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Prospective Swiss cohort study of living-kidney donors: study protocol

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ABSTRACT

Background: Offering living kidney donation raised the concern that donors are exposed to unknown risks. All Swiss transplant centres therefore decided to start a prospective cohort study of living kidney donors in Switzerland. This paper describes the rationale for and implementation of this cohort study.

Methods/design: All kidney donors in Switzerland are registered and examined before donation and biennially after donation starting in the first year after nephrectomy. Before each follow-up visit, the study centre sends a package to the kidney donor containing the health questionnaire, blood and urine tubes and a prepaid envelope for sending the samples to the central laboratory. The donor makes an appointment with their family physician, who examines the donor and reports findings such as pain and other complaints, blood pressure, creatinine, albumin, all major health events and the state of mental and social well-being to the study centre. The family doctor draws the blood sample and mails it with the urine sample in the prepaid envelope. All data are centrally managed. All abnormal findings in the follow-up of individual donors are regularly discussed with the principal investigator, and necessary clinical changes made and recorded in the database. The health insurance of the recipient covers all costs of the donor follow-up. The main outcomes are the occurrence of albuminuria, hypertension and renal insufficiency. The secondary outcomes are major somatic and social events such as death, cardiovascular disease, stroke and depression.

Discussion: This prospective cohort offers unique opportunities to assess the risks of living kidney donation and will allow us to examine the risks associated with the methods used for nephrectomy in Switzerland (various forms of open surgery and laparoscopic nephrectomy). The prospective collection of all clinically relevant data and the regular monitoring of donors will allow timely interventions at early stages before serious kidney and general health problems occur.

ARTICLE SUMMARY

Article focus

- To describe the rationale and set-up of the Swiss Living Kidney Donor Cohort Study.

Key messages

- The question of whether kidney donation increases health risks such as hypertension and renal failure is still unsettled.
- Data for this countrywide prospective cohort study over the period of at least 18 years will answer many still open questions concerning living kidney donor outcome.

Strengths and limitations of this study

- This countrywide cohort study includes all consenting Swiss living kidney donors.
- This is a long-term follow-up allowing the assessment of clinically relevant outcomes of donation such as hypertension and renal failure.
- We cannot completely rule out residual confounding in this observational study.

BACKGROUND

Living kidney donors have been used in Switzerland since 1967 but at a low rate. This, however, changed in the early 1990s. Rapid expansion of live kidney transplantation took place mainly in two large Swiss transplant centres Basel and Zürich. The latter had strictly disapproved all living organ donations for the two previous decades on ethical grounds. The increase in live donor transplantation was not universally regarded as a benefit. A lawyer wrote in the Swiss Medical Journal that 'organ removal from a living person for transplantation is an intended bodily injury according to civil and criminal law'.[1] Concerns were raised over the safety of live organ donation for the donors. The available published data from retrospective studies were largely incomplete. In these studies, the percentage of donors without follow-up data ranged from 21%[2 3] to 31%,[4] to 42%[5 6] up to 77%.[7] Indeed, given the available evidence, fair counselling of potential living donors is challenging.

Since living-donor transplantation was mainly propagated by the Basel transplant centre, we felt obliged to offer a long-term follow-up of the health state of living organ donors for all Swiss transplant centres. This idea was well accepted by the other five Swiss centres (Bern, Geneva, Lausanne, St Gallen and Zürich), and consequently, the cohort study by the name of the Swiss Organ

Living Donor Health Registry (SOL-DHR) was initiated in April 1993.

This paper describes the rationale for, and implementation of, this prospective cohort study. We aim to assess the prevalence of complications of living kidney donation and to identify risk profiles associated with unfavourable outcomes. We will assess the results of different surgical options for donation. In particular, the study is designed to prospectively quantify the risks to donors after living kidney donation: the development of hypertension, albuminuria, renal failure and psychological diseases. The infrastructure will also assist in the management of individual donors at an early stage if such complications occur.

