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CLINICAL PRACTICE UPDATE IN
ENDOCRINOLOGY & DIABETES

OSTEOPOROSIS

Breaking Through the Tough Questions

Bisphosphonates were first developed in the 1960's by the detergent industry to manage calcium deposits. By the 1990's, their ability to bind to bone became apparent but their inhibition of both resorption and formation led to osteomalacia. "Second generation" bisphosphonates (risedronate, alendronate, zoludronate) have 1000-fold greater potency for inhibition of bone resorption vs formation. The result is BMD increases of 4-10%, typically associated with a 40-60% reduction in fractures.

Hasnain Khandwala
MB, BS, FRCPC

Jodi Fox
MD, D. ABIM

SHOULD I CONTINUE BISPHOSPHONATE TREATMENT AFTER 5 YEARS? SHOULD I CONSIDER A "DRUG HOLIDAY" FOR STABLE PATIENTS?

These medications become buried in bone very effectively and their true duration of bone effect is not clearly understood. They are released from bone gradually, over years, by both bone remodelling and by release from osteoclasts.

Both alendronate and risedronate have been demonstrated to be safe and effective for long durations – up to 10 years and up to 7 years, respectively. In an extension study of 247 postmenopausal women, alendronate resulted in continued increases in BMD. The total 10-year increase in LS density was 13.7%; compared to 10% after the first 5 years.

"stopping therapy led to gradual LOSS of prior BMD gains"

Similarly, in an extension study of 164 post-menopausal women, after 7 years of continuous risedronate treatment, LS BMD increased by 11.5% and bone turnover markers were still suppressed by 54% from baseline levels.

Although there is currently no consensus on length of therapy, the FLEX follow-up of the landmark FIT trial (1099 postmenopausal women) showed that stopping therapy led to gradual loss of prior BMD gains. One measure of fracture was also measurably higher in the group that stopped therapy (clinically detected vertebral fractures 5.3% vs. 2.4%).

There is no current standard of practice regarding stopping therapy or taking a "drug holiday" after long-term bisphosphonate therapy. Here are a few pointers to help provide individual clinical judgment:

1 ▸ Many women began bisphosphonate therapy when HRT therapy fell into disfavour following the disappointing results of the Women's Health Initiative. Many of these women, in retrospect, carry a lower degree of fracture risk. In these patients, with

no other risk factors for fracture, it may be reasonable to stop bisphosphonate therapy and follow BMD clinically.

2 ▸ Observational studies have suggested that the fracture benefit seen with alendronate may not persist if therapy duration was <2 years. If therapy is indicated, a minimum duration of 5 years should be considered.

3 ▸ Women at highest risk for fracture have not been studied in a "stop therapy" format and should be continued on therapy if well-tolerated.

WHAT ABOUT OSTEONECROSIS OF THE JAW (ONJ)?

ONJ awareness has become a point of concern amongst our patients. Osteonecrosis, or "avascular necrosis", is a pathological process associated with several therapies. Although the underlying mechanism is unknown, compromise of bone vasculature results in marrow cell death. Associated symptoms include swelling, pain, local infection and possible fracture of the mandible and maxilla. Almost all reported cases have occurred in patients who are either immune-compromised or receiving IV bisphosphonate as a chemotherapy agent (multiple myeloma and metastatic breast cancer).

"almost all reported cases have occurred in patients who are either IMMUNE-COMPROMISED or receiving.. CHEMOTHERAPY.."

In one prospective study, ONJ risk was highest with underlying dental disease, malignancy, and extended duration of therapy. There has been a greater association with zoledronic acid therapy (Aclasta) as a chemotherapy agent, possibly due to its higher potency. Little data exists for risk of ONJ with IV bisphosphonate at osteoporosis doses.

