CHAPTER **45**

# NONUNION RISK FACTORS

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Nonunions secondary to fractures and failed arthrodesis will be discussed. Co-morbidities, medications, and iatrogenic, patient induced factors leading to nonunions will be reviewed.

## CO-MORBIDITIES

Due to the nature of the podiatric profession and prevalence of the disease, diabetes is likely to be the most common co-morbidity that will be involved in the patient that develops a nonunion in our practices. The American Diabetes Association's 2007 National Diabetes Fact Sheet states the disease affects 7.8% or 23.6 million Americans. Diabetes retards bone healing. It has been shown that the glycation end products found in diabetes can retard bone healing between 40 to 60% (1). In the experimental animal model peri-implant bone was shown to be significantly decreased in two studies (2, 3) and another showed significantly decreased healing of tendon to bone in the rotator cuff. The strength of bone in fracture healing in the experimental rat model has been shown to be reduced in two studies (4, 5). In the diabetic patient population both tibial pilon fractures and ankle fractures have shown increased complication rates that included nonunion and delayed union (6, 7). Studies are currently underway to evaluate the efficacy of fibroblast growth factors in increasing bone growth in diabetes and osteoporosis and early results are promising (8, 9). This line of research may eventually lead to the discovery of other treatment options for this subset of patients and ultimately all patients at risk for non-union (8).

As baby boomers age, the increase in the elderly population will lead to an increase of osteoporosis in the podiatric practice. Osteoporosis strikes many subsets of the world population, including women, the elderly, and those with arthritis, autoimmune diseases, HIV, and the immuno-compromised. This disease predisposes people to an increased risk of low trauma and fragility fractures and increases the likelihood for nonunions. Approximately 40% of white women and 13% of white men ages 50 years will have a fragility or insufficiency fracture secondary to osteoporosis in the US. Studies using the rat model have shown decreased healing potential in the early (10, 11), middle, and late (12, 13) phases of bone healing. One retrospective study showed increased time to healing of femur fractures in a group of patients over 65 with osteoporosis at a mean of 19.4 weeks versus sub 40-year-old patients with normal bone mineral density at 16.2 weeks (14). Another prospective randomized trial involving 113 patients showed increased rate of nonunion and complications with 76% of the 33 failures occurring in patients with osteoporosis (15).

As podiatrists, we should also be alerted to the possibility of insufficiency fractures of the calcaneus in the absence of trauma (16) in patients with osteoporosis. These patients will typically present with "ankle" pain with tenderness noted along the superior-lateral aspect of the calcaneus with positive bone scan and magnetic resonance imaging and negative radiology findings for up to 2 months.

Rheumatoid arthritis has increased risk for osteoporosis secondary to both the disease process and its treatment in the form of prednisone and methrotrexate. There is a correlation between bony erosions and decreased bone mineral density leading to higher risk for fracture (17). A recent study has also implicated glycation end products similar to those seen in the diabetic patient for the osteoporosis seen in the rheumatoid population (18).

Several retrospective studies have looked at fusion rates in the rearfoot. Relative to the ankle fusions one author published two separate papers. In one, a series of 25 tibiocalcaneal fusions with a retrograde intramedullary nail resulted in one nonunion and three deep infections (19). The second study reviewed 35 ankle fusions 13 performed percutaneously and 22 open fixated with compression screws. Nine went on to nonunions with no difference between the open versus percutaneous groups. Citing the nonunion rates and decreased patient satisfaction the authors did not recommend compression screw fixation for ankle fusion in the rheumatoid population. Another retrospective study of 32 ankle fusions compared the rate of fusion with external fixation (19) versus internal fixation via 6.5 millimeter cancellous compression screws (13). They had four failures all secondary to infection in the external fixation group. Three failed to fuse with one secondary to infection in the internal fixation group. They found no

differences in fusion rates or complications comparing the two groups (20). The tibio calcaneal nail was modified with four fins in the calcaneus and inserted in 15 ankles without a nonunion and two wound complications (21).

