

# OSTEOPOROSIS AND OSTEOPENIA IN PREMENOPAUSAL WOMEN: A REVIEW OF RISK FACTORS AND MANAGEMENT CONSIDERATIONS FOR THE CHIROPRACTOR

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## ABSTRACT

**Objective:** In the United States, Doctors of Chiropractic (DCs) are healthcare providers who may manage patient with osteoporosis or osteopenia. Many physicians are familiar with management approaches pertaining to postmenopausal osteoporosis, but the evidence available for premenopausal osteoporosis and osteopenia are limited. This review aims to provide an overview of prevalence, diagnostic strategies, risk factors and management considerations for premenopausal females as relevant to DCs.

**Methods:** A search of the PubMed database from January 1, 2003 to December 31, 2019, was conducted using search terms osteoporosis, osteopenia, and premenopausal women. Additional searches were performed as necessary for supplementary information regarding interventions. Data were synthesized based on content relevant to chiropractic practice and presented as a narrative review.

**Results:** Dual-energy x-ray absorptiometry (DXA) screening is indicated in cases of fragility fracture or significant secondary causes of low bone mineral density in the premenopausal population. For women that are 30-40 years old, perhaps 0.5% have DXA scores consistent with osteoporosis and 15% with osteopenia. Of these cases, 50-90% are influenced by genetic predisposition, increased age, low weight and body mass index, malnourishment, medication use, and related systemic diseases impacting nutrient metabolism, hormone regulation, and autoimmune inflammatory conditions. Management of osteoporosis and osteopenia in at-risk premenopausal women includes referral for primary systemic diseases requiring medical intervention, conservative management targeting nutritional treatment

and lifestyle recommendations critical to bone health, and referral for DXA screening and pharmacological interventions as indicated.

**Conclusion:** There is currently limited evidence regarding osteoporosis and osteopenia in premenopausal women. DCs can employ diagnostic strategies and conservative management strategies, some of which may decrease the risk of development or progression of osteoporosis and osteopenia in this population. The use of conservative strategies for co-managing secondary causes may have the potential to improve long-term management of these conditions. (*J Contemporary Chiropr* 2020;3:64-74)

**Key Indexing Terms:** Osteoporosis; Osteopenia; Premenopausal; Chiropractic; Nutrition; Prevention

## INTRODUCTION

Osteoporosis, a systemic skeletal disease affecting bone infrastructure, results in gross decline of bone mineral density and leads to increased risk for bone fragility and subsequent fracture. An estimated 200 million people worldwide had osteoporosis in 2017, including 54 million men and women in the United States. Current estimates place half of Americans older than 50 years at risk for osteoporotic fractures with economic impact projected to reach over \$25 billion annually by 2025. (1)

In the United States, Doctors of Chiropractic (DCs) are among the healthcare providers who manage patients with osteoporosis. In a 2015 survey conducted by the National Board of Chiropractic Examiners, 72% of chiropractors report co-managing osteoporosis or osteomalacia with other healthcare professionals. Of these cases, an approximate 37% were initially diagnosed by the DC. (2)

Currently, osteoporosis research focuses predominantly on morbidity and mortality associated with pathologic fractures in postmenopausal and geriatric female

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populations. However, since the literature available on osteoporosis, and its precursor osteopenia, in the premenopausal female population is modest at best, DCs may not be familiar with this material. Premenopause encompasses the time between menarche and menopause, and is inclusive of perimenopause, which is the 5-7 years immediately preceding menopause. There are 2 main transitions associated with perimenopause. The first transition is into perimenopause and occurs at an average age of 447 and is associated with fluctuations in follicle-stimulating hormone (FSH) and an increased variability in menstrual cycles. The second major transition in perimenopause occurs at an average age of 49 and typically occurs with the first missed period and a consistent elevation of FSH. A woman is considered to be in menopause 1 year after the first missed period. On average, this will occur at age 51 and is accompanied by high FSH, low estrogen, and low progesterone. (46) This review aims to provide an overview of prevalence, diagnostic strategies, risk factors and management considerations for premenopausal females as relevant to a DC.

