FROM THE EXPERTS IN ENDOCRINOLOGY

2024 ENDOCRINE CASE MANAGEMENT: MEET THE PROFESSOR

ENDOCRINE SOCIETY

FROM THE EXPERTS IN ENDOCRINOLOGY

ENDO 2024

ENDOCRINE
CASE MANAGEMENT

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ENDO 2024
CONTENTS

ADIPOSE TISSUE, APPETITE, OBESITY, AND LIPIDS

ADRENAL

BONE AND MINERAL METABOLISM

CARDIOVASCULAR ENDOCRINOLOGY

DIABETES MELLITUS AND GLUCOSE METABOLISM

GENERAL ENDOCRINOLOGY

NEUROENDOCRINOLOGY AND PITUITARY

PEDIATRIC ENDOCRINOLOGY

REPRODUCTIVE ENDOCRINOLOGY

THYROID

TUMOR BIOLOGY

APPENDIX

ENDO 2024
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2024 Endocrine Case Management: Meet the Professor Faculty

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Baylor College of Medicine

Saumya Agrawal, MD
Creighton University School of Medicine

Mona Al Mukaddam, MD, MS
University of Pennsylvania Health System

Grazia Aleppo, MD
Northwestern University

Nasreen Alfaris, MD, MPH
King Fahad Medical City

Dalal S. Ali, MD, MSc
McMaster University

Trevor E. Angell, MD
Keck School of Medicine of University of Southern California

Ambika P. Ashraf, MD
University of Alabama at Birmingham

Natalie Hecht Baldauff, DO, MBA
University of Pittsburgh Medical Center Children's Hospital of Pittsburgh

Linda A. Barbour, MD, MSPH
University of Colorado School of Medicine and Anschutz Medical Campus

Cesar Luiz Boguszewski, MD, PhD
Federal University of Parana

A. Enrique Caballero, MD
Brigham and Women's Hospital and Harvard Medical School

Frederic Castinetti, MD, PhD
Aix Marseille University

Layal Chaker, MD, PhD
Erasmus University Medical Center

Uriel Clemente-Gutierrez, MD
University of Texas MD Anderson Cancer Center

Roderick Clifton-Bligh, BSc (med), MBBS, PhD
Royal North Shore Hospital and University of Sydney

Kevin Colclough, DClinSci
Royal Devon University Healthcare National Health Service Foundation Trust

Martine Cools, MD, PhD
Ghent University Hospital and Ghent University

Kenneth Cusi, MD
The University of Florida

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Bambino Gesù Children's Hospital and Queen Mary University of London

Nancy Samir Elbarbary, MBBCh, MSc, MD, PhD
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University of Michigan

James W. Findling, MD
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Maria Fleseriu, MD
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Joseph Henske, MD
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Sasha R. Howard, MBBS, PhD
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Bernice L. Huang, MD
University of Texas MD Anderson Cancer Center

Christopher Hvisdas, PharmD
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Sean J. Iwamoto, MD
University of Colorado School of Medicine, Anschutz Medical Campus and Rocky Mountain Regional Veterans Affairs Medical Center

Malavika Kesavan, MD
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McMaster University

Alexandra N. Krez, BA
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Amanda La Greca, MD
University of Colorado School of Medicine

Carol J. Levy, MD, CDCES
The Icahn School of Medicine at Mount Sinai

E. Michael Lewiecki, MD
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Sarah E. Mayson, MD
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Alon Y. Mazori, MD
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Michael T. McDermott, MD
University of Colorado Denver School of Medicine

Moisés Mercado, MD
National Autonomous University of México

Alia Munir, MBBCh, PhD
Sheffield Teaching Hospitals National Health Service Foundation Trust

Lynnette K. Nieman, MD
National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health

Kashyap A. Patel, PhD
Royal Devon University Healthcare National Health Service Foundation Trust and University of Exeter Medical School

Robin Peeters, MD, PhD
Erasmus University Medical Center

Nancy D. Perrier, MD
University of Texas MD Anderson Cancer Center

JoAnn V. Pinkerton, MD
University of Virginia Health

Tamar Reisman, MD
Weill Cornell Medicine

Jane E. B. Reusch, MD
University of Colorado, Anschutz Medical Campus

Eyal Robenshtok, MD
Rabin Medical Center

Micol S. Rothman, MD
University of Colorado School of Medicine

Omair A. Shariq, MD, MS
Mayo Clinic

Jennifer A. Sipos, MD
The Ohio State University

Emily M. Stein, MD, MS
Hospital for Special Surgery

Anand Vaidya, MD, MMSc
Brigham and Women's Hospital and Harvard Medical School

Elena V. Varlamov, MD
Oregon Health & Science University

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ENDO 2024
OVERVIEW

OVERVIEW

Endocrine Case Management: Meet the Professor is designed to provide physicians with a concise and high-quality review of more than 40 common and rare endocrine disorders to help you keep your practice current. It consists of case-based clinical vignettes and rationales written by experts in all areas of endocrinology, diabetes, and metabolism.

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The Endocrine Society is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The Endocrine Society has received Accreditation with Commendation.

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LEARNING OBJECTIVES

Endocrine Case Management: Meet the Professor will allow learners to assess their knowledge of all aspects of endocrinology, diabetes, and metabolism.

Upon completion of this educational activity, learners will be able to:

- Recognize clinical manifestations of endocrine and metabolic disorders and select among current options for diagnosis, management, and therapy.
- Identify risk factors for endocrine and metabolic disorders and develop strategies for prevention.
- Evaluate endocrine and metabolic manifestations of systemic disorders.
- Use existing resources pertaining to clinical guidelines and treatment recommendations for endocrine and related metabolic disorders to guide diagnosis and treatment.

TARGET AUDIENCE

Endocrine Case Management: Meet the Professor provides case-based education to clinicians interested in improving patient care.

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As a provider of CME accredited by the Accreditation Council for Continuing Medical Education, the Endocrine Society has a policy of ensuring that the content and quality of this educational activity are balanced, independent, objective, and scientifically rigorous. The scientific content of this activity was developed under the supervision of the Endocrine Society's Annual Meeting Steering Committee.

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Trevor E. Angell, MD Research Investigator: Immunovant, Inc.

Ambika P. Ashraf, MD Moderator, AMRYT PES Webinar in October 2023; Consultant, BioMarin, one time commitment.

Cesar Luiz Boguszewski, MD, PhD Consulting Fee: Novo Nordisk, Ipsen; Research Investigator: Crinetics; Speaker: Ipsen, Novo Nordisk, Recordati.

Frederic Castinetti, MD, PhD Advisory Board Member: HRA Pharmaceuticals; Grant Recipient: HRA Pharmaceuticals.

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Lynnette K. Nieman, MD Grant Recipient: Crinetics Pharmaceuticals; Other: UpToDate.

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Yumie Rhee, MD, PhD Ambassador: American Society of Bone and Mineral Research; Committee: Korean Endocrine Society, Korean Society of Bone and Mineral Research; Editor: *JCEM Case Reports.*

W. Edward Visser, MD, PhD Royalties (Institution): Egetis Therapeutics

Selma Feldman Witchel, MD Editor: *Journal of the Endocrine Society, Sex Development, Steroids*; Research Investigator: Neurocrine Sciences; Contributor: UpToDate; Speaker: Canadian Society of Endocrinology and Metabolism, EndoBridge Conference.

