GREETINGS FASIG MEMBERS!

In this issue, we have an important message from Dave Sinacore about why and how we all have an important role in evaluating and directing care in our patients who have diabetes. Please heed the message: your patients will thank you.

Frank

Dem Bones, Dem Bones, Dem Foot Bones: Recognizing the Foot Bone-Kidney Connection

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I am certain most of you are familiar with the spiritual song "Dem Bones." You remember…"Toe bone connected to the foot bone; foot bone connected to the heel bone; heel bone connected to the ankle bone, etc…etc." These lyrics composed by songwriter James Weldon Johnson (1871-1938) were believed to be inspired by the prophet Ezekiel [Ezekiel 37:1-14] when he visits the "Valley of the Dry Bones."[1]

Well, today Ezekiel and songwriter Mr. Johnson would likely describe that *"the foot bone connected to the kidney"*… This connection would be entirely accurate and profoundly prophetic, specifically impacting our patients with diabetes mellitus, peripheral neuropathy, and chronic kidney disease (CKD). Physical therapists and particularly members of the Foot and Ankle Special Interest Group of the Academy of Orthopaedic Physical Therapy should be keen to recognize and understand this important connection, since it has long been recognized that end-stage renal disease is a major risk factor and contributor to non-traumatic lower extremity (foot) amputation in individuals with both phenotypes (ie, type 1 and 2) of diabetes mellitus.[2] When the complications of diabetic peripheral neuropathy combine with progressive diabetic nephropathy (the most common type of CKD), the risk for foot ulceration and lower extremity amputation (LEA) increase dramatically.[3]

Renal osteodystrophy (the older term was renal rickets) occurs in nearly 90% of individuals with diabetes mellitus and CKD with a progressively increasing prevalence in the later stages of CKD (ie, stage 4 and stage 5).[4] Historically and currently, bone histology from bone biopsy of the ilium remains the gold standard method for diagnosing and classifying the type of renal osteodystrophy (ROD). Radiological diagnosis of ROD using dual-energy x-ray absorptiometry (DXA) or quantitative computed tomography to assess the loss of bone mass (bone mineral density [BMD]) in the hip or lumbar spine has become more routine for follow-up in those individuals with established disease.[5] However, as our methods of regional BMD assessments have improved, it is now apparent that foot bones lose both cortical and trabecular bone mass at a rate that may exceed the loss in the hip and lumbar spine.[6,7] In fact, pedal osteolysis may be the incipient biomarker of ROD in the foot resulting in neuropathic fractures, acute Charcot neuroarthropathy and chronic foot deformities leading to sequelae such as plantar ulcerations and osteomyelitis that too often culminate in partial or complete foot amputation.[8]

What is the foot bone-kidney connection?

Like most physiological and metabolic cascades, the bone-kidney axis is highly complex. Despite the complexities of these endocrine interactions, a decreasing functional nephron mass in CKD clearly impairs the kidney's ability to filter metabolic toxins and interferes with the kidney's vital role in regulating the body's serum phosphate and calcium stores. The burden placed on the remaining functioning nephrons to regulate and maintain serum phosphate and calcium levels, stress the bone-kidney axis by triggering the skeleton's osteocytic secretion of several circulating factors including fibroblast growth factor 23 (FGF23) and sclerostin.[9,10] The FGF23 is an osteocyte-derived hormone that regulates phosphate excretion, whereas sclerostin is an important osteocyte-secreting protein (one of the circulating wingless-related integration site [WNT] inhibitor proteins) that inhibits new bone formation and remodeling. In CKD, elevated secretion of sclerostin not only derives from skeletal osteocytes, but also may arise from the smooth muscle cells in the vascular media causing excessive vessel stiffness and difficulty regulating blood flow to the foot. In CKD, high levels of sclerostin are directly associated with vascular and extra-vascular calcification.[10]

What is the link of CKD-MBD to foot bones?

