Abnormalities in biomarkers of mineral and bone metabolism in kidney donors

see commentary on page 734

Bertram L. Kasiske[1,12], Rajiv Kumar[2,12], Paul L. Kimmel[3], Todd E. Pesavento[4], Roberto S. Kalil[5], Edward S. Kraus[6], Hamid Rabb[6], Andrew M. Posselt[7], Teresa L. Anderson-Haag[1], Michael W. Steffes[8], Ajay K. Israni[1,9], Jon J. Snyder[9], Ravinder J. Singh[10] and Matthew R. Weir[11]

[1]Department of Medicine, Hennepin County Medical Center, Minneapolis, Minnesota, USA; [2]Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA; [3]Division of Kidney Urologic and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA; [4]Department of Medicine, Ohio State University, Columbus, Ohio, USA; [5]Department of Medicine, University of Iowa, Iowa City, Iowa, USA; [6]Department of Medicine, Johns Hopkins University, Baltimore, Maryland, USA; [7]Department of Surgery, University of California, San Francisco, San Francisco, California, USA; [8]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota, USA; [9]Minneapolis Medical Research Foundation, Minneapolis, Minnesota, USA; [10]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA; and [11]Department of Medicine, University of Maryland, Baltimore, Maryland, USA

Previous studies have suggested that kidney donors may have abnormalities of mineral and bone metabolism typically seen in chronic kidney disease. This may have important implications for the skeletal health of living kidney donors and for our understanding of the pathogenesis of long-term mineral and bone disorders in chronic kidney disease. In this prospective study, 182 of 203 kidney donors and 173 of 201 paired normal controls had markers of mineral and bone metabolism measured before and at 6 and 36 months after donation (ALTOLD Study). Donors had significantly higher serum concentrations of intact parathyroid hormone (24.6% and 19.5%) and fibroblast growth factor-23 (9.5% and 8.4%) at 6 and 36 months, respectively, as compared to healthy controls, and significantly reduced tubular phosphate reabsorption (–7.0% and –5.0%) and serum phosphate concentrations (–6.4% and –2.3%). Serum 1,25-dihydroxyvitamin D_3 concentrations were significantly lower (–17.1% and –12.6%), while 25-hydroxyvitamin D (21.4% and 19.4%) concentrations were significantly higher in donors compared to controls. Moreover, significantly higher concentrations of the bone resorption markers, carboxyterminal cross-linking telopeptide of bone collagen (30.1% and 13.8%) and aminoterminal cross-linking telopeptide of bone collagen (14.2% and 13.0%), and the bone formation markers, osteocalcin (26.3% and 2.7%) and procollagen type I N-terminal propeptide (24.3% and 8.9%), were observed in donors. Thus, kidney donation alters serum markers of bone metabolism that could reflect impaired bone health. Additional long-term studies that include assessment of skeletal architecture and integrity are warranted in kidney donors.

Kidney International (2016) **90,** 861–868; http://dx.doi.org/10.1016/j.kint.2016.05.012

KEYWORDS: FGF23; hyperparathyroidism; mineral metabolism; parathyroid hormone

There are compelling reasons to understand the short- and long-term effects of kidney donation on donors.[1,2] First, it is important to know the adverse consequences of donation to appropriately inform potential donors of inherent risks of donation. Second, kidney donation is an opportunity to better understand the physiological effects of mild reductions in kidney function without the confounding effects of underlying kidney disease.

Whether kidney donors with a glomerular filtration rate less than 60 ml/min per 1.73 m^2 should be classified as having chronic kidney disease as suggested in current guidelines is controversial.[3,4] One reason to classify someone as having chronic kidney disease is to alert individuals and caregivers to possible preventable or treatable complications. Individuals with chronic kidney disease typically have abnormalities of calcium and phosphorus regulation.[5] Previous studies have reported that kidney donors have increased concentrations of serum parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF23).[6–14] Studies report that donors have reduced serum concentrations of 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$, calcitriol].[7–11,13] Most studies, however, have been small, with short-term follow-up. Only 1 study has been prospective and controlled, and only 1-year follow-up has been reported.[14] None of these studies has reported a comprehensive assessment of mineral metabolism.

To examine the possible health-related consequences of kidney donation we conducted a prospective, controlled study of living kidney donors and paired normal controls (Assessing

Correspondence: *Bertram L. Kasiske, Department of Medicine, Hennepin County Medical Center, 701 Park Avenue, Minneapolis, Minnesota 55415, USA. E-mail: bkasiske@cdrg.org. Or Rajiv Kumar, MS 1-120, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905, USA. E-mail: rkumar@mayo.edu*

[12]Joint first authors.