METHODS

Prospective cohort study

There was a priori consensus among the founding members that a lifelong assessment of the health state of all consenting eligible living kidney donors should be made at regular time intervals in the context of a prospective cohort study. The protocol and questionnaires were approved by the Ethical Committee of the University Hospital of Basel and the Swiss Academy of Medical Science (SAMW). No informed consent is required, as a lifelong follow-up of the living donor's health state is required by the Swiss Transplant Law and may be studied as long as data are analysed anonymously. However, to ensure compliance with the long-term follow-up protocol, donors are informed about the aims of the protocol and the registry before their donation. In addition, kidney donors have at any time after donation the option to stop participating by simply ignoring the invitation from SOL-DHR to visit their family physician.

Donors from all six kidney transplant centres have been included in the SOL-DHR since 1993. Until the end of 2010, a total of 1332 living kidney donors have been included (Basel, n=521; Berne, n=119; Geneva, n=111; Lausanne, n=151; St Gallen, n=79; Zurich, n=360).

Main objectives

The main objectives were as follows:

- obtain prospective outcome data from consecutive living kidney donors in Switzerland;
- quantify the risks for early and late complications owing to nephrectomy;
- improve the information given to future potential donors before agreeing to donate a kidney and to produce standardised evidence-based educational materials;
- install a system of timely intervention in case of development of markers of increased risk or new health problems;
- compare outcomes from different methods of nephrectomy;
- provide a neutral platform for donors to express complaints and receive help.

Data-collection principles

Before kidney donation, the transplant centre is responsible for including patients in the study and for the first medical examination before kidney donation (see basic medical questionnaire below). At the time of discharge after nephrectomy, the transplant centre submits a second questionnaire (the early-complications questionnaire). Thereafter, the SOL-DHR centre organises a lifelong follow-up after nephrectomy at 1 year, 3 years, 5 years, 7 years, 10 years and biennially thereafter. The kidney donors are examined by their family physicians in the vicinity where they live. Before each follow-up visit, the SOL-DHR centre sends a package to the kidney donor asking the donor to make an appointment with the present family physician of their choice. This contains the brief information for the donor and the family physician, a health questionnaire, tubes for blood and urine samples, and a prepaid envelope for sending the samples at room temperature to the central laboratory (Viollier AG Basel, Switzerland). The basic biennial follow-up questionnaire is filled in by the family physician. Every 5 years, the donor fills in the additional Eight-Item Short-Form (SF-8) and social-status questionnaire (see below).

If no response from the donor is received within 2 months after the follow-up material was sent out, SOL-DHR initiates a search for the donor, contacting the recipient, the donor's health insurance and the public registries to identify whether the donor has died and, if so, the cause of death.

Results from the blood and urine analysis by the central laboratory are sent to the family physician and to the cohort manager at SOL-DHR.

Participation of family physicians

Whereas kidney recipients usually live in the area of the transplant centre, kidney donors often do not. Donors are not likely to adhere to a recommendation to travel lifelong biennially to a distant transplant centre for follow-up, particularly since travel expenses are not covered. We believe that adherence will be much greater if a follow-up can be coordinated by the patient's own local family physician. Family physicians, aided by trainees at the transplant centre, follow the protocols provided by the study centre.

Collected data

Laboratory data

We analyse creatinine in blood and urine, albumin and protein in urine centrally. The method used to quantify creatinine in blood changed over the years: 1993–1996 Jaffee, 1997–2003 enzymatic assay (Roche AG Basel, Switzerland), 2004–2005 'Jaffe compensated' (Roche), 2006–August 2007 'Jaffe corrected' (Siemens, Schweiz AG, Zürich, Switzerland), and since September 2007 an enzymatic assay (Siemens). In order to avoid systematic

errors owing to different assays prior to the database entry all values are converted to values traceable to isotope dilution mass spectrometry (IDMS) as recommended by the Kidney Disease: Improving Global Outcomes consensus conference[8] using calibration data supplied by the assay's manufacturers (data available on request). Albumin in urine is measured by turbidimetry after antigen–antibody reaction using the endpoint method (Roche).Whenever during a follow-up a laboratory result (creatinine or albumin/creatinine ratio) exceeds the expected range in an individual donor, the sampling and the laboratory analysis are repeated.

