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Review Article

Osteoporosis in Menopause & Beyond

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Bone is living tissue with its own blood and nerve supply. Bone renews itself continuously by the cells in the body which remove the old bone and replace it with new bone. When new bone formation declines with age & menopause, bones become weak, fragile and porous called osteoporosis. This osteoporotic bone is easily breakable. Menopause, due to estrogen deficiency predisposes osteoporosis but women don't feel until they suffer from fracture and it's complications. That is why osteoporosis is called a silent killer and difficult to combat. According to International osteoporosis foundation by 2050, the worldwide incidence of hip fracture in men is projected to increase by 310% and by 240% in women compared to 1990. Worldwide, osteoporosis causes more than 8.9 million fractures annually, resulting in 1 fracture in every 3 seconds [1] which is very alarming. After the age of 50, one in 3 women and one in five men suffer from Osteoporosis [2].

Women today can expect to live > 1/3 of their lives in the postmenopausal state. So huge number of women over age 50 years will experience osteoporosis and subsequently fractures. So to combat dreadful consequences of Osteoporosis, timely screening, diagnosis and intervention is very important. Prevention of osteoporosis may ameliorate the sorrows of osteoporosis. But addressing osteoporosis is a great challenge in menopausal women.

What is Osteoporosis ;

Actually osteoporosis means loss of bone tissue, which makes the bone brittle.

Literally Osteoporosis is defined as

"A systemic skeletal disease characterized by low bone mass (measured as bone mineral density– BMD) and micro architectural deterioration of bone tissue with a consequent of increase in bone fragility and susceptibility to fractures involving the wrist, spine, hip, pelvis, ribs or humerus.''[3, 4]

The World Health Organization defines osteoporosis using bone mineral density (BMD) T score. T score represents a standard deviation (SD) that calculates how much a result varies from the average or mean bone mineral density of a healthy young adult. T score of 0 means that BMD is equal to the norm for a healthy young adult. The more SDs below 0, indicated as negative numbers, the lower the BMD and higher the risk of fracture.

Normal bone density: T-score between "1 SD and +1 SD ("1 SD ≤normal T-score ≤+1 SD)

Osteopenia: T-score is between "1 and "2.5, including "2.5

Osteoporosis: T-score is <–2.5

Severe osteoporosis: T-score is <"2.5, and the patient has suffered an osteoporosis-related fracture.

It is very important for all men and women to know the risk factors so that they may modify those risk factors thereby may reduce the risk of fracture. Those risk factors of Osteoporosis are-

Not modifiable factors:

Advanced age
Ethnicity
Female
Early menopause (<45 years)
History of fracture at adult
Positive family history
Diminished Peak Bone Mass (PBM) at skeletal maturity
Chronic inflammatory diseases

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Modifiable factors:

Malnutrition
Smoking
Excess alcohol intake
Estrogen/testosterone deficiency
Low calcium intake
Inactivity/immobilization, impaired neuromuscular function
Long-term medication use
Low body mass index

Also who are consuming high caloric diet they are shown to have lower bone mass and higher rates of fracture[5].

Why we are so concern about Osteoporosis?

The consequences of osteoporosis are very dreadful. Bone fracture is the most serious complication. Fractures can occur at any bone site, but are most common in the hip and vertebrae. Fractures may lead to chronic pain, disability, depression, prolong home stay, reduced quality of life, and increased mortality. Nobody wants to be bed bound, everybody wants the freedom and mobility. But fracture makes the life measurable and bed bound.

Hip fractures occur usually after a fall. Hip fractures are associated with 15% to 20% increased mortality rate within 1 year, followed by a 2.5-fold increased risk of future fractures. Approximately 20% to 50% hip fracture patients require long-term nursing home care and suffer from decreased quality of life, social isolation, depression, and loss of self esteem [6]. Multiple vertebral thoracic fractures may result in restrictive lung disease and back pain (acute and chronic), which results prolonged disability, poor self-image, social isolation, depression, and positional restriction. Compression fractures in addition increases mortality [7].

The direct cost of treating osteoporotic fractures of people is very high. It's a huge economic burden. It is reported that between 5000 and 6500 billion USD is spent for the treatment of osteoporosis per year in Canada, Europe and the USA. So it is prudent to prevent fractures that may prevent the personal, social and huge economic burden.