## METHODS

A search of the PubMed database of a 16-year period from January 1, 2003 to December 31, 2018, was conducted using search terms osteoporosis, osteopenia, and premenopausal women. Papers limited to the English language were included that addressed prevalence, diagnosis and/or management relevant to primary or secondary osteoporosis or osteopenia, where premenopausal women were included. Additional searches were performed as necessary for supplementary information regarding interventions. Data were synthesized based on content relevant to chiropractic practice and presented as a narrative review. One author performed the initial search regarding premenopause and osteoporosis or osteopenia. Additional searches were performed for each risk factor with insufficient management recommendations, as determined by the study team. These searches were again performed using the search terms osteoporosis, osteopenia, premenopause, and included a fourth search term for the individual risk factor of interest. Articles were included if they contained content that was pertinent to chiropractic practice.

## RESULTS

The PubMed search identified 17 papers that included, at least in-part, premenopausal subjects. Additional searches for specific conditions and interventions identified an additional 28 papers. The results of the papers are summarized by topic below.

## DISCUSSION

### Prevalence

Studies have shown that premenopausal women lose between 0.25- 1.6% of their bone mineral density (BMD) per year, whereas on average approximately 10% of BMD is lost during the transition to menopause. (3) Using dual-energy x-ray absorptiometry (DXA) T-score criteria, 0.5% and 15% of women aged 30-40 years old fulfill the criteria for osteoporosis and osteopenia respectively, and it is estimated 30-50% of those 50 years or older have osteoporosis. (3,4)

### Pathophysiology

Studies investigating causative factors for the pathophysiologic process of osteoporosis and osteopenia in premenopausal women are limited. Postmenopausal osteoporosis has been well described, with estrogen deficiency being a large contributory factor in the pathogenesis of the condition. (3) Multiple primary and secondary risk factors that could contribute to the development and severity of osteoporosis or osteopenia in the premenopausal population have been identified, but the data is still limited.

### Risk Factors (summarized in Table 1)

#### *Heredity*

Acquisition of peak bone mass may be up to 80% attributable to genetic predisposition. (5) This has been documented in twin and family studies, where parallel deficiencies impacting processes integral for bone formation, such as vitamin D receptor genes, estrogen receptor genes, collagen type-1 alpha-1 genes, and the genes responsible for regulation of growth hormone/insulin growth factor-1 (IGF-1), have been observed. (6) Additionally, white and Asian individuals are at a higher risk of developing osteoporosis compared to black individuals. (7) It is important to discuss family history of osteopenia and osteoporosis at patient intake to assess genetic predisposition. For women, peak bone mass is achieved in the lumbar spine between 33 and 40 years of age, and in total hip between 16 to 19 years of age (7) Following the attainment of peak bone mass, it is estimated that premenopausal women lose 0.25-1.6% of BMD per year. (40)

#### *Age, Weight, Body Mass Index (BMI)*

There is a strong association between decreased BMD and increased age, low weight and low BMI, particularly in the geriatric female population. Lifestyle factors, such as nutritional status and lack of physical activity, could negatively influence hormone levels and consequently have negative implications on bone modeling and remodeling at an early age, predisposing young adults to bone fragility. In a 2018 study, low total lean mass had a strong positive correlation with lowest BMD

levels amongst premenopausal women with rheumatoid arthritis. (8)

#### *Dietary and Nutritional*

Calcium, vitamin D, and protein are critical to the maintenance of bone density. If one or multiple of these nutrients are deficient over a long period of time, this may have deleterious effects on bone integrity.

- Calcium

Calcium is predominantly stored in bone and largely impacts bone strength and bone remodeling processes. (9) The body tightly regulates serum calcium levels; therefore, it is very unlikely for one to have overt serum calcium deficiency. If substantial calcium deficiency is suspected, a serum calcium laboratory test corrected for albumin may be ordered. Calcium is either bound to albumin or exists as ionized calcium. If albumin levels are low, calcium levels could incorrectly appear to be low as well. (10)

An efficient means to assess daily intake is through a Food Frequency Questionnaire (FFQ), which may be done via online or written formats. When researchers compared 3-day food diaries to both an online FFQ and a written calcium FFQ, online FFQ and written FFQ reported a difference in intake <70mg/day and approximately 190mg/day, respectively. (11) The intentional brevity of questionnaires poses limitations to data collections, with 3-day journaling allowing for reporting of more foods compared to questionnaires.