Definitions

Estimation of glomerular filtration rate (GFR)

To estimate GFR, we use the MDRD equation for IDMS-traceable creatinine values:[9]

$$\mathrm{eGFR(mL/min/1.73\ m^2)} = 175\times(\mathrm{Scr}/88.4)^{-1.154}\times(\mathrm{Age})^{-0.203}\times(0.742^{*})\times(1.212^{+}) * \mathrm{If\ female} + \mathrm{If\ African}$$

Microalbuminuria (=high albumin excretion)

We assume a daily urinary excretion of 10 mmol creatinine/day as being normal for donors (using this mean value for both genders taken together; an underestimate for males, and an overestimate for females). We will report albuminuria as albumin:creatinine ratios using the cut-off point defined by the report of the scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration.[10] The cut-off point for microalbuminuria or high albumin excretion is >30 mg/g (≥3.3 mg/mmol). For clarity, we will use the term microalbuminuria, which is commonly used in Europe, rather than the term 'high albumin excretion' used in North America. The cut-off point for macroalbuminuria (proteinuria) or very high albumin excretion is >300 mg/g (>33.9 mg/mmol).

Hypertension

Donors who have a systolic pressure above 140 mm Hg or diastolic pressure above 90 mm Hg or both or who are taking any antihypertensive drug are classified as hypertensive. In any case of new-onset hypertension, we ask the family physician to perform a 24 h ambulatory blood pressure recording. If hypertension is confirmed, we recommend antihypertensive treatment with and ACE inhibitor or an angiotensin-receptor blocker.

HEALTH-STATUS DATA

At each visit, the family physician is asked to measure the actual weight, height and blood pressure (three times in the sitting position), and the bare abdomen of the donor in an upright posture to look for an incisional hernia or abdominal wall bulging caused by the nephrectomy. When the donor is complaining about pain in any specific place (eg, lumbar back pain), it should be examined and evaluated whether it is or could be causally related to nephrectomy. We ask for careful documentation of new symptoms, comorbidities or other problems (somatic, mental or social).

Questionnaires

Basic medical questionnaire to be collected before donation

The basic medical questionnaire collects information on body weight, sitting blood pressure (three times), description of the nephrectomy scare, pain or new problems since the last examination and an inventory of all drugs currently taken. The questionnaire before donation also includes 'major disease and back pain,' since we realise that back pain is such a common complaint that we need information before donation in order classify back pain after donation in a meaningful way.

Early-complication questionnaire to be collected at the time of hospital discharge after nephrectomy (since 1998)

This questionnaire collects data on the side and method used for nephrectomy and all complications occurring peri- and postoperatively including blood transfusions, whether the endoscopic procedure had to be changed intraoperatively and whether surgical revision was necessary. Early postoperative pain, which reflects pain at the site of incision and sometimes in case of endoscopic nephrectomy additional shoulder pain due to body positioning during surgery, is assessed using the visual analogue scale. The questionnaire is filled out usually 2 weeks after nephrectomy. For grading early complications, we use the Clavien scale.[11] Every early complication observed in a donor is classified along the Clavien scale (Grade I=1, grade II=2, grade IIIa=3, grade IIIb=3.5, grade IVa=4, grade IVb=4.5, etc). If multiple complications occur in the same donor, the single Clavien scores are added to what is called the Clavien sum per donor score. We also calculate the simple sum of observed complications per donor. The two sums have different interpretations. For a given group of donors, for example, older than 60 years, the mean simple sum of complications shows the frequency of early complications seen in older donors, whereas the mean Clavien sum shows their severity.

Basic biennial follow-up questionnaire

We ask the family physician to measure body weight and sitting blood pressure (three times), examine the nephrectomy scar and take an interim medical history in order to complete the medical questionnaire. This includes questions about pain and all serious health problems (eg, stroke, cardiovascular events, diabetes or malignancies) since the last examination. Back pain is considered to be related to the nephrectomy only if specified by the donor or their physician as being clearly more intense than before donation. (Pain related to nephrectomy can be caused by instability of the abdominal wall after large lumbar incision with partial muscular palsy.) The family physician records all drugs

currently taken, performs a bedside dipstick examination of the urine, fills the blood and urine phials, and sends both phials to the central laboratory. If the urinary dipstick turns out to be positive for blood, protein, white blood cells or other abnormalities, we request that the family doctor make an additional microscopic examination of the urinary sediment. All clinical data are sent to the SOL-DHR study centre.

