Risk Factors for Amputation in the Diabetic, Neuropathic Foot in Patients with Chronic Kidney Disease

Victor Cheuy[1], Rodney Gross[1], Saghi Sadoughi[1], Gabriella Ramil[1], David Sinacore[2], Mary Hastings[3], Galateia Kazakia[1]
[1]University of California, San Francisco, CA, [2]High Point University, High Point, NC, [3]Washington University in St. Louis, St. Louis, MO
victor.cheuy@ucsf.edu

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INTRODUCTION: Non-traumatic lower extremity amputations (NLEA) in people with diabetes have increased 50% since 2009 in the United States. People with diabetic neuropathy (DN) and chronic kidney disease (CKD) are 15 times more likely to have a NLEA compared to diabetes alone and have a 71% 3-year mortality rate after an NLEA. The effect of CKD on pedal bone quality has not been studied in this population, representing a large gap in knowledge in NLEA prevention. Impaired skeletal health and foot dysfunction could contribute to structural deformities and ulceration, known precursors to NLEA. The purpose of this study was to determine if DN and CKD negatively affect pedal bone quality, plantar pressures, and joint kinematics beyond DN alone.

METHODS: This study was conducted with approval from the UCSF institutional review board (IRB #19-27927) and all participants gave informed consent prior to participation. This cross-sectional, observational study recruited three groups: controls (CON), those with DN without CKD (DN), and those with DN and CKD (DN+CKD). Group designation was determined by diagnosis of diabetes, the Michigan Neuropathy Screening Instrument (MNSI), and serum creatinine to estimate glomerular filtration rate (eGFR) using the CKD-EPI equation. High resolution peripheral quantitative computed tomography (HR-pQCT, XCT II, Scanco Medical AG) evaluated second metatarsal cortical and trabecular bone microarchitecture at distal, proximal, and mid-diaphysis sites using a binarization approach based on a Laplace-Hamming segmentation. Dynamic gait plantar pressure data were collected on an HR Mat System (Tekscan), mapping the foot into hind-, mid-, and forefoot regions. Three-dimensional joint kinematics and kinetics during gait were collected on a motion capture system (Vicon) with force plates (AMTI), and processed with QTM (Qualisys AB) and Visual3D (C-Motion) software. Fisher Exact tests and ANOVA with Tukey's HSD post-hoc pairwise comparisons were used to determine differences between groups.

RESULTS SECTION: 14 people were enrolled in the study (Table 1; CON: n=4; DN: n=4; DN+CKD: n=6). Groups were equivalent for all demographics. DN+CKD had the highest cortical porosity compared to CON (4.4% vs 2.3%, p=.005) and DN (4.4% vs 2.8%, p=.026). Hindfoot pressure time integral was highest in DN+CKD compared to CON (13.8 vs 6.5 PSI-sec, p=.004). DN+CKD had the greatest deficits in rearfoot dorsiflexion during stance (6.9 vs 18.0 deg, p=.043) and swing phases (4.3 vs 16.4 deg, p=.009), and less ankle power (2.1 vs 3.4 W/kg, p=.004) compared to CON.

DISCUSSION: People with DN+CKD exhibited poorer bone quality, increased plantar pressures, and greater ankle joint dysfunction. Taken together, these foot changes may be the earliest contributors to structural deformities, ulcers, and ultimately NLEA. The main study limitations are the cross-sectional study design and small sample size. Future directions are to longitudinally investigate how CKD severity and progression relate to bone quality, plantar pressure, and joint function in the DN+CKD population, and determine how these factors relate to clinically relevant poor foot outcomes.

SIGNIFICANCE/CLINICAL RELEVANCE: CKD prevention and treatment is key to NLEA prevention; CKD-induced bone deterioration synergistically combines with the negative effects of DN on ankle function and plantar pressure in patients at highest risk for NLEA. Assessment of key bone, pressure, and foot function metrics have the potential to identify early risk factors for NLEA, when prevention methods are most effective.

REFERENCES: Geiss LS, et al. Resurgence of Diabetes-Related Nontraumatic Lower-Extremity Amputation in the Young and Middle-Aged Adult U.S. Population. Diabetes Care. 2019;42(1):50-4. | Harding JL, et al. Trends of Nontraumatic Lower-Extremity Amputation in End-Stage Renal Disease and Diabetes: United States, 2000-2015. Diabetes Care. 2019;42(8):1430-5. | Sadoughi S, et al. A Laplace-Hamming Binarization Approach for Second-Generation HR-pQCT Rescues Fine Feature Segmentation. J Bone Miner Res. 2023 Apr 27. Epub ahead of print.

