Effects of Preexistent Hypertension on Blood Pressure and Residual Renal Function After Donor Nephrectomy

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Background. Living kidney donor selection has become more liberal with acceptation of hypertensive donors. Here, we evaluate short-term and 1- and 5-year renal outcome of living kidney donors with preexistent hypertension.
Methods. We compared outcome of hypertensive donors by gender, age, and body mass index with matched control donors. Hypertension was defined as predonation antihypertensive drug use. All donors had glomerular filtration rate (^{125}I-iothalamate) and effective renal plasma flow (^{131}I-hippuran) measured 4 months before and 2 months after donation. A subset of donors had serum creatinine measured 1 year after donation or a renal function measurement 5 years after donation.
Results. Included were 47 hypertensive donors and 94 control donors (both 53% male; mean age, 57±7 years; and body mass index, 28±4 kg/m^2). Pre- and early postdonation, systolic blood pressure, and mean arterial pressure were significantly higher in hypertensive donors. Control donors showed a rise in diastolic blood pressure after donation, and thus the predonation difference was lost postdonation. Both at 1 year (29 hypertensive donors, 58 controls) and 5 years after donation (13 hypertensive donors and 26 controls) blood pressure was similar. Renal function was similar at all time points.
Discussion. In summary, hypertensive living kidney donors have similar outcome in terms of blood pressure and renal function as control donors, early and 1 and 5 years after donation.

Keywords: Living kidney donors, Donor outcome, Hypertension, Glomerular filtration rate.

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The number of patients reaching end-stage renal disease and, thus, in need for renal replacement therapy has increased over the past decades. Because of both a shortage in deceased donor organs and the recognition of superior results, living kidney donors have become more important. To enlarge the donor pool, selection criteria for potential donors have become less strict, leading to an older and more overweight donor population (*1*). Many centers extended their criteria further and accept potential donors with well-regulated hypertension as well. This situation raises a new set of issues. Hypertension is a known risk factor for renal disease. Furthermore, previous studies have shown an increase in blood pressure postdonation in nonhypertensive donors (*2–5*). Nevertheless, longitudinal studies have shown that living kidney donors are not at increased risk of developing hypertension postdonation compared with the general population. However, little is known about the postdonation course of blood pressure of donors with preexistent hypertension. Moreover, it is unknown whether hypertensive donors are at increased risk of impaired residual renal function postdonation. Textor et al. (*6*) have shown that at 1 year after donation, the presence of preexistent hypertension has no adverse effects on blood pressure or glomerular filtration rate (GFR). Data on effective renal plasma flow (ERPF) and filtration pressure are, however, not available.

Here, we evaluate short-term and 1- and 5-year outcome in terms of blood pressure and renal function of living kidney donors with preexistent hypertension, compared with matched control donors.

RESULTS

Donor characteristics before and 2 months after donation are shown in Table 1. There was no difference in mean

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TABLE 1. Donor characteristics before and after 2 mo of donation

	Hypertensive donors	Control donors	*P*
N (% female)	47 (47)	94 (47)	1.00
Age at donation (yr)	57±7	56±7	0.71
BMI at donation (kg/m^2)	28±3	28±3	0.58
Pre-Unx			
Systolic BP (mm Hg)	139±16	129±12	<0.01
Diastolic BP (mm Hg)	82±10	77±8	<0.01
MAP (mm Hg)	101±11	94±8	<0.01
GFR (mL/min)	118±19	113±25	0.23
ERPF (mL/min)	419±87	406±91	0.45
FF (%)	29±4	28±4	0.40
ΔGFR_{DOPA} (mL/min)	10±10	9±11	0.96
$\Delta ERPF_{DOPA}$ (mL/min)	95±70	92±56	0.81
Urinary protein excretion (g/24 hr)	0.1 [0.0–0.3]	0.1 [0.0–0.2]	0.42
2 mo post-Unx			
Systolic BP (mm Hg)	135±13	128±12	<0.01
Diastolic BP (mm Hg)	81±9	80±9	0.36
MAP (mm Hg)	99±9	96±9	0.03
GFR (mL/min)	73±13	70±13	0.21
ERPF (mL/min)	267±48	263±53	0.61
FF (%)	28±3	27±3	0.30
ΔGFR_{DOPA} (mL/min)	1.3±4.1	1.8±4.0	0.29
$\Delta ERPF_{DOPA}$ (mL/min)	38±32	35±22	0.68
Urinary protein excretion (g/24 hr)	0.0 [0.0–0.2]	0.0 [0.0–0.2]	0.45
5 yr post-Unx			
N	13 (46)	26 (46)	1.00
Systolic BP (mm Hg)	137 [132–143]	131 [121–136]	0.07
Diastolic BP (mm Hg)	80 [74–90]	77 [74–84]	0.50
MAP (mm Hg)	102 [90–106]	94 [90–101]	0.27
GFR (mL/min)	81 [72–94]	78 [64–95]	0.53
ERPF (mL/min)	258 [250–299]	258 [223–306]	0.74
FF (%)	30 [29–33]	31 [28–32]	0.74
Urinary protein excretion (g/24 hr)	0.0 [0.0–0.1]	0.0 [0.0–0.2]	0.26