The SF-8 questionnaire has been collected every 5 years after donation since 2002. The validated SF-8 multiple choice questionnaire is used to calculate the Physical Component Summary and Mental Component Summary

We ask three supplementary multiple-choice questions, which are analysed separately: (1) In comparison with 1 year ago, how would you describe your actual health? (2) How has your emotional relationship with the kidney recipient changed since donation? (3) Would you donate a kidney again, if you still had two kidneys?

Social-status questionnaire

Since 2002, we have used an instrument developed by SOL-DHR that contains multiple-choice questions about the actual professional activity, working capacity, efficiency and physical fitness of the donor, along with two open questions: (1) drawbacks because of donation (eg, financial, insurance, pension fund or professional disadvantages) and (2) donor's suggestions for possible improvement for SOL-DHR activities (What can SOL-DHR do better for you?).

Data monitoring and quality assurance

All incoming data are checked by staff for completeness and plausibility, and are entered into an electronic database. In case of missing or implausible data, we call the office of the family physician and attempt to rectify this. Once or twice a month, staff discuss any donor with an abnormality with the principal investigator. Urgent cases are discussed immediately, and interventions are initiated without delay. All outcomes are stored within the database.

The 'principle of intervention' is a key feature of this cohort study. Thus, we not only observe our cohort but also intervene actively, as soon as any risk factor changes or clinical problem develops. Study leaders make recommendations for interventions which are then implemented by the family physician. Recommendations may include performing a diagnostic procedure such as 24 h ambulatory blood pressure measurement in order to confirm hypertension, to perform an ultrasound of the remaining kidney or to repeat the chemical analysis. The letter may also contain a recommendation for treatment.

Funding of SOL-DHR and reimbursement for follow-up examinations

The SOL-DHR expenses are funded by the Swiss Foundation for the follow-up care of living organ donors (SNO). The SNO is supported by the government, research and industry funds as well as the Swiss Society of Nephrology. The detailed list of sponsors is given at the end of the manuscript. The running costs of SOL-DHR are kept low, as organisation and medical activities of SOL-DHR have been provided on a volunteer basis by GTT since 1993 and by DT since 2000.

The basic concept is to cover the costs of kidney donor follow-up via the insurance company of the kidney recipient, because they would have paid ongoing dialysis costs had no living donation taken place. Coverage includes all costs including those of late complications of the donor that are causally related to the donation. Hence, Swiss transplant law requires the health insurance of the kidney recipients to cover the bills from the family physicians for biennial donor follow-up (according to a fixed payment schedule) as long as the recipient is alive. After the recipients' death, the bills for the donor follow-up are covered by SNO. The bills for donor follow-up examination are sent to the SOL-DHR centre, which forwards the bill to the health insurance of the kidney recipient. The costs for the chemical analysis in blood and urine of donors have been covered by Viollers AG Basel since 1993. The cost for drugs required by the donor is paid by the compulsory health insurance of the donor, whether the drug treatment is related to donation or not.

Handling missing responses

If no response is received by 2 months after an invitation has been sent (a filled out questionnaire from the donor, the family physician or laboratory) SOL-DHR staff call the donor. If the donor declines to participate further, they will be marked 'inactive' in the cohort database, and follow-up is suspended. If the donor later changes their mind, and gets in touch with us again (eg, after moving back to Switzerland), the status is changed back to 'active' immediately.

Control population

To control for the risk of developing hypertension, we plan to use two different reference groups. First, we will compare the incidence and prevalence of hypertension in our cohort with that of the Monitoring of Trends and Determinants in Cardiovascular Disease Study (data from a normal Swiss population).[12–14] Second, since living donors are positively selected from the normal population, we consider them to be 'healthier' than the normal population, resulting in a potential underreporting of health risks. To directly compare the normal outcome of such a healthy cohort, pooled data from the SOL-DHR's own healthy donor population taken prior to nephrectomy (n=1332) are used to analyse the outcome of this positively selected donor population after donation.