In outpatient osteoporosis populations, there have been <100 adjudicated cases of ONJ, a risk estimated to be as low as 0.7 in 100,000 patient-years. Patients initiating bisphosphonate therapy should be made aware of the risk of ONJ but the American Society of Bone and Mineral Research suggests that a baseline dental visit is unnecessary.

Invasive dental procedures in a bisphosphonate user remain controversial. The American Association of Oral and Maxillofacial Surgeons suggests that long-term users (>3years) should discontinue their oral bisphosphonate for three months prior to surgery with resumption of the medication after recovery. Despite a lack of supportive evidence, a brief "therapy holiday" is unlikely to be harmful.

WHEN SHOULD I TREAT OSTEOPENIA?

Osteoporosis has been arbitrarily defined as BMD of 2.5 standard deviations or more below the mean BMD of young (mean 30 years old), healthy women (t-score < -2.5). Low bone mass (osteopenia) is then defined as a t-score between -1.0 and -2.5. Although fracture risk is greater in osteoporosis, there are far greater postmenopausal women in the osteopenia range. The vast majority of fractures actually happen to women with osteopenia and many of these fractures can be prevented.

Therapy guidelines have shifted from being BMD-based, using old WHO criteria, to now better address an individual's specific fracture risk. We therefore use the BMD result and clinical information to determine who carries the highest risk for fracture – and therefore, are most likely to benefit from therapy. For Canadian populations, we have chosen to use European population fracture predictive data to combine age, sex and BMD result to determine fracture risk, for patients over 50 years of age. Fracture risk is defined as low, medium, or high, based on 10-year risk of <10%, 10-20% and >20%. Fracture risk is poorly understood in younger populations. Two additional risk factors significantly increase fracture risk for BMD – prior fragility fracture and exogenous glucocorticoid therapy. Either would suggest an increase in risk category by one level. Other multiple risk factors can be considered as well, including advanced age, smoking, excess alcohol consumption, reduced mobility and hyperparathyroidism.

Most patients in the "low" or "moderate" fracture risk categories will not achieve substantial benefit in fracture risk reduction from bisphosphonate therapy. Alternatives may include non-pharmacologic therapy for low bone mass – adequate calcium intake, vitamin D supplementation, exercise (especially weight-bearing), smoking cessation, and moderation of alcohol intake.

HOW MUCH CALCIUM & VITAMIN D SHOULD I BE RECOMMENDING? WHAT ARE THE UPPER LIMITS?

An optimal diet for treatment (or prevention) of osteoporosis includes an adequate intake of calcium and vitamin D. Postmenopausal women (and older men) should take adequate supplemental elemental calcium (generally up to 500 to 1000 mg/day), such that their total calcium intake, including food calcium, approximates 1500 mg/day. 300mg of Calcium can be obtained from items such as 1 cup milk, 1 cup fortified soy or OJ, 175ml yogurt, 50g cheese. The remainder of the diet typically provides an additional 300-400mg/day. Supplemental calcium has marginally higher bioavailability when taken in divided doses, and at mealtime.

"significant Vitamin D deficits seen in Canadian populations"

Of note, one large study based in New Zealand has demonstrated that higher calcium intakes (dietary intake plus supplements>1000mg/day) are associated with an increased risk of ischemic CAD events. This association hasn't been seen in other large studies and the results may have been skewed by higher CV risks in the "calcium supplement " group but it does seem reasonable to cap calcium intake at a total of 1500mg/day (dietary plus supplements).

Probably of greater importance is correcting the significant Vitamin D deficits seen in Canadian populations, especially in the winter months. Women with osteopenia should take supplements of 1000IU daily or higher as needed to bring their serum vitamin D levels into the normal range. Many populations, including children and teenagers, have been shown to be low in vitamin D, and to benefit from vitamin D supplementation. Vitamin D supplementation guidelines have not yet formally evolved and individual judgment should be used regarding using vitamin D supplementation to normalize 25-hydroxy vitamin D levels.