The bottom part shows 5 yr post-donation values for a smaller subset of donors. Characteristics before and early after donation of this smaller group were similar as presented in the table. Values represent mean±SD; median [IQR] or n (%). *P* values represent hypertensive donor values vs. control donor values (independent samples *t* test, Mann-Whitney *U* test, and χ^2 test).

BMI, body mass index; MAP, mean arterial pressure; GFR, glomerular filtration rate; ERPF, effective renal plasma flow; FF, filtration fraction; Unx, unilateral nephrectomy (i.e. kidney donation); BP, blood pressure; ΔGFR_{DOPA}, stimulated GFR−basal GFR; $\Delta ERPF_{DOPA}$, stimulated ERPF−basal ERPF; IQR, interquartile range.

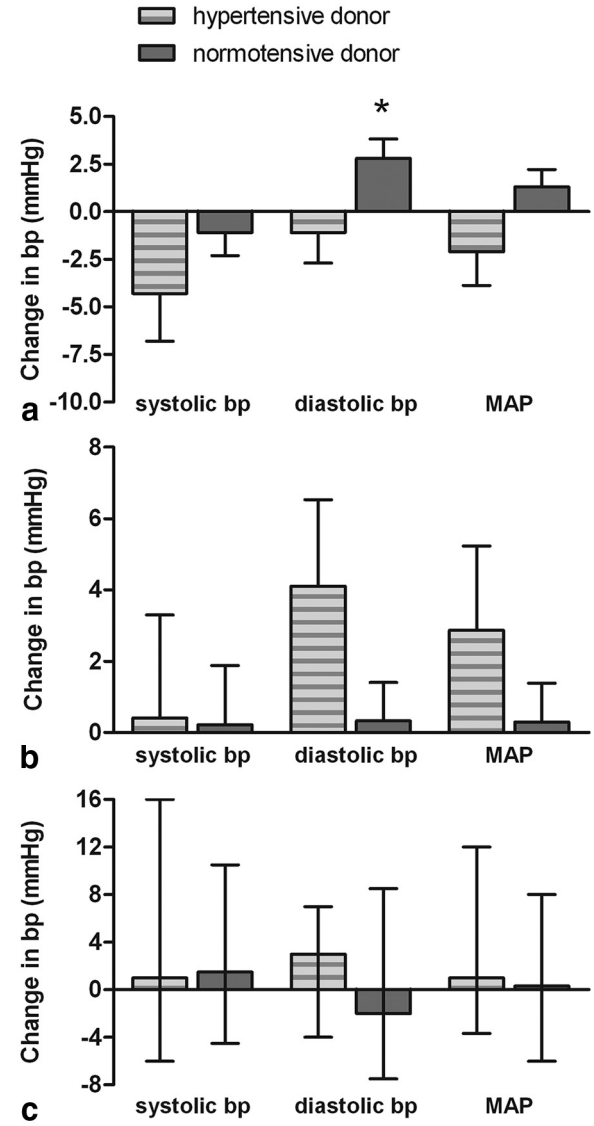

FIGURE 1. Changes in donor blood pressure over time. (a) From predonation to 2 months after donation (n=141); (b) from 2 months after donation to 1 year after donation (n=87); (c) from 2 months after donation to 5 years after donation. (a and b) mean±SEM, (c) median [interquartile range (IQR)]. bp, blood pressure; *$P<0.05$ vs. hypertensive donors.