Prevalence of Osteoporosis

Worldwide variation in the incidence and prevalence of osteoporosis is difficult to determine, because of problems with under diagnosis and under reporting. The best way to compare osteoporosis in different population groups is by looking at the fracture rates in older individuals. As osteoporosis is not a life-threatening condition, data from developing countries are scarce. Worldwide, osteoporosis causes more than 8.9 million fractures annually, resulting in an osteoporotic fracture every 3 seconds. Osteoporosis is estimated to affect 200 million women worldwide. As women are living longer so the incidence of osteoporosis will be increased markedly in coming decade. Prevention is the most important to ameliorate the dreadful consequences. National Health and Nutrition Examination Survey (NHANES) found that 48.3% of adults aged 65 and over had osteopenia or low bone density at the lumbar spine or femur neck. Women had a higher age adjusted prevalence of low bone mass at either skeletal site (52.3%) than men (44.0%). Adults aged 80 years and over had a higher unadjusted prevalence of low bone mass (52.7%) than adults aged 65 to 79 years (46.7%)[8].

How to prevent Osteoporosis ?

Complete prevention of Osteoporosis is not possible. But if appropriate strategies are adopted, we may slow the progression of the disease process. Prevention need to be started early in young adulthood. Once peak bone mass (PMB) has been attained (I e, at 25-30 years) the goal of prevention is to reduce the rate of bone loss. All women should be advised to eliminate or minimize the potentially reversible risk factors.

Prevention strategies include –proper nutrition, exercise, and lifestyle modification. All older adults,

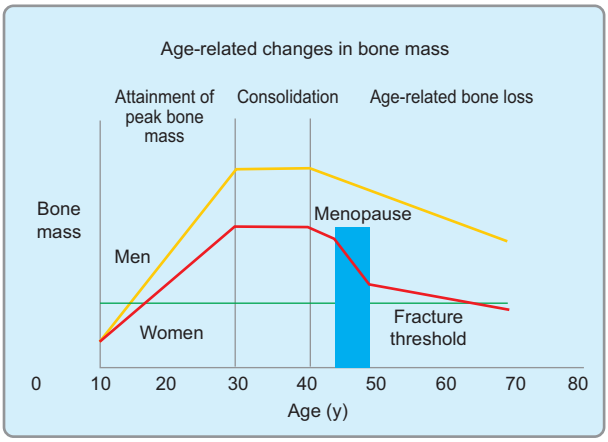

Figure 1: *Age-related changes in bone mass*

with osteoporosis, should be counseled for fall prevention strategies, reduction of sedative-hypnotic medications[9,10].

Diet

A healthy diet in childhood is an important contributor to peak bone mass, and maintaining a healthy diet, can help to reduce bone loss in later life. Adequate dietary protein (1gm/kg body weight), calcium, vitamin D, magnesium, fruits, and vegetables have a positive influence on bone health. Optimum diet, regular exercise and good sunlight exposure achieve 'high peak bone mass' that build strong bone and decrease the risk of osteoporosis. Eating at least 400 g, or 5 portions, of fruits and vegetables per day, reduces the risk of NCDs (non-communicable disease), and helps ensure an adequate daily intake of dietary fiber. Diet should must contain plenty vegetables, fresh fruits, yogurt and raw vegetables as snacks.

PBM is achieved usually by young age of 25, later it remains almost static and starts declining at perimenopause and menopause period. Nutrition strategies must include adequate calcium, magnesium and vitamin D intake. The recommended calcium intake for postmenopausal women is 1000-1200 mg/d, & vitamin D is 800 IU daily, which can be difficult to achieve by diet alone so supplementation is necessary [5]. We need to ensure that women is taking adequate nutrition particularly calcium and vit D. Low vit D is associated with impaired calcium absorption, a negative calcium balance, and a compensatory rise in parathyroid hormone, results in excessive bone resorption. WHO proved that adequate calcium and vit D prevented fracture. We must know that, not only calcium, but also Magnesium is the another master mineral for perfect Bone Health.

Therefore adequate magnesium (320mg) is also necessary to keep the bone strong. The study showed that deficiency of this master molecule enhances the rate of osteoporosis[11].

