ENDOCRINE Interhospital Conference Case 1

A 37-year-old Thai woman with low-trauma left hip fracture

- Approach Early-Onset Osteoporosis
- DMPA and Fracture Risk
- Adult-onset Hypophosphatasia (HPP)

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19 July 2024

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Conditions that Increase Risk of Osteoporosis in Younger Adults

Table 1. Conditions that Increase Risk of Osteoporosis in Younger Adults

Inflammatory/autoimmune disease
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Cystic fibrosis
- Crohn's disease
- Ulcerative colitis
- Ankylosing spondylitis

Endocrine dysfunction
- Cushing's syndrome (iatrogenic or due to organic pathology)
- Hypogonadism and functional hypothalamic amenorrhea
- Type 1 diabetes mellitus
- Growth hormone deficiency
- Hyperthyroidism
- Hyperparathyroidism
- Complete androgen insensitivity
- Subtherapeutic transgender hormone therapy

Malabsorptive disease
- Celiac disease

Psychiatric disease
- Schizophrenia
- Anorexia nervosa

Other
- Cancer and cancer-treatment
- Gastric bypass surgery
- Thalassemia
- Human immunodeficiency virus
- Systemic mastocytosis
- Solid organ or bone marrow stem cell transplant

Some causes of secondary causes of low BMD in adults

Endocrine	Nutritional conditions	Hematologic diseases	Disorders of collagen metabolism	Drugs
Hypogonadism	**Vitamin D deficiency**	**Multiple myeloma**	Osteogenesis imperfecta	**Glucocorticoids**
Hypercalciuria	Malnutrition	**Thalassemia**	Homocystinuria	**Antiepileptic drugs**
Hyperthyroidism	Malabsorption	Leukemia	Ehlers-Danlos syndrome	**Aromatase inhibitors**
Hyperparathyroidism	Gastric surgery	Lymphoma	Marfan syndrome	Chemotherapy
Cushing's syndrome	Anorexia nervosa	Mastocytosis		Immunosuppressant
DM type1, 2	**Chronic liver disease**			Depo-Provera
Acromegaly	IBD			GnRH agents
GH deficiency	Alcoholism			PPI
	Rheumatologic diseases	**Others**		TZD
	Rheumatoid arthritis	**AIDS/HIV**		
	SLE	**COPD**		
	Ankylosing spondylitis	**Organ transplantation**		
		ESRD		

- **History taking and PE**
- **Laboratory investigation**

Adapted from AACE Guidelines on Osteoporosis 2016

Fertil Steril 2008;90: 2060-7.
JBMR Plus 2022;6: e10594.

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TABLE 2

Absolute and percentage change in BMD at L1–L4 spine and femoral neck.

Endpoint	Time (h)	Adjusted group means (SE)[a] Untreated	DMPA	OC	*P* values
Spine absolute values, g/cm^2	0	0.98 (0.007)	0.97 (0.013)	1.01 (0.007)	
	6	1.00 (0.007)	0.96 (0.013)	1.02 (0.007)	DMPA vs. OC ($P=.005$)
	12	1.02 (0.008)	0.95 (0.013)	1.03 (0.008)	DMPA vs. OC ($P<.001$), DMPA vs. control ($P=.003$)
	18	1.03 (0.008)	0.95 (0.013)	1.03 (0.008)	DMPA vs. OC ($P<.001$), DMPA vs. control ($P<.001$)
	24	1.04 (0.008)	0.94 (0.014)	1.03 (0.008)	DMPA vs. OC ($P<.001$), DMPA vs. control ($P<.001$)
Spine % change, 0–24 mo	—	6.3 (0.53)	−1.5 (1.01)	4.2 (0.70)	DMPA vs. OC ($P<.001$), DMPA vs. control ($P<.001$)
Femoral neck absolute values, g/cm^2	0	0.92 (0.010)	0.92 (0.017)	0.96 (0.010)	
	6	0.93 (0.010)	0.90 (0.017)	0.96 (0.010)	
	12	0.94 (0.011)	0.90 (0.018)	0.96 (0.011)	
	18	0.95 (0.011)	0.86 (0.019)	0.97 (0.011)	DMPA vs. OC ($P<.001$), DMPA vs. control ($P=.003$)
	24	0.96 (0.012)	0.86 (0.020)	0.97 (0.012)	DMPA vs. OC ($P<.001$)
Femoral neck % change, 0–24 mo	—	3.8 (0.80)	−5.2 (1.57)	3.0 (1.02)	DMPA vs. OC ($P<.001$), DMPA vs. control ($P<.001$)

