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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 and set-up of this cohort.

Methods/Design All consenting eligible kidney donors are registered and examined before and biennially starting in the first year after nephrectomy. In the lead-up of a follow-up visit, the study center sends a little parcel to the kidney donor containing the health questionnaire, blood and urine tubes and a pre-paid envelope for sending the probes to the central laboratory. The donor makes an appointment with his family physician. At the consultation, body weight and sitting blood pressure is measured, followed by an inspection of the nephrectomy scare. Then, the questionnaire assessing the current health status including medications is filled. Blood and urine samples are sent to the central laboratory for examination. A urine dip-stick test is made and, if positive for blood, protein, white blood cells and other abnormalities, an microscopic examination is performed. All data are centrally managed at the cohort headquarter. All abnormalities are regularly discussed with the principle investigator and all necessary measures are taken. Any intervention is stored in the database. The health-insurance of the organ-recipient covers all costs of the donor-follow-up. Main outcomes are the occurrence of albuminuria, hypertension and renal insufficiency.

Discussion This prospective cohort offers unique opportunities assessing the risks of living kidney donation and allows examining risk differences for all available methods used for nephrectomy in Switzerland (various forms of open surgery and endoscopic nephrectomy). Moreover, the systematic collection of all clinically relevant data and the monitoring of participants on a regular basis allow timely interventions if critical parameters of kidney function or general health change for the worse.

BACKGROUND

Living kidney donors were used in Switzerland since 1967 but at a low rate. This, however, changed in the early nineties. Rapid expansion of live kidney transplantation took place especially in one large Swiss transplant centre, where live kidney was formerly strictly disapproved over two decades because of ethical reasons. But the rising number of live donor transplantation was not well accepted from all sides. 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 retrospectively collected data came from fare away and were largely incomplete. The percent of missed donors ranged from 21% [2 3] to 31% [4], to 42% [5 6] up to 77% [7]. Prospective cohort studies of living donors were not generally regarded as necessary. Thus, any fair counselling of potential living donors was impossible for us, all the more that no Swiss data on donor risk were available at that time.

Since living donor transplantation was mainly propagated by the Basel transplant centre, we felt obliged to offer a long-time follow-up of the health state of living organ donors for all Swiss transplant centres. This idea was well accepted by the other 5 Swiss centres (Bern, Geneva, Lausanne, St. Gallen and Zürich) and consequently, the cohort study by the name of SOL-DHR (Swiss Organ Living Donor Health Registry) was initiated in April 1993.

This paper describes the rationale and set-up of this prospective cohort study aiming at assessing the prevalence of complications of living kidney donation and aiming at identifying risk profiles associated with unfavourable outcomes.

METHODS / DESIGN

Prospective cohort study: There was an a priori consensus among the founding members that health state of all consenting eligible living kidney donors should be assessed life-long at regular time intervals in the context of a prospective cohort study. The responsible Ethics committees approved the protocol and we are obtaining informed consent from all participants.

Main objectives

- Gaining prospective outcome data from living kidney donors in Switzerland
- Assess and quantify the risks for early and late complications due to organ removal
- Improve the information given to potential donors before agreeing to donate a kidney
- Install a system of timely intervention in case of deterioration in state of health
- Compare the consequences of different methods of organ removal on state of health
- Provide a neutral platform, where donors can express complains and receive help

Data collection principles

Study inclusion and a first medical examination before kidney donation is done by the transplant centre. Thereafter the study centre organises the 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 (free choice of donor to select the doctor) in the vicinity where they live. In the lead-up of a follow-up visit, the study centre sends a little parcel to the kidney donor containing the brief information for the donor and the family physician, a health questionnaire, blood and urine tubes and a pre-paid envelope for sending the probes to the

central laboratory (Viollier AG Basel). The donor makes an appointment with his family physician.

The family physician is requested to measure body weight, sitting blood pressure (3 times), examine the nephrectomy scare, ask all questions necessary to file-out the medical questionnaire including the question about pain or new problems since the last examination, to note all drugs currently taken, make a dip-stick examination of the urine and finally fill a blood and a urine tube and send both tubes to the central laboratory. If the urinary dip stick turns out to be positive for blood, protein, white blood cells and other abnormalities, the doctor has to make an additional microscopic examination of the urinary sediment. All clinical data, including the health state questionnaire, are sent to the study centre SOL-DHR.

The central laboratory sends all results of the analyses to the family physician and to the cohort manager.

Participation of family physicians

Whereas kidney recipients live usually in the area of the transplant centre, kidney donors often do not. Asking donors to travel lifelong biannually to the distant transplant centre for control has little chance to be followed, particularly since travel expenses are not covered. Follow-up controls done by the family physician working in the vicinity of the donor improve donor's willingness to participate manifold. Family physicians as well as young medical assistants at the transplant centre follow the protocols provided by the study centre.

Collected data

Laboratory data

We quantify creatinine in blood and urine, albumin and protein in urine. The method used to quantify Creatinine in blood changed over the years: 1993 -1996 Jaffee, 1997 -2003 enzymatic assay (Roche), 2004 – 2005 "Jaffe compensated" (Roche), 2006 – 2007 "Jaffe corrected" (Siemens). Since September 2007 enzymatic assay (Siemens). In order to avoid systematic errors due to different assays prior to the data base entry all values are converted to values traceable to isotope dilution mass spectrometry (IDMS) as recommended by the KDIGO 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 Diagnostics). Protein in urine is measured by turbidimetry after exposure to benzethoniumchloride.