Bu Beng Yeap, MBBS, PhD Advisory Board: Novo Nordisk, Bayer, Lilly; Research Support: Lawley Pharmaceuticals; Advisor: Lawley Pharmaceuticals; Speaker: AstraZeneca, Besins, Philippine Society for Endocrinology, Diabetes and Metabolism, View Street Medical; Past-President: Endocrine Society of Australia; Editor: *Asian Journal of Andrology, Journal of Gerontology Medical Sciences*; Editorial Board: *Journal of Gerontology Medical Sciences, Journal of Clinical Endocrinology and Metabolism, Maturitas.*

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COMMON ABBREVIATIONS

ACTH = corticotropin

ACE inhibitor = angiotensin-converting enzyme inhibitor

ALT = alanine aminotransferase

AST = aspartate aminotransferase

BMI = body mass index

CNS = central nervous system

CT = computed tomography

DHEA = dehydroepiandrosterone

DHEA-S = dehydroepiandrosterone sulfate

DNA = deoxyribonucleic acid

DPP-4 inhibitor = dipeptidyl-peptidase 4 inhibitor

DXA = dual-energy x-ray absorptiometry

FDA = Food and Drug Administration

FGF-23 = fibroblast growth factor 23

FNA = fine-needle aspiration

FSH = follicle-stimulating hormone

GH = growth hormone

GHRH = growth hormone–releasing hormone

GLP-1 receptor agonist = glucagonlike peptide 1 receptor agonist

GnRH = gonadotropin-releasing hormone

hCG = human chorionic gonadotropin

HDL = high-density lipoprotein

HIV = human immunodeficiency virus

HMG-CoA reductase inhibitor = 3-hydroxy-3-methylglutaryl coenzyme A reductase

inhibitor

IGF-1 = insulinlike growth factor 1

LDL = low-density lipoprotein

LH = luteinizing hormone

MCV = mean corpuscular volume

MIBG = *meta*-iodobenzylguanidine

MRI = magnetic resonance imaging

NPH insulin = neutral protamine Hagedorn insulin

PCSK9 inhibitor = proprotein convertase subtilisin/kexin 9 inhibitor

PET = positron emission tomography

PSA = prostate-specific antigen

PTH = parathyroid hormone

PTHrP = parathyroid hormone–related protein

SGLT-2 inhibitor = sodium-glucose cotransporter 2 inhibitor

SHBG = sex hormone–binding globulin

T_3 = triiodothyronine

T_4 = thyroxine

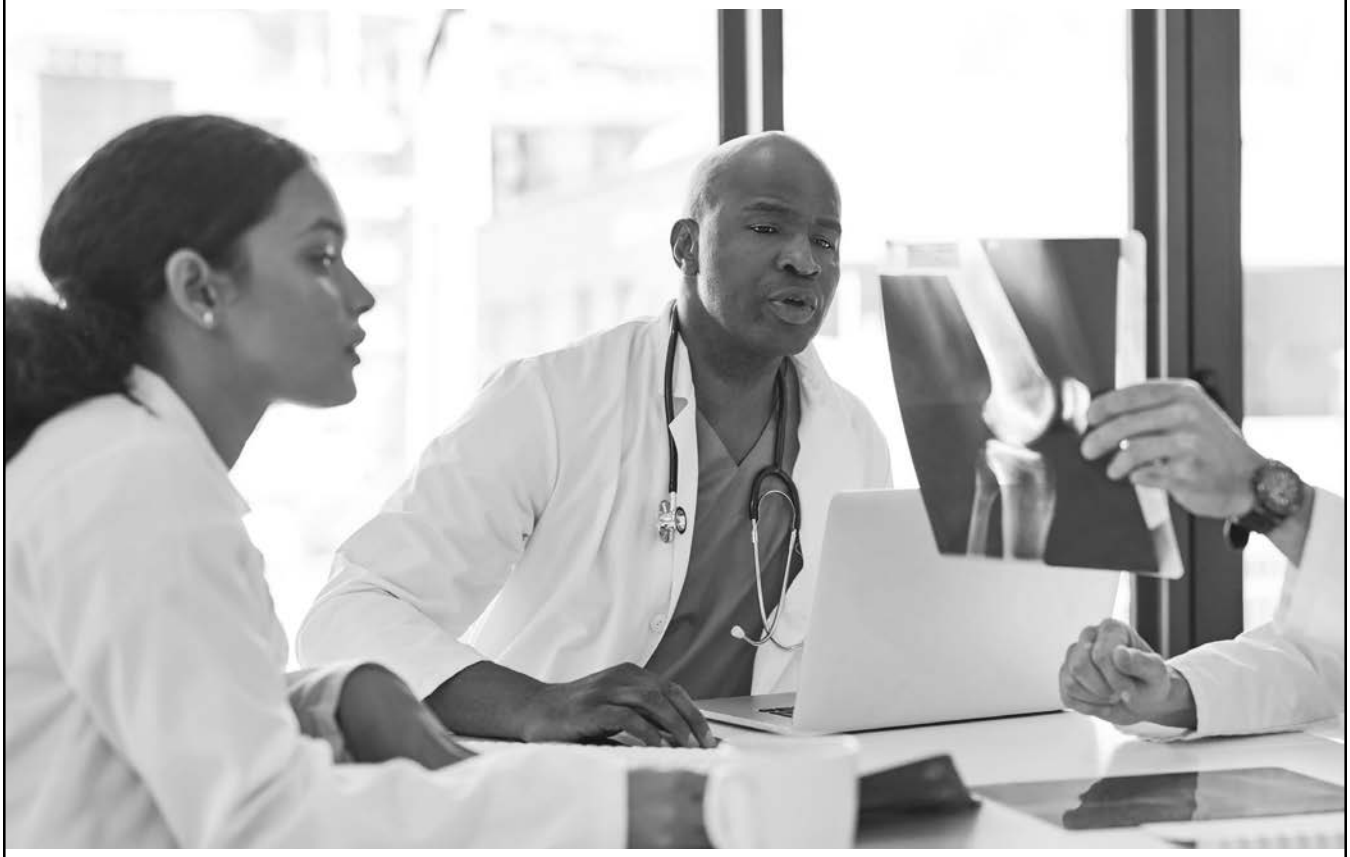
TPO antibodies = thyroperoxidase antibodies

TRH = thyrotropin-releasing hormone

TRAb = TSH-receptor antibodies

TSH = thyrotropin

VLDL = very low-density lipoprotein



BONE AND MINERAL METABOLISM

Strategies for Osteoporosis Treatment: Risk Stratification and Treatment Sequence Matter

Mona Al Mukaddam, MD, MS. University of Pennsylvania Health System, Philadelphia, PA; Email: Mona.almukaddam@pennmedicine.upenn.edu

Christopher Hvisdas, PharmD. Penn Presbyterian Medical Center, University of Pennsylvania Medical Center, Philadelphia, PA; Email: Christopher.Hvisdas@pennmedicine.upenn.edu

Educational Objectives

After reviewing this chapter, learners should be able to:

- Identify appropriate initial osteoporotic therapy based on risk stratification.
- Review evidence for sequential therapy in patients with osteoporosis.
- For patients at very-high risk, recommend osteoanabolic treatments and consider long-term treatment goals in all treatment decisions, including fracture risk reduction, bone mineral density targets, minimization of short- and long-term adverse drug events.
- Apply treatment recommendations to clinical case vignettes.

Significance of the Clinical Problem

Pharmacologic recommendations for osteoporosis treatment vary considerably based on many clinical and nonclinical factors, including individual prescriber preferences, familiarity with advanced treatment options, varying treatment guideline recommendations, global availability, and ability to overcome access issues such as cost and insurance restrictions. Many different treatment guidelines from national and international societies recommend varying approaches for medication management of postmenopausal osteoporosis. Emerging literature continues to suggest that risk stratification and pharmacologic treatment sequences matter to achieve optimal patient outcomes. However, the generalizability of guideline recommendations and lack of robust clinical data make the incorporation of individualized treatment sequence recommendations in guidelines difficult. This creates confusion among health care professionals and patients, and justifiably allows the creation of insurance compendium requirements that preferentially dictate certain therapy that may be inappropriate based on individual patient factors.

Practice Gaps

- Many initial prescribers of osteoporosis medications are not comfortable screening for, stratifying, and subsequently treating osteoporosis with advanced injectable treatments. Current guidelines do not provide specific treatment recommendations based on individual risk.
- Some clinical guidelines do not tier treatment approaches and broadly list bisphosphonates as preferred first-line treatment options even for patients with very severe osteoporosis.

Treatment considerations include severity, sequences, and impact on the next therapy.

- Overcoming insurance restrictions and tier criteria requires specialized knowledge and dedication of time to ensure appropriate treatment is received.

