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This clinical e-newsletter from The North American Menopause Society (NAMS) presents questions and cases commonly seen in a menopause specialist's practice. Recognized experts in the field provide their opinions and practical advice. Chrisandra L. Shufelt, MD, the Editor of *Menopause e-Consult,* encourages your suggestions for future topics. Note that the opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Shufelt.

Case:

A 42-year-old premenopausal woman has just been diagnosed with osteoporosis after a wrist fracture. What are the current treatment approaches for premenopausal osteoporosis?

Management Issues by:

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Osteoporosis is a common condition associated with an increased risk of fracture in postmenopausal women. A fragility fracture in a premenopausal woman indicates that bone strength is impaired and requires further evaluation to understand why bone strength is impaired in a supposedly estrogen replete female. Osteoporosis in premenopausal women is diagnosed in the presence of fragility fractures and not simply a low bone mineral density (BMD) in the premenopausal patient population.

The World Health Organization definition of osteoporosis based on bone density alone does not apply to premenopausal women. (1)

The criteria for the diagnosis of low bone density in premenopausal women are different to those used in postmenopausal women. (1)

A normal BMD in the premenopausal patient population is a BMD value which is within 2 standard deviations of the age matched reference range.(ie Z-score higher then -2) Low BMD in the premenopausal female is defined as a BMD value (at the lumbar spine, total hip, femoral neck or one third radial site) equal to or lower then 2 standard deviations below the age matched reference value (ie a Z-score of -2 or lower). This may be due to achievement of a lower peak bone mass or due to bone loss following achievement of normal bone density and requires further assessment.(2)

It is necessary to confirm whether the forearm fracture which our case patient experienced was indeed a fragility fracture and occurred with minimal trauma, such as with a fall from standing height or from the third step or lower if the patient was running down the stairs at the time of the fall. An assessment of other prior fractures, if any, is also necessary, and each past fracture needs to be evaluated and categorized as fragility or traumatic.

Osteoporosis as well as low BMD in premenopausal women should always be further evaluated as it may be due to an underlying disease, condition or medications. In addition to genetic predisposition, environmental factors such as inadequate calcium intake, alcohol and/ or tobacco excess, and low body weight in the teenage and young

adult years can contribute to the achievement of a low peak bone mass.

Clinical or subclinical estrogen deficiency can also contribute to achieving a lower peak bone mass or to the development of bone loss in the premenopausal years.

After confirming the clinical diagnosis of osteoporosis, it is essential to exclude the presence of diseases or conditions that contribute to bone loss and impaired bone strength (Table 1).[1]

The two key factors that determine the achievement and maintenance of bone strength in women are gonadal status and body weight. Other important factors that can result in the development of osteoporosis and impaired bone strength include diseases associated with impaired bone formation or excessive bone loss, as well as drugs that increase the risk of osteoporosis and fragility facture. Referral to a metabolic bone clinic is appropriate for patients experiencing fragility fractures or progressive bone loss in the premenopausal years.

Table 1. Important Secondary Causes of Bone Loss

Diseases/Conditions

- Hypogonadism (primary and secondary)
- Primary hyperparathyroidism
- Thyrotoxicosis
- Hypercortisolism
- Growth-hormone deficiency
- Osteomalacia
- Myeloproliferative disorders
- Connective tissue disorder

Malabsorptive states (eg, Celiac disease)

- Hepatic disorders (eg, primary biliary cirrhosis)
- Inflammatory bowel disease
- Renal disease
- Hypercalciuria
- Osteogenesis imperfecta

Medications

- Glucocorticoids
- Thyroxine (excessive)
- Anticonvulsants (eg, phenytoin, phenobarbital)
- Heparin (long term)
- Lithium
- Cytotoxic chemotherapy
- Gonadotropin-releasing hormone agonists
- Depot medroxyprogesterone acetate

Begin by determining the age of menarche and evaluating the regularity of the menstrual cycle as well as the presence of menopausal symptoms. Contraceptive use needs to be reviewed in particular (for example, prolonged use of depot medroxyprogesterone acetate can contribute to decreases in bone density).