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IMAGES AND TABLES:

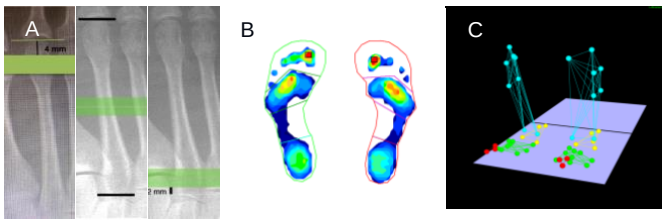

Figure 1. (A) HR-pQCT scout scan of second metatarsal at distal, mid-diaphysis, and proximal sites; **(B)** plantar pressure mapping of gait; **(C)** multi-segment lower extremity biomechanics model (blue: shank, yellow: rearfoot, green: forefoot, red: toe).

Table 1. Demographics	CON	DN	DN+CKD
N	4	4	6
Age (yrs)	58 (4)	69 (6)	69 (9)
Sex	2 M, 2 F	2 M, 2 F	4 M, 2 F
BMI (kg/m^2)	30 (13)	27 (2)	28 (2)
MNSI	0.5 (0.9)	5.2 (1.3)*	5.2 (2.6)*
HbA1c (%)	5.5 (0)	6.5 (0.6)	7.0 (1.2)
Diabetes Duration (yrs)		16 (8)	18 (4)
eGFR (mL/min/1.73m^2)			61 (21)

*p < .05 compared to CON; BMI: body mass index; HbA1c: glycated hemoglobin; MNSI: Michigan Neuropathy Screening Instrument; eGFR: estimated glomerular filtration rate.

Table 2. Results	CON	DN	DN+CKD
Cortical (*mid-diaphysis*)			
Ct.Ar (mm^2)	38.4 (14.5)	47.7 (7.8)	44.2 (6.2)
Ct.vBMD (mg HA/cm^3)	1002 (31)	988 (14)	974 (67)
Ct.Po (%)	**2.3 (0.3)**	**2.8 (1.0)**	**4.4 (0.9)*‡**
Trabecular (*distal*)			
Tb.vBMD (mg HA/cm3)	211 (29)	237 (11)	218 (65)
Tb.Sp (mm)	0.44 (0.07)	0.44 (0.03)	0.43 (0.03)
Tb.N (1/mm)	2.01 (0.29)	1.96 (0.12)	1.99 (0.07)
Trabecular (*proximal*)			
Tb.vBMD (mg HA/cm3)	237 (62)	251 (32)	244 (74)
Tb.Sp (mm)	0.48 (0.13)	0.48 (0.08)	0.54 (0.19)
Tb.N (1/mm)	1.99 (0.52)	1.96 (0.27)	1.91 (0.48)
Rearfoot Pressure			
Peak Pressure (PSI)	39.5 (9.2)	46.0 (7.0)	58.0 (20.7)
PPG (PSI/in)	79 (21)	112 (64)	163 (81)
PTI (PSI-sec)	**6.5 (0.7)**	**11.7 (2.1)***	**13.8 (2.0)***
Forefoot Pressure			
Peak Pressure (PSI)	45.5 (7.8)	56.7 (15.9)	61.3 (21.5)
PPG (PSI/in)	228 (54)	358 (186)	335 (150)
PTI (PSI-sec)	8.0 (2.8)	14.7 (4.0)	12.3 (3.1)
Peak Dorsiflexion			
Rearfoot, *stance* (deg)	**18.0 (3.3)**	**13.2 (4.4)**	**6.9 (5.7)***
Rearfoot, *swing* (deg)	**16.4 (3.8)**	**11.6 (3.0)**	**4.3 (4.1)***
Peak Ankle Power (W/kg)	**3.4 (0.5)**	**1.9 (0.1)***	**2.1 (0.3)***

p < .05 compared to *CON or ‡DN. Ar: area; vBMD: volumetric bone mineral density; Po: porosity; Sp: separation; N: number. PPG: peak pressure gradient; PTI: pressure time integral.