Discussion

Numerous postmenopausal osteoporosis guidelines exist with notable differences throughout the world. The references are not all-inclusive but demonstrate an explanation for common prescribing variance observed in clinical practice. For the purposes of this educational content, the focus will remain on 5 treatment guidelines for postmenopausal osteoporosis, including Endocrine Society, American Academy of Endocrinology (AACE), International Osteoporosis Foundation (IOF) and European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO), American College of Physicians (ACP), and Bone Health and Osteoporosis Foundation (BHOF). Other guidelines are also commonly referenced depending on the country of origin for clinical practice and specialty prescribing location but are outside the scope of the content presented herein. The *Table* (*following page*) summarizes the 5 guidelines for risk stratification from each society along with corresponding treatment recommendations.[1-5]

The importance of risk stratification is summarized in the 2019 IOF and ESCEO guidelines and for the fracture to be expressed as an absolute risk probability with occurrence over time, commonly 10 years.[5] It is important to understand that fracture risk varies by country and that multiple risk assessment tools differ in predictive value.[5]

Patient-specific properties that contribute to bone strength include bone mineral density (BMD), bone geometry and mineralization, the microarchitecture of the bone commonly assessed with trabecular bone scores, and markers of bone turnover, such as C-telopeptide (CTX). BMD correlates to fracture risk with increasing risk inversely related to decreasing BMD.[6] Assessment of bone microarchitecture requires methodologies not routinely used in clinical practice. Non-BMD factors that increase fracture risk include advancing age, sex, low BMI, history of fragility fracture or other previous atraumatic fractures, parental history of hip fracture, glucocorticoid therapy, cigarette smoking status, and alcohol use. Incorporating these risk factors independent of BMD increases the sensitivity of fracture risk assessment, which should improve and optimize treatment intervention strategies.[6] These are reflected in treatment guidelines but remain nonspecific without reference of risk factors to guide specific treatment recommendations in some guidelines.

Consider the current structure of the 5 guidelines summarized in the *Table*. Similarities and differences are observable. There is a degree of risk stratification for most guidelines; however, the definition of low vs high risk varies, as do the corresponding treatment recommendations. Currently, all but one guideline recommends denosumab as a potential first-line treatment option. ACP is the only societal organization to the author's knowledge that recommends denosumab as the preferred second-line option given risks of interruption, impacts on future treatments, and reversibility. Likewise, 3 of the 5 treatment guidelines (BHOF, IOF, ESCEO, and ACP) recommend osteoanabolic treatment as the preferred initial treatment in patients at very high risk for fracture or those with a history of osteoporotic fracture based on observed treatment differences.[2,4,5]

Multiple guidelines highlight the differences in cost-effectiveness among the agents with a note of lack of proven difference in efficacy among the major treatment options for postmenopausal osteoporosis. There are limited head-to-head comparisons of interventions which is why a resulting hierarchy of treatments has not been developed; however, data suggest treatment sequences matter.

Table. Summarized Guideline Risk Stratification and Treatment Recommendations

	Endocrine Society	AACE	IOF and ESCEO	ACP	BHOF
Date published	2020	2020	2019	2023	2022
Low Risk	• No prior hip or spine fracture • BMD T-score at hip and spine both above –1.0 • 10-year hip fracture <3% and 10-year risk factor of major osteoporotic fracture <20%	Not defined	Not defined	Baseline fracture risk assessment is based on diagnosis of osteoporosis, history of osteoporotic fractures (clinical or incidental) multiple risk factors for fractures or failure or intolerability of osteoporosis medications rather than scores from available tools	No previous spine or hip fracture; T-score at hip and spine above –1.0; FRAX below treatment threshold
Moderate risk	• No prior hip or spine fracture • BMD T-score at hip and spine both above –2.5 • 10-year hip fracture <3% and 10-year risk factor of major osteoporotic fracture <20%	Not defined			No previous spine or hip fracture; T-score between –1 and –2.5; FRAX above treatment threshold
High risk	• Prior hip or spine fracture • BMD T-score at hip and spine below –2.5 • 10-year hip fracture ≥3% and 10-year risk factor of major osteoporotic fracture ≥20%	• Lumbar spine or femoral neck or total hip T-score of –2.5 or below, or a history of fragility fracture, or high FRAX fracture probability defined as 10-year major osteoporotic fracture risk ≥20% or hip fracture risk ≥3% (nonuse regions may have different thresholds) • No prior fractures but risk factors present such as advanced age, frailty, glucocorticoids, very low T-scores, or increased fall risk			Prior spine or a hip fracture or lumbar spine or hip T-score of –2.5 or below; FRAX 10-year absolute fracture risk above the treatment threshold
Very high risk	Multiple spinal fractures and a BMD T-score at the hip or spine of –2.5 or below	Very high-risk factors include advanced age, frailty, glucocorticoids, very low T-scores, or increased fall risk		Very high risk based on older age, a recent fracture (eg, within the past 12 months), history of multiple clinical osteoporotic fractures, multiple risk factors for fracture, or failure of other available osteoporosis therapy	Multiple spine fractures/hip fracture and T-score of –2.5 or lower at lumbar spine or hip

	Endocrine Society	AACE	IOF and ESCEO	ACP	BHOF
Treatment recommendations	• Low risk: reassess fracture risk in 2-4 years • Moderate risk: reassess fracture risk in 2-4 years or bisphosphonate (oral or intravenous) • High very high risk: bisphosphonates, denosumab, teriparatide or abaloparatide, romosozumab	• Low and moderate risk: no recommendation for treatment • High risk or no prior fractures: bisphosphonates, denosumab • Very high risk or prior fractures: denosumab, abaloparatide, teriparatide, romosozumab, zoledronic acid	High risk: anabolic agent	• First-line: bisphosphonates • Second line: denosumab • Primary osteoporosis with very high risk of fracture: use romosozumab teriparatide or abaloparatide followed by a bisphosphonate	• Low and moderate risk: reassess fracture risk in 2-4 years • High risk: initial treatment with bisphosphonates or denosumab • Very high risk: teriparatide, abaloparatide, or romosozumab
Recommends bisphosphonates first line	Yes	Yes	Yes	Yes	Yes
Recommends denosumab first-line	Yes	Yes	Yes	No	Yes
Prioritizes osteoanabolic therapy as initial therapy for patients with a history of fracture or very high-risk	No	No	Yes	Yes	Yes

Treatment Sequence

Bisphosphonates are the most consistently recommended first-line therapy for postmenopausal osteoporosis treatment secondary to their broad-spectrum antifracture efficacy data. Additionally, these are the only oral medications with robust antifracture data and are often preferred by patients due to route of administration. Oral bisphosphonates are associated with limited patient and prescriber obstacles for accessing therapy such as insurance prior authorization requirements and complicated office administration billing or instructions for use. They are associated with little to no patient out-of-pocket expense. Most societal guidelines recommend bisphosphonates as first-line therapy; however, there are treatment concerns when considering long-term effects on patient care and the efficacy and safety of treatment sequence.

Bisphosphonates are embedded in the bone matrix and are associated with recirculation for many years. This recirculation impacts bone resorption, a part of the therapeutic process that PTH analogues depend on, particularly during the initial phase of anabolic therapy where biomarkers are increased. Most studies and guidelines support the finding that bisphosphonates blunt the effect of osteoanabolic therapy.[1-5] Based on the impairment of biomarkers in patients receiving PTH analogues after receiving bisphosphonates compared with PTH analogue alone, it is hypothesized that the ability of osteoanabolic medications to increase BMD optimally is reduced. Confirmation of this finding is further supported by more recent romosozumab studies, where BMD gains in the hip and spine were significantly less in patients pretreated with bisphosphonates 1 year before romosozumab initiation.[7] This finding supports the need to identify and treat appropriately selected patients with osteoanabolic medications prior to bisphosphonates but is only reflected in certain guideline recommendations.

Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor–kappa β (RANKL) that blocks osteoclast differentiation and decreases bone resorption. In the 36-month, prospective placebo-controlled FREEDOM Trial, denosumab did the following: (1) decreased CTX by 86% at 1 month and by 72% at 36 months; (2) increased BMD by 9.2% in the spine and 6.0% in the total hip; and (3) decreased fracture risk by 68% in the spine, 40% in the hip, and 20% for nonvertebral locations compared with placebo.[8] In the FREEDOM extension trial, denosumab resulted in sustained incremental increases in BMD by 22% at the spine and 9% at the total hip over 10 years.[9] After stopping denosumab, preosteoclasts rapidly mature into osteoclasts, which results in increases in bone resorption markers and is associated with BMD decline to pretreatment levels within 2 years. This increases the risk of developing vertebral fractures as evidenced by a larger proportion of patients experiencing multiple vertebral fractures upon discontinuation of denosumab (60.7%) compared with placebo (38.7%) ($P = .049$).[9,10] Bone turnover markers may remain elevated for 30 months after the last denosumab dose. This is responsible for an increased risk of multiple compression fractures between 7 and 18 months after the last denosumab dose.[10] It is important to consider the risk factors for rebound bone loss and vertebral fractures after denosumab discontinuation to individualize treatment approaches:

- Younger age
- Duration of denosumab therapy
- Greater improvement in hip BMD while on therapy
- Greater decline in hip BMD off therapy
- History of vertebral fractures
- Lower BMD at baseline
- High CTX at denosumab initiation

A history of bisphosphonate therapy prior to denosumab can decrease the degree of improvement in BMD with denosumab, which may be associated with less rebound bone loss upon cessation of denosumab. The authors' general recommendation is to consider denosumab as a second-line therapy for antiresorptive agents, particularly in younger patients, consistent with ACP guideline recommendations.

Additionally, DATA-SWITCH and romosozumab studies demonstrated that osteoanabolic therapy in patients with a high or very high fracture risk should be considered prior to or in addition to denosumab.[11-13] This is important to consider in young patients given the reversibility of the medication that would require lifelong therapy or transition to other therapy. The importance of sequences and risk of developing osteonecrosis of the jaw or atypical femoral fracture appear to be increased with cumulative exposure and length of therapy. Discontinuation of denosumab should be considered when adverse effects occur or if treatment goals are achieved but require bridge to alternative therapy to reduce the risk of rebound bone resorption and subsequent development of fractures. The optimal sequence for transition remains definitively unanswered, but existing data suggest some optimal approaches to reduce this risk. DATA-SWITCH demonstrates that the overlap of denosumab with an osteoanabolic agent likely is the most favorable approach in patients on denosumab who remain at very high fracture risk.[11] Bisphosphonates (oral and intravenous) can be effective options, especially if a course of denosumab is less than 2 years. However, in patients on long-term denosumab therapy, frequent monitoring of bone resorption markers is necessary to guide the dosing frequency of intravenous zoledronic acid.[14] Finally, low-dosage denosumab, 30 mg every 6 months over 24 months, resulted in modest improvement in spine BMD while maintaining hip BMD regardless of the therapy duration. Follow-up studies are ongoing to evaluate the efficacy of intravenous zoledronic acid following low-dosage denosumab.

Clinical Case Vignettes

Case 1

A 67-year-old woman with postmenopausal osteoporosis presents with a 6-month history of back and hip pain. The patient is concerned with preserving activities of daily living. She remains an active cigarette smoker (1 pack per day for the last 43 years). She had a myocardial infarction 10 months ago. Osteoporosis was diagnosed on her most recent DXA (*see Table*).

She previously delayed treatment with oral alendronate recommended by her primary care physician because she was concerned about adverse effects.

On physical examination, her blood pressure is 157/97 mm Hg and pulse rate is 84 beats/min. Her height is 65.7 in (167 cm), and weight is 107 lb (48.5 kg) (BMI = 17.4 kg/m^2). She has reportedly lost 2 in (5.08 cm) of height. She appears healthy and is in no apparent distress. She can easily rise from a seated position unassisted with good tandem gait with balance.

There is a history of low vitamin D and elevated alkaline phosphatase (documented 3 years ago) that normalized with vitamin D correction. Currently, calcium and vitamin D intake are adequate, and she exercises daily. She received a steroid injection for left hip pain 3 times in the last 3 years. There is no history of oral steroids, anticoagulation, thyroid medication, proton-pump inhibitors, or anticonvulsants. The secondary workup for osteoporosis and comorbid conditions was unrevealing.

X-ray reveals an L1:L2 compression fracture.

Which of the following is the most appropriate treatment recommendation for this patient?

A. PTH analogue
B. Denosumab
C. Romosozumab
D. Raloxifene

Answer: A) PTH analogue

Which of the following is the most compelling factor that supports the use of the recommended agent?

A. Compression fracture
B. Vegan diet
C. Age
D. BMD

Answer: A) Compression fracture

PTH analogues are preferred for this patient given the severity of her osteoporosis and history of compression fracture, which is the most compelling indication for therapy. The patient is treatment-naïve and as such, it is anticipated that she would get the greatest response from a PTH analogue as initial therapy. Bisphosphonates are often considered as initial therapy but would not be the preferred option due to the potential for blunting the benefits of teriparatide. In addition, this patient already experienced a compression fracture and is at very high risk for subsequent fractures. Thus, she needs optimization of treatment sequence with the most effective options. To optimally reduce her risk, it is recommended to start with the agent that would

Date/machine	Trabecular bone score (TBS)	Lumbar spine	Femoral neck	Total hip
Lunar	1.132	0.875 g/cm^2 T-score = –2.5 L1-L2 0.749 g/cm^2 T-score = –3.5 Degenerative disease L3-L4	Left 0.729 g/cm^2 T-score = –2.2 Right 0.673 g/cm^2 T-score = –2.6	Left 0.761 g/cm^2 T-score = –2.0 Right 0.704 g/cm^2 T-score = –2.4

most greatly impact BMD and with robust and timely fracture risk reduction. The VERO trial demonstrated greater fracture risk reduction and effectiveness with teriparatide compared with the oral bisphosphonate risedronate (24 months, new vertebral fractures 5.4% in teriparatide group vs 12.0% in the risedronate group (risk ratio 0.44; $P < .0001$).[15] Romosozumab could be considered; however, this patient has a contraindication to therapy given the cardiovascular event in the last 12 months. Denosumab may also be a referenced option, but it would not be the authors' preferred first-line therapy. First, DATA-SWITCH suggests that using denosumab prior to a PTH analogue will result in significant decreases in BMD. This limits the option for the next sequence of treatment. Second, the patient is young with a history of compression fractures, which places her at very high risk of rebound bone loss and development of further compression fractures with denosumab discontinuation. This is a significant concern with denosumab cessation, and hence duration of denosumab therapy would be unclear and create complications for transitions to alternative therapy.

Case 2

A 70-year-old woman with stress-induced cardiomyopathy and cardiac arrest 12 years ago presents for follow-up of postmenopausal osteoporosis. Osteoporosis was diagnosed by DXA with the lowest T-score of –2.9 at the lumbar spine and no history of fragility fractures. A PTH analogue was recommended twice, but the patient remains apprehensive of a daily self-administered injection. She also declines treatment with intravenous zoledronic acid due to concerns with intravenous infusions. Subsequently, the patient started denosumab 6 years ago. No adverse outcomes were reported, and she has been tolerating denosumab every 6 months except for a 2-month delay during the COVID pandemic and for dental work. Physical examination findings and laboratory evaluation are unremarkable. The most recent DXA (this year, after 9 doses of denosumab), demonstrates significant improvement with the lowest T-score of –2.3 at the spine, –2.2 at the left femoral neck, and –1.4 at the left total hip. She has heard about the adverse effects of osteonecrosis of the jaw and she would like to stop denosumab if possible.

How long should denosumab be continued for this patient?

A. Lifelong
B. 10 years
C. 5 years
D. Dependent on several factors

Answer: D) Dependent on several factors

The duration of denosumab therapy depends on several factors. Given results from the FREEDOM extension, there are efficacy data to suggest that treatment of 10 years (and potentially longer) is appropriate and safe. Consideration of cumulative exposure doses, as well as managing the need for invasive dental work and development of atypical femoral fracture is vital. Additionally, a system for ensuring appropriate administration and continuation of denosumab is an important aspect of management to prevent interruption or delay to avoid the risk of rebound fracture.[16] The patient is responding well to treatment overall as evidenced by no development of fractures and T-score improvement to greater than –2.5; thus, discontinuation of denosumab and transition to alternative therapy can be considered.

Which of the following would be the most appropriate pharmacological treatment option for transition?

