The Effect of a 26-Hour Fast in Living Kidney Donors

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ABSTRACT

Background. Living kidney donation is widely practiced, and short- and long-term outcomes are acceptable. Within the living kidney donor population there are unique ethnic groups who practice customs that affect kidney function. In Judaism, Yom Kippur (Day of Atonement) is a 25- to 26-hour fast practiced yearly. There are no studies describing the effect of this fast on LKDs.

Methods. Living kidney donors were approached via e-mail. Exclusion criteria were conditions considered prohibitive of fasting. Control participants were potential living kidney donors approved by the standard medical evaluation but that had not yet donated. Blood and urine samples were obtained at 3 time points: baseline: 3 months before fast; fasting: 1 hour after fast; and follow-up: 14 days after fast.

Results. In total, 85 living kidney donors and 27 control participants were included. Donors were older (42.8 vs 38.8 years) and had a higher baseline creatinine (103 vs 72 umol/L). All other parameters were the same. The percent change between fasting and nonfasting creatinine was smaller in living kidney donors than in control participants (0.12% vs 0.21% change, $P = .04$). Values of sodium, albumin, and osmolarity were not different between groups. Time from donation did not influence results.

Conclusions. Living kidney donors practicing a day fast showed a different pattern regarding the change in creatinine levels. This pattern cannot be considered hazardous for living kidney donors. The emotional wellbeing of living kidney donors is of utmost importance, and this first report of the safety of a 24-hour fast is reassuring. These findings may be of interest to other religious groups, for example, the Muslim community which observes Ramadan.

KIDNEY transplantation is currently accepted as the best renal replacement therapy that can be offered to eligible patients suffering from end-stage renal disease (ESRD) [1]. Living kidney donation, introduced in 1954, is widely accepted and has been shown to be superior to transplantation from a deceased donor [2]. Living kidney donors undergo unilateral nephrectomy without direct medical benefits, but the short- and long-term outcomes in respect to longevity and quality of life are considered acceptable [3,4]. Potential donors are screened extensively medically and psychologically before donation, with particular emphasis made on healthy lifestyle conduct. In addition, yearly medical follow-up after donation is highly advised. Factors that can affect postdonation kidney function, such as blood pressure, proteinuria, and various metabolic issues, are examined at length in the medical literature [5-7]. However, scarce information exists regarding nonclassic factors such as short-term fasting.

Rates of living kidney donation are rising worldwide. In Israel, a dramatic increase in living donation numbers and rates has been

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seen in the past 4 to 5 years. A major contribution to this exceptional phenomenon is the foundation and continuous activity of a voluntary nonprofit organization named Matnat Chaim (Hebrew for Gift of Life). It was established by a kidney transplant recipient, with the main goal being to connect altruistic kidney donors to patients in need of kidney transplant. For reasons described elsewhere [8], most donors via Matnat Chaim are from the Orthodox Jewish community. In Judaism there are several holy days, and the "Day of Atonement," or Yom Kippur, is the holiest of them all. It is a day of introspection and asceticism for purifying the soul: "For on this day He will forgive you, to purify you, that you be cleansed from all your sins before God" (Leviticus 16:30). On this day an observant Jew fasts for 25 hours, avoiding any food or drinks. There are several other days during the year on which observant Jews are commanded to fast, either for 25 or 12 hours. A similar situation can be found in the Muslim religion, where Ramadan is a month-long daytime fast (~12 hours).

The medical community in Israel is now facing a new and unique situation: an exponentially growing population of orthodox kidney donors who cannot and will not compromise the religious obligation of repeated yearly fasting. It is the belief of the teams in the transplant community that ensuring the emotional welfare of donors is as important as monitoring blood pressure, proteinuria, and kidney function. We decided to study the effect of this 25-hour fast on the single kidney of those donors in order to try and relieve the donors' concerns resulting from the repeated prolonged fasting they practice. To our knowledge, this study is the first to address this question.