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LMC GUIDE TO BONE BUILDING EXERCISES

Starting an exercise program is very benefical for many reasons. One reason is the prevention of Osteoporosis.

TYPES OF EXERCISES

1. **Cardiovascular** - includes as walking, stair climbing, dancing; least 3 days/week for 30 minutes
2. **Resistance** - includes weight lifting, band exercises; 2-3 days/week with 1-3 sets of 10-15 reps
3. **Stretching** - includes Tai Chi, yoga; 4 – 7 days/week

- Exercises should be spread out through the week, alternating between cardio and resistance days.
- Warm up and cool down for 5-10 mins of low-intensity exercise followed by a stretching routine.
- Progession can be made based on each individual.
- Do a variety of exercises to reduce bordem and risk of injury.

BICEP CURL

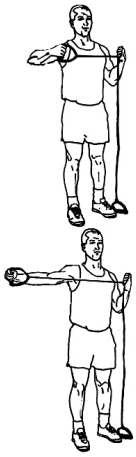
Stand on the band while holding onto the band with palms facing up. Keeping abdominals tight and knees slightly bent. Bend arms and bring palms toward shoulders in a bicep curl. Position feet wider for more tension.

Return to start and repeat.

TRICEP EXTENSION

Stand or sit and hold the band at your left shoulder with your left hand. Hold the end of the band with your right hand, elbow out to the side at shoulder level and bent. Press your right hand out to the side, straightening your elbow. Keep the elbow at shoulder level.

Repeat, and then change arms.



SEATED ROW

Sit with your back rested against the chair and your feet flat on the floor. Have the band anchor in front at chest height. Hold your arms out in front, with your hands just below chest level and the band slightly stretched. Pull your hands towards you, keeping your elbows close to your side.

Return to start and repeat.

HALF SQUAT

Stand on the centre of the band, feet shoulder-width apart, arms at your side, with the band fully stretched. Keep your abdominals tight and chest up. Slowly bend your knees until your thighs are at 45° angle. Keep your heels down, with your body weight over the ankles and your lower back in a natural arch.

Return to starting position and repeat.

STORK STAND

With a chair near by, stand on one leg with your other leg bent at the knee. Make sure you do both sides. To increase the difficulty try: closing your eyes, or moving the raised leg in and out or while tossing a ball from each hand.

BACK POSTURE

Sit in a chair with your hands behind your neck. Inhale while gently moving your elbows backward. Hold the position for a few seconds, breathing normally, before returning to your starting position.

Repeat 5 to 10 times, based on your ability.

My Weekly Schedule:

	Sun	Mon	Tue	Wed	Thurs	Fri	Sat
Cardio							
Resistance							
Stretching							

Who Should Be **Treated** for Osteoporosis?

3 STEPS:

1. Determine 10-year absolute fracture risk based on BMD & age & sex (see tables below)
2. If fracture risk is high – consider therapy
3. Escalate risk by 1 category for either of (a) fragility fracture or (b) glucorticoid therapy

Who Should be **Assessed** for Osteoporosis?

1. All patients > 65 years of age – baseline BMD and R/A based on findings (q3 – 5 years)
2. All patients < 65 years of age & with 1 Major Risk Factor:

- Fragility fracture or Family History of osteoporotic fracture
- Glucocorticoid therapy > 3 months
- Malabsorption
- Primary hyperparathyroidism
- Propensity to fall, instability
- Hypogonadism or menopause < 45 years of age

or with 2 Minor Risk Factors:

- Rheumatoid arthritis
- Prior hyperthyroidism
- Chronic anti-convulsant therapy
- Concerning dietary calcium intake
- "Bone toxins"– alcohol, caffeine, nicotine
- Low weight (< 57kg) or weight loss (>10%)