- Vitamin D

In addition to calcium, vitamin D has a key regulatory role in many bone mineralization and remodeling mechanisms. Vitamin D is essential for the absorption of calcium and phosphates in the gastrointestinal tract, as well as the reabsorption of calcium at the kidneys. Serum 1,25(OH)D is an appropriate laboratory test when a vitamin D deficiency is suspected. A 2011 report from the Institute of Medicine indicated optimal serum 1,25(OH)D levels vary, with one half of the population having optimal vitamin D status at 40nmol/liter and the other half having optimal status at 50 nmol/liter. (12) In 1 study, serum 1,25(OH)D levels below 50 nmol/liter were measured in 87% of 153 Bangladeshi premenopausal garment factory workers. (13) It is important to note that aside from a potential effect on BMD, low levels of vitamin D have also been associated with decreased muscle strength and increased risk of falls, which can additionally increase an individual's risk of fracture. (9)

- Protein

Protein intake impacts bone maintenance and remodeling through regulation of insulin growth factor-1 levels. (14) Although protein plays a key role in bone mineral density maintenance, studies assessing the optimal amount for bone health are inconclusive. For this reason, the National Osteoporosis Foundation recommendations do not include increase in protein consumption above standard clinical guidelines as a standard care protocol. (15) If patients have multiple risk factors or dietary protein intake is of concern, the Food Frequency Questionnaire has been shown to be moderately correlated with true protein intake. (16)

#### *Anorexia Nervosa (AN)*

AN is a mental health disorder in which an individual significantly restricts food intake. It typically affects individuals in adolescence, when peak bone mass is attained. The food restrictions involved with AN can lead to deficiencies in vitamins, minerals, and hormones that have a direct influence on BMD. One study investigated BMD in 130 women diagnosed with AN and found 92% were osteopenic per the World Health Organization's definition, and almost 40% were osteoporotic. (6) In cases where AN is known or suspected, it is imperative to refer to a qualified mental health provider and dietary specialist for treatment and management. Depending on severity, BMD monitoring can be done initially through serum assessment of critical nutrients in bone remodeling processes known to be impacted by malnutrition, including: serum 1,25(OH)D, alkaline phosphatase (ALP), serum calcium, serum phosphate, intact parathyroid hormone (iPTH), thyroid stimulating hormone (TSH), FSH and estradiol. If fragility fracture has occurred or is of significant concern, a DXA can be performed and a primary care practitioner may consider recombinant IGF-1 and hormone replacement therapy. (4)

#### *Medication*

- Glucocorticoids

Glucocorticoids impact bone by disrupting reproductive hormone production and inhibiting osteoblasts and calcium absorption. Glucocorticoids are prescribed for many inflammatory conditions, some of which (e.g. inflammatory bowel disease and rheumatoid arthritis) are also risk factors for osteoporosis and osteopenia. Studies have demonstrated a rapid decrease in BMD 3-6 months after initiation of glucocorticoid medication, with one study supporting a relationship between higher dose and increased risk of fracture. (17) There is currently no standard to assess the risk of decreased BMD with glucocorticoids use in a premenopausal population. The American College of Rheumatology recommend premenopausal females of childbearing potential

taking at least 7.5mg of prednisone or equivalent per day for 3 months or longer, should be considered for adjunctive bisphosphonates therapy to prevent drug-induced osteoporosis. (17) Limited evidence is available to support reversal of bone loss, further emphasizing the need for adjunct preventative treatment. This is of particular concern if the course of treatment is expected to exceed 3 months.

- Depot Medroxyprogesterone Acetate (DMPA)

DMPA is an injectable form of contraception composed solely of progestin, and acts by inhibiting gonadotropin secretion leading to low levels of estrogen, with increased bone turnover as a possible side effect. (18) The National Osteoporosis Foundation's implementation recommendations cite multiple studies that indicate a consistent negative impact on bone with the use of DMPA (5), with one study observing a dose-response relationship with DMPA and BMD changes. (19) DMPA use is not an indication for DXA screening unless accompanied by other significant secondary causes of osteoporosis, osteopenia, or past or present fragility fracture. Osteoporosis risk factors and estrogen levels should be assessed when considering injectable contraception, particularly in adolescents and premenopausal women, until more research is conducted.

