AJKD
Original Investigation

Gout After Living Kidney Donation: A Matched Cohort Study

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Background: In the general population, high serum uric acid concentration is a risk factor for gout. It is unknown whether donating a kidney increases a living donor's risk of gout as serum uric acid concentration increases in donors after nephrectomy.

Study Design: Retrospective matched cohort study using large health care databases.

Setting & Participants: We studied living kidney donors who donated in 1992 to 2010 in Ontario, Canada. Matched nondonors were selected from the healthiest segment of the general population. 1,988 donors and 19,880 matched nondonors were followed up for a median of 8.4 (maximum, 20.8) years.

Predictor: Living kidney donor nephrectomy.

Outcomes: The primary outcome was time to a diagnosis of gout. The secondary outcome in a subpopulation was receipt of medications typically used to treat gout (allopurinol or colchicine).

Measurements: We assessed the primary outcome with health care diagnostic codes.

Results: Donors compared with nondonors were more likely to be given a diagnosis of gout (3.4% vs 2.0%; 3.5 vs 2.1 events/1,000 person-years; HR, 1.6; 95% CI, 1.2-2.1; $P < 0.001$). Similarly, donors compared with nondonors were more likely to receive a prescription for allopurinol or colchicine (3.8% vs 1.3%; OR, 3.2; 95% CI, 1.5-6.7; $P = 0.002$). Results were consistent in multiple additional analyses.

Limitations: The primary outcome was assessed using diagnostic codes in health care databases. Laboratory values for serum uric acid and creatinine in follow-up were not available in our data sources.

Conclusions: The findings suggest that donating a kidney modestly increases an individual's absolute long-term incidence of gout. This unique observation should be corroborated in future studies.

Am J Kidney Dis. 65(6):925-932.

INDEX WORDS: Cohort study; donor outcomes; gout; allopurinol; colchicine; health administrative data; diagnostic codes; health outcomes; hyperuricemia; living kidney donor; kidney donation; nephrectomy; renal transplantation; uric acid.

High serum uric acid concentration is a potent risk factor for gout, for which the 10-year incidence rates are estimated to be 49%, 5%, and 1% for uric acid levels $\geq$ 9, 7.0 to 8.9, and $<$ 7.0 mg/dL, respectively.[1,2] A decline in glomerular filtration rate (GFR) results in less uric acid excretion and a higher serum uric acid concentration.[3,4] These changes are evident with the 25% to 40% reduction in GFR that occurs after living kidney donation.[5-9] As early as 6 months after nephrectomy, donors versus nondonor controls demonstrate an 8.2% higher serum uric acid level (mean values of 5.3 $\pm$ 1.1 [standard deviation] vs 4.9 $\pm$ 1.2 mg/dL; $P < 0.001$) and a 20% higher serum uric acid level a mean of 7 years after nephrectomy (Table S1, available as online supplementary material); mean uric acid level is 1.0 mg/dL higher in donors compared with nondonor controls.[8,10] However, whether donating a kidney appreciably increases a person's risk of gout is unknown. We undertook this study to investigate

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Received September 10, 2014. Accepted in revised form January 15, 2015. Originally published online March 26, 2015.

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0272-6386
http://dx.doi.org/10.1053/j.ajkd.2015.01.017

whether kidney donors have a higher risk of gout than nondonors with similar indicators of baseline health.

METHODS

Design and Setting

We conducted a retrospective matched cohort study using manual chart review and linked health care databases in Ontario, Canada, where citizens have universal access to hospital care and physician services. The reporting of this study followed guidelines for observational studies.[11] The research ethics board approved the prespecified protocol and waived the need for informed consent.

Data Sources

We ascertained patient characteristics, covariate information, and outcome data from records in 7 linked databases. Trillium Gift of Life Network is Ontario's organ and tissue donation registry and captures information for all living kidney donors in the province at the time of donation. We supplemented the data at this registry by manually reviewing perioperative charts of all living kidney donors who underwent donor nephrectomy at 1 of 5 major transplantation centers in Ontario in 1992 through 2010 to ensure data accuracy and completeness. Demographics and vital status information were retrieved from Ontario's Registered Persons Database. We used the Ontario Drug Benefit database to identify prescription drug use. This database contains highly accurate records of outpatient prescriptions dispensed to all patients 65 years or older, with a basic error rate $< 1\%$.[12] Diagnostic and procedural information during hospital admissions was gathered from the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) and Same Day Surgery (CIHI-SDS), whereas information regarding emergency department visits was gathered from the National Ambulatory Care Reporting System. The Ontario Health Insurance Plan database contains health claims for both inpatient and outpatient physician services. These databases have been used extensively for epidemiologic and health services research, including the study of living kidney donor outcomes.[13-19]