Received 9 March 2016; revised 26 April 2016; accepted 5 May 2016; published online 28 June 2016

Long Term Outcomes in Living Kidney Donors [ALTOLD]).[15,16] We previously reported that for up to 3 years after donation, serum PTH concentrations were elevated in donors compared to pre-donation values and compared to controls.[16] Because of these observations, and previous reports of elevated PTH and FGF23 concentrations among donors, we measured serum concentrations of intact PTH, intact FGF23, 25-hydroxyvitamin D [25(OH)D], $1,25(OH)_2D_3$, the tubular reabsorption of calcium and phosphorus, and markers of bone resorption and formation in donors and controls. The results show that 3 years after kidney donation, donors have increased PTH and FGF23 and reduced $1,25(OH)_2D_3$ concentrations, and concomitant increases in serum markers of bone resorption, which if persistent could place donors at risk of increased bone loss in future years.

RESULTS

Participant characteristics

Donors and controls were similar at baseline (Table 1). Donors were more likely to have a blood relationship to the transplant recipient than were controls. The numbers of participants taking an oral vitamin D, a calcium supplement, or both were similar in controls and donors. There were no differences in body weight or body mass index. The participants differed from living donors in the United States in some important ways: compared to all living donors in the United States, study participants were less likely to be male, more likely to be white, and more likely to be younger.[15]

Glomerular filtration rate declined as expected after donation, but increased slightly among donors and declined slightly in controls between visits at 6 and 36 months after donation (Table 2). Serum albumin concentration appeared to decline slightly over time, but was not different in donors versus controls. C-reactive protein, urine protein, and urine albumin concentrations were similar in donors and controls and changed little before and after donation.

PTH, FGF23, and fractional reabsorption of phosphate

At 6 and 36 months serum PTH concentrations had increased in donors compared to controls (Figure 1 and Table 3). Serum FGF23 concentrations were also higher in donors than controls at 6 and 36 months. Increases in serum PTH and FGF23 were associated with a reduction in the tubular reabsorption of phosphate in the donor group, but not in the control group. The serum phosphate concentration was lower in donors than controls at 6 months but not different at 36 months. Serum calcium and fractional tubular resorption of calcium were not affected by kidney donation (Table 3).

Vitamin D, calcium, and fractional excretion of calcium

Serum $1,25(OH)_2D_3$ concentrations were similar in donors and controls before kidney donation, but at 6 and 36 months $1,25(OH)_2D_3$ concentrations were lower in donors compared to controls (Figure 1 and Table 3). Serum 25(OH)D concentrations were similar in donors and controls before kidney donation (Table 3). In the donor group, by 6 and 36 months, 25(OH)D concentrations had increased, while 25(OH)D concentrations remained unchanged in controls.

Markers of bone metabolism

We measured markers of bone resorption and bone formation in donors and controls before and at 6 and 36 months after kidney donation. Bone resorption was assessed by measuring serum aminoterminal cross-linking telopeptide of bone type I collagen (NTX), carboxyterminal cross-linking telopeptide of bone type I collagen (CTX), and tartrate-resistant acid phosphatase 5b (TRAP 5b), while bone formation was assessed by measuring osteocalcin (OC), bone alkaline phosphatase (BAP), and procollagen type I N-terminal propeptide (P1NP). Serum NTX and CTX were increased in donors compared to controls at both 6 and 36 months (Figure 2 and Table 3). TRAP 5b concentrations did not change in donors or controls. OC concentrations were higher in donors than controls at 6 and 36 months (Table 3), while P1NP concentration was higher at 6 months but not different at 36 months (Table 3). BAP concentrations were higher in donors than controls at 6 and 36 months, but BAP concentrations were also higher in donors than controls at baseline (Figure 2 and Table 3). Altogether the findings are consistent with increased bone turnover in donors compared to controls.

DISCUSSION

The principal findings of the current study at 3 years after kidney donation are that donors show (i) increased serum

Table 1 | Participant characteristics[a]

Characteristic	Controls (N = 173)	Donors (N = 182)	P Value
Male sex	60/173 (34.7%)	62/182 (34.1%)	0.91
Non-white ethnicity	8/173 (4.6%)	11/182 (6.0%)	0.64
Blood relative of the transplant recipient	40/173 (23.1%)	98/182 (54.1%)	<0.001
Vitamin D supplement used before donation	6/173 (3.5%)	7/182 (3.9%)	0.85
Vitamin D supplement used at 6 months after donation	8/170 (4.7%)	7/180 (3.9%)	0.71
Vitamin D supplement used at 36 months after donation	26/173 (15.0%)	17/182 (9.3%)	0.11
Calcium supplement used before donation	14/173 (8.1%)	6/182 (3.3%)	0.05
Calcium supplement used at 6 months after donation	15/170 (8.9%)	8/180 (4.5%)	0.10
Calcium supplement used at 36 months after donation	21/173 (12.1%)	16/182 (8.8%)	0.30
Age at baseline before donation (years)	43.4 (41.5–45.2)	43.6 (42.0–45.3)	0.84
Body mass index at baseline before donation (kg/m^2)	26.7 (26.0–27.5)	26.6 (26.0–27.2)	0.81

[a]Values are numbers (and % in parentheses) of controls or donors with the characteristic, or means (and 95% confidence intervals) for age and body mass index.