A. Teriparatide
B. Romosozumab
C. Oral bisphosphonate
D. Intravenous zoledronic acid

Answer: D) Intravenous zoledronic acid

How often should intravenous zoledronic acid be administered?

A. Once
B. Every 12 months
C. Every 3 months
D. Dependent on monitored bone markers

Answer: D) Dependent on monitored bone markers

DATA-SWITCH demonstrates that transitioning to teriparatide is not the optimal treatment approach. Likewise, data from phase 2 and 3 studies of romosozumab suggest that after 2 doses of denosumab BMD did not decline with romosozumab, but there was a blunting in the degree of BMD improvement. No data are available regarding romosozumab after long-term therapy with denosumab. Oral bisphosphonates are a potential option, likely more effective after short-term denosumab therapy, but there is no option to adjust the frequency of bisphosphonate administration based on monitoring of bone turnover markers and subsequent elevations, which is a vital aspect of denosumab discontinuation and management. Hence, intravenous zoledronic acid is the optimal approach, as it can be given more frequently based on bone turnover markers.

Case 3

An 83-year-old woman presents for a follow-up visit for management of postmenopausal osteoporosis and low BMD. She was last seen in the office 12 months ago. She has received 2 doses of intravenous zoledronic acid over the last 2 years with reports of lower-extremity cramps 1 week after each infusion. She confirms this is tolerable and does not have concerns about continuing. The last infusion of intravenous zoledronic acid was given 11 months ago. Her lowest T-score at the time of diagnosis was –2.8 at the lumbar spine with no history of atraumatic fractures. She saw the dentist 2 months before the current visit and confirmed no plans for invasive dental work. The patient denies any concerning hip or pelvic pain consistent with an atypical femur fracture. She has a history of atrial fibrillation and developed a stroke 6 months ago and is now treated with apixaban. She remains active with physical therapy and optimizing nonpharmacological treatment recommendations, including adequate supplementation of vitamin D and calcium. Follow-up DXA demonstrates a significant decline in BMD with the lowest T-score of –3.0 in femoral neck. The patient's CTX is 1269.1 pg/mL (reference range, 104-1008 pg/mL).

Which of the following is the most appropriate pharmacological treatment option?

A. Romosozumab
B. Denosumab
C. Continuation of intravenous zoledronic acid
D. PTH analogue

Answer: B) Denosumab

Which of the following statements best supports the need to transition to alternative therapy?

A. Significant decline in BMD suggests failure of current therapy
B. Bone turnover marker is elevated suggesting bisphosphonate is not optimally suppressing bone turnover
C. The patient has not had a fracture, so is responding to therapy and does not need to switch
D. The patient is having adverse effects from bisphosphonates

Answer: A) Significant decline in BMD suggests failure of current therapy

The patient has a history of cardiovascular disease with a stroke in the past 12 months, so romosozumab is contraindicated. The significant decline in BMD suggests the failure of antiresorptive therapy, and treatment escalation or transition is required. While CTX is elevated,

these markers have not been validated to assess fracture risk and thus are not the primary reason for transition. PTH analogues will have less effect on BMD in the hip where the patient's BMD is lowest, so it would not be the optimal next step. Given her age and specific presentation, this is a scenario where denosumab is the preferred next treatment step.

Key Learning Points

- Risk stratification, future considerations, and treatment goals are important for deciding initial treatment.
- Risk factors, cost, insurance coverage, comorbidities, and patient preferences should be considered with all decisions.
- Long-term treatment goals should be considered to guide all treatment decisions.

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Primary Hyperparathyroidism in Pregnancy

Dalal S. Ali, MD, MSc. Division of Endocrinology and Metabolism, McMaster University, Hamilton, ON, Canada; Email: dalal.ali@boneresearch.ca

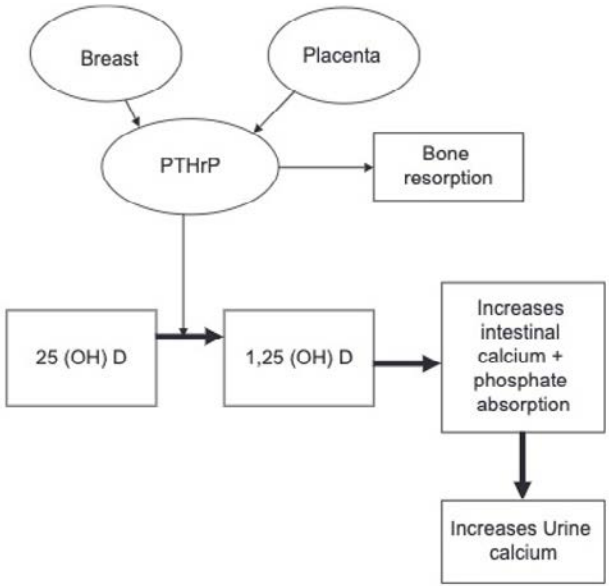
Aliya A. Khan, MD. Division of Endocrinology and Metabolism, McMaster University, Hamilton, ON, Canada; Email: aliya@mcmaster.ca

Educational Objectives

After reviewing this chapter, learners should be able to:

- Explain the changes in calcium homeostasis during pregnancy.
- Evaluate and diagnose primary hyperparathyroidism (PHPT) during pregnancy.
- Manage PHPT during pregnancy, both medically and surgically.
- List the indications for genetic testing in women of childbearing age presenting with PHPT.

Figure 1. Calcium Homeostasis During Pregnancy



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Significance of the Clinical Problem

Physiology

During pregnancy, PTH levels can decline in association with the physiological rise in PTHrP (*Figure 1*). The PTHrP level rises as early as 3 to 13 weeks' gestation and peaks in the third trimester. In pregnancies complicated by PHPT, the diagnosis is confirmed in the presence of hypercalcemia with elevated or (nonsuppressed) PTH.[1]

Epidemiology

PHPT is a leading cause of hypercalcemia in the nonpregnant population.[2] An increase in the incidence of PHPT in pregnancy was noted in a Canadian retrospective study evaluating 13,792,544 deliveries. Of these, 368 deliveries occurred in women with PHPT, representing an increase in the overall incidence of PHPT from 1.6 to 5.2 per 100,000 births ($P < .0001$) over the past 16 years.[3] Women with PHPT had a higher prevalence of comorbidities such as obesity, pregestational hypertension, and diabetes when

compared with the control group. They also had a higher rate of preterm delivery (odds ratio, 1.69; 95% CI, 1.24-2.29), preeclampsia (odds ratio, 3.14; 95% CI, 2.30-4.28), and cesarean delivery (odds ratio, 1.69; 95% CI, 1.36-2.09). Another retrospective study that included 28 pregnancies showed a higher rate of preterm delivery and preeclampsia in women with PHPT treated medically during pregnancy.[4] Infants born to mothers with PHPT were more likely to experience growth restriction (odds ratio, 1.83 [95% CI, 1.08-3.07]) and be diagnosed with a congenital anomaly (odds ratio, 4.21 [95% CI, 2.09-8.48]) as noted in one retrospective study.[3]

Practice Gaps

- Diagnosing PHPT during pregnancy and excluding familial hypocalciuric hypercalcemia (FHH) types 1, 2, and 3 requires careful evaluation.
- Diagnosing and managing PHPT in pregnancy requires close follow-up.
- Medical management of PHPT in pregnancy is currently being further studied.

Discussion

Diagnosis

The diagnosis of PHPT in pregnancy is confirmed in the presence of hypercalcemia (elevated serum ionized calcium or calcium adjusted for albumin) with a nonsuppressed serum PTH.[5] PHPT results from a solitary parathyroid adenoma in approximately 85% of cases, with hyperplasia occurring in approximately 15% of patients. Fortunately, parathyroid cancer is extremely rare.[6] In those younger than 40 years, an underlying pathogenic variant resulting in the development of PHPT is present in approximately 10% of individuals.[7] These variants may result in the development of a syndromic or nonsyndromic form of PHPT. Syndromic forms include multiple endocrine neoplasia (MEN type 1, MEN type 2A, or MEN type 4) or hyperparathyroidism–jaw tumor syndrome. Nonsyndromic forms of PHPT or isolated PHPT also require further evaluation and in particular exclusion of familial hypocalciuric hypercalcemia (FHH). FHH is considered if the calcium-to-creatinine clearance ratio is less than 0.01 in the presence of hypercalcemia and a nonsuppressed PTH. If the calcium-to-creatinine clearance ratio is inconclusive (between 0.01 and 0.02), it is important to consider other causes of a low calcium-to-creatinine clearance ratio, including vitamin D inadequacy, kidney impairment, or inadequate calcium intake. Consideration may be given to completing DNA analysis of the *CASR*, *AP2S1*, and *GNA11* genes with exclusion of the 3 forms of FHH, namely FHH types 1, 2, and 3.