In 2006, the Kidney Disease: Improving Global Outcomes (KDIGO) working group described a new syndrome of Chronic Kidney Disease-Mineral Bone Disorders (CKD-MBD).[11] This evolving syndrome now links progressive renal disease to atherosclerotic cardiovascular disease and mineral-bone disorders resulting in early-onset and accelerated morbidity and mortality. The definition of CKD-MBD syndrome (which now incorporates all forms of ROD) includes any of the following: (1) abnormalities of calcium, phosphorus, parathyroid hormone (PTH), or vitamin D metabolism; (2) abnormalities in bone turnover, mineralization, volume, linear growth, or strength; and (3) vascular and extravascular calcification.[11]

Chronic Kidney Disease-Mineral Bone Disorders in the foot may begin as early as stage 2 CKD due to a small rise in serum FGF23 and sclerostin.[9,10] These serum increases may trigger a secondary hyperparathyroidism (2HPT) resulting in an elevated plasma concentration of parathyroid hormone (ie, PTH). Parathyroid hormone increases the activity and number of osteoclasts resulting in a compensatory increase in serum calcium concentration [Ca^{2+}] but with an accelerated bone loss (osteolysis) from the body's stores including the small bones of the foot.[6] Prolonged mobilization of calcium phosphate from hydroxyapatite stores in foot bones result in an accelerated osteolysis and a concomitant increase in foot vessel calcification.[12] Both of these effects increase the risk of well-known and potentially compounding effects resulting from neuropathy and vascular disease leading to foot deformities, ulceration. and ultimately LEA.

As evidence for a CKD-MBD-foot bone connection, the

author has reported preliminary evidence that pedal osteolysis may start as early as stage 2 CKD when the estimated glomerular filtration rate falls to between 89-60 ml/min. Using quantitative ultrasonometry, calcaneal BMD decreases (compared to stage 1) by 12% in stage 2, by 20% in stage 3, and can average 40% loss in BMD by stage 5 or end-stage renal disease were found.[13] Compared to stage 1 CKD, there is an increasing prevalence of pedal vessel calcification beginning as early as stage 2 CKD and progressing in prevalence to 68% in stages 3, 4, and 5 CKD. The presence of pedal vessel calcification on foot radiographs of diabetic neuropathic individuals has a diagnostic odds ratio =7.2x for having CKD-MBD in the foot compared to individuals with diabetic stage 1 CKD.[13] The author believes that progressive CKD-MBD results in an increasing prevalence of pedal impairments including mid foot deformities, Charcot neuroarthropathy, and pedal vessel calcifications that ultimately result in LEA.[14,15] Physical therapist-foot and ankle specialists should continue to seek the most effective interventions to attenuate the impact of pedal CKD-MBD and to prevent non-traumatic LEA in their patients with diabetes and peripheral neuropathy.

What can physical therapists do for the foot bone-kidney connection?

With an understanding that the diabetic foot is an early target for CKD-MBD, the physical therapist-foot and ankle specialist has an evolving and important role in recognizing pedal CKD-MBD and preventing non-traumatic LEA in their patients. Routine assessment of the neural, vascular, and musculoskeletal health of your patients' feet is the key to early recognition and prevention. Any combination of diabetes, neuropathy, vascular disease, and progressive CKD should alert the patient of a need for further follow-up. A referral to the patients' primary care physician or other health care specialist including endocrinologist, podiatrist, orthopedic surgeon specialist, or vascular surgeon for more thorough evaluations including diagnostic imaging of the feet using radiography, DXA, CT, or quantitative ultrasonometry may be necessary. Alerting your patients and their health care team of any evidence of CKD-MBD-related foot impairments may initiate early interventions that can prevent many of the sequelae which lead to primary LEA.

As with most musculoskeletal impairments, recognition and early interventions are key to preventing subsequent complications. Screening for diabetic peripheral neuropathy (**Figure 1**), foot deformities, inflammation, callus and high stress (pressure) patterns on the foot, fit, and type of footwear, ulcerations in the skin and ankle-brachial indices (**Figure 2**) in each foot of every patient seen with diabetes may alert the physical therapist of developing complications in the foot.