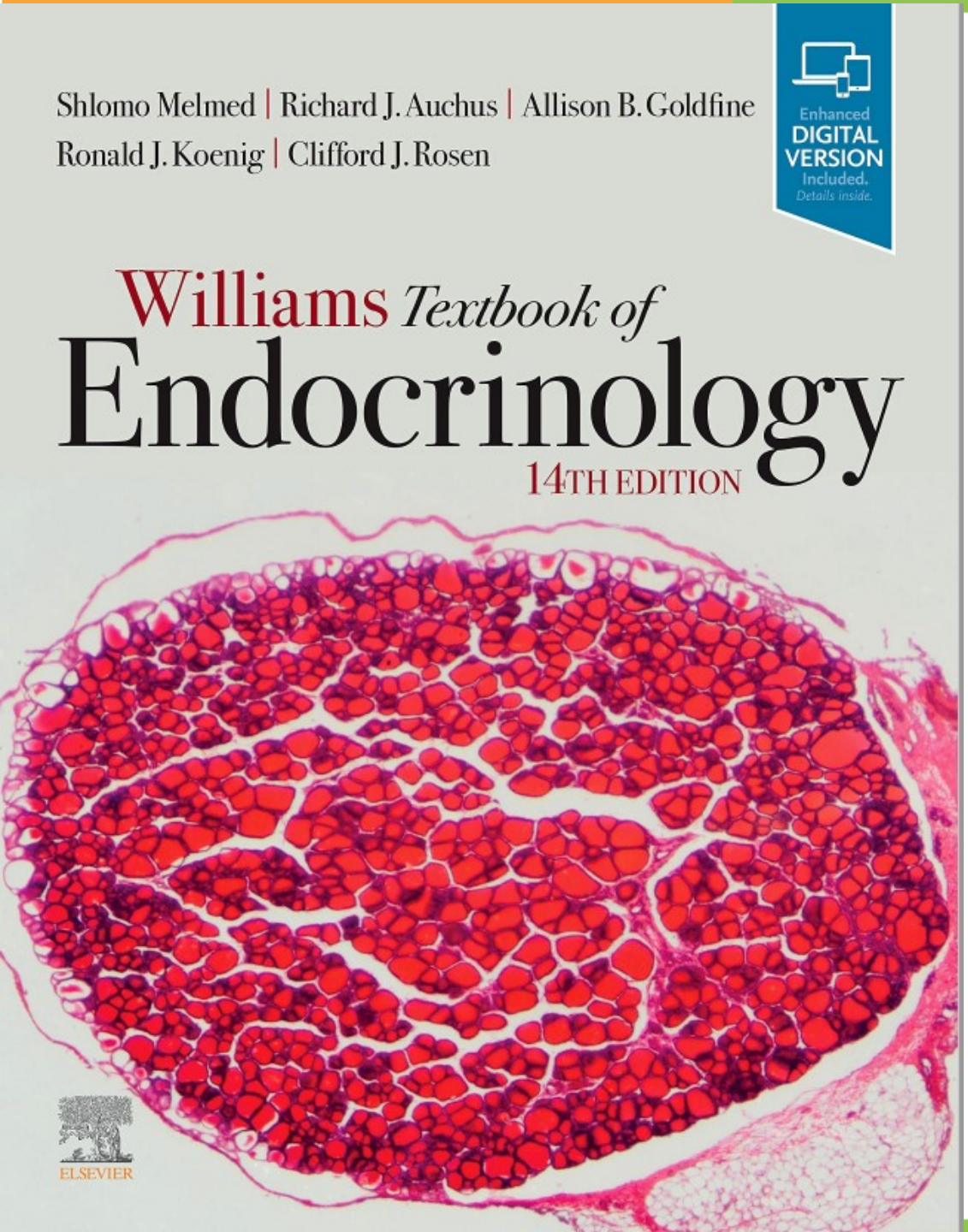
[a] Values adjusted for age, race, body weight, tobacco use, physical activity, and baseline BMD.

Cromer. Bone and contraception in adolescents. Fertil Steril 2008.

Over 24 months, mean percentage change in spine BMD was as follows: DMPA, -1.5%; OC, +4.2%; and untreated, +6.3%. Mean percentage change in femoral neck BMD was as follows: DMPA, -5.2%; OC, +3.0%; and untreated, +3.8%. Statistical significance was found between the DMPA group and the other two groups. In the DMPA group, mean percentage change in spine BMD over the first 12 months was -1.4%; the rate of change slowed to -0.1% over the second 12 months. **No bone density loss reached the level of osteopenia.**