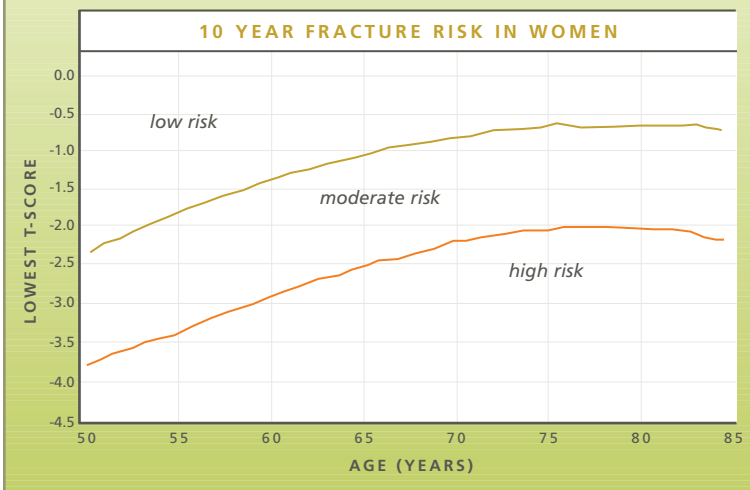
10 YEAR FRACTURE RISK IN WOMEN

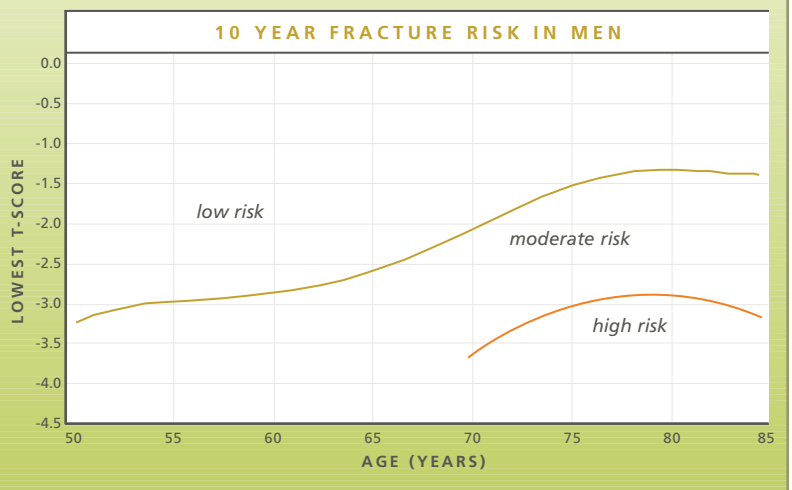
AGE	LOW <10%	MODERATE 10 TO 20%	HIGH >20%
50	>-2.3	-2.2 to -3.9	<-3.9
55	>-1.9	1.9 to -3.4	<-3.4
60	>-1.4	-1.4 to -3.0	<-3.0
65	>-1.0	-1.0 to -2.6	<-2.6
70	>-0.8	-0.8 to-2.2	<-2.2
75	>-0.7	-0.7 to -2.1	<-2.1
80	>-0.6	-0.6 to -2.0	<-2.0
85	>-0.7	-0.7 to -2.2	<-2.2

*L1-4 (minimum 2 valid vertebrae), total hip, trochanter and femoral neck

10 YEAR FRACTURE RISK IN MEN

AGE	LOW <10%	MODERATE 10 TO 20%	HIGH >20%
50	>-3.4	<=-3.4	- -
55	>-3.1	<=-3.1	- -
60	>-3.0	<=-3.0	- -
65	>-2.7	<=-2.7	- -
70	>-2.1	-2.1 to -3.9	<-3.9
75	>-1.5	-1.5 to -2.9	<-3.2
80	>-1.2	-1.2 to -3.0	<-3.0
85	>-1.3	-1.3 to -3.3	<-3.3





Additional areas for concern:

- Patients with diabetes
- Glitazone users
- Patients with eating disorders
- Using long-acting injectable OCP's

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DIABETES ▪ METABOLISM ▪ ENDOCRINOLOGY

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