Maternal and Fetal Outcomes

Pregnancy in women with PHPT may be associated with several maternal complications, including hyperemesis gravidarum, nephrolithiasis, and/or pancreatitis,[5] as well as fetal complications, including neonatal hypocalcemia (in severe cases), tetany, intrauterine growth restriction, and fetal demise.[5] Early recognition of PHPT is associated with a reduced rate of complications compared with that observed in older literature. However, medically managed PHPT still seems to be linked to an increased risk of preeclampsia and miscarriage rates. The literature reports postpartum hypercalcemic crises as a potential complication of PHPT in pregnancy, likely occurring when the active transplacental transfer of calcium from the mother to the fetus is lost after placental delivery.[8]

Management

Medical

Mild cases of PHPT in pregnancy have been reported in the literature and have been successfully managed medically. Medical management includes ensuring adequate hydration, cessation of thiazide diuretics, calcium supplements and lithium if possible, and/or

pharmacotherapy. Several pharmacological agents have been used in this context.[9] This includes calcitonin, a class B category drug that does not cross the placenta and can be used for a short duration to manage hypercalcemia.[9] Cinacalcet, a calcimimetic agent that reduces PTH secretion, has also been cautiously used in women with severe PHPT during pregnancy.[10] This is a class C category drug that crosses the placenta, and data on long-term safety in pregnancy are unfortunately lacking. Bisphosphonates (class C drug) are another category of medications used in hypercalcemia management. However, bisphosphonates carry a theoretical risk of affecting the fetal endochondral bone formation and should therefore be avoided.[9] Denosumab, a category D drug, should not be used during pregnancy due to its association with fetal skeletal adverse outcomes in animal studies.[9]

Surgical

Timely surgical intervention in the second trimester has been associated with favorable outcomes in patients with moderate to severe hypercalcemia during pregnancy (calcium adjusted for albumin greater than 11 mg/dL (>2.75 mmol/L) based on the Fifth International Workshop on the management of PHPT in pregnancy.[11] Other guidelines from Europe have a different threshold for recommending parathyroidectomy in pregnancy (calcium adjusted for albumin greater than 11.42 mg/dL (>2.85 mmol/L).[12] Surgery remains the only curative option for PHPT and is well-tolerated during pregnancy (ideally in the second trimester) with minimal adverse events. Parathyroid resection under local anesthesia may be possible to reduce risks of anesthesia-related complications during pregnancy.[13,14] Parathyroidectomy has also been reported in the third trimester in patients for whom medical therapy has failed and severe hypercalcemia is present. In such patients, surgery also appears to be safe in experienced hands with no negative maternal or fetal outcomes.[15] However, associated complications were reported in some cases, including preeclampsia, preterm labor, and severe neonatal hypocalcemia with third-trimester surgery.[15] These complications may be attributed to delayed presentation and prolonged exposure to maternal hypercalcemia.

Localization in Pregnancy

The diagnosis of PHPT is confirmed based on the biochemical profile, and imaging is only used to guide the surgical approach. Neck ultrasonography serves as the first-line imaging modality, with a sensitivity of 76% to 87% in identifying abnormal parathyroid tissue and a specificity of 94% to 96%.[5] If neck ultrasonography fails to identify a parathyroid adenoma, neck MRI[12] or CT with appropriate abdominal shielding would be appropriate.[16]

Clinical Case Vignettes

Case 1

A 30-year-old woman (G2A1L0) presents at 32 weeks' gestation with progressive leg pain of 2 months duration, and now requires wheelchair use. Her early pregnancy was complicated by nausea with intermittent vomiting. Two years ago, she presented with flank pain and a kidney stone was identified on kidney ultrasonography.

On physical examination, her blood pressure is 140/92 mm Hg and other vitals are stable. There is no cervical lymphadenopathy and there is a fullness in the left lower lobe of the thyroid. The left distal femur has a palpable, deep, soft-tissue mass that is mildly tender. The quadriceps tendon is intact. Motor examination documents 3/5 power in the left leg. The left quadriceps is tender. She has normal findings on sensory exam and musculoskeletal exam, including normal knee and hip function and intact reflexes. She has a gravid uterus.

Laboratory test results (sample drawn at admission):

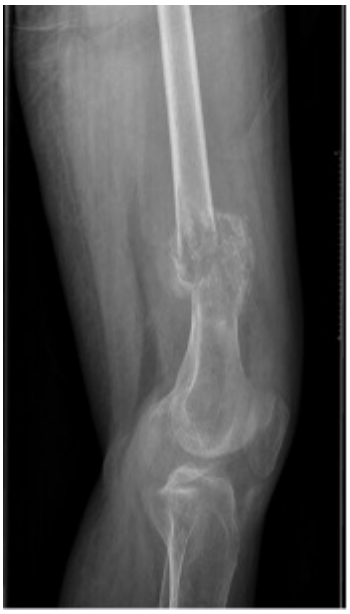
Serum-corrected calcium = 16.83 mg/dL (8.62-10.4 mg/dL) (SI: 4.2 mmol/L [2.15-2.6 mmol/L])
PTH = 1394.6 pg/mL (15-65 pg/mL) (SI: 147.9 pmol/L [1.6-6.9 pmol/L])

Estimated glomerular filtration rate = 71 mL/min per 1.73 m^2 (>60 mL/min per 1.73 m^2)
Serum alkaline phosphatase = 183 U/L (50-136 U/L) (SI: 3.06 μkat/L [0.84-2.27 μkat/L])
Serum phosphate = 3.31 mg/dL (3-4.5 mg/dL) (SI: 1.07 mmol/L [0.81-1.45 mmol/L])
Magnesium = 1.14 mg/dL (1.7-2.2 mg/dL) (SI: 0.47 mmol/L [0.85-1.10 mmol/L])
25-Hydroxyvitamin D = 14.72 ng/mL (30-50 ng/mL) (SI: 36.8 nmol/L [75-125 nmol/L])
Serum AST, normal
Bilirubin, normal

Biochemical workup for MEN type 1 is unremarkable. Genetic test results are outstanding.

Femur x-ray demonstrated a large, aggressive bone lesion within the distal femoral diaphysis, with aggressive periosteal reaction and cortical thinning of approximately 7 cm (*Figure 2*). Histopathology identifies it as a brown tumor, with additional bone lesions found on a skeletal survey involving the right shoulder, right humerus, skull, and pelvis.

Figure 2. Femur X-ray



X-ray showing large, aggressive bone lesion in the distal femoral diaphysis (brown tumor). Courtesy of Dalal S. Ali and Aliya A. Khan, McMaster University, Ontario, Canada.

Neck ultrasonography shows a TR-4 right solid and cystic neck nodule favored to represent an exophytic thyroid nodule rather than a parathyroid adenoma, TR-2. Subsequent CT neck reveals a 4-cm parathyroid adenoma with no overt malignant features.

Which of the following is this patient's most likely diagnosis?

A. Severe PHPT
B. Solid-organ cancer with bone metastasis
C. Ectopic PTH-secreting tumour
D. Milk-alkali syndrome

Answer: A) Severe PHPT

This patient's biochemical profile is consistent with PTH-dependent hypercalcemia (thus, Answer A is correct).

Case 1 (continued)

In addition to intravenous fluid hydration and discontinuation of any drugs that may contribute to hypercalcemia, which of the following is the best course of action?