age or body mass index (BMI) at donation, reflecting a good match between hypertensive and control donors. Despite the use of mean 1.3±0.7 antihypertensive drugs, hypertensive donors had higher blood pressures before donation (all $P<0.01$). Postdonation, control donors showed a significant increase in diastolic blood pressure ($P<0.05$) whereas hypertensive donors had stable blood pressure. The difference in diastolic blood pressure was, thus, lost postdonation. Figure 1(a) shows the change in blood pressure from pre- to early postdonation. In hypertensive donors, no rise in blood pressure occurred, whereas the control donors showed a significant rise in diastolic blood pressure and nonsignificant rise in mean arterial pressure (MAP). Basal renal function and renal reserve capacity were similar both pre- and postdonation, as was urinary protein excretion. None of the donors had urinary protein excretion exceeding 0.5 g/24 hr. Figure 2(a) displays pre- and postdonation renal function graphically. The change in renal function of hypertensive donor parallels the change of control donors.

Use of antihypertensive drugs is shown in Table 2. On average, hypertensive donors used 1.3±0.5 antihypertensive

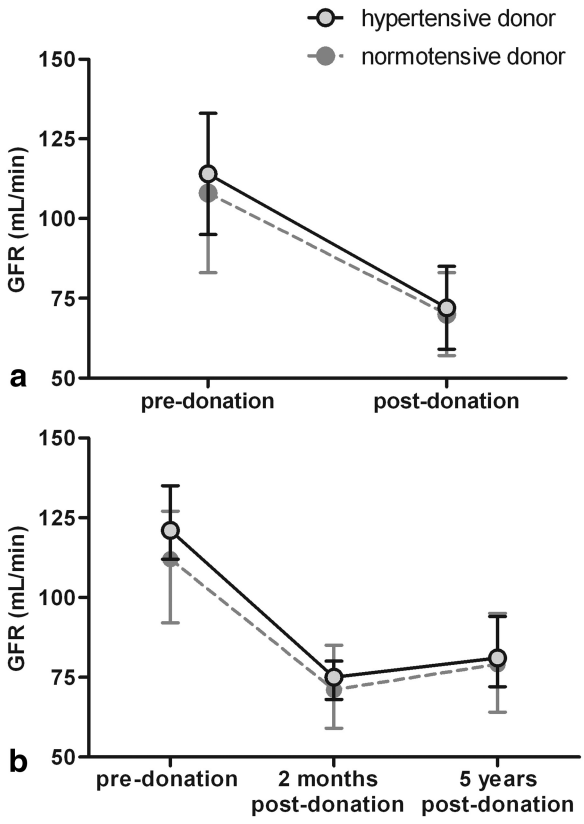

FIGURE 2. Change in glomerular filtration rate (GFR) over time. (a) Pre- and 2 months after donation GFR for the whole group (n=141), values represent mean±SD; (b) pre- and 2 months and 5 years after donation GFR for a subset of donors (n=39), values represent median [IQR].

drugs, preferably an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. The mean number of antihypertensive drugs did not increase over time, though there was a slight shift to more use of diuretics. Furthermore, several donors stopped their antihypertensive medication, especially at 1 year after donation. At 5 years after donation, however, all but one hypertensive donors were using antihypertensive drugs again. Before and 2 months after donation, none of the control donors used antihypertensive drugs. At 1 year after donation, one control used a calcium channel blocker, whereas at 5 years after donation four donors used one antihypertensive drug.

Pre- and postdonation characteristics for donors with 1-year follow-up are shown in Table 3. Again, predonation systolic blood pressure and MAP were higher in hypertensive donors ($P<0.01$). This difference was again lost postdonation, though the difference in MAP reached statistical significance again at 1 year after donation. Diastolic blood pressure was similar between hypertensive and control donors at all time points. Figure 1(b) displays blood pressure course from 2 months after donation to 1 year after donation. In hypertensive donors, diastolic blood pressure showed a nonsignificant rise to 1 year after donation, whereas control donors remained stable. Renal function and urinary protein excretion at 1 year after donation, expressed as serum creatinine and estimated GFR by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, was similar between the groups.