Population

Donors

We included all permanent residents who donated a kidney from July 1, 1992, through April 30, 2010, at any of the 5 major transplantation centers in Ontario. The date of nephrectomy served as the start date for follow-up and was designated the index date. Prior to matching, 35 living kidney donors with a predonation diagnosis of gout or a prescription for a medication typically used for the treatment of gout (eg, allopurinol or colchicine) were excluded. This was done to assess de novo gout in follow-up. There were too few donors with predonation gout to permit meaningful analyses of their outcomes after donation. We also excluded donors with recognized risk factors for gout, such as those with a predonation diagnosis of alcoholism ($n = 10$) or those with evidence of a prescription for medications that may increase uric acid levels ($n = 86$), such as thiazides.

Healthy Nondonors

Selecting the appropriate nondonors with whom donors can be compared is central to any study reporting risks associated with donor nephrectomy.[20] Donors undergo a rigorous medical screening and selection process and thus are inherently healthier than the general population. To address this issue, we used techniques of restriction and matching to select the healthiest segment of the general population. We randomly assigned an index date to the entire Ontario adult general population according to the distribution of index dates in the donors. We then identified comorbid conditions and measures of health care access from the beginning of available database records (July 1, 1991) to the index date. This provided an average of 12 years of medical records for baseline assessment, with 98.4% of individuals having at least 2 years of data for review. Among the general population, we excluded adults with a history of gout ($n = 210{,}814$) or any medical conditions prior to the index date that could preclude donation, including diabetes and hypertension (Table S2). Those who had a nephrectomy, kidney transplantation, kidney biopsy, dialysis, or a previous nephrology consultation also were excluded. Furthermore, we excluded any individual who had evidence of frequent physician visits (>4 visits in the previous 2 years) or who failed to see a physician at least once in the previous 2 years. The latter criterion was applied to ensure that healthy nondonors in our study were accessing physicians for routine health care needs, including preventive health measures. From a total of 9,484,623 Ontarians during the period of interest, this selection process resulted in the exclusion of 45.2% of adults ($n = 4{,}291{,}484$) as eligible nondonors. From the remaining adults, we matched 10 healthy nondonors to each donor based on age (within 2 years), sex, index date (within 6 months), rural (population $< 10{,}000$) or urban residence, and income (categorized into fifths of average neighborhood income).

Outcomes

All patients were followed up until death, emigration from the province, or the end of the study period (March 31, 2013). The primary outcome was time to the first health care encounter (physician visit, emergency department visit, or hospitalization) in follow-up at which a diagnostic code of gout was recorded in a health care database by medical coders or those submitting claims for physician reimbursement (Table S2). The secondary outcome was receipt of a prescription for allopurinol or colchicine, 2 medications typically used to treat gout. This secondary outcome was examined in the subpopulation that reached 65 years or older in follow-up.

Statistical Analysis

We compared standardized differences in baseline characteristics between donors and healthy nondonors. Differences $> 10\%$ suggest meaningful imbalance.[21] We used Cox proportional hazards regression models, stratified on matched sets, to calculate the hazard ratio (HR) with 95% confidence interval (CI) for the time to first gout diagnosis. The proportional hazards assumption was not violated (nonsignificant donor $\times$ log [follow-up time] interaction term; $P = 0.5$). We expressed the risk of developing an outcome in both relative and absolute terms. Absolute risk also was expressed as the number needed to harm (ie, the reciprocal of the absolute risk increase). This measure indicates how many individuals need to donate a kidney for 1 patient to experience an event, who otherwise would not have been harmed if all individuals did not donate a kidney (a lower number indicating greater harm). The number needed to harm was calculated for ease of interpretation and not to imply causality. In the subpopulation in which all individuals in a matched set reached 65 years or older in follow-up, we used conditional logistic regression accounting for matched sets to calculate the odds ratio (OR) and 95% CI for receipt of a prescription for allopurinol or colchicine. We repeated the primary analysis in 4 prespecified subgroups defined by the presence or absence of a family history of kidney disease, median age at index date (≤43 vs >43 years), sex, and index date (1992-2003 [median follow-up, 13.6 (interquartile range [IQR], 11.4-16.4) years] vs 2004-2010 [median follow-up, 5.8 (IQR, 4.3-7.3) years]). Information for family history of kidney disease was available for only donors (living related vs living unrelated donor), and in each subgroup analysis, sets of nondonors were categorized according to the characteristic of their matched donor (so as not to break matched sets in subgroup analysis). We examined whether subgroup-specific rate ratios differed among subgroups using a series of pairwise standard z tests. We examined the characteristics