A. Start calcitonin
B. Start cinacalcet
C. Start a trial of calcitonin and normalize vitamin D
D. Start intravenous bisphosphonate therapy

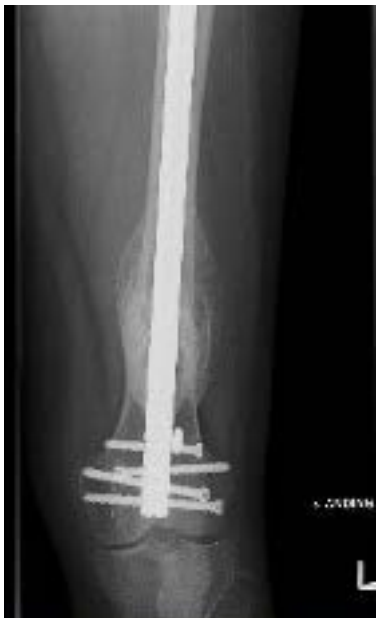
Answer: C) Start a trial of calcitonin and normalize vitamin D

Calcitonin and vitamin D supplementation (Answer C) is safe during pregnancy. Correction of vitamin D inadequacy has been associated with reduced incidence of hungry bone syndrome following parathyroidectomy.

This patient had severe PTH-mediated hypercalcemia, confirmed to be PHPT. She was treated with intravenous fluids, and calcitonin was added. Cinacalcet was introduced after an inadequate response to previous measures, with a maximum dosage of 30 mg twice daily. Subtotal parathyroidectomy was performed at 33

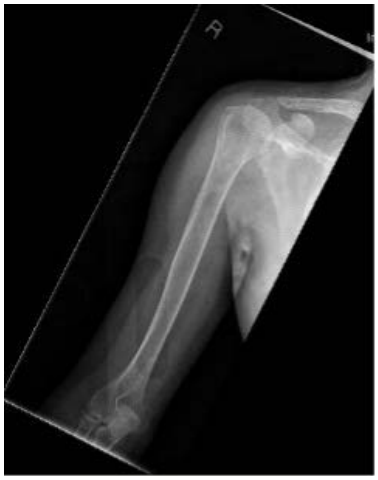
weeks' gestation. PTH dropped to 44.3 pg/mL (4.7 pmol/L) postoperatively, signifying cure. The histopathologic report was consistent with an atypical parathyroid adenoma, and there was no evidence of malignancy. After parathyroidectomy, the patient experienced premature rupture of membranes and cesarean delivery was completed at 34 weeks' gestation. On day 8 post parathyroidectomy, the patient developed hungry bone syndrome requiring calcium and vitamin D supplementation. Unfortunately, she also experienced a mechanical fall, resulting in a pathological fracture of the femur at the site of the brown tumor (*Figure 3*). *Figures 4* and *5* represent the right humeral lesion before and 6 months after parathyroidectomy.

Figure 3. X-ray After Parathyroidectomy



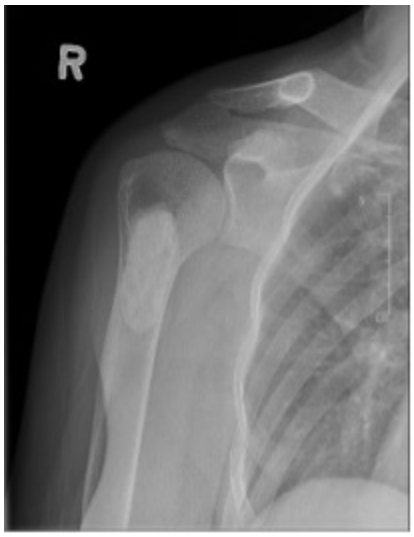
X-ray showing an intramedullary rod in the left femur. Exuberant bony callus formation in the distal diaphysis is noted with progressive bony healing. Courtesy of Dalal S. Ali and Aliya A. Khan, McMaster University, Ontario, Canada.

Figure 4. X-ray Before Parathyroidectomy



X-ray showing inhomogeneous increased density lesion in the proximal humerus, measuring approximately 5.3 × 2.2 cm. There is no obvious cortical involvement. Image courtesy of Dalal S. Ali and Aliya A. Khan, McMaster University, Ontario, Canada.

Figure 5. X-ray 6 Months After Parathyroidectomy



X-ray showing a densely sclerotic and elongated oval-shaped intramedullary focus at the level of the right humeral neck, measuring approximately 5.5 × 2 cm when compared with previous imaging, consistent with posttreatment changes with brown tumor. Image courtesy of Dalal S. Ali and Aliya A. Khan, McMaster University, Ontario, Canada.

Case 1 (continued)

Which of the following complications of maternal PHPT is a concern?

A. Post-term pregnancy
B. Neonatal hypocalcemia
C. Arrhythmias due to prolonged QT interval in the mother
D. Seizures

Answer: B) Neonatal hypocalcemia

Neonatal hypocalcemia (Answer B) can develop due to suppression of the fetal parathyroid glands in the presence of maternal hypercalcemia. The baby was admitted to neonatal intensive care with hypoparathyroidism, requiring pharmacological intervention with calcium and active vitamin D. Hypoparathyroidism resolved at 3 months of age.

Case 2

A 32-year-old woman (G1P0) presents at 27 weeks' gestation with incidental hypercalcemia and high PTH. Nausea and vomiting worsened at the 18th week of gestation. There is no end-organ involvement. Her corrected calcium is 12.18 mg/dL (3.04 mmol/L) and PTH concentration is 161.2 pg/mL (17.1 pmol/L). She is managed with intravenous fluids and remains symptomatic with no improvement in hypercalcemia.

Which additional investigations should be completed before surgery?

A. Exclusion of MEN and FHH by laboratory profile and DNA analysis
B. Sestamibi scan
C. Exclusion of MEN and FHH by laboratory profile
D. Family mapping

Answer: C) Exclusion of MEN and FHH by laboratory profile

Exclusion of familial causes of hypercalcemia is advised in young individuals.

Case 2 (continued)

Which of the following is the best next management step?

A. Surgery
B. Intravenous zoledronate
C. Cinacalcet
D. Calcitonin

Answer: A) Surgery

Parathyroidectomy (Answer A) in the second trimester is considered safe in pregnant women with severe PHPT. Parathyroidectomy was performed at 30 weeks' gestation with excellent maternal and fetal outcomes. Postoperatively, PTH dropped to 18.8 pg/mL (2.0 pmol/L), signifying cure (*Figure 6, following page*). Histopathologic findings were consistent with parathyroid adenoma. She had a spontaneous vaginal delivery at 39 weeks' gestation, and no neonatal hypocalcemia was noted. The baby was healthy and had normal APGAR scores. The biochemical workup for MEN was unremarkable, and DNA analysis is pending.

Case 2 (continued)

Which of the following complications is NOT a concern for the mother?