MATERIALS AND METHODS

The study was approved by the ethics committee of Hadassah Hebrew University Medical Center (protocol #0468-17-HMO). Potential participants were approached via email through the Matnat Chaim organization. Inclusion criteria were age ≥18 years and providing informed consent. Exclusion criteria were conditions considered prohibitive of fasting, such as pregnancy or chronic illness, and failing to provide informed consent. Although this was not a formal exclusion criterion, donors were actively encouraged not to fast, and therefore not to participate, if time from donation was <12 months. The control group consisted of people wishing to donate a kidney who had been tested and approved by the standard medical evaluation but had not yet donated. Clinical and demographic data (age, weight, blood pressure, smoking status, current medical conditions and medications, and time and place of donation) were obtained via self-reported questionnaires.

Blood and urine samples were obtained at 3 time points: 1. baseline data (time point #1): serum creatinine up to 3 months before the fast. Blood was drawn at community clinics, at the convenience of the participant. 2. Post-fast data (time point #2): blood and urine samples were taken up to 1 hour after the 25-hour fast. Samples were collected the next day and transferred to the central laboratory at our medical center. Serum was separated and stored at −4°C until analysis. 3. Follow-up data (time point #3): blood and urine samples were taken 14 days after the fast. Samples were transferred the next day to the central laboratory at our medical center. Serum was separated and stored at −4°C until analysis. Urine samples were stored at −4°C until analysis. Blood and urine samples were analyzed for sodium, potassium, urea, creatinine, glucose, albumin (Cobas 6000, Cobassystem, Roche Diagnostics, Sussex, United Kingdom), and osmolality (OsmoPRO, Advanced Instruments, Roche Diagnostics, Sussex, United Kingdom). All participants provided written informed consent.

Sample size calculation: The primary outcome of the study is the variance in the pattern of fasting-related serum creatinine changes between donors and control participants. Accordingly, the null hypothesis was that absolute alterations in serum creatinine brought on by fasting would be similar between the groups.

Statistical analysis: clinical and demographic variables are described as percentages (ratios) or mean ± standard deviation and range. Characteristics were compared between groups (ie, donors vs control participants) applying unpaired Student's *t* tests or Mann-Whitney *U* tests, as appropriate. To account for repeated measurements and for interactions between predictor variables, we applied repeated measures ANOVA, using R (The R Foundation) and SPSS (IBM, Armonk, NY, United States).

RESULTS

Two hundred kidney donors and 65 candidates for donation (control participants) were approached by e-mail approximately 2 months prior to Yom Kippur. A total of 146 and 27 (respectively) replied and signed the informed consent form. Eighty-five and 27 were included in the final analysis. Reasons for exclusion from final analysis were mainly inability to provide blood samples at a

Table 1. Study Population

Characteristics	Control Participants (n = 27)	Donors (n = 85)	*P* value
Age, current (y)	38.8 ± 9.5 (25-60)	42.8 ± 9.3 (26-70)	.056
Sex (male/female)	21/6	70/15	.804
Time since donation (mo)	N/A	31.3 ± 26.4(2-193)	
Weight (kg)	74.4 ± 11.7 (55-100)	76.7 ± 11.0 (48-100)	.35
BMI at donation (kg/m^2)	N/A	25.5 ± 2.7 (17.4-32.4)	
BMI, current (kg/m^2)	24.9 ± 3.2 (20.3-32.7)	25.7 ± 2.9 (17.3-32.5)	.27
Smoking status (no/yes)	25/2	82/3	.753
Systolic BP	118 ± 10 (98-140)	119 ± 10 (99-140)	.74
Diastolic BP	73 ± 9 (60-90)	76 ± 7 (62-91)	.149
Current medical issues (no/yes)	26/1	77/8	.586
Creatinine time point 1 (μmol/l)	72 ± 13 (47-97)	103 ± 17 (67-141)	< .001
eGFR (CKD-EPI, mL/min/1.73 m^2)	108± 12 (74-127)	75± 15 (52-118)	< .001

Values are reported as mean ± standard deviation (range) or ratios.