- Antiepileptic drugs (AEDs)

AEDs have been associated with decreased vitamin D levels, specifically carbamazepine and phenobarbital. In one population study, 41% of the 46 premenopausal participants taking AED, demonstrated decreased bone mineralization with 12 and 7 having osteopenia and osteoporosis respectively. When analyzing all 130 subjects in the study regardless of menopausal status, those who had been undergoing treatment >25 years had a 2.1 odds of developing an abnormal BMD. (20) Due to the risks associated with vitamin D deficiency in populations prescribed AEDs, dietary or supplemental interventions should be employed as indicated. If patient has multiple additional risk factors for osteoporosis or osteopenia, DXA may be considered (10).

- Proton-Pump Inhibitors (PPI)

PPI use changes the pH of the stomach and can lead to calcium malabsorption and impact BMD. Evidence has shown a 20% increased risk of hip fracture, regardless of duration of PPI use, and a dose-dependent response with up to a 30% increased risk of hip fracture at the highest PPI dosage. (21) No standard is established for screening or monitoring BMD in patients currently on PPIs, but cumulative risk and benefit of the individual patient should be considered before starting this course

of treatment. Dietary calcium intake should be assessed in those taking PPIs.

### *Gastrointestinal Disorders*

- Celiac Disease (CD)

CD is an autoimmune condition where the body attacks cells of the intestinal lining in the presence of gluten, leading to malabsorption of key nutrients needed for bone remodeling processes. One study revealed 3.4% of 266 patients with osteoporosis, compared to 0.2% of controls, tested positive for CD via endoscopic biopsy. The severity of osteoporosis in those subjects with diagnosed CD correlated with anti-tissue transglutaminase levels ( $R^2 = 0.37$ ). (22) Positive testing for antigliadin, antienomysial, or transglutaminase antibodies should increase suspicion of CD, with upper GI biopsy demonstrating atrophic villi being gold standard for diagnosis of the disease. Adherence to a strict gluten-free diet is the only therapeutic approach for CD. Nutrient deficiencies due to malabsorption that have been identified through appropriate laboratory testing should be corrected through dietary intake or supplementation as indicated.

- Irritable Bowel Disease (IBD)

Those with IBD, which includes Crohn's disease and ulcerative colitis (UC), are at a higher risk of osteopenia and osteoporosis due to decrease absorption of calcium, increased osteoclastic activity, and the increased use of glucocorticoids when symptomatic. (23) When compared to controls, patients with UC and Crohn's disease had an increased odds, 14.93 and 24.38 respectively, of having osteopenia (24). A population study looking at osteoporosis in 1230 patients with pre-existing IBD showed a small, but statistically significant increased risk of having osteoporosis at the lumbar spine, femoral neck, trochanter or total hip (OR, 1.20; 95% CI, 1.02-1.40). (23) Standard laboratory tests for IBD are anti-saccharomyces cerevisiae antibody test for Crohn's disease and perinuclear anti-neutrophil cytoplasmic antibody test for UC. It is particularly important to assess and treat underlying vitamin D deficiency and be aware of those taking glucocorticoids for medical management of either condition.

### *Endocrine Disorders*

- Hypogonadism

Estrogen and estradiol play a significant role in bone homeostasis and deficiency at a young age and can significantly impact an individual's ability to obtain optimum peak bone mass. (25) Estrogen deficiency is common in conditions like AN, Turners Syndrome, and primary ovarian insufficiency. Laboratory tests which include FSH and estradiol panel along with serum

calcium, should be considered if hypogonadism is suspected. Referral of a patient with hypogonadism to an endocrinologist is appropriate, as estrogen therapy may be considered to ensure optimal peak bone mass for adolescents or for bone maintenance for young adult and middle-aged women. (25)

- Hyperthyroidism

Hyperthyroidism can result in increased activity of osteoclasts and osteoblasts, resulting in an estimated decrease of 10-30% in BMD. (10) A meta-analysis demonstrated decreased BMD scores in the spine of patients with untreated hyperthyroidism, while those who underwent pharmacological treatment had increases in BMD that reached normal levels after 1 year. (26) In 1 study, the 10-year fracture risk in premenopausal women with subclinical hyperthyroidism was significantly higher than controls. (27) If hyperthyroidism is suspected or present, refer to endocrinologist for co-management and assess other associated nutritional deficiencies.