Current and past body weight requires careful assessment—a history of anorexia nervosa may have prevented the formation of this woman's genetically determined peak bone mass or contributed to bone loss in the young adult years. Taking a careful drug history also is advised. Glucocorticoid therapy is associated with impairment of bone quality and bone quantity, with progressive decreases in bone density and in osteoblast and osteocyte function, and can contribute to the development of fragility fractures. Other drugs that can affect bone health include anticonvulsant therapy, selective serotonin reuptake inhibitors (SSRIs), thiazolidinedione, and gonadotropin-releasing hormone agonists, as well as chemotherapy.

It is important to evaluate for the presence of other diseases that can contribute to the development of fragility fracture (Table 1).[1] These include a history of hyperthyroidism or hyperparathyroidism and respiratory conditions such as asthma or chronic obstructive lung diseases that require glucocorticoid therapy, as well as Cushing's syndrome. Malabsorption states can also be associated with an increased risk of osteoporosis because of impaired absorption of vitamin D, calcium, and phosphorus. Inflammatory conditions such as rheumatoid arthritis or systemic lupus erythematosus can contribute to osteoporosis. Vitamin D is hydroxylated in the liver and the kidney, and renal and liver diseases are associated with osteoporosis. Connective tissue diseases such as osteogenesis imperfecta are associated with bluish grey sclerae, hearing impairment, joint laxity, easy bruisability, and dental disease as well as skeletal fragility and need to be identified and treated.

Lifestyle factors such as excessive alcohol intake and smoking can contribute to osteoporosis and require assessment as well.

After a detailed history and physical, additional laboratory tests are completed to exclude other causes of bone loss (Table 2).[2] Spinal x-rays are completed in the presence of height loss (> 2 cm) or back pain in order to identify the presence of vertebral fractures. A BMD test should also be completed to assess bone density at baseline and to monitor patient progress.

Table 2. Workup for Low BMD in Premenopausal Women

Laboratory investigations

- Serum calcium (corrected for albumin)
- Complete blood count
- Erythrocyte sedimentation rate
- Phosphate
- Magnesium
- Liver function tests
- Thyrotropin-stimulating hormone
- Estradiol, FSH
- Renal function-(eGFR)
- 25-hydroxyvitamin D
- Parathyroid hormone

24-hour urine collection for

- Calcium
- Creatinine

Additional investigations

- Celiac profile
- 24 hour urine for free cortisol
- DNA analysis for Col 1A1 and 1A2 genes

Treatment requires correction of any underlying abnormalities identified in the workup of osteoporosis. If a cause is not identified, and progressive bone loss is present, then a tetracycline-labeled bone biopsy may be necessary in order to evaluate bone formation and bone resorption and ensure that mineralization abnormalities are not present.

Appropriate calcium and vitamin D supplementation is advised in addition to smoke cessation and limiting alcohol intake, as well as soft drinks and coffee. Achievement of an ideal body mass index (BMI) is necessary for those with low BMI.

Bisphosphonates have been evaluated in premenopausal women with glucocorticoid-induced osteoporosis, and in this specific situation, bisphosphonates are effective in normalizing bone remodeling and reducing the risk of fragility fracture. Bisphosphonates do, however, have long-term skeletal retention and in a premenopausal woman planning a future pregnancy, the drug may be released from the skeleton and potentially affect the developing fetal skeleton. These agents should not be used in a pregnant woman and should be used only with great caution in a woman planning a future pregnancy.