BMI, body mass index; BP, blood pressure; CKD-EPI, chronic kidney disease epidemiology collaboration equation; eGFR, estimated glomerular filtration rate; N/A, non applicable.

Table 2. Serum creatinine levels at 3 time points

	Control Participants (n = 27)	Donors (n = 85)	*P* value
Creatinine, time point 1(μmol/l)	72 ±12 (48-97)	103 ±17 (67-141)	< .001
Creatinine, time point 2(μmol/l)	86 ±14 (57-114)	115 ±18 (67-149)	< .001
Creatinine, time point 3(μmol/l)	80 ±13 (59-111)	113 ±19 (71-156)	< .001

Values are reported as mean ± standard deviation (range).

minimum of 2 time points (donors). Among control participants, the main reason for exclusion was failing to complete most of the medical evaluation before donation (and thus not serving as ideal controls). Clinical and demographic characteristics of the study population are shown in Table 1.

There was a clear predominance of male donors and control participants. Donors were older (borderline statistically significant) than control participants and had higher baseline (prefasting) creatinine, whereas all other parameters were not significantly different between the 2 groups. Most of the study population had normal or well-controlled blood pressure, had a normal body mass index, and were nonsmokers.

The effects of the fast on serum creatinine levels are shown in Table 2 and in Fig 1. Mean serum creatinine levels were higher in male vs female participants (blue vs red lines, Fig 1), donors vs control participants and after vs before fasting. These findings are all expected, particularly the baseline creatinine difference between donors and control participants, because postdonation compensatory hypertrophy does not restore kidney function to predonation levels.

Next, the kinetics of change in creatinine and estimated glomerular filtration rate (eGFR) were explored. We calculated the percent change in creatinine levels and eGFR (CKD-EPI) in donors vs control participants at the 3 time intervals (Table 3, Fig 2). Interestingly, the change between fasting and nonfasting creatinine was smaller in kidney donors than in control participants. This was true whether the nonfasting creatinine levels were 3 months before the fast (time point 2 vs 1) or up to 2 weeks after the fast (time point 3 vs 2), and was almost statistically significant.

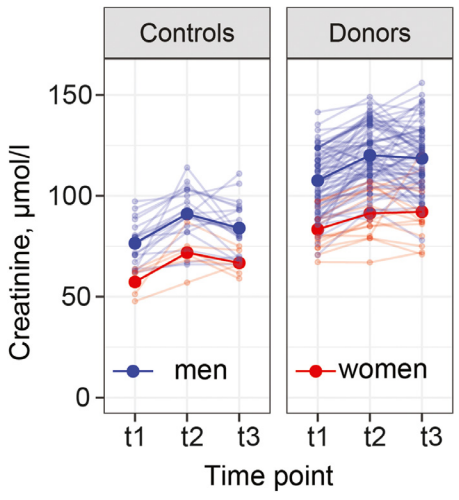

Fig 1. Individual creatinine levels at the 3 time points tested, displayed by group and sex. The bold lines represent group- and sex-specific medians.

In addition to changes in creatinine levels and eGFR, we examined whether other physiological indicators of kidney function, such as the ability to concentrate urine and retain sodium, are influenced by kidney donation and fasting. These parameters were evaluated at time point 2 (immediately after fasting) and time point 3 (2 weeks after the fast). Values for osmolarity in blood and urine samples as well as sodium and albumin in the urine are shown in Table 4. Trends in urine osmolarity are displayed in Fig 3 (male in blue, female in red). Donors and control participants adequately concentrated urine, as reflected by high urine osmolarity, with no significant discrepancy between groups. As expected, albuminuria was not present at either time point in either group. Urine sodium concentration was numerically higher in control participants, but this was not statistically significant.