A meta-analysis, based on 18 prospective cohort studies revealed a nonlinear relation between alcohol consumption and the risk of hip fracture. Light alcohol consumption (0.01–12.5 g/d) is not that harmful it may be associated with a slightly reduced risk of fracture. Women taking heavy alcohol (>50 g/d) has high risk of fracture particularly increased hip fracture risk[12].

Cigarette smoking is an important risk factor for osteoporosis. Smoking causes reduction in circulating levels of 1,25-dihydroxyvitamin D and parathyroid hormone (PTH). This is actually a modifiable risk factor. All should know that smoking causes significant reductions in bone mineral density when compared with nonsmokers[13].

Any comorbidity needs to be well controlled. Type 1 diabetes mellitus is associated with low BMD and the risk increases with the duration of the disease. Data from Health Survey done in Norway showed a significant increase in hip fracture rates among females with type1diabetes (relative risk 6.9, confidence interval 2.2–21.6) compared with nondiabetic female patients. Though the exact mechanism of bone loss is unknown [14]. Therefor all must control her diabetes and blood pressure .

Exercise

Mature women should be recommended exercise for multiple health benefits not only for Osteoporosis. Regular weight bearing and muscle strengthening exercise improves, strength, posture, balance and maintain or improve bone strength, reduce the fall and fracture risks.

150 minutes of moderate-intensity aerobic physical activity throughout the week or doing at least 75 minutes of vigorous-intensity aerobic physical activity two days in a week or an equivalent combination of moderate and vigorous intensity activity is recommended. Aerobic activity should be performed in bouts of at least 10 minutes. Incorporation of Muscle-strengthening activities, like lifting weights or working with resistance bands should be done involving major muscle groups (gluteus, quads, hamstrings, back, chest) two or more days a week is recommended. Most studies reported the benefits of exercise.

Shanb AA et al showed moderate weight bearing exercise improves DXA derived measurements of BMD at the spine and hip. Feskanich D and et al in their Observational cohort studies showed that, moderate weight bearing exercise reduces the risk of hip fracture. Another RCT of 105 subjects by Kemmler W expressed (Exercise = 59 vs. control: n = 46) representing 1680 participant in 16-year follow-up RR (EG) showed overall low-trauma fracture was less 0.51 (95% CI: 0.23- 0.97), p = .046)[15,16,17].

Structured exercise and balance programs (eg, tai chi, yoga) can help to reduce increase balance and prevents the falls. Regular weight-bearing exercise and

back posture exercises on most days should be advocated. Also important to know whether the performed exercise is effective, increased pulse rate is the good indicator of effective exercise [15,16, 17].

Screening of osteoporosis

Screening of osteoporosis directs us to be vigilant with the women who are screen positive. How can we do the screening for osteoporosis? Fracture risk assessment tool (FRAX) is widely popular screening tool. Risk assessment of osteoporosis can be done by (FRAX) tool, which is a tool that helps to predict a patient's 10-year risk of hip or other major osteoporotic fracture. It has been validated for untreated patients aged 40 to 90 years in multiple countries and for multiple ethnicities. It can be obtained at www.sheffield.ac.uk/FRAX.

Screening for osteoporosis need to be done in all women aged 65 and older. Screening should be conducted at the hip and spine using Dual energy-X-ray Absorptiometry (DXA), which also helps in diagnosis of Osteoporosis. It can be done earlier if women are having risk factors.

Trabecular bone score (TBS)

Trabecular bone score (TBS) is an index of bone microarchitecture. It is measured from a lumbar spine DEXA image and thus no extra scan is required. TBS is particularly useful in patients with BMD values in the low osteopenia range (T score between -2.0 and -2.5) in whom a low TBS indicates possible need to consider commencing treatment. TBS is unreliable in individuals with a body mass index (BMI - kg/m2) of over 35. TBS ≥1.350 is normal; TBS between 1.200 and 1.350 is considered to partially degraded microarchitecture and TBS ≤1.200 defines degraded microarchitecture.

How to diagnose Osteoporosis ?