STATISTICAL CONSIDERATIONS

Continuous data will be presented with medians, interquartile ranges or means and standard deviations as appropriate, and categorical data as rates and

percentages. The association of independent variables with the outcome variables will be reported using correlation coefficients. Main outcomes are the occurrence of albuminuria, hypertension and renal insufficiency as specified above. Secondary outcomes are major somatic and social events such as death, cardiovascular disease, stroke and depression collected from the questionnaires. All outcomes are considered to be dichotomous.

Results from univariate analysis will inform multivariable modelling. Assessment of causal associations will be performed using multivariable models including potential confounders along with the independent variables of interest. Prognostic scores will be built using either multivariate logistic regression analysis or Cox proportional hazard models. Models will be validated in cross-samples. Calibration and discrimination of the cross-validated prognostic instruments will be assessed using the Brier Score. Time-series analysis will be performed using random-effects regression models where appropriate.

Sample-size calculations

The analysis is based on the example of hypertension. We assume that one additional kidney donor out of 15 (controls) will develop hypertension. We further assume a follow-up after the accrual interval of 10 years. Prior data indicate that the median time for onset of hypertension (survival time) on the control treatment is 5 years. If the true median survival times on the experimental and control treatments are 5 and 10 years, respectively, we will need to study 29 subjects developing hypertension and 435 control subjects to be able to reject the null hypothesis that the experimental (post-surgery) and control (presurgery) survival curves are equal with probability (power) 80%. The Type I error probability associated with this test of this null hypothesis is 0.05.

DISCUSSION

This paper describes the rationale for, and organisation of, a lifelong prospective cohort study of living kidney donors in Switzerland. This study offers unique opportunities to assess the frequency of occurrence of unfavourable outcomes following donation and allows risk factors associated with them to be determined. More specifically, we are particularly interested in increasing our understanding of the long-term effect of donation on renal function and the risk of developing hypertension or albuminuria, and exploring whether adverse outcomes depend on the method of nephrectomy applied. Moreover, the systematic collection of all clinically relevant data and the monitoring of participants on a regular basis allow timely interventions if kidney functions or general health change for the worse.

Overview of the existing evidence

In the 1980s and early 1990s, many interesting papers were already available.[2–7 15–23] They all tried to quantify the morbidity and mortality of living kidney donation or unilateral nephrectomy. Most data derive from single centres in the USA, some from Norway or Australia. Unfortunately, all published data were collected retrospectively, resulting in incomplete data sets, and the data were affected by selection bias. Based on these retrospective studies, kidney donation is now generally accepted as a relatively safe procedure, but long-term data prospective studies of consecutive patients are lacking.[24–27]

Up to now, prospective long-term follow-up of living donors has not been regarded generally as a necessity. A prospective long-term follow-up study of living donors as set out in the present protocol is likely to improve the quality of the data on the short- and medium-term safety of living kidney donation, but also allows for timely intervention if an individual donor experiences a potential problem. Data generated will inform policy on optimal long-term donor follow-up.

In addition, new questions such as the effect of various surgical techniques have arisen recently. Several methods of endoscopic (including robotically assisted) nephrectomy have been introduced and have been shown to be relatively safe.[28–38] Single-centre reports mainly concentrate on a single technology rather than providing unbiased comparisons of different methods.[30 33–36] To our knowledge, no national prospective cohorts have yet reported on these issues, and those that are planned will compare only two methods.[32]

The question of whether kidney donation increases the risk for hypertension, which had already been debated in the 1980s,[4 16 22] is still unsettled owing to the limited number of studies.[29] We think that the results of this large, nationwide, prospective cohort study will address many important unanswered questions about outcomes in living kidney donors.

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Competing interests None.

Patient consent Obtained.

Ethics approval Ethics approval was provided by the Ethical Committee of the University Hospital of Basel and the Swiss Academy of Medical Science.

Contributors GTT was involved in the conception and design of the study, drafted the protocol, supervised the revisions and approved the final manuscript. DT was involved in the conception and design of this study, revised the draft critically for intellectual content and approved the final revised manuscript. CN was involved in the conception of the study, revised the draft critically for intellectual content and approved the final manuscript.

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