- Hyperparathyroidism

Hyperparathyroidism can result in increased bone resorption and typically presents with osteoporosis of the distal radius. (28) When assessing DXA scores, it is advised to use the t-score as it will reflect difference from peak bone mass. (28) Parathyroid hormone (PTH) should be run concurrently with serum calcium and serum phosphate to assess parathyroid function. Co-management with an endocrinologist is advised, along with increased dietary intake or exogenous supplementation of calcium and phosphate as indicated.

- Growth Hormone (GH) deficiency

GH impacts bone growth and remodeling through hepatic production of IGF-1 (25). A six-year randomized controlled trial investigating GH therapy in children born small for gestational age, observed lower IGF-1 levels and lumbar spine BMD at baseline, with both measurements increasing significantly in the treatment group at the end of the trial ( $p < 0.001$ ). (29) Laboratory testing showing GH hormone deficiency should be followed by a GH stimulation test. If deficient levels persist following exogenous stimulation, primary GH deficiency is likely. Referral to an endocrinologist is appropriate in these instances.

- Diabetes Mellitus Type-1 (T1DM)

T1DM is traditionally a childhood disease and can present with a concurrent decrease in IGF-1 levels and significant increase in GH secretion, negatively impacting BMD. In a 2017 meta-analysis, subjects with T1DM had a 0.055 g/cm<sup>2</sup> lower BMD of the femoral neck compared to controls. (30) In a 2014 study, increased

levels of Hemoglobin A1c (HbA1c) were correlated with decreased levels of osteocalcin, a marker of bone formation. (31) Poorly controlled T1DM in adolescence, resulting in higher HbA1c levels, can have a negative impact on the individual's ability to reach optimal peak bone density. (25) It is important in this population to maintain controlled HbA1c levels through medication management provided by endocrinologist or primary care provider and education on dietary approaches to proper glucose management.

### *Inflammatory Diseases*

- Rheumatoid Arthritis (RA)

RA is an autoimmune condition which involves an inflammatory process in which synovial tissue attaches to bone surfaces surrounding joints and creates pannus. Although the mechanism of bone loss with RA is unknown, the common use of steroid therapy for managing RA symptoms may contribute to the increased incidence of osteoporosis and osteopenia in this population. (32) A 2018 randomized control trial observed RA disease severity as an indicator of the magnitude of BMD decline. Of 96 premenopausal females with RA, 25% had osteopenia at the spine, 32.3% at the hip, and 56.3% at the wrist, and 7.3% had osteoporosis at the spine, 6.3% at the hip, and 17.7% at the wrist. (10) If RA is suspected, laboratory testing should include antinuclear antibodies (ANA) and rheumatoid factor with referral to a rheumatologist and subsequent DXA screening as indicated. If currently undergoing treatment for RA with methotrexate or other steroidal anti-inflammatory drugs, additional nutritional support for depleted calcium, magnesium, and vitamin K stores is advised.

- Systemic Lupus Erythematosus (SLE)

SLE is a complex autoimmune condition, involving multiple organ systems. Several studies have found multiple disease-related factors are correlated with low BMD amongst those with SLE. The combination of low BMI, commonly prescribed corticosteroids for symptom management, and limited sunlight exposure, could increase the potential of this population developing osteopenia or osteoporosis. (33,34). In a 2008 study of premenopausal Mexican women with SLE, 40% and 5% had osteopenia and osteoporosis at some site, respectively. (34) If SLE is suspected, laboratory testing should include ANA and referral to a rheumatologist. If currently undergoing treatment for SLE, maintaining optimal vitamin D levels, proper protein intake, and incorporating strength training is essential in maintaining muscle mass and BMD.