N =58, aged 12-18 yrs

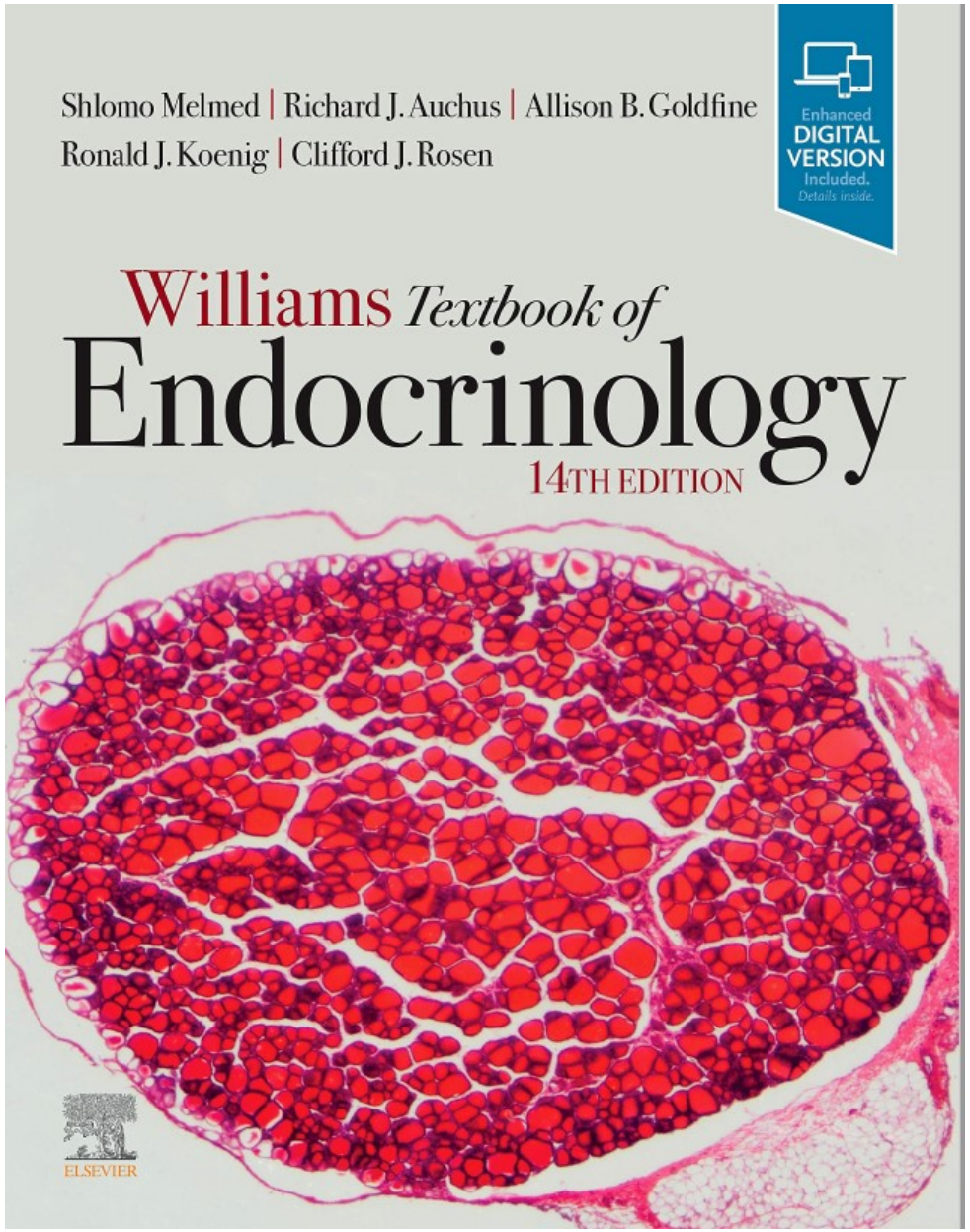
Fertil Steril 2008;90: 2060-7.
JBMR Plus 2022;6: e10594.



Injectable Contraceptives in Adolescents

Discontinuation rates for DMPA in adolescents are high, with half of adolescents discontinuing the method by 12 months.[273] However, because DMPA suppresses ovulation for an extended period of time, prior use of DMPA protects many adolescents from unintended pregnancy despite inconsistent use. Weight gain is the most commonly cited reason for adolescents to discontinue DMPA, and it may be more common in obese adolescents.[115] Although loss of bone density has been a concern in adolescents using DMPA, the position statement of the Society for Adolescent Medicine is that DMPA represents an extremely effective contraceptive, and that clinical concerns about loss of BMD must be placed within the context of likely bone recovery on discontinuation, low risk of fractures, and benefits of preventing unintended pregnancy among adolescents.[274]

