RESPONSE TO COMMENT ON CHAN ET AL.

FGF23 Concentration and *APOL1* Genotype Are Novel Predictors of Mortality in African Americans With Type 2 Diabetes. Diabetes Care 2018;41:178–186

Jasmin Divers[1] *and Barry I. Freedman*[2]

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We thank Drs. Zheng and Wang for their comments (1) regarding fibroblast growth factor 23 (FGF23) compared with serum phosphorus concentration for prediction of mortality in the African American–Diabetes Heart Study (AA-DHS). Mildly elevated mean serum phosphorus concentrations and calcium-phosphorus products, well within their normal ranges, are cardiovascular disease risk factors and predict death in populations without chronic kidney disease (CKD) (2,3). The AA-DHS cohort permitted investigation of novel and conventional risk factors for cardiovascular disease and mortality in those with recent African ancestry at increased risk based upon the presence of type 2 diabetes (4). AA-DHS participants did not have advanced nephropathy at recruitment (median [25th, 75th percentile] estimated glomerular filtration rate 91.3 [76.4, 111.3] mL/min/1.73 m^2), permitting analyses with low likelihood of confounding from CKD. Although Zheng and Wang (1) state that "serum phosphorus is the main stimulus for FGF23 secretion," regulation of FGF23 is a complex and incompletely understood process, particularly in the earliest stages of CKD (5). With the exception of patients with end-stage kidney disease, serum phosphorus concentrations have not shown immediate and consistent effects on the secretion of FGF23 (5).

We performed additional analyses to address their questions on the effects of serum phosphorus and the calcium-phosphorus product on mortality in the AA-DHS (4). The median [25th, 75th percentile] levels of serum phosphorus and calcium-phosphorus product were 3.6 [3.2, 3.9] mg/dL and 33.8 [30.4, 37.7] mg/dL, respectively. Distributions were not statistically different between those who died and those still alive for both serum phosphorus levels (3.6 [3.2, 3.9] vs. 3.5 [3.1, 3.8] mg/dL; $P = 0.24$) and calcium-phosphorus product (33.9 [30.6, 37.8] vs. 32.3 [28.4, 36.1] mg/dL; $P = 0.07$). In contrast, strong differences were observed for plasma FGF23 levels in those alive versus those who died (107.3 [79.0, 154.0] vs. 162.3 [97.3, 362.0] RU/mL; $P = 5 \times 10^{-5}$). FGF23 was weakly correlated with serum phosphorus and calcium-phosphorus product in these participants ($r = 0.17$ and 0.15, respectively; both $P < 0.01$). Adjusting for age, sex, and African ancestry proportion in a multivariate analysis, as was performed for FGF23 (see Table 3 in Chan et al. [4], models 1 and 2), serum phosphorus and calcium-phosphorus product were not significant predictors of mortality in the AA-DHS. We observed hazard ratios for mortality of 0.91 (95% CI 0.69, 1.21) and 0.82 (0.62, 1.10) for serum phosphorus and calcium-phosphorus product, respectively ($P > 0.15$ in both). In the fully adjusted models, the hazard ratios were 0.80 (95% CI 0.59, 1.09) for serum phosphorus and 0.74 (0.54, 1.02) for calcium-phosphorus product; P values were 0.16 and 0.06, respectively.

A total of 508 AA-DHS participants had both FGF23 and serum phosphorus measurements, and 54 deaths were recorded during a median 6.6-year follow-up. In contrast, the Cholesterol And Recurrent Events (CARE) study that assessed serum phosphorus and mortality in individuals with prior myocardial infarctions had better power (2); CARE included 4,127 individuals (136 African American) with 375 deaths during a 5-year follow-up.

In conclusion, plasma FGF23 significantly predicted mortality in the AA-DHS, whereas serum phosphorus and the calcium-phosphorus product did not. These results support use of FGF23 to predict mortality in African Americans with type 2 diabetes who lack nephropathy.

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[1]*Department of Biostatistical Sciences, Division of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, NC*
[2]*Section on Nephrology, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC*

Corresponding author: Barry I. Freedman, bfreedma@wakehealth.edu.

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