TABLE 2. Use of antihypertensive medication before and 2 mo and 1 or 5 yr after donation

	Hypertensive donors	Control donors
Pre-Unx		
N	47	94
Number of donor using AH drugs	47 (100)	0 (0)
Number of AH drugs	1.3±0.7	0±0
Use of ACEi/ARB	27 (57)	0 (0)
Use of β-blocker	19 (40)	0 (0)
Use of calcium channel blocker	8 (17)	0 (0)
Use of diuretic	9 (19)	0 (0)
2 mo post-Unx		
N	47	94
Number of donor using AH drugs	42 (89)	0 (0)
Number of AH drugs	1.3±0.5	0±0
Use of ACEi/ARB	26 (55)	0 (0)
Use of β-blocker	15 (32)	0 (0)
Use of calcium channel blocker	7 (15)	0 (0)
Use of diuretic	12 (26)	0 (0)
1 yr post-Unx		
N	29	58
Number of donor using AH drugs	17 (59)	1 (2)
Number of AH drugs	0.8±0.8	0±0.1
Use of ACEi/ARB	10 (34)	0 (0)
Use of β-blocker	8 (28)	0 (0)
Use of calcium channel blocker	2 (7)	1 (2)
Use of diuretic	4 (14)	0 (0)
5-yr post-Unx		
N	13	26
Number of donor using AH drugs	12 (92)	4 (15)
Number of AH drugs	2 [1–3]	0 [0–0]
Use of ACEi/ARB	8 (62)	2 (8)
Use of β-blocker	7 (54)	2 (8)
Use of calcium channel blocker	2 (15)	0 (0)
Use of diuretic	8 (62)	0 (0)

Values represent mean±SD, median [IQR], or n (%). There were no differences in pre- and early post-donation drugs use between donors available and unavailable for 1 and 5 yr post-donation follow-up.

Unx, unilateral nephrectomy (i.e. kidney donation); AH drugs, antihypertensive medication; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; IQR, interquartile range.

A small subset of donors had data on renal function and blood pressure 5 years after donation. Characteristics are shown in Table 1. From 2 months after donation up to 5 years after donation, blood pressure remained stable for hypertensive donors and controls (Fig. 1c). At 5 years after donation, no difference in renal function or urinary protein excretion was observed. Figure 2(b) shows a parallel course in renal function to 5 years after donation.

To evaluate the effect of blood pressure as such, correlation and regression analysis was performed. No associations were found between predonation GFR and blood pressure.

TABLE 3. Donor characteristics before and 2 mo and 1 yr post-donation

	Hypertensive donors	Control donors	*P*
N (% female)	29 (41)	58 (41)	1.00
Age at donation (yr)	58±6	57±7	0.81
Pre-Unx			
Systolic BP (mm Hg)	138±18	130±12	0.02
Diastolic BP (mm Hg)	80±10	77±8	0.09
MAP (mm Hg)	100±12	95±8	0.03
Serum creatinine (mg/dL)	0.9±0.2	1.0±0.2	0.10
CKD-EPI (mL/min/1.73 m^2)	85±13	79±13	0.03
Urinary protein excretion (g/24 hr)	0.1 [0.0–0.3]	0.0 [0.0–0.2]	0.23
2 mo post-Unx			
Systolic BP (mm Hg)	134±14	129±12	0.10
Diastolic BP (mm Hg)	80±9	81±8	0.61
MAP (mm Hg)	98±10	97±9	0.65
Serum creatinine (mg/dL)	1.4±0.3	1.4±0.3	0.56
CKD-EPI (mL/min/1.73m^2)	51±11	49±9	0.46
Urinary protein excretion (g/24 hr)	0.0 [0.0–0.2]	0.0 [0.0–0.2]	0.37
1 yr post-Unx			
Systolic BP (mm Hg)	134±15	129±15	0.10
Diastolic BP (mm Hg)	84±10	80±8	0.08
MAP (mm Hg)	101±10	96±8	0.05
Serum creatinine (mg/dL)	1.3±0.2	1.3±0.2	0.31
CKD-EPI (mL/min/1.73 m^2)	58±10	55±11	0.22
Urinary protein excretion (g/24 hr)	0.1 [0.0–0.1]	0.1 [0.0–0.1]	0.64

Values represent mean±SD, median [IQR], or n (%). *P* values represent hypertensive donor values vs. control donor values (independent samples *t* test, Mann-Whitney *U* test, and χ^2 test).

Unx, unilateral nephrectomy (i.e. kidney donation); MAP, mean arterial pressure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; BP, blood pressure; IQR, interquartile range.