### Other Considerations

- Depression

Major Depressive Disorder (MDD) has been associated with osteoporosis but is still rarely listed as a risk factor. The association is, in part, due to the side-effect of medications used to treat psychiatric disorders, but research has shown multiple physical co-morbid conditions associated with depressive behavioral patterns. (35) A 2015 case control study observed subjects with depression had a 1.45 odds of subsequent fracture (p=0.05). (35) In a 36-month prospective study of premenopausal women, those with MDD compared to controls had a significantly higher prevalence of osteopenia which was associated with decreased levels of vitamin D and calcium, and increased levels of PTH and 8am plasma adrenocorticotrophic hormone (ACTH). (36) In addition to referring to a mental health professional, one should order appropriate laboratory testing to assess the bone health of patients with diagnosed depression.

- Breastfeeding

In pregnancy, a woman's ability to absorb calcium is increased, and it returns to baseline during lactation. While breastfeeding, a mother may be at increased risk for depleted calcium stores in bone, which weakens the trabeculae. Many studies show that this is reversed

**Table 1.** Risk factors for developing osteoporosis or osteopenia

<b>Unmodifiable</b>	Genetics
	Age
<b>Dietary and Lifestyle</b>	Calcium Deficiency
	Vitamin D Deficiency
	Protein Deficiency
	Anorexia Nervosa
<b>Medication</b>	Glucocorticoids
	Depot Medroxyprogesterone Acetate (DMPA)
	Antiepileptic Drugs (AEDs)
	Proton-Pump Inhibitors (PPI)
<b>Gastrointestinal Disorders</b>	Celiac Disease
	Irritable Bowel Syndrome
<b>Endocrine Disorders</b>	Hypogonadism
	Hperthyroidism
	Hyperparathyroidism
	Growth Hormone Deficiency
	Diabetes Mellitus Type-1
<b>Inflammatory Disease</b>	Rheumatoid Arthritis
	System Lupus Erythematosus
<b>Other Considerations</b>	Depression
	Breastfeeding

between 6-12 months postpartum and pregnancy-associated osteoporosis is rare. However, clinicians should take the increased risk of depleted bone calcium stores associated with breastfeeding into consideration with patients who could be at high risk due to the presence of additional risk factors. Currently, the literature does not indicate a decreased risk of calcium depletion in bone with calcium supplementation during breastfeeding. Thus, it may be advisable for those with already established osteoporosis to avoid breastfeeding. (4)

### Diagnosis

Assessing low BMD through DXA is the gold standard for diagnosing osteoporosis and osteopenia, reporting within 1-2% precision. (14) DXA results are reported two ways, a T-score and a Z-score. The Z-score shows BMD compared to expected BMD for the patients' age and sex and is more appropriate for the premenopausal population. There are no overt signs or symptoms of osteopenia or osteoporosis, and first sign of premenopausal osteoporosis is often fragility fracture. Guidelines advise BMD screening and a diagnosis of osteoporosis in premenopausal women be reserved for cases of fragility fracture or significant secondary causes of low BMD. (37,38) If a DC is aware of previous fragility fracture or significant secondary causes associated with decreased BMD, a DXA may be ordered to assess BMD to confirm diagnosis.

### Management

#### Spinal Manipulation

There is no literature that suggests spinal manipulation is a treatment for osteoporosis and/or osteopenia. For the premenopausal patient with osteoporosis/osteopenia who additionally has a musculoskeletal disorder that may be amenable to treatment with spinal manipulation, no literature exists on the risk and efficacy of spinal manipulation in this particular patient population. No literature was found that reported a serious adverse event from spinal manipulation in this patient population.

#### Management of Osteoporosis and Osteopenia (summarized in Table 2)

Many of the modifiable risk factors mentioned above are largely attributable to dietary or nutritional deficiencies that commonly involve suboptimal levels of vitamin D and/or calcium. This can occur through poor diet or secondary to medications or systemic diseases. DCs are well equipped to address lifestyle factors, such as dietary interventions or physical activity, and to conservatively manage those at risk for osteoporosis. However, it is important to identify primary diseases that necessitate referral for potential pharmacological treatment, such as endocrinological disorders, gastrointestinal disorders, and inflammatory arthropathies, and to refer for

medication management in cases where conservative strategies unsuccessfully deter the progression of osteoporosis.