Next, we explored the effect of time elapsed from donation and trends in absolute creatinine levels or percent change in creatinine levels in relation to fasting. As can be seen in Fig 4, we did not detect any influence of time from donation.

Of particular interest are the donors who decided to fast less than 1 year from donation (n = 9). Intriguingly, percent change in creatinine levels in the 9 donors fasting less than 1 year from donation was similar to the control group, and not in concordance with the donor group (Table 5). This was different than our findings depicted in Fig 2.

DISCUSSION

Living kidney donation is viewed as a safe procedure both medically and psychosocially. After donation, the initial loss of nephron mass and reduction in glomerular filtration rate (GFR) are balanced by compensatory hypertrophy. Within 10 to 14 days after donation, GFR rises to 70% of predonation values, and after a longer follow-up it stabilizes at 75% to 85% of predonation values [9]. In the long term, kidney donors may be at a higher risk for ESRD, but the absolute rise in ESRD is small and considered acceptable, provided the donor is well informed of both relative and absolute risks. The donor population includes unique ethnic groups, such as Jewish and Muslim individuals who practice customs that may affect kidney function. In the Jewish religion, Yom Kippur is a 25 to 26 hour fast practiced yearly. It is considered the holiest day in the year and revered by secular and nonsecular Jews alike. To date, there are no studies that describe the effect of short-term fasting on this

Table 3. Percent change in serum Creatinine between timepoints

	Control Participants (n = 27)	Donors (n = 85)	P value
ΔCreatinine, time 2 vs 1 (% baseline)	21 ± 18 (3-82)	12±12 (−13 to 78)	.024
ΔCreatinine, time 3 vs 2 (% baseline)	−9 ± 17 (-53-30)	−1 ± 13 (−25 to 52)	.058
ΔCreatinine, time 3 vs 1 (% baseline)	12 ± 16 (-14-57)	11 ± 15 (−27 to 72)	.69

Values are reported as mean ± standard deviation (range). Student *t* test

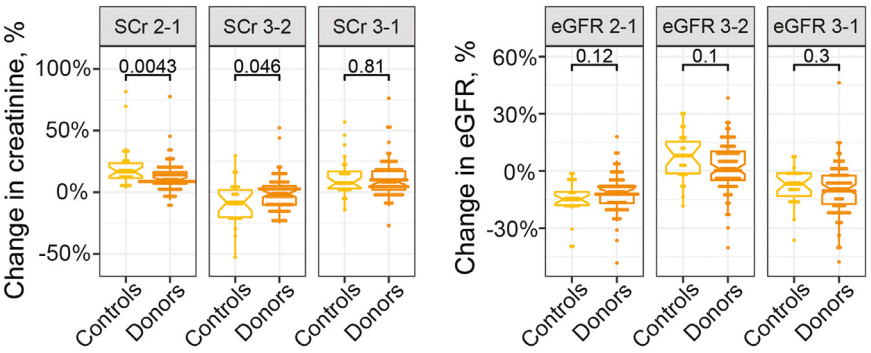

Fig 2. Left: ratio between creatinine levels at all 3 time intervals. Right: change in estimated glomerular filtration rate (eGFR) (chronic kidney disease epidemiology collaboration equation [CKD-EPI]) at all 3 time intervals.