Predonation systolic blood pressure correlated negatively with early postdonation GFR ($R=-0.22$, $P<0.01$). This association was lost after correction for age. Neither diastolic blood pressure nor MAP was significantly related to renal function. No significant associations were found between serum creatinine and CKD-EPI at 1 year and pre- and postdonation blood pressures. The group with 5-year follow-up was too small for continuous analysis.

DISCUSSION

In this study, we compared postdonation outcome of living kidney donors with preexistent hypertension with matched control donors. Although hypertensive donors had higher blood pressure before and 2 months after donation, these differences were lost at 1 and 5 years after donation. At none of the evaluated time points, differences were seen in renal function or urinary protein excretion between hypertensive and normotensive donors. Where normotensive donors showed a rise in diastolic blood pressure, hypertensive donors retained stable blood pressure throughout the follow-up. Thus, postdonation course of renal function and blood pressure of hypertensive donors is comparable with normotensive donors, including the long-term adaptive increase of GFR between year 1 and 5 after donor nephrectomy.

Earlier studies evaluating the postdonation follow-up of living kidney donors had some conflicting results. Although several studies reported an increase in blood pressure postdonation of 5 to 10 mm Hg (*2–5*, *7*), others found no increase (*8*, *9*). The latter studies, however, had rather short follow-up (maximum 1 year), which may explain the lack in increase in blood pressure. The incidence rate of postdonation hypertension varies from 15% (*10*) to 22% (*11*) and 45% (*12*). This incidence seems to increase with increasing time postdonation, and indeed the highest reported incidence was after a mean follow-up of 14 years (*12*). Although hypertension is, thus, present postdonation, incidence rates are similar to the general population when correcting for age and gender (*3*, *13–15*). One study, however, found a higher incidence of hypertension in male donors compared with matched controls. Donors with postdonation hypertension had higher macroalbuminuria and urinary protein excretion than normotensive donors in three studies (*5*, *11*, *13*). Here, however, we found no difference in urinary protein excretion. Textor et al. (*6*) compared donors with preexistent hypertension with normotensive donors, and found no increase in blood pressure or differences in renal function or urinary protein excretion. However, the definition of hypertension was made on blood pressure cutoffs, and only three patients used antihypertensive drugs predonation. One study reported that donors with postdonation hypertension are at increased risk for an estimated GFR less than 60 mL/min/1.73m^2 (*16*). In this study, however, we found no difference in renal function in the short- and long-term postdonation.

The finding that hypertensive donors are not at increased risk for renal function impairment postdonation is reassuring for the current donor selection practice. Because of a shortage in donor organs, many centers accept more marginal donors nowadays. Although this study shows no deleterious effects of predonation hypertension, we like to emphasize that donors in our center undergo strict selection, comprising renal function measurements and strict blood pressure management. Where one might expect lower renal function in middle-aged hypertensive subjects, our donors actually had good renal function predonation. This contradiction can be explained by the selection bias due to the screening. Thus, we stress the need for thorough donor screening before accepting donors with hypertension. Furthermore, postdonation follow-up of living kidney donors remains important, and enables identification of subjects at risk for renal function loss or hypertensive complications.

Previous studies have shown the importance of ambulatory blood pressure measurements as part of the donor screening (*17–19*). Unfortunately, ambulatory measurements were not available for all donors of this study. Before donation, and 2 months and 5 years after donation, blood pressure was measured during renal function measurement. Donors were seated in a quiet environment in semisupine positions and were at rest for at least 2 hr before the blood pressure measurement started. Blood pressure was recorded for at least half an hour. At 1 year after donation, only office blood pressures were available.

Our study has several limitations, the most important being the relatively small sample size, the monocentric character, and the lack of standardized ambulatory blood pressure measurements. Furthermore, the conclusions cannot be extrapolated to patients with African ethnicity.

In conclusion, hypertensive living kidney donors show a similar course in postdonation renal function and blood pressure as normotensive donors. Thus, hypertensive donors are not at increased risk of renal function loss up to 5 years after donation. More long-term studies, with longer follow-up of donors with hypertension before donation, are necessary to ensure long-term donor safety.