Williams Textbook of Endocrinology
14th Edition 2020



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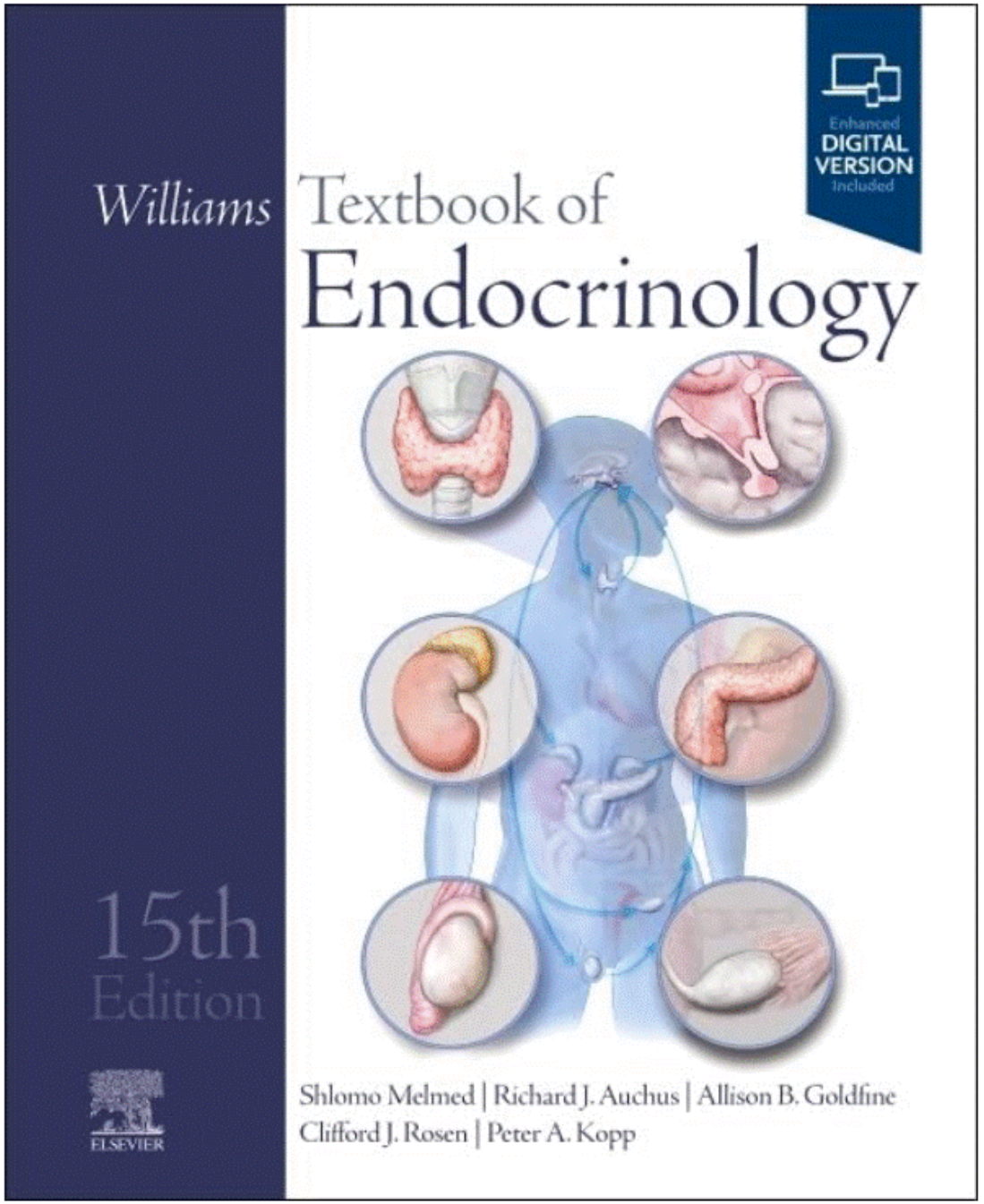

reassurance that loss of BMD associated with DMPA use is reversible. [153] [154] [155]

Changes in BMD resulting from use of DMPA are clinically important if they increase risk for fracture. No published data address whether premenopausal DMPA impacts subsequent fracture risk in postmenopausal patients. Although the association between decline in BMD and risk of fracture is well established in postmenopausal women, [156] the association is less robust in healthy premenopausal women. [132] Observational studies have mixed findings on the association of DMPA use and fracture risk in reproductive age individuals. Three observational studies used large national databases to examine the association between DMPA or LNG-IUD use and fracture. [157] [158] [159] Two of these were based on the same large UK database. [157], [158] Using case-control methods, ever users of DMPA had a higher risk of fracture compared with never users (odds ratio [OR] 1.44). [157] Using the same British database but a retrospective cohort analysis, a second group also observed DMPA users had an increased risk for fracture (OR 1.41). However, this second report noted that the elevated risk was present at baseline, *before* DMPA use; accordingly, the elevated fracture risk could not have been caused by DMPA. [158] A Danish case-control study also noted that ever use of DMPA was associated with increased risk for fracture (OR 1.44). However, the authors of this Danish report suggested the subgroup of women choosing DMPA, 0.1% of the study sample,

