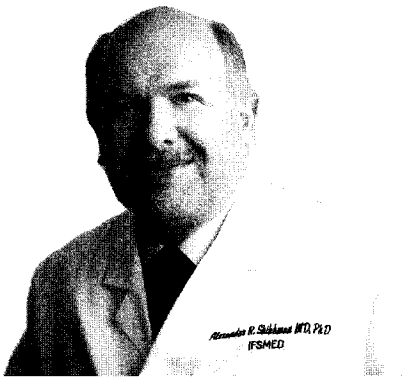

Risk Factors for Osteoporosis and Celiac Disease

By Alexander R. Shikhman, MD, PhD, FACR

It has been recognized for several decades that both children and adults with celiac disease have a significantly increased frequency of osteoporosis and increased risk of fractures as compared to the age-matched non-celiac healthy individuals. Based on published data the prevalence of osteoporosis among celiac patients varies from as low as 4% to as high as 70%. The data from our clinic indicate that prevalence of osteoporosis among adults with gluten intolerance and celiac disease is in the vicinity of 30-40%.

Characteristics and causes of osteoporosis

Osteoporosis is a bone disease characterized by the reduced bone mineral density and impaired bone architecture that leads to an increased risk of fracture. The three main mechanisms by which osteoporosis develop include an inadequate peak bone mass, excessive bone resorption and inadequate formation of new bone during remodeling.

At a given age, bone mass results from the amount of bone acquired during growth (the peak bone mass) minus the acquired bone loss due to variety of reasons including age-related processes, malabsorption syndromes, chronic steroid use etc. The rate and magnitude of bone mass gain during the pubertal years may markedly differ from one individual to another. It has been demonstrated that pediatric onset of celiac disease and poor compliance with gluten-free diet during childhood do significantly reduce peak bone mass.

One of the main causes of osteoporosis is an alteration in bone remodeling due to imbalance between bone formation and resorption, with a predominance of resorption resulting in a reduction in bone mass and increased risk of fractures. Formation of the new bone is facilitated by specialized cells, osteoblasts, which actively synthesize bone matrix. Bone resorption is mediated by other specialized cells, osteoclasts.

One of the main regulators of bone remodeling is the RANK/RANKL/OPG system. During bone remodeling, bone marrow cells and osteoblasts produce RANKL(receptor activator for nuclear factor kB ligand), which bonds with a transmembrane receptor of the osteoclast precursor, RANK(receptor activator of nuclear factor kB), causing their differentiation and activation. Osteoprotegerin (OPG) binds to RANKL before it has an opportunity to bind to RANK, and hence suppresses its ability to increase bone resorption.

Normal bone remodeling is based on the permanent renovation of the skeleton and consists of an initial phase of bone resorption followed by a phase of formation, both of which are regulated by general (endocrine) factors and local (paracrine) factors. The main endocrine factors include parathyroid hormone [PTH] and vitamin D as well as estrogens and, to a lesser extent, testosterone, thyroid hormones, growth hormone and leptin. Local factors include various cytokines (IL-1, IL-6 and TNF-a playing a role) key growth factors that regulate the process.

There are several well-characterized risk factors which contribute to the development of osteoporosis in celiac patients. These include:

1. Malabsorption of vitamin D and secondary hyperparathyroidism

Villous atrophy in celiac patients reduces the active absorption surface and induces steatorrhea (exces fat in feces), which has a chelating effect on calcium and vitamin D, making their absorption difficult. This reduces levels of the vitamin D transporting protein (calbindin and calciumbinding protein) and increases PTH synthesis which, in turn, lead to increased bone resorption causing osteoporosis.

"Risk Factors", continued

2. Malabsorption of vitamin K
Malabsorption of fat soluble vitamins including vitamin K is a common finding in celiac patients. Three vitamin-K dependent proteins have been isolated in the bone: osteocalcin, matrix Gla protein (MGP), and protein S.

Osteocalcin is a protein synthesized by osteoblasts. The synthesis of osteocalcin by osteoblasts is regulated by the active form of vitamin D—1,25-dihydroxy-cholecalciferol. The mineral-binding capacity of osteocalcin requires vitamin K-dependent gamma-carboxylation of three glutamic acid residues.

MGP has been found in bone, cartilage, and soft tissue, including blood vessels. The results of animal studies suggest MGP facilitates normal bone growth and development.

The vitamin K-dependent anticoagulant protein S is also synthesized by osteoblasts, but its role in bone metabolism is unclear. Children with inherited protein S deficiency suffer complications related to increased blood clotting as well as decreased bone density.

The data on the role of vitamin K in osteoporosis came from the clinical observations indicating that a chronic use of vitamin K antagonists such as warfarin increases risk of vertebral and rib fractures. Accordingly, vitamin K supplementation significantly lowers risk of vertebral and hip fractures.

3. Magnesium deficiency
Magnesium deficiency may be an additional risk factor for celiac-associated osteoporosis. This may be due to the fact that magnesium deficiency alters calcium metabolism and the hormones that regulate calcium. Several human studies have suggested that magnesium supplementation may improve bone mineral density. Magnesium deficiency is easily detected with laboratory tests (eg, low serum magnesium, low serum calcium, resistance to vitamin D) or clinical symptoms (eg, muscle twitching, muscle cramps, high blood pressure, irregular heartbeat). Screening for magnesium deficiency should be routinely included in the screening of celiac patients with osteoporosis.