Your patients' musculoskeletal health is a physical therapist's primary concern. Recognizing the diabetic foot-kidney connection early will potentially save your patients' feet. As the chorus of the song suggests, "Dem bones, dem bones gonna walk around, Now hear the word of the Lord." With your help, your patients are "gonna walk around" for many for years to come.

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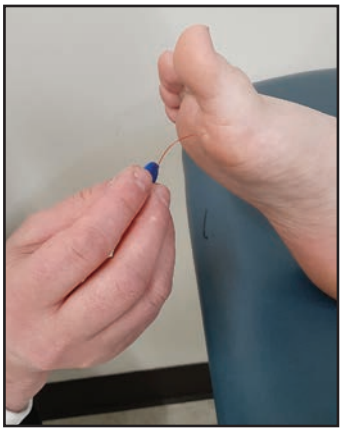
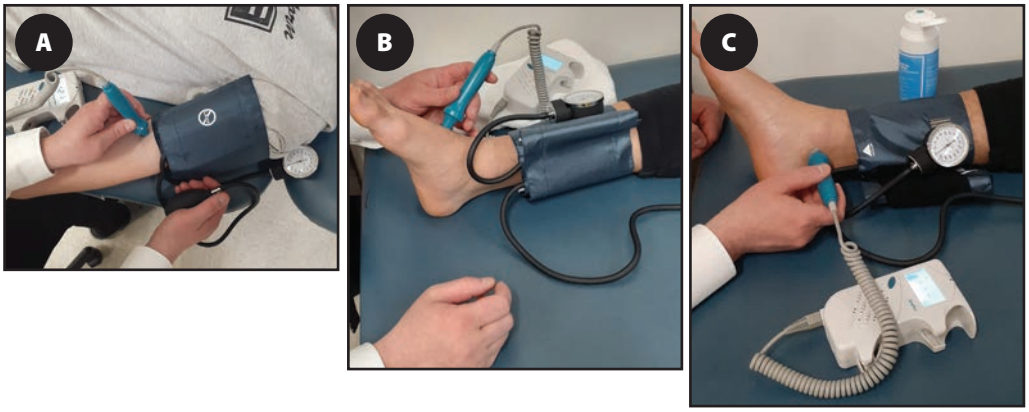
Figure 1. Protective Sensation Testing



Place the 10-g monofilament perpendicular to the plantar surface until you achieve the primary C shape: asking the patient to report if they feel the monofilament. Test multiple locations, lending less credence to testing over callouses. 1+ insensate locations warrants consultation on foot care and footwear. For more information check out #11 in this link: https://diabetesjournals.org/care/issue/44/Supplement_1

Figure 2. Ankle-Brachial Index Testing



Use a handheld Doppler to auscultate brachial (A) and dorsalis pedis (B) and/or posterior tibial (C) artery systolic blood pressure. For each leg separately, divide the highest ankle pressure (dorsalis pedis or posterior tibial) by the highest brachial pressure (across both arms). Values greater than 1.4 or below 0.8 warrant medical referral. For more specifics check out this link: http://stanfordmedicine25.stanford.edu/the25/ankle-brachial-index.html.

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Highlights

- The diabetic neuropathic foot is at highest risk for non-traumatic lower extremity amputation.
- Chronic kidney disease-mineral bone disorder contributes to the highest risk for LEA in the diabetic neuropathic foot.
- Physical therapists should screen ALL their patients with diabetes for impairments including neuropathy, deformities, inflammation, callus (pressure) patterns, fit and type of footwear, ulcerations in the skin and ankle-brachial indices in each foot.
- If the physical therapist finds any combination of foot impairments, they should alert the patient to seek follow-up by their primary care physician and health care team.

What is an Infographic?

An infographic is a visual image such as a chart of diagram used to represent information or data. The infographics are tailored for the audience - "clinician focused" and "patient focused" version can be used to help inform care for each group.

Contact Megan Peach if you have an idea or want to help generate an Infographic (megan@excelptmt.com).