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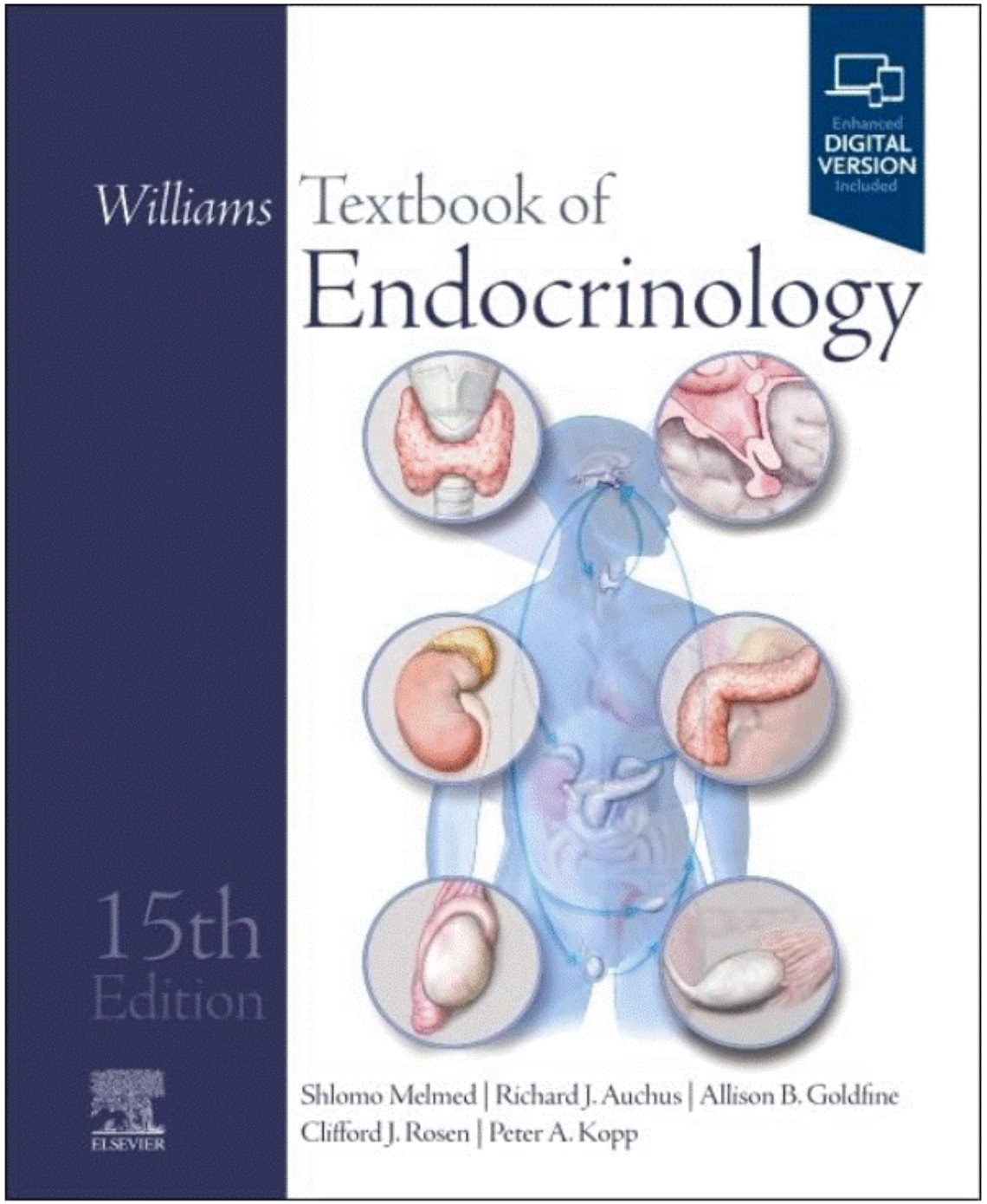

Effect on Skeletal Health

When counseling patients considering initiation or continuation of injectable contraception, clinicians should discuss the benefits and the risks of DMPA, including the FDA "black box" warning, and use clinical judgment and shared decision making to assess appropriateness of use. The effect of DMPA on BMD and skeletal health should not prevent clinicians from recommending DMPA initiation or continuing use beyond 2 years (USMEC category 2 for adolescents <18 years of age and women >45 years of age; category 1 for women age 18–45 years). [9] Routine assessment of BMD is not recommended in adolescents and young patients using DMPA. Although low-dose estrogen supplementation has been observed to limit BMD loss in adolescent DMPA users, [160] , [161] estrogen supplementation during DMPA use is not recommended because of potential adverse effects, as well as a paucity of data from clinical trials assessing skeletal health outcomes.

For patients with comorbidities and conditions that may impact skeletal health, including an elevated risk of falls, wheelchair use, chronic corticosteroid use, renal disease, or malabsorption, individualized counseling and clinical management along with shared decision making is appropriate. Age-appropriate calcium and vitamin D dietary intake, regular weight-bearing exercise, and smoking cessation should be encouraged for all patients. Although these recommendations may benefit the health of patients in general, studies demonstrating that

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BOX 16.2

Summary and Recommendations for DMPA Use

BMD, **bone mineral density;** *DMPA,* **depot medroxyprogesterone acetate;** *IM,* **intramuscular;** *SC,* **subcutaneous.**

1. DMPA is an excellent method of contraception for patients who desire a long-term, reversible contraceptive method.

2. DMPA primarily acts by inhibiting follicular maturation and ovulation through inhibition of gonadotropin secretion; it also affects cervical mucus.

3. DMPA is available in two formulations: 150 mg/1 mL for IM injection and 104 mg/0.65 mL for SC injection.

4. DMPA can be administered as long as the provider is reasonably certain the patient is not pregnant. The dose is repeated every 3 months (13 weeks), with a 2-week grace period.