Table 4. Physiological Indicators of Kidney Function at 3 Time Points

	Control Participants	Donors	*P* value
Osmolarity, blood, time point 2	298 ± 5 (288-309)	298 ± 4 (287-313)	.57
Osmolarity, blood, time point 3	295 ± 4 (287-306)	297 ± 4 (290-307)	.11
ΔOsmolarity, blood, time point 2 − 3 (mOsm/L)	3.0 ± 5.6 (−6 to 16)	1.0 ± 5.2 (−10 to 15)	.119
Osmolarity, urine, time point 2	994 ± 143 (598-1233)	945 ± 141 (435-1226)	.117
Osmolarity, urine, time point 3	828 ± 229 (345-1227)	703 ± 280 (96-1174)	.067
ΔOsmolarity, urine, time point 2 minus 3(mOsm/L)	178 ± 263 (−546 to 574)	241±271 (−463 to 828)	.497
Sodium, urine, time point 2	138 ± 51 (24-223)	121 ± 44 (39-264)	.1
Sodium, urine, time point 3	141 ± 63 (47-294)	122 ± 57 (10-258)	.159
ΔSodium, urine, time point 2-3 (mmol/L)	−2 ± 78 (−135 to 143)	2 ± 61 (−149 to 149)	.847
Albumin/creatinine ratio, urine, time point 2 (mg/g)	7.7 ± 7.0 (2-31)	6.9± 8.4 (1-59)	.64
Albumin/creatinine ratio, urine, time point 3(mg/g)	5.6± 4.0 (0-20)	7.6± 11 (0-82)	.47
ΔAlbumin/creatinine ratio, urine, time point 2-3 (mg/g)	2.5 ± 6.5 (−6 to 25)	−0.5 ± 8.9 (−29 to 24)	.280

Values are reported as mean ± standard deviation (range).

population, let alone the living kidney donor cohort. We aimed to describe the short-term effects of a 25 to 26 hour fast among living kidney donors.

Creatinine levels and eGFR of donors is predictably higher and lower, respectively, than control participants, reflecting the postdonation reduction in nephron mass (Fig 1, Table 2). Less predictable was the attenuated response of changes in creatinine and eGFR among donors (Table 3, Fig 2). Donors had a smaller difference (ie, creatinine rose less in the fasting state, and there was a smaller reduction in eGFR). Whether this change is also clinically significant is debatable. It is known that serum creatinine is a suboptimal biomarker to portray an acute and potentially subtle kidney injury; it thus has poor sensitivity for the early diagnosis of acute kidney injury. The higher baseline value of creatinine in the donors may have dampened the magnitude of fast-induced rise in creatinine. We did not check more sensitive markers of acute kidney injury such as urinary neutrophil gelatinase-associated lipocalin levels. Of note, creatinine levels and eGFR did not return completely to baseline levels, as depicted in Fig 1. Reassuringly, this was observed in both donors and control participants, and can be attributed to study design and the fact that creatinine levels at time point 1 were obtained from community clinics, whereas blood and urine samples at time points 2 and 3 were analyzed at one central laboratory. This conclusion is supported by the lack of difference between donors and control participants in percent change in creatinine or eGFR at time points 3 to 1 (Table 3, Fig 2).

Examining physiological parameters of kidney function, such as urine osmolarity, we did not detect a significant change between groups. Urine osmolarity was adequately high in the fasting state (Table 3). However, urine osmolarity was slightly lower, with borderline statistical significance, in the donor

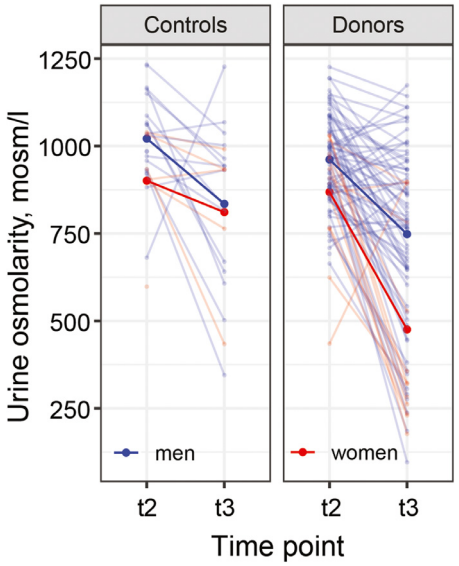

Fig 3. Urine osmolarity at time points 2 (after fast) and 3 (2 weeks after fast). The bold lines represent group- and sex-specific medians.