*Primary Systemic Diseases*

Conditions requiring medical interventions should be referred to the appropriate specialty. Disorders such as primary GH deficiency T1DM would warrant referral to an endocrinologist for consideration of recombinant human GH and insulin therapy, respectively. AN and MDD should be referred to the appropriate mental health practitioner, and inflammatory arthropathies such as RA and SLE merit a rheumatologic referral.

*Conservative Strategies*

Dietary interventions can be utilized as adjunct therapy in those with vitamin D, calcium, and protein deficiencies due to decreased dietary consumption, malabsorption, or side effects of medication. Vitamin D is in high quantities in egg yolk, salmon, mackerel, and cod liver oil, and calcium can be found in nuts, legumes, broccoli, kale, and other leafy greens. (12) Protein intake can come from animal and non-animal sources but should comprise all essential amino acids. A protein intake of 12-15% of total energy intake is recommended in women for optimum bone health. (39) To assess a patient's dietary intake, it is advised to have the patient keep a food journal or conduct a standardized questionnaire such as the 24-hour recall or food frequency questionnaire. (11)

If the patient is significantly deficient in vitamin D or calcium, or taking medications that have a great impact on absorption or synthesis of these nutrients, exogenous supplementation can be used. Due to the tight regulation of serum calcium, it is unlikely laboratory values will indicate a deficiency, so dietary questionnaires and medication side effects should inform the decision for supplementation. The current recommendation by The National Osteoporosis Foundation is that women who are 18-50 years old should consume 1000 mg of calcium per day for osteoporosis prevention. (40) The opinions on a best practice for exogenous supplementation of vitamin D vary. For women with serum vitamin D levels above 30 ng/mL, the suggested maintenance dose ranges from 800-1000 IU/day. (41) If under 20 ng/mL, the American Association of Clinical Endocrinologists recommends 50,000 IU weekly for 8 weeks. An alternative recommendation is bolus dosing of 300,000-600,000 IU over 6-10 weeks, followed by 800-4,000 IU per day. (42) If a patient is actively under glucocorticoid treatment, guidelines advise an intake of 1200-1500 mg/day of calcium and 800-1000 IU daily of vitamin D while taking glucocorticoids to combat the potential deficiencies of these nutrients due to the medication. (40)

All women at risk for osteoporosis and osteopenia should be prescribed exercise interventions. This exercise should be weight-bearing or high-impact. Literature shows a 1-2% increase in BMD in premenopausal women

**Table 2.** Assessment of conditions and management strategies

Background	Assessment	Management
Calcium Deficiency	3-day food journal, serum calcium corrected for albumin	1000 mg/day for prevention Food: broccoli, kale, leafy greens, nuts, legumes
Vitamin D Deficiency	Serum 1,25(OH)D	>30 ng/mL: 800-1000 IU/day <20 ng/mL: 50,000 IU/week for 8 weeks Foods: egg yolk, salmon, mackerel, cod liver oil
Protein Deficiency	Food Frequency Questionnaire	Animal and non-animal protein comprising all essential amino acids
Anorexia Nervosa	Blood laboratory markers related with malnutrition and bone health; serum 1,25(OH)D, ALP, serum calcium, serum phosphate, iPTH, TSH, PSH, estradiol	Refer to mental health and nutrition specialists
Glucocorticoids	Serum calcium corrected for albumin, FSH, estrogen, estradiol	See appropriate management of calcium deficiency
Depot Medroxyprogesterone Acetate	FSH, estradiol	Refer to endocrinologist or gynecologist to discuss other options for birth control
Antiepileptic Drugs	Serum 1,25(OH)D	See appropriate management for vitamin D deficiency
Proton-Pump Inhibitors	3-day food journal to assess dietary calcium, serum calcium corrected for albumin	See appropriate management for calcium deficiency