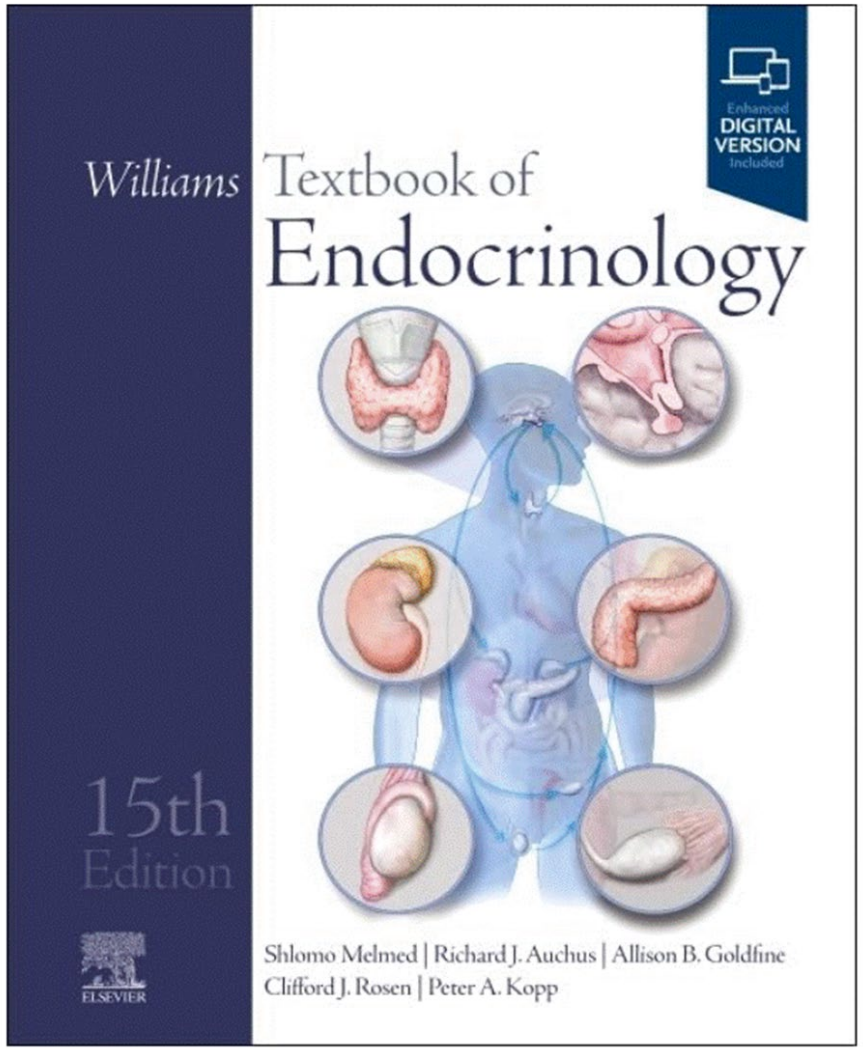
5. Although DMPA does not permanently affect endocrine function, return of fertility may be delayed.

6. Menstrual changes occur in all patients using DMPA and are the most frequent cause for discontinuation.

7. Because DMPA induces amenorrhea, it can be used for managing a variety of gynecologic and nongynecologic disorders, such as heavy menstrual bleeding, dysmenorrhea, and iron deficiency anemia.

8. There is no high-quality evidence that use of DMPA increases the risk of developing cancer, cardiovascular disease, or sexually transmitted infection. DMPA use significantly reduces the risk of developing endometrial cancer.

9. There is an association between current DMPA use and decreased BMD; losses in BMD are temporary, reverse after discontinuation of DMPA, and have not been linked to postmenopausal osteoporosis or fractures.



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Monogenetic etiologies of early-onset osteoporosis

- Young adults presenting with early-onset osteoporosis in the absence of a secondary cause may also have a primary or genetic etiology of bone fragility.
- Monogenetic or primary osteoporosis classically presents in childhood. However, clinical severity of some genetic forms of osteoporosis can be variable, and patients can have an initial presentation in young adulthood.
- In a study of 123 men and women with idiopathic osteoporosis, candidate gene sequencing identified 11 patients with rare or novel variants in *COL1A2, PLS3, WNT1, or DKK1,* plus an additional 16 patients with very rare or novel variants in *LRP5*.
- In a cohort of 75 women with idiopathic low bone mass, whole-exome sequencing identified eight subjects with heterozygous likely pathogenic variants or variants of undetermined significance in relevant genes (***LRP5, PLS3, FKBP10, SLC34A3, and HGD***).

27/123 = 22%
8/75 = 11%

JBMR Plus 2018;2:12-21.
Bone 2021;154: 116253.

Monogenetic etiologies of early-onset osteoporosis

Table 2. Frequencies and classification of rare variants and affected genes identified in LBMD study population

Pathway	Gene name	LBMD (n = 394)	
		DCV	VUS
ECM	*BMP1*		1
	COL1A1	22	4
	COL1A2	12	4
	EXT2[a]	1	
	PLOD1		1
Mineralization	*ALPL*	8	
	ENPP1	2	2
	CASR[a]	1	1
	SLC34A1		2
	SLC34A3[a]	3	
Wnt	*DVL1*[a]		1
	LRP5	17	1
	LRP6		3
	WNT1	9	
TGF-β	*FBN1*		3
	FBN2		3
	TGFBR2		1
Other	*LMNA*[a]	1	1
	NOTCH2	1	
	PLS3	4	
	ZNF469	1	
	Total	82	28
		20.8%	7.0%

Abbreviations: DCV, disease-causing variant (American College of Medical Genetics class IV and V); ECM, extracellular matrix; LBMD, low bone mass disorder; TGF-β, genes involved in TGF-β signaling.
[a]No currently known LBMD gene, but involvement in skeletal development/homeostasis.