Osteoporosis is often underdiagnosed and undertreated, not only in our country it is happening all over the world. After sustaining fragility fracture, around 80% of patients are still not diagnosed and treated for osteoporosis and the underlying disease that caused the fracture and morbidities. It is estimated that only 1/3 of vertebral fractures come to clinical attention. So early diagnosis is cornerstone to prevent the disease progression. The diagnosis of osteoporosis can be made by detailed history taking. Presence of a fragility fracture particularly at the spine, hip, wrist, humerus, rib, or pelvis without measurement of BMD strongly indicates osteoporosis [18]. Physical examination also provides some clue for the diagnosis of osteoporosis. Following Physical Examination are indicators of Osteoporosis:

1.Loss of height Look for Kyphosis & Dowager's hump may be signs of vertebral fracture,

2.Occiput to wall distance in standing position inability to touch –implies thoracic fracture

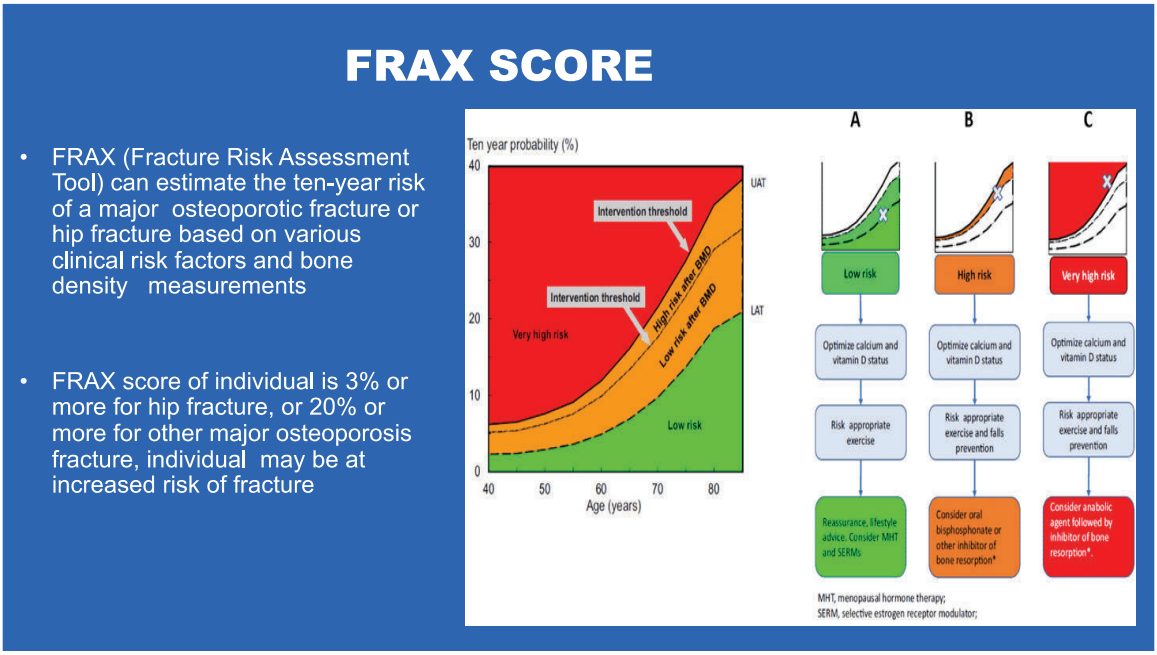

Figure 2: *FRAX score*

3.Women can lose up to 1.0 to 1.5 inches to be measured annually. Loss of 1.5 inches (3.8 cm) or more calls for evaluation by a lateral thoracolumbar radiograph or DEXA.

4.Inability to insinuate four fingers of hand between lower rib cage & anterior superior iliac crest implies lumbar fracture.

5. Weight should also be recorded; women with low BMI are susceptible for osteoporosis.

Several professional organizations also support making the diagnosis when the 10- year probability of a major osteoporotic fracture is greater than 20% for major joints or the 10-year probability of hip fracture is greater than 3% [19,20,21]

Investigations for Osteoporosis

All postmenopausal women should be evaluated for osteoporosis risk in order to determine the need for BMD testing and/or vertebral imaging. In general, women having the more risk factors, her fracture risk will be greater. Many experts recommend laboratory evaluation of complete blood count, serum calcium, phosphorous, and alkaline phosphatase, and a 25-hydoxyvitamin D level. Further investigations may be needed when there is suspicion for hyperthyroidism, celiac disease, multiple myeloma, or hyperparathyroidism [19,20,21]. Bone Turnover Markers: Blood tests for markers such as serum C-telopeptide (CTX) and serum N-telopeptide (NTX) can provide information about bone resorption rates.