A. Kidney stones
B. Fractures
C. Preeclampsia
D. Basal ganglia calcifications

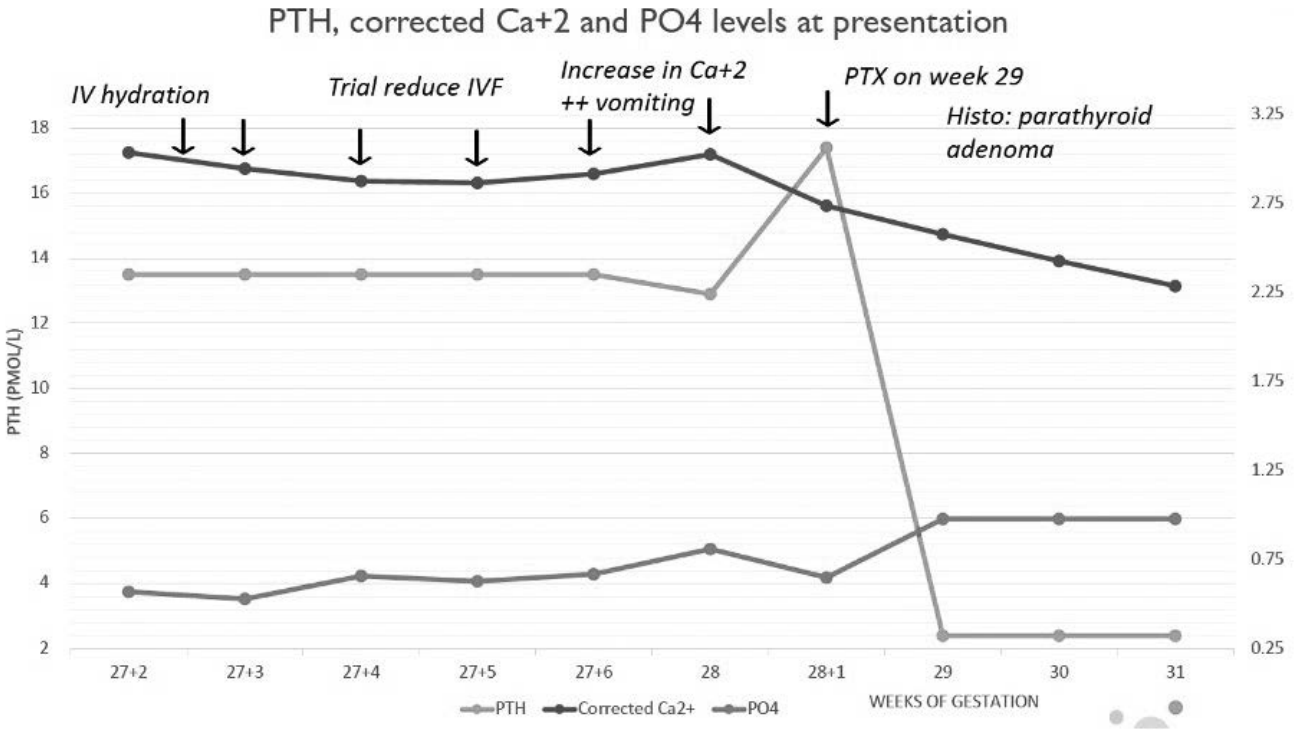
Answer: D) Basal ganglia calcifications

Basal ganglia calcifications (Answer D) are seen in hypoparathyroidism, not in PHPT.

Case 3

A 37-year-old pregnant woman (G2P1) is referred at 10 weeks' gestation for the evaluation and management of hypercalcemia in pregnancy. High serum calcium with high PTH were identified during the workup of dizziness. The

Figure 6. Patient's Laboratory Data Before and After Parathyroidectomy



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25-hydroxyvitamin D concentration was low at presentation, and she was started on vitamin D_3, 1000 IU daily. The serum-corrected calcium fluctuated between normal and mildly elevated, while the serum ionized calcium was consistently mildly elevated. Nausea was present before pregnancy, and it significantly worsened during pregnancy, with no response to doxylamine. She currently has polyuria, excessive thirst, and nocturia. She drinks almost 3 L of fluids daily. She has mild abdominal pain and constipation. There is no history of kidney stones or fractures. She has had no changes in mental status. There is no history of lithium, thiazide, or calcium supplement use. She has no family history of hypercalcemia or parathyroid disorders and has never had an emergency department visit or hospital admission for hypercalcemia.

Laboratory test results:

Serum ionized calcium = 6.2 mg/dL (4.6-5.4 mmol/L)
(SI: 1.56 mmol/L [1.15-1.35 mmol/L])
PTH = 78.2 pg/mL (SI: 8.3 pmol/L)
25-Hydroxyvitamin D = 24 pg/mL (SI: 60 nmol/L)
Urinary calcium = 230 mg/24 h (SI: 5.76 mmol/d)
Urinary creatinine = 1.1 g/24 h (SI: 9.7 mmol/d)
Magnesium = 1.87 mg/dL (SI: 0.77 mmol/L)
Phosphate = 2.2 mg/dL (SI: 0.71 mmol/L)
Estimated glomerular filtration rate = 111 mL/min per 1.73 m^2
Creatinine = 0.7 mg/dL (SI: 62 μmol/L)
Calcium-to-creatinine clearance ratio = 0.014

She is advised to increase her fluid intake and avoid dehydration. Genetic testing excludes FHH.

At 13 weeks' gestation, she starts experiencing increasing nausea and vomiting, the following laboratory values are documented:

Serum ionized calcium = 6.2 mg/dL
(SI: 1.56 mmol/L)
Serum corrected calcium = 11.9 mg/dL
(SI: 2.97 mmol/L)
Calcium-to-creatinine clearance ratio = 0.019

At what serum calcium concentration (corrected for albumin) is parathyroidectomy considered during pregnancy?

A. 13 mg/dL (3.25 mmol/L)
B. >11 mg/dL (>2.75 mmol/L)
C. 10.8 mg/dL (2.7 mmol/L)
D. >13 mg/dL (>3.25 mmol/L)

Answer: B) >11 mg/dL (>2.75 mmol/L) based on the 5th International Workshop on PHPT management

Parathyroidectomy is recommended during pregnancy, preferably in the second trimester, if the serum-corrected calcium concentration exceeds 11 mg/dL (>2.75 mmol/L) (Answer B).

Case 3 (continued)

Which of the following is the first-line imaging modality for localizing parathyroid adenomas when considering parathyroidectomy during pregnancy?

A. Neck ultrasonography
B. 4D-CT with abdominal shielding
C. Neck MRI
D. ^{99m}Tc-MIBI

Answer: A) Neck ultrasonography

Neck ultrasonography (Answer A) is the safest imaging modality during pregnancy and should be used as the first-line imaging if parathyroidectomy is being considered. Neck ultrasonography revealed no clear parathyroid adenoma in this patient, but neck MRI identified the parathyroid adenoma.

Parathyroidectomy was completed at 15 weeks' gestation. Histopathology was consistent with right lower lipoadenoma. Postoperative PTH dropped to 22.6 pg/mL (2.4 pmol/L), signifying cure, and the following laboratory values were documented:

Serum ionized calcium = 5.2 mg/dL (SI: 1.29 mmol/L)
Serum corrected calcium = 9.42 mg/dL (SI: 2.35 mmol/L)
Serum phosphate = 4.03 mg/dL (SI: 1.3 mmol/L)

Key Learning Points

- Medical management of PHPT in pregnancy is limited to hydration and calcitonin with close monitoring. There is limited evidence regarding the use of cinacalcet in pregnancy.
- Parathyroidectomy is well-tolerated in the second trimester of pregnancy in women with severe PHPT.
- Imaging options prior to surgical intervention for PHPT in pregnancy include neck ultrasonography, MRI, or CT with proper abdominal shielding.

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Osteoporosis in Underserved Populations

E. Michael Lewiecki, MD. University of New Mexico Health Sciences Center, Albuquerque, NM; Email: mlewiecki@gmail.com

Micol S. Rothman, MD. University of Colorado School of Medicine, Aurora, CO; Email: micol.rothman@cuanschutz.edu

Educational Objectives

After reviewing this chapter, learners should be able to:

- Identify disparities in the management of patients with osteoporosis.
- Recommend strategies for identifying and treating patients in underserved populations who are at high risk for fracture.

Significance of the Clinical Problem

Osteoporosis is a chronic systemic skeletal disorder characterized by low bone mineral density (BMD) and poor bone quality that results in loss of bone strength and increased risk of fractures. The consequences of fractures include chronic pain, impaired quality of life, loss of independence, and death. The global burden of osteoporosis and related fractures is vast and increasing, in large part due to aging of the population, with marked differences among world regions, countries, and population groups within countries. It is estimated that more than 200 million women have osteoporosis worldwide and that about 10 million adults in the United States have osteoporosis.

Despite the availability of excellent tools to assess fracture risk and many approved medications to reduce fracture risk, most patients at risk for fractures are not recognized and not treated. This large treatment gap constitutes a global crisis in the care of patients with osteoporosis.

Practice Gaps

- NonWhite women with osteoporosis are undertreated due to underuse of diagnostic services and potential bias in fracture risk assessment tools.
- Treatment of osteoporosis is low in populations with low income and low levels of education.
- Transgender and gender-diverse (TGD) individuals may be at risk for low BMD and may not receive appropriate skeletal health care screenings.

Discussion

Many factors contribute to the osteoporosis treatment gap, including fear of drug adverse effects, poor understanding of the balance of benefits and risks with treatment, poor appreciation of the potentially serious consequences of fractures, failure to recognize that a prior fracture is due to osteoporosis, conflicting clinical practice guidelines, limited available time for physician-patient encounters, and competing health care priorities. The gap in osteoporosis care is especially large in nonWhite women and in populations that are underserved due to factors