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Clinical Research Article

ENDOCRINE SOCIETY

OXFORD

Genetic Diagnostics in Routine Osteological Assessment of Adult Low Bone Mass Disorders

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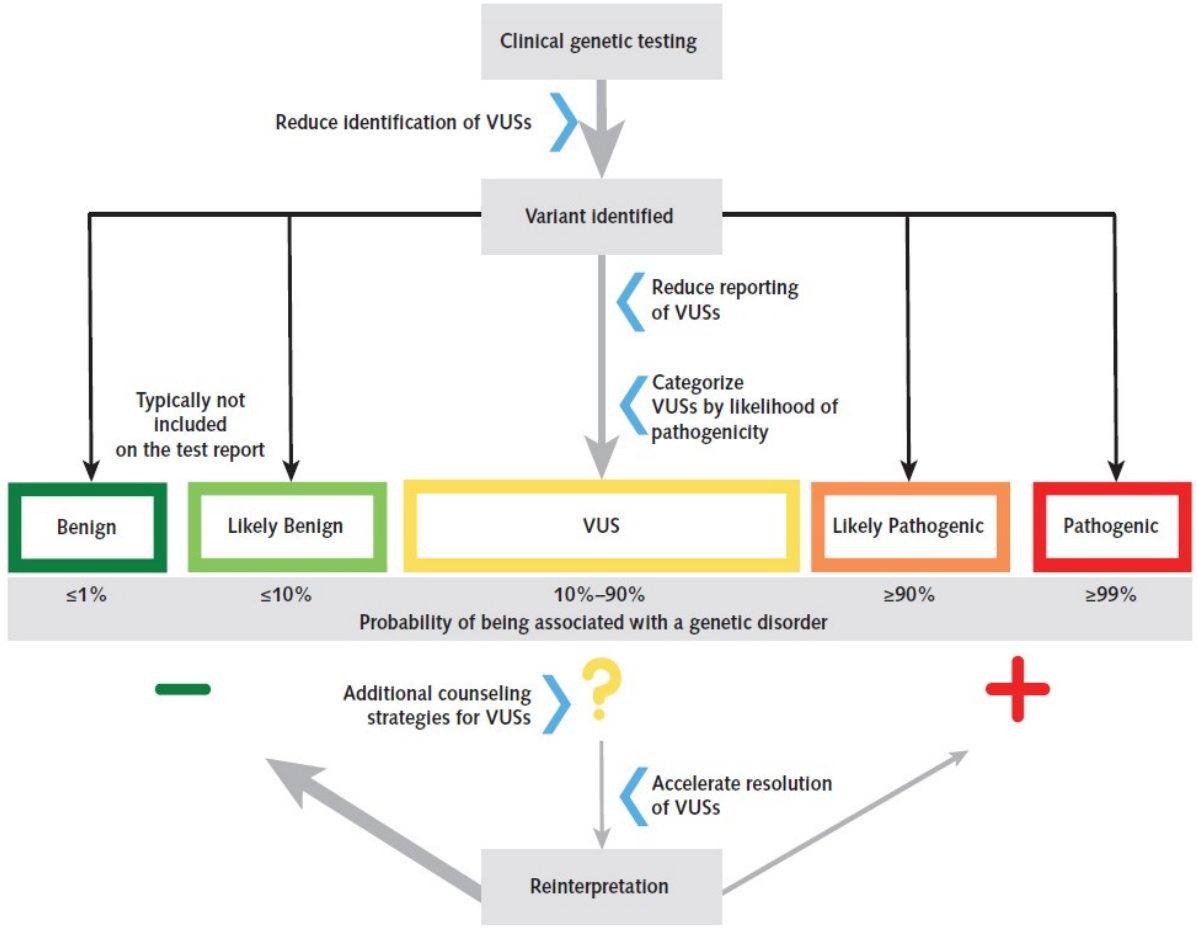
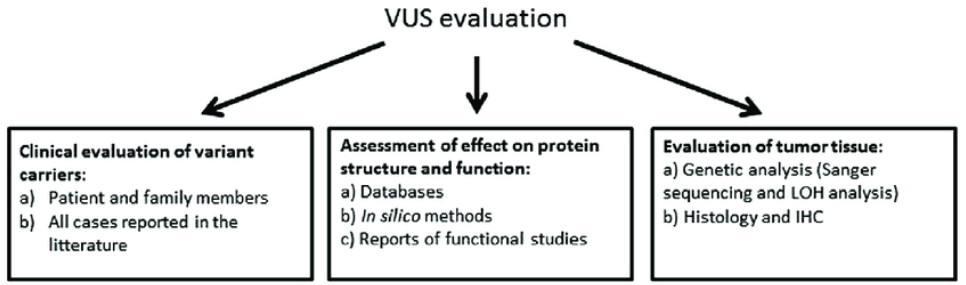
The Challenge of Genetic Variants of Uncertain Clinical Significance (VUS)

Figure. Strategies for managing VUSs identified in genomic testing.