Regarding Imaging we may advice according to indication and if body parts are affected.

DEXA(Dual-Energy X-ray Absorptiometry), Quantative ultrasound, X-ray of bones/ joints (Particularly Lateral X-ray of lumbar and thoracic spine), CT Scan and MRI can be done. DEXA is still the Gold standard investigation.

Interpretations of a DEXA Scan

Interpreting the results of a DEXA scan is crucial for assessing bone health and determining the risk of osteoporosis and fractures. Here's a detailed explanation of how to interpret the results of a DEXA scan:

T-Score:

The primary parameter used for interpreting DEXA scan results is the T-score; The T-score compares the bone density to the woman with that of a young, healthy adult of the same sex and ethnicity.

The World Health Organization (WHO) diagnosis of osteoporosis based on T-scores is as follows:

Normal: T-score above -1.0 SD

Osteopenia: T-score between -1.0 SD and -2.5 SD

Osteoporosis: T-score at or below -2.5 SD

Good history, clinical examination and assessment of DEXA and in some occasion bone turnover markers are very important to reach the diagnosis. Regarding serum biomarkers most experts recommend, laboratory evaluation with a complete blood count, a chemistry panel that includes calcium, phosphorous, magnesium and alkaline phosphatase, and a 25-hydoxyvitamin D level. Further evaluation is indicated when there is suspicion for hyperthyroidism, celiac disease, multiple myeloma, or hyperparathyroidism.

TREATMENT

The bedrock of the treatment of Osteoporosis is life style modification. Once the diagnosis of osteoporosis is made, all women and men should be counseled about nonpharmacologic preventive measures, including exercise, diet, cessation of smoking, and prevention of fall.

Pharmacologic treatment; when to start?

NAMS recommends consideration of bone-specific medication in women with osteoporosis or low bone mass who have either a 10-year probability of a hip fracture of 3% or higher or a 10-year probability of a major osteoporosis related fracture of 20% or higher, based on the US-adapted World Health Organization algorithm[22].

NOFSA recommends treatment should be started at T-score < -2.5 or who are having known fragility fracture. Both women and men with osteoporosis should be offered pharmacologic treatment. Reduction in fracture risk with pharmacologic therapy has only been demonstrated with diagnosis based on DXA in the osteoporotic range or with previous fragility fracture. The drugs are:

1. ANTIRESORPTIVE Agents (Inhibitors of bone resorption)
   * MHT (Menopause Hormone Therapy)- Estrogen+Progesterone (if estrogen is intact)
   * SERM and TSEC - SERM (selective estrogen receptor modulators)- Raloxifene
   * Bisphosphonates
   * Alendronate
   * Risedronate
   * Zoledronic Acid
   * Ibandronate
   * Denosumab
   * Ant Rankle

2. ANABOLIC Agents (Stimulator bone formation)

Parathyroid hormone
Teriparatide
Abaloparatide and the monoclonal antibody Romosozumab.

1. Antiresorptive agents

MHT may be used for prevention and treatment of osteoporosis in the early postmenopause symptomatic women when there is no contraindication. MHT should not be started solely for bone protection after 10 years of menopause. Sex hormone replacement may help to prevent bone loss in men and women who have other indications for their use (eg, hypogonadism in men, hot flashes in women), but not been used for established osteoporosis due to lack of efficacy [23]. MHT is indicated as primary therapy to prevent bone loss in women with premature menopause and Premature ovarian insufficiency. Estrogen / Progestin Interventions trial showed, bone density increased at the lumbar spine and femur in women who used MHT or 3 years. WHI (Women Health Initiative) study back in 2002 showed bone density at the lumbar spine and femur increased by 4.5% and 3.7%, respectively, with the MHT than the placebo group. The standard dose of MHT increases bone density by inhibiting bone resorption and reducing bone remodeling process. The response of bone density to estrogen is dose-dependent. In the Postmenopausal Estrogen/Progestin Interventions trial, bone density increased at the lumbar spine and femur in women who received ET or EPT (0.625 mg CEE/MPA or micronized progesterone) for 3 years compared with the control group[24]. In the WHI study, bone density at the lumbar spine and femur increased by 4.5% and 3.7%, respectively, with the standard-dose EPT (0.625 mg CEE + 2.5 mg MPA) compared with the control group[25] In the WHI study, the risk of facture significantly decreased by 33% at the lumbar spine and 35% at the femur using EPT and by 38% at the lumbar spine and 39% at the femur using ET. This protective effect rapidly disappeared after stopping MHT, and the long-term follow-up study of WHI reported that the ET group showed a continued reduction effect of all fractures after stopping therapy, whereas the EPT group showed no reduction in all fractures[26].