MATERIALS AND METHODS

In this study, 49 consecutive living donors with preexistent hypertension and 98 matched controls were included. Controls were matched by gender, age, and BMI. All donors donated at the University Medical Center Groningen between 1998 and 2010. Hypertension was defined as antihypertensive drug use predonation. Donors were found eligible to donate with a well-regulated blood pressure achieved by a maximum of two antihypertensive drugs. Blood pressure could was not allowed to exceed 145/85 mm Hg at repeated measurements and ambulatory blood pressure measurement. Renal function was measured as described later, 4 months before and 2 months after donation. In the earlier mentioned period, a cutoff of 80 mL/min of true GFR was used for acceptation of a potential donor in our center. There was no absolute upper limit for donor age, an upper limit for BMI has been set at 30 kg/m^2 at 2008. Beforehand, no upper limit for BMI was used. Furthermore, proteinuria exceeding 0.5 g/24 hr, or signs or end organ damage due to hypertension such as left ventricular hypertrophy, led to rejection of potential donors. One year after donation, donors came for an outpatient visit without measurement of GFR. Data were available for 29 subjects and 48 controls. For 13 subjects and 26 controls, 5-year follow-up, with renal function measurement, was available as well. Procedures were conducted in accordance with the Helsinki declaration.

Renal Function Measurement

GFR was measured by constant low-dose infusion of the radiolabeled tracer ^{125}I-iothalamate, as originally described by Donker et al. and more recently by Visser et al. (*20–22*) Simultaneously, ERPF was measured as the clearance of ^{131}I-hippurate. For the measurements, subjects were seated in a quiet room in, in a semisupine position. After drawing a blank blood sample, the priming solution containing 0.04 mL/kg body weight of the infusion solution (0.04 MBq of ^{125}I-iothalamate and 0.03 MBq of ^{131}I-hippurate per mL saline) plus an extra 0.6 MBq of ^{125}I-iothalamate, was given followed by constant infusion at 12 mL/hr. To attain stable plasma concentrations of both tracers, a 2 hr stabilization period followed, after which the clearance periods start. Clearances were measured over the next 2 hr and calculated as (U×V)/P and (I×V)/P, respectively. U×V represents the urinary excretion of the tracer, I×V represents the infusion rate of the tracer, and P represents the tracer value in plasma at the end of each clearance period. GFR was calculated from UV/P of ^{125}I-iothalamate and corrected for voiding errors by multiplying the urinary clearance of ^{125}I-iothalamate with the ratio of the plasma and urinary clearance of ^{131}I-hippurate. The day-to-day variability for GFR is 2.5%. Next to basal renal function, renal reserve capacity was measured pre- and 2 months after donation as part of the screening and early follow-up. To obtain reserve capacity, the earlier mentioned baseline procedure was extended for 2 hr. During this period, dopamine was infused at a rate of 1.5 μg/kg per min. At 5 years after donation, reserve capacity was not measured. Blood pressure was measured for 30 min during the renal function measurement, in rest and semisupine positions, with a semiautomated device (Dinamap 1846; Critikon Inc., Tampa, FL).

Calculations

Filtration fraction (FF) was calculated as the ratio of GFR and ERPF; filtration fraction=([GFR/ERPF]×100). MAP was calculated as MAP=([$^1/_3$][systolic blood pressure−diastolic blood pressure]+diastolic blood pressure). Renal reserve capacity was calculated as the response in renal function to dopamine (ΔGFR_{dopa} and $\Delta ERPF_{dopa}$) as: (stimulated renal function−basal renal function). Because at the outpatient visit, 1 year after donation no renal function measurement was performed, we estimated GFR from serum creatinine by use of the CKD-EPI equation (*23*). The following calculations were used:

Female with serum creatinine less than or equal to 0.7 mg/dL: $GFR=144\times(0.993)^{age}\times(\text{Serum creatinine}/0.7)^{-0.329}$

Female with serum creatinine more than 0.7 mg/dL: $GFR=144\times(0.993)^{age}\times(\text{serum creatinine}/0.7)^{-1.209}$

Male with serum creatinine less than or equal to 0.9 mg/dL: $GFR=141\times(0.993)^{age}\times(\text{serum creatinine}/0.9)^{-0.4111}$

Male with serum creatinine more than 0.9 mg/dL: $GFR=141\times(0.993)^{age}\times(\text{serum creatinine}/0.9)^{-1.209}$

Statistical Analysis

Analyses were performed using PASW Statistics version 18 and GraphPad Prism version 5 for Windows. Data are given as mean±SD or median [interquartile range]. Independent samples *t* test, Mann-Whitney *U* test, and chi-square test were used to analyze for differences between groups. Differences within groups were tested with paired samples *t* test and Wilcoxon signed ranks test.

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