Teriparatide PTH(1-34) may be considered in women with recurrent fragility fractures and has been found to be effective in increasing BMD in premenopausal women with osteoporosis. It was also found to improve bone microarchitecture in this patient population. Further research is however required with teriparatide in larger numbers of patients. (3) It is not recommended for younger women or girls in whom the epiphyses have not closed. (4)

In women aged younger than 50 years with clinical or subclinical estrogen deficiency, estrogen supplementation is strongly advised. Further research is required to evaluate the value of pharmacologic therapy in premenopausal women with osteoporosis. Currently, data evaluating the effectiveness of pharmacologic therapy in premenopausal osteoporosis are very limited. Further research will enable the development of evidence-based guidelines for the management of osteoporosis in premenopausal women.

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Question:

How can practitioners advise women on skin health during the menopause transition and afterward? What is the most effective cosmetic treatment for melasma and wrinkles?

Commentary by:

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Maintaining healthy-appearing skin, especially on the face, neck, and hands, while transitioning through menopause, is a desire of many of our patients. The aging process begins in the third decade and becomes visible in the fourth.[1] Dry skin, shallow and deep wrinkles, thinning, skin pigmentation unevenness, and reduced ability to withstand trauma bother patients in varying degrees, from cosmetic annoyance to reduced quality of life.

Histologic changes occur in the dermis and the epidermis that result in the flattening of the epidermis, irregular desquamation, reduced hydration (from loss of the interstitial extracellular matrix), and glycosaminoglycan-degraded fibroblasts, causing disordered collagen with diminished production and diminished elasticity.[1,2]

Skin aging is a result of modifiable and unmodifiable factors. Chronologic aging, ethnicity, and anatomic variations are unchangeable. However, modifiable factors affect skin health tremendously. Smoking reduces skin's elasticity and abates blood flow, thus depriving nutrient delivery to tissues.[3] Repeated ultraviolet B (UVB) exposure depletes hyaluronic acid in dermal connective tissue, resulting in reduced moisture content. Crazily, many women still ignore the long-term consequences of UV exposure and seek a tan. Exposure to UV from tanning beds or sunlight exposure is responsible for most of the appearance of aging skin.

Substantial loss, as much as 30%, of types I and III collagen occurs in the first few years postmenopause. Later, the collagen loss continues at close to 2% per year.[1] Hormonal changes play a substantial role in this. Estrogen receptor (ER) density is higher on genital organs, legs, and the face, particularly in the epidermis, sebaceous hair follicles, and sweat ducts. It is much less abundant in the dermis and sweat glands,[2] but no cell is spared from the menopause transition.

Studies on systemic estrogen therapy in women with mild loss of skin collagen showed that estrogen prevented further loss, and in women with more significant loss of collagen, it corrected the loss and maintained the effects. Topical estrogen increases types I and III collagen, improves hydration and elasticity, and thickens the epidermis; however, topical estrogen use may lead to hyperpigmentation and unknown levels of systemic absorption.[4] One study indicated that topical estrone induced expression of matrix metallo-proteinase-1, a collagen-degrading enzyme, in sun-exposed skin.[5] No FDA-approved topical estrogen exists for nongenital skin application.

Phytoestrogen research shows some promising effects. Genistein and S-equol activate ERβ receptors and improve skin elasticity and wrinkle depth when consumed. Furthermore, resveratrol appears to have potent antioxidant

effects in fibroblasts and may show promise in supplements for skin health.[4]

Dizzying arrays of antiaging cosmetic options fill store shelves. Unfortunately, reliable studies confirming efficacy of these products are rare. Studies have been conducted on several chemicals, but the actual product formulations, product bases, and even the packaging affect efficacy in real-life use.

Topical retinoids include tretinoin (retinoic acid), isotretinoin, retinol, retinaldehyde, tazarotene, and adapalene. Topical application increases collagen I formation, likely reducing collagen breakdown. Reduction of melanocytic hypertrophy balances skin color. Normalization of elastic tissue improves skin texture.

Tretinoin is the most effective topical antiaging therapy, even more effective than estrogen, although skin irritation is a common adverse effect. Tretinoin benefit appears to be dose dependent, and ongoing treatment is needed to maintain benefits.