The osteoporotic fracture with combined HT vs. placebo was reduced at the hip (HR 0.67, unadjusted 95% CI 0.47–0.96) and at the vertebrae and wrist (HR 0.65, unadjusted 95% CI 0.46-0.92 and HR 0.71, 95% CI 0.59-0.85, respectively [27]. Also Estrogen therapy may improve balance and reduce the tendency to fall.

Raloxifene is a Selective estrogen receptor modulators (SERM), it is effective for reduction of osteoporosis related fractures. Raloxifene inhibits bone resorption and reduced the risk of vertebral fracture, but there is no evidence that it reduces the risk of hip fracture, and for that reason, it is considered a second-line agent. It is unclear how long SERMs can be safely administered; many clinicians discontinue therapy at 8 years because of lack of safety data beyond that time frame[23].

Which drug to use?

Commonly used drugs

Oral Bisphosphonate (risedronate, alendronate, ibandronate, and zoledronic acid) forms should be taken in the morning with at least 8 ounces of water, in an upright position, with no other ingestions for at least 40 minutes. These are very effective and can be used as 1st line drugs.

The intravenous (IV) bisphosphonates (zoledronic acid and abandronate) can be utilized for patients who cannot tolerate oral bisphosphonates (i.e., inability to sit up for 40 minutes). IV bisphosphonates are sometimes associated with hypocalcemia and influenza-like symptoms[23].

The maximum duration of therapy is 10 years for oral bisphosphonates and 6 years for IV bisphosphonates.

Denosumab

Denosunab is as a human monoclonal antibody that acts on the key bone resorption mediator RANKL, thus inhibiting osteoclast formation and survival. It has been shown to increase BMD and reduce the incidence of fracture in postmenopausal women. Because of the increased risk of fractures following discontinuation of therapy, continuing therapy or administration of another agent following discontinuation should be considered[28,29].

2. Anabolic Agents

Parathyroid hormone, Teriparatide and abaloparatide are anabolic agents, which stimulate bone formation and activate bone remodeling. These drugs are very expensive so we are not using these drugs as 1st line. Women with severe osteoporosis (T < -2.5 with a fragility fracture) and when patients can't tolerate other therapies, or in patients who fail to respond to other

therapies anabolic drugs are prescribed. Adverse effects include mild upper GI symptoms, hypercalcemia, and depression. They are not advocated to use longer than 24 months, as there is risk of osteosarcoma.

Bazedoxifine is a SERM that is used in Europe and Japan for women with osteoporosis. It is also available in Bangladesh and used in combination with estrogen for the prevention of osteoporosis.

Romosozumab is a promising drug and it increases the bone mass density and reduce vertebral and nonvertebral fractures. But it is very expensive and has been associated with an increased risk of serious cardiovascular events[30].

Conclusion:

To combat osteoporosis is very challenging but possible. Bone loss/fracture is an inevitable consequence of increased longevity. Women are more prone to develop osteoporosis. Osteoporosis and its complications cause profound sufferings. They remain silent but are common causes of morbidity and mortality. So all should adopt preventive strategies by maintaining, "bone healthy life style" with optimum food, regular exercise and avoiding bone toxic agents. Adequate calcium, vitamin D, sunlight, practicing weight bearing exercise, avoiding tobacco, excess alcohol consumption and sedentary life style is paramount important. Women should be screened for osteoporosis beginning at age 65 or earlier if having risk factors. Once diagnosis of osteoporosis is made, they should be offered pharmacologic therapy. MHT has tremendous role for osteoporosis and fracture prevention so it should be offered to women when indicated. All elderly should adopt fall prevention strategies.

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