Another study using a Kuntscher tibio-calcaneal nail and early mobilization had an 80% fusion rate with two nonunions in eleven. Triple arthrodesis with staple fixation and autologous bone grafting had a 100% successful fusion in 32 feet with all patients relating they would have the procedure again (22). Arthrodesis rates although generally acceptable in the rheumatoid patient do present with increased complications and as expected somewhat higher failure rates.

Primary hyperparathyroidism, although rare at 100,000 cases or 1 in 2,719 Americans, can lead to significant bone loss and hypercalcemia. As the name implies this disease is of the hyperparathyroid gland due to adenoma, hyperplasia, or less likely carcinoma of the parathyroid gland. This population will have elevated parathyroid hormone and calcium levels secondary to increased bone resorption.

Secondary hyperparathyroidism occurs when the parathyroid is responding to decreased calcium or increased phosphate levels. The most common cause for this is chronic renal failure. Failing kidneys do not convert enough Vitamin D to its active form and do not adequately excrete phosphorus both leading to hypocalcemia. This in turn stimulates the parathyroid glands leading to increased bone resorption. Other causes for secondary hyperparathyroidism include malabsorption of calcium found in chronic pancreatitis, small bowel disease, and more often now with bariatric surgery specifically gastric bypass. Long term lithium use will also cause decreased calcium levels and the secondary form.

Finally tertiary hyperparathyroidism occurs when the parathyroid has been up-regulated for a long time even if the original insult is corrected as is sometimes seen following kidney transplant. In these cases the parathyroid hypertrophy is irreversible. Regardless of the cause of the overactive parathyroid the hormone secreted leads to decreased bone density. One study addressed the incidence of secondary hyperparathyroidism in postmenopausal females about to undergo total knee replacement. They evaluated renal function, intact parathyroid hormone, calcium and phosphorous levels and found 35% of these patients to have secondary hyperparathyroidism. They recommended pre-operative screening for elevated intact parathyroid hormone before total knee replacement (23). Certainly, many of our patients will tell you that they have compromised kidney function and should have this evaluated for secondary hyperparathyroidism before proceeding. The underlying hypocalcemia can be addressed and in most cases will reverse the hyperparathyroidism. Conversely, parathyroidectomy and hypoparathyroidism and pseudohypoparathyroidism result in hypocalcemia and negative changes in bone.

Vitamin D plays an important role in bone health. Rickets, a childhood disease, and the adult form, osteomalacia, are secondary to malnutrition with decreased calcium and Vitamin D are more often seen in developing countries. However, we are now seeing more cases of rickets in the US and Europe. There is also a rise in subclinical Vitamin D deficiency especially in the colder climates and during the winter months. There is increased attention being given to the role that subclinical Vitamin D deficiency is playing in bone health, increased fracture risks in both the clinical and laboratory setting. Within the last few years three major laboratories have seen significant increases in testing with increases of 74% (Mayo Clinic), 80% (Quest) and 90% (LabCorp). One prospective study compared Vitamin D levels in controls of age-matched 41 inpatient and 41 outpatient males and 41 hip fracture patients. Subclinical Vitamin D (defined as <50 nmol/L serum 25-hydroxyvitamin D) was 63% in the fracture group, compared with 25% in the control groups. The investigators concluded that subclinical Vitamin D deficiency and resulting secondary hyperparathyroidism was the leading risk factor for hip fractures compared to age, body weight, tobacco, comorbidity, corticosteroids, and alcohol (24).