Isotretinoin (a tretinoin metabolite) improves photodamaged skin and increases epidermal thickness.

Retinol and *retinaldehyde* are common ingredients in nonprescription skincare products. Topical retinaldehyde has been shown to have benefits similar to tretinoin with less irritation. Retinol is easily degradable and biologically inactive on light exposure.[6] Retinol peel treatments increase the amount of skin lipids and improve dryness.[7] *Retinyl propionate* is a less-irritating and less-effective ingredient in over-the-counter (OTC) products.[3] All retinoids increase sun sensitivity, so any user must wear sunscreen. *Retinyl palmitate* is included in some sunscreens because of observed antioxidant properties.[3]

Topical antioxidants show promise in antiaging products. *Nicotinamide* (vitamin B_3) appears to prevent melanosome transfer, resulting in improvement in hyper-pigmentation.[3] Limited data show that *tocopherol* (vitamin E) improves wrinkling and reduces sunburn symptoms.[3]

Vitamin C application improves lipid production by stimulating synthesis of ceramides. It can reduce wrinkles from UVB exposure and improve roughness and fine lines. *Ascorbyl tetraisopalmitate* (oil-soluble vitamin C) stimulates collagen synthesis and reduces collagen breakdown by decreasing production of matrix metalloproteinase.[8] As ascorbic acid is notoriously unstable in OTC preparations, using a product with L-ascorbic acid may deliver a more efficacious amount of the product.[3]

Argan oil, rich in antioxidants and ferulic acid, appears to improve elasticity when consumed. Argan oil is available as a topical application, although data are preliminary as to its effectiveness.[9]

Encouraging evidence exists for the benefits of pine bark extract in the form of *Pycnogenol*, which contains a variety of substances beneficial to skin. Pycnogenol use stimulated collagen and elastin-rich extracellular matrix proteins and enhanced skin hydration in study participants, more so in participants with very dry skin.[10]

Also, eating a diet high in antioxidant-rich foods and staying hydrated with water delivers nutrients to the skin.

Popular **alpha-hydroxy acids** are derived from organic sources, for example, lactic acid in dairy products, malic acid and citric acid in fruit, and glycolic acid in sugar cane. Lactic acid and glycolic acid are the most potent; glycolic acid is the smallest, best-penetrating molecule.[1] The number of skin layers affected depends on the concentration of the acid. Weakening epidermal intercellular adhesions is the proposed theory to explain the exfoliating effects of alpha-hydroxy acids. They also appear to stimulate collagen and hyaluronic acid synthesis to reduce wrinkles and improve skin thickness.

Alpha-hydroxy acids tend to be less irritating than retinoids. Newer formulations of *polyhydroxyacids* may be less irritating than older types.[6] For hyperpigmentation, cholic acid, derived from the Aspergillus fungus, has been shown to reduce production of melanin through tyrosinase inhibition.[1]

Peptides are topical amino acids that absorb into the skin to produce potentially significant effects. Although opinions are conflicting regarding efficacy and long-term safety, peptides appear to introduce genetic information into cells and modify their behaviors. Carrier peptides deliver collagen, elastin, and other bioactive molecules into the cell. Signal peptides aim to stimulate matrix protein, collagen, and elastin synthesis. Enzyme-inhibitor peptides inhibit proteinases. Neurotransmitter-inhibitor proteins paralyze the underlying muscles for a smoothing effect.[11]

Certainly, several interventions are available to create and maintain beautiful skin during and after menopause. Sunscreen and reducing UV exposure greatly reduces skin aging. A few dietary supplements to improve skin health are supported by data. Tretinoin is the most effective topical agent but can cause skin irritation. Weaker retinoids and alpha-hydroxy acids improve skin thickness, reduce wrinkles, and are well tolerated.

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What are your clinical challenges with premenopausal osteoporosis? Post on our Member Forum (www.menopause.org/member-login?ReturnUrl=%2fforum) to discuss the topics from April *Menopause e-Consult*.

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