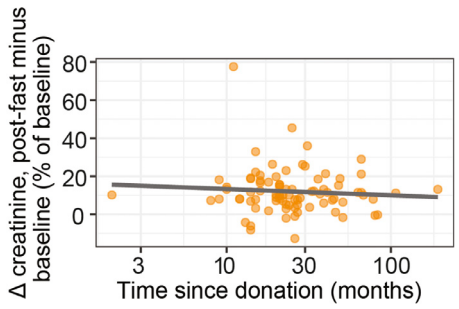

Fig 4. Time interval from donation to the Yom Kippur fast and percent change in creatinine levels from baseline to post-fasting.

population at time point 3 (14 days after fast). This may reflect donor daily lifestyle habits of adequate hydration practices. As expected, albuminuria was not influenced by fasting in donors or in control participants.

Time from donation did not influence any of the parameters examined, including change in creatinine levels (Fig 4), osmolarity of blood and urine, or urine sodium concentration (not shown). Mean time from donation in our cohort was 31 months, with most of the cohort donating 2 to 3 years before the study and having a relatively preserved eGFR (mean 75 mL/min/1.73 m^2). It may well be that this time span is short to allow detection of substantial and clinically relevant alterations of kidney function in the fasting state.

A prespecified exclusion criterion for participating in the study was a short time from donation (<12 months). This is concordant with clinical practice (although with no real scientific basis) of advising donors not to fast in the first year after donation. Nevertheless, there were 9 donors who insisted on fasting. We decided to report their results (Table 5). Surprisingly, the changes in serum creatinine and eGFR were similar to those of the control group, that is, they did not display the attenuated response to fast detected in the whole donor cohort. These results need to be further explored in a larger group with adequate statistical power. However, it was reassuring to see that donors fasting less than 1 year from donation do not display an alarming change in creatinine or eGFR. It may be appropriate to conduct a similar study in this specific population, thus further informing donors about the safety of fasting within 1 year after donation.

Of note, in accordance with previous studies, parameters of cardiovascular and metabolic function such as blood pressure and body mass index were within normal limits, and similar to the values before donation, echoing the notion that, at least in the short term, kidney donation is a safe procedure.

A strength of our study was the control group, all carefully screened and approved for donation that at the time of the study were awaiting nephrectomy, thus serving as ideal control participants. Still, our study has several limitations. First, as mentioned above, most participants had preserved eGFR, reflecting a short time from donation. It is imperative to conduct a similar study, preferably in the same cohort, 5 to 15 years from now, when the long-term impact of kidney donation might take its toll.

Also, baseline creatinine of the participants was obtained from blood tests in community clinics. It was not standardized among the participants, and may be analyzed differently than the methods used in our central laboratory. This was addressed by an internal control of comparing the percent difference in creatinine between time point 3 and time point 1, as seen in Fig 2a and Table 3.

There may be a selection bias, because only participants who chose to reply to the electronic survey were included. It cannot be ruled out that healthier donors who felt ready to fast were disproportionately included in the study.

Table 5. Data of 9 Donors <1 Year From Donation

	Donors <1 Year (n = 9)	Donors ≥1 Year (n = 76)	Control Participants (n = 26)
Δ creatinine, post-fast vs baseline (% of baseline)	21.2 ± 25.1	11.2 ± 9.8*	21.1 ± 18.5
ΔCKD-EPI eGFR, post-fast vs baseline (mL/min/1.73 m^2)	−15.3 ± 17.6	−8.7 ± 7.8*	−16.4 ± 11.5

Values are reported as mean ± standard deviation.
CKD-EPI, chronic kidney disease epidemiology collaboration equation; eGFR, estimated glomerular filtration rate.
* $P < .01$ vs control participants (Steel-Dwass pairwise ranking test)

CONCLUSIONS

This prospective study in kidney donors demonstrates no clinically meaningful influence of kidney donation on the transient effects of fasting on kidney function. It may thus provide reassurance of the short-term safety of a 26-hour fast among healthy kidney donors.

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