Osteogenesis imperfecta, a genetic disorder compromising the connective tissue structure secondary to malformed Type I collagen, results in a very high nonunion rate (25-28). Paget's disease or what is now called osteodystrophia deformans is an inflammatory reaction possibly secondary to a virus results in a three phase reaction in bone. Increased osteoclastic activity is followed by a mixed clastic and blastic cycle and ultimately a burned out phase where there is hyperdense bone. Many patients may be subacute and not symptomatic. They will have elevated alkaline phosphatase levels with normal calcium and phosphate levels. By itself this is not a direct contraindication to surgery, but the surgeon must bear in mind that the disease process does alter bone remodeling and results in a higher complication rate.

As podiatrists we are acutely aware of the role the vascular system plays in lower extremity healing and pathology. We screen all our patients for peripheral vascular disease; however, we must also consider the role of anemia and any myelodysplasias (29-32), which can either slow or prevent bone healing. Although clinical data was lacking, one prospective randomized experimental study induced anemia in the rat model and demonstrated significantly reduced osteogenesis in the anemia model (29).

## PATIENT DERIVED RISK FACTORS

As of 2005, the US Department of Human Services reported that just over 20% of Americans or 45 million Americans smoked tobacco. Tobacco use is the single most devastating user-controlled health risk. One study showed an increase in nonunion rate for hindfoot fusions at 2.7 times the rate than in non smokers. The same study found a residual increase in those who quit smoking, albeit decreased when compared to those who continued to smoke, in nonunion rates (33). Using the Austin bunionectomy as an elective surgical model and radiographic bone healing as the criteria, Krannitz et al found that in the smoking population time to bone healing was 1.7 times longer (34). There is no paucity of data on the negative effects of tobacco on bone healing, fractures and arthrodesis in both the animal model and patient population. It behooves the podiatric surgeon to seriously consider the possible sequela of nonunion in the smoking population. In the author's practice all fusion procedures involving the midfoot and proximal require that the patient quit smoking prior to surgical intervention. All patients undergoing surgery are advised of the increased risk of tobacco use on bone and wound healing.

The correlation between obesity and bone quality or osteoporosis is currently under investigation with data showing equivocal results. One recent animal model found that in mice fed a high fat diet had an associated decrease in bone mineral density (35). There may also be a genetic relationship between obesity and osteoporosis (36). It is clear that the obese patient does present with higher incidence of orthopedic complaints including fractures (37-40). There is clear evidence of bone loss secondary to gastric bypass for morbid obesity secondary to decreased Vitamin D and calcium and up-regulation of parathyroid hormone (see secondary parathyroidism under co-morbidities). Gastric banding has not shown the same effect on bone quality. Another practical consideration of the obese patient is whether the patient will be able to remain nonweight bearing following surgical intervention and the possible increased load on the fracture or fusion site during the transition to full weight bearing. One retrospective study including 279 patients undergoing surgical repair of ankle fractures did not find any significant differences in complications, functional outcomes or time to healing in the obese population (41).

Excessive alcohol consumption can lead to an increase in osteoporosis and decreased ability for bone healing. As would be expected there is also an increase in fall risk and subsequent fractures in this population. An animal model using rats showed that elevated alcohol consumption decreased total bone mineral content with decreased bone formation at periosteal and cancellous sites (42). One retrospective study showed increase healing time in tranvserve tibial fractures in alcohol abusers (43). A meta-analysis performed in 2007 showed that consuming 0.5 to 1.0 servings of alcohol per day had a lower hip fracture rate then abstainers but 2.0 servings per day increased hip fracture rates. Interestingly, there was increased bone mineral density with alcohol use but because the reviewed articles failed to stratify the amount of alcohol it could not determine if higher consumption resulted in decreased density (44).

A form of iatrogenic osteoporosis we also need to consider is disuse osteopenia whenever we require immobilization and/or nonweight bearing. Aggressive return to activity may result in fractures. There have been cases of calcaneal and tibial stress fractures reported in the literature following treatment for acute leg fractures. Certainly other causes of disuse osteopenia must also be considered such as hemiplegia following stroke, spinal cord injuries or any condition that may immobilize the patients. This can also increase risk of nonunion secondary to the osteoporosis.

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