- Pathogenic variant
- Likely pathogenic variant
- Variant of uncertain significance (VUS)
- Likely benign variant
- Benign variant



Ann Intern Med 2022;175: 994-1000.

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Adult-onset Hypophosphatasia (HPP)

- Hypophosphatasia (HPP) is an inherited condition which causes a defect in bone calcification (mineralization). It is a genetic disorder caused by mutation in the *tissue-non-specific alkaline phosphatase gene (TNSALP)*. It causes impaired bone mineralization, fractures, tooth loss, muscle weakness and possibly other adverse health outcomes.

- The role of ALP is to hydrolyze phosphomonoesters with the release of inorganic phosphate. HPP is caused by the presence of loss-of-function mutations in the *ALPL* gene, resulting in decreased enzyme activity and consequent accumulation of the natural substrates of the enzyme.

- HPP is a rare metabolic bone disease, with an estimated prevalence of between 0.3 and 1/100,000 in severe forms, and more recent reports suggesting that moderate forms are substantially more frequent. Adult forms are milder, often missed by doctors or confused with osteoporosis.

Nat Rev Endocrinol 2016;12: 233-46.

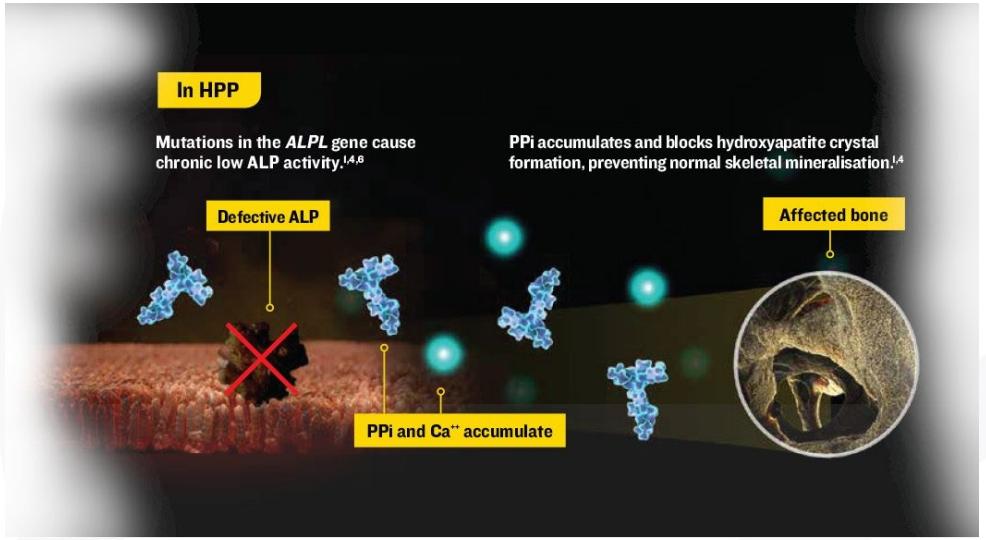
Adult-onset Hypophosphatasia (HPP)

Universiteit Leiden The Netherlands

- According to the latest update of the Leiden Open Variation Database (LOVD) web site, about 700 loss-of-function variants of the ALPL gene have been described to date.
- Plasma Pyridoxal 5´ Phosphate (PLP) concentrations, the active form of vitamin B6 and one of the main substrates of TNSALP, were the most sensitive marker to elevate in HPP.

Table 1. Clinical Types of Hypophosphatasia

Perinatal	In utero and at birth
Infantile	<6 months
Childhood/juvenile	>6 months to >18 years
Adult	>18 years
Odontohypophosphatasia (dental only)	Any age



https://databases.lovd.nl/shared/genes/ALPL

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Bisphosphonate use in patients with HPP

- In 2012, atypical femur fractures (AFF) have been reported in a patient with HPP who was treated with alendronate, suggesting that HPP may be a risk factor for this rare type of fracture, especially in the setting of treatment with a bisphosphonate.
- **HPP predisposes to AFF during antiresorptive therapy**; hence, bisphosphonates and denosumab are contraindicated in this condition. Enzyme therapy with recombinant ALP (asfotase alfa) is currently prohibitively costly.
- Treatment with anabolic bone agents such as teriparatide has been reported, but whether normally mineralized bone is formed requires further study.

J Bone Miner Res. 2012;27: 987 -94.
BMC Musculoskelet Disord 2016;17: 332.
Endocr Pract 2016;22: 941-50.
Endocrinol Diabetes Metab Case Rep 2021;2021: 21-0096.

Take Home Messages

- This case highlights the potential fracture risk from **long-term use of DMPA** in susceptible patients with pre-existing higher risk for fractures.
- Identification of rare *ALPL* VUS challenges in deciphering the clinical relevance whether this patient has adult-onset hypophosphatasia and bisphosphonate should be discontinued.
- The underrepresentation of non-European ancestry groups in current genomic databases complicates interpretation of their genetic test results.
- The patient's clinical presentation remains the most important context for interpreting sequencing results.