4. Chronic diarrhea and metabolic acidosis
Chronic diarrhea in patients with celiac disease results in significant bicarbonate losses and development of metabolic acidosis. Bone is a major site for the extracellular buffering of the retained acid. Therefore, one of the main compensatory mechanisms maintaining a stable serum bicarbonate level in the face of an uncorrected metabolic acidosis is the dissolution of bone buffers and net efflux of calcium from bone. Bicarbonate supplementation in patients with metabolic acidosis decreases urinary calcium, phosphorus and hydroxyproline wasting supporting the concept of negative effects of acidosis on bone health.

5. Hypogonadism
Decline of estrogen production and activity is one of the main events in the development of age-related osteoporosis. It is well known that estrogen deficiency is important in the pathogenesis of osteoporosis not only in women but also in men. Increase in bone mineral density in young men and declines in older men are related to circulating free estrogen, not testosterone. In general, patients with celiac disease are characterized by low levels of circulating estrogens which contributes to the development of premature osteoporosis.

6. Chronic use of Proton Pump Inhibitors
Proton pump inhibitors (PPIs) are one of the most widely used classes of drugs. The commonly used PPIs include such drugs as Omeprazole (brand name: Prilosec), Lansoprazole (brand name: Prevacid), Dexlansoprazole (brand names: Kapidex, Dexilant), Esomeprazole (brand name: Nexium), Pantoprazole (brand name: Protonix) and Rabeprazole (brand name: AciphHex). Chronic use of PPIs for gastroesophageal reflux disease and other related conditions has been associated with impaired calcium and magnesium absorption and increased risk of vertebral and nonvertebral fractures.

7. Chronic use of Selective Serotonin Reuptake Inhibitors
Selective Serotonin Reuptake Inhibitors (SSRIs) are frequently used in celiac patients for treatment of depressive disorders. The commonly used SSRIs include such drugs as Citalopram (brand name: Celexa), Escitalopram (brand name: Lexapro), fluoxetine (brand name: Prozac), fluvoxamine (brand name: Luvox), Paroxetine (brand name: Paxil) and Sertraline (brand name: Zoloft). It has been demonstrated that SSRIs increase extracellular 5-HT (5-Hydroxytryptophan) levels that have deleterious skeletal effects. The skeletal serotonergic system consists of 5-HT receptors and the 5-HT transporter (5-HTT) in osteoblasts and osteocytes. 5-HTT is a transmembrane protein targeted by SSRIs. 5-HT restrains osteoblastic activity,

"Risk Factors", continued

thus leading to bone loss.

8. Autoimmune mechanisms
Autoimmune mechanisms have been long suspected as risk factors contributing to development of osteoporosis in celiac patients. Near a decade ago, it was demonstrated that sera from celiac patients with osteoporosis contains significantly high titers of antibodies against bones as compared to non-celiac osteoporotic patients. The immunostaining was localized in areas where an active mineralization process occurred and was similar to the distribution of the native bone tissue transglutaminase. Recently, it has been described that a subset of patients with celiac disease has autoantibodies to osteoprotegerin, which block the inhibitory effect of osteoprotegerin on signaling by the receptor activator of nuclear factor (NF)-kappaB (RANK), and are associated with severe osteoporosis and high bone turnover.

9. Chronic inflammation
Chronic inflammatory diseases, including celiac disease, are associated with overproduction of proinflammatory cytokines such as TNF-a, interleukin(IL)-1, IL-6, IL-11, IL-15 and IL-17 among others which activate osteoclasts and accelerate bone resorption leading to osteoporosis.

In conclusion, osteoporosis associated with celiac disease is not a coincidental problem. It is a consequence of disease-specific (autoantibodies to osteoprotegerin), disease-nonspecific (malabsorption of vitamin D, K and magnesium, hypogonadism, chronic inflammation, chronic diarrhea and metabolic acidosis) and jatrogenic (overuse of PPIs and SSRIs) events accelerating resorptive processes in the skeleton. Correction of the aforementioned risk factors in celiac patients can reverse the development of osteoporosis and reduce the risk of osteoporosis-associated fractures.

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A Fond Farewell to My Fellow Journal Readers

By Connie Sarros

Dear Friends and Readers,

I have been writing articles for Scott Adams since the 2002 Summer Issue of the Scott-Free Press. The Scott-Free Press evolved into the Journal of Gluten Sensitivity. I felt honored when Scott asked me ten years ago to contribute to his quarterly journal and it's been a privilege to write articles for his publication ever since.

Due to personal health reasons and restrictions, I find that I need to retire. My husband and I can no longer travel the country speaking at conferences and to support groups (which we dearly loved to do) nor can I commit to writing more books, articles, or menus. Consequently, I will no longer be contributing articles to the Journal of Gluten Sensitivity.

My following books will still be available at Celiac.com and/or www.Amazon.com:

- Gluten-free Cooking for Dummies
- Student's Vegetarian Cookbook for Dummies
- Wheat-free Gluten-free Dessert Cookbook
- Wheat-free Gluten-free Reduced Calorie Cookbook
- Wheat-free Gluten-free Cookbook for Kids and Busy Adults (revised version)

My first book was published in 1996. My journey since then has been incredible. I have met so many in the celiac community and I feel blessed to be able to call you friends. Many of you have told me that I helped to change your life – let me assure you that your kind words, your phone calls, your thoughtful notes, and your feedback throughout the years have had a vital impact on my life, too. Thank you for all of your support through these years.

Connie Sarros has traveled the country for years speaking to celiac support groups. She has a DVD "All You Wanted to Know About Gluten-free Cooking" and has written the following books:

- *Newly Diagnosed Survival Kit*
- *Wheat-free Gluten-free Dessert Cookbook*
- *Wheat-free Gluten-free Recipes for Special Diets*
- *Wheat-free Gluten-free Reduced Calorie Cookbook*
- *Wheat-free Gluten-free Cookbook for Kids and Busy Adults*
- *Gluten-free Cooking for Dummies*

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