Celiac Disease	Anti-tissue transglutaminase, antigliadin antibodies, antienomysial antibodies	Refer to gastroenterologist for upper-GI biopsy Education on a gluten-free diet and assessment for nutrient deficiencies due to malabsorption
Irritable Bowel Syndrome	Anti-saccharomyces cerevisiae antibody (Crohn's), perinuclear anti-neutrophil cytoplasmic antibody (UC), serum 1,25(OH)D	Refer to gastroenterologist and assessment of nutrient deficiencies due to malabsorption
Hypogonadism	FSH, Estradiol, Serum calcium corrected for albumin	Refer to endocrinologist
Hyperthyroidism	TSH, Total T4, Total T3, Free T4, Free T3	Refer to endocrinologist and address appropriate nutrient deficiencies through diet or supplementation
Hyperparathyroidism	Serum calcium corrected for albumin, serum phosphate	Refer to endocrinologist and see appropriate management for calcium deficiency
Growth Hormone Deficiency	Growth hormone	Refer to endocrinologist
Diabetes Mellitus Type-1	HbA1c	Refer to endocrinologist or primary care provider and provide education on dietary approaches to reduce sugar intake
Rheumatoid Arthritis	Rheumatoid Factor, antinuclear antibodies (ANA), serum calcium corrected for albumin, serum magnesium, serum vitamin K	Refer to rheumatologist and address appropriate nutrient deficiencies through diet or supplementation
Systemic Lupus Erythematosus	ANA, serum 1,25(OH)D, dietary protein	Refer to rheumatologist, and address nutritional support for deficiencies. Refer for or provide strength training program.
Depression	Serum 1,25(OH)D, serum calcium corrected for albumin, PTH, 8am plasma ACTH	Refer to mental health professional Address appropriate nutrient deficiencies through diet or supplementation
Breastfeeding	Serum calcium corrected for albumin	See appropriate management for calcium deficiency Those with established osteoporosis may be advised to avoid breastfeeding

following resistance and/or high-impact exercise. (43) whereas there was no demonstrated change in BMD with non-impact sports such as swimming. (44)

#### Pharmaceutical Interventions

Evidence for use of pharmaceutical interventions for premenopausal women is not well understood. Most literature recommends medications aimed at bone resorption should be reserved for chronic secondary causes of osteoporosis or osteopenia, but the main focus should be the treatment of primary disease factors. Chronic inflammatory conditions, such as RA or IBD, can necessitate high levels or long-term glucocorticoid use which is known to impact BMD. In these instances, a physician will most commonly prescribe bisphosphonates. For premenopausal women the Food and Drug Administration currently only approves the use of bisphosphonates in those receiving

glucocorticoids, and most studies only support their use in women with history of fragility fracture or with a known ongoing process of bone loss. Particular caution is used in this population due to the ability of the medication to cross the placenta and have a teratogenic effect in pregnancy. Rat models have demonstrated the accumulation of bisphosphonates in skeletal bone, making this pharmaceutical intervention a last resort and having increased diligence with suspending use well before intention to conceive. Long-term use of bisphosphonates has been associated with osteonecrosis of the jaw and atypical femoral fractures. (18,45)

#### Follow-up

In those who have undergone DXA testing and demonstrated significant BMD loss, it is advisable to monitor DXA every 18-36 months to assess BMD status. Once BMD has reached reasonable standards or

stabilized, follow-up scans may be suspended. However, patients should continue preventative measures using diet, exercise, and pertinent long-term medication. (45)

## CONCLUSION

This paper presents a summary of the evidence on osteoporosis and osteopenia in a pre-menopausal female population. These data have importance to DCs in diagnosis and management of such cases. Risk factors are largely attributable to modifiable dietary and nutritional deficiencies, most commonly involving compromise of vitamin D and calcium. This can occur primarily through daily intake or secondarily by medications or conditions that impact absorption of these nutrients. Patients are not always placed on preventative protocols for the medications they are on, despite research supporting the benefits of exogenous supplementation for preventing BMD loss.

Although more research needs to be conducted in the premenopausal population, awareness of conservative approaches to managing the increased risk of BMD loss due to secondary causes of osteoporosis and osteopenia may improve the long-term incidence of osteoporosis and osteopenia in this population. These management strategies may be of value to maintain as women enter menopause and are at a higher risk for BMD decline.

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## CONFLICT OF INTEREST

The authors have no additional conflicts of interest, financial or otherwise, to disclose.

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