the DV)	88	22
Margarine, fortified, 1 tablespoon	60	15
Liver, beef, cooked, 3.5 ounces	49	12
Sardines, canned in oil, drained, 2 sardines	46	12
Eggs, 1 large (vitamin D is found in yolk)	41	10
Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 0.75-1 cup (more heavily fortified cereals might provide more of the DV)	40	10
Cheese, Swiss, 1 ounce	6	2

* IUs – International Units.
† DV – Daily Value, DVs were developed by the U.S. Food and Drug Administration to help consumers compare the nutrient contents among products within the context of a total daily diet.

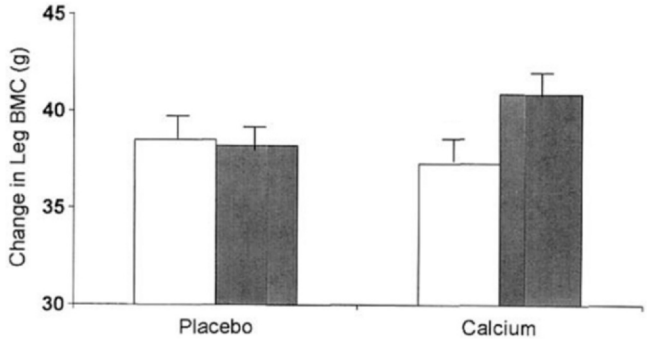

Figure 4. This graph represents young children given either a placebo or supplemental calcium. The gray bars represent those that participated in higher physical activity. Calcium supplementation combined with physical activity resulted in higher bone mineral content (BMC) [38].

health. There is an increase in sporting activities and intensity at a younger age with a subsequent decrease in level of participation and intensity as children reach high school. This decrease in physical activity correlates with a significant increase in childhood obesity and associated medical issues associated including poor bone health. The American Academy of Pediatrics' position statement on the safety and benefits of resistance training for children and adolescents' states that resistance training is an important component of sport and exercise training. The goal is to engage children at a younger age and promote a culture of activity [37]. In one randomized trial, changes in bone mass were only seen if there was physical activity along with consumption of calcium intake $\geq$1100 mg/d [38]. They found that increased periosteal and endosteal tibia circumferences occurred with physical activity and this finding was independent of calcium intake. This finding demonstrates that physical activity stimulates bone growth in diameter, but increasing bone mineral relies on both physical activity and calcium intake (Fig. 4) [38]. Strength training has been shown by others to have the potential to increase bone mineral density [37,39]. Other benefits of improving strength include improvements in motor skills, gains in speed and power, building self-esteem, reducing risk of injury, and injury rehabilitation [37.]

Conclusion

Bone mass attained early in life is one of the most important determinants of lifelong skeletal health. Peak bone mass is achieved by the end of the second decade and cannot be rebuilt later in life. When adolescents reach their age of peak height velocity, they obtain 90% of their adult stature but only 57% of their total bone mineral content [40]. This discrepancy leads to an increased risk of fractures during this period. Bone continues to remodel throughout our lifetime, and this is regulated by PTH, vitamin D3, and IGF-1. Modifiable factors related to bone health include nutrition/diet, body weight, exercise, and hormonal status. These need to be maximized to optimize peak bone mass and decrease osteoporosis risks. Nonmodifiable factors include gender, ethnicity, and the person's genetic makeup, which may account for up to 70% of bone mass variance. Diet, exercise, and adequate calcium and vitamin D intake are all ways to contribute to bone health starting from birth [37]. Vitamin D deficiency and insufficiency is common in the pediatric population and contributes to more severe fractures and osteoporosis risks later in life. Healthcare practitioners should take an active role in bone health education to optimize patients' potential to reach their highest peak bone mass. Information for patient education can be found in Orthokids to help educate the community.

Author contributions

Julie Balch Samora: Writing – Review and Editing, Conceptualization. **Louise Reid Boyce Nichols:** Conceptualization, Supervision, Writing – Original draft, Writing – Review and Editing. **Timothy Hereford:** Writing – Original draft, Writing – Review and Editing. **Alec Kellish:** Resources, Writing – Review and Editing.

Declarations of competing interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: L. Reid Nichols reports a relationship with Smith and Nephew Inc. that includes speaking and lecture fees. Louise Reid Nichols reports a relationship with OrthoPediatrics that includes speaking and lecture fees. L. Reid Nichols reports a relationship with NuVasive that includes speaking and lecture fees. Editor, JPO, LRN. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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