Definitions

Estimation of the glomerular filtration rate (GFR)

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

eGFR (mL/min/1.73 m2) =

$175 \times (Scr/88.4)^{-1.154} \times (Age)^{-0.203} \times (0.742^{*}) \times (1.212^{+})$ * If female + If African

Micro-albuminuria and macro-albuminuria

We assume a daily urinary excretion of 10 mmol Creatinin/24h as being normal for donors (mean value for both genders taken together, - underestimating it for males, overestimating for females). The cut-off-point for albuminuria to be called micro-albuminuria is set to an albumin/creatinine-quotient of at least 5 mg albumin / mmol creatinine. Assuming a daily

urinary excretion of 10 mmol creatinine, this cut-off gives an estimation of 50 mg albumin per day instead of the commonly used 30 mg. We refrain from using a cut-off of 3 mg albumin / mmol creatinine, as many donors having a creatinine excretion below 10 mmol/d would be misclassified as having microalbuminuria, while donors with a quotient of 5mg/mmol run a very high chance that this is correct and not just a borderline state fluctuating between mini-micro-albuminuria and no micro-albuminuria.

For the definition of macro-albuminuria, which is identical with the term proteinuria, we use 300 mg albumin / 10 mmol creatinine or 30 mg albumin / mmol creatinine.

Hypertension

Donors having a systolic pressure above 140 mm Hg or diastolic above 90 mmHg or both or taking any antihypertensive drug are classified as hypertensive. In any case of new onset hypertension, we ask the family physician to perform a 24h pressure recording. If hypertension is confirmed, we recommend antihypertensive treatment with ACEI or an Angiotensin receptor antagonist (ARA).

Health state data

At each visit, the family physician is asked to measure the actual weight, height and blood pressure (3 times in sitting position). Moreover he is requested to examine the bare abdomen of the donor in an upright posture in order to look for an incisional hernia or abdominal wall bulging caused by the nephrectomy. When the donor is complaining about pain at any specific place (i.e. lumbar back pain), it should be examined and evaluated, whether it is or could be causally related to nephrectomy. New complains, disease or any problems (somatic, mental, social) need to be mentioned carefully in a separate line of the form.

Questionnaires

- The basic medical questionnaire:

  Containing information on body weight, sitting blood pressure (3 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 realize 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 (since 1998):

  This questionnaire is asking about 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. Postoperative pain 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 [10]. Every early complication observed in a donor is classified along the Clavien scale (Grade 1 =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 as compared to the simple sum of observed complications per donor score. The two sums have different interpretations. For a given (sub) population of donors, i.e. older than 60 years, the "mean sum of complications" shows the frequency of early complications seen in elderly donors, the mean Clavien sum" however, their severity.

- SF-8 questionnaire (since 2002).

  (The questionnaire is supplemented by three own questions: In comparison to the last year how would you describe your actual health, how has your emotional relation to the kidney recipient changed since donation? Would you donate a kidney again, if you still had two kidneys?). These questions are obviously not used for calculating the PSC (Physical Component Summary) or MCS (Mental Component Summary), but are considered separately.

- Social status questionnaire (since 2002).

  This instrument has been developed by ourselves and contains questions about the actual professional activity, working capacity, efficiency, and physical fitness and two open questions: 1) draw backs because of donation and 2) desires addressed to SOL-DHR (what can SOL-DHR do better ?)

Data monitoring and quality assurance

All incoming data are checked by cohort staff for completeness and plausibility, and are entered thereafter into an electronic database. In case of lacking information, staff calls to the office of the family physician and tries to receive any missing data. All cases with an abnormality are discussed with the principle investigator once or twice a month. 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 do not only observe our cohort, but we also intervene actively, as soon as any potential danger is turning up. Interventions are planned to be provided by the family physician based on the recommendation of the study leaders. Recommendations my include performing a diagnostic procedure like the 24h blood-pressure measurement in order to confirm hypertension or to

perform a sonongraphy of the remaining kidney or simply to repeat the chemical analysis. The letter may contain a recommendation for treatment, i.e. a renoprotective antihypertensive drug (ACEI or ARA), when blood pressure is high and already accompanied by micro-albuminuria. We ask the colleague to select the specific agent among ACEI or ARA he is most familiar with.

Reimbursement

Doctors' bill for this examination is sent to the study headquarater, which forwards this bill to the health insurance of the kidney recipient. The amount which can be asked by the family physician for this service is now fixed with the majority of Swiss health insurances at about 150 Swiss Francs (~115 Euros). The Sponsor Fund of this cohort study covers the examination costs if a recipient dies. The basic concept is to charge the costs of kidney donor follow-up to the insurance of the kidney recipient, because they would have to pay the dialysis costs if no living donation had taken place. Coverage includes all costs including those of late complications that are causally related to the donation.

Handling missing responses

If within 2 months no response is received after invitation (neither a filled out questionnaire from the donor nor the family physician or laboratory) SOL-DHR staff calls the donor. If the donor declares, that he does not longer want to participate he or she will be marked "inactive" in the cohort database and follow-up is suspended. If the donor, however, changes his or her mind, and gets in touch with us again (i.e. after moving back to Switzerland) the status is changed back to "active" immediately at any time.

Statistical Considerations

Epidemiologic data and patients' descriptives available on continuous scales will be presented with medians, interquartile ranges or means and standard deviations as appropriate. Categorical data will be presented as rates and percentages. Association of individual (independent) variables on the outcome variables will be reported using correlation coefficients. Results from univariate analysis will inform multivariate modelling. Assessment of causal associations will be performed using multivariate 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.

Discussion

This paper describes the rationale and set-up of a lifelong prospective cohort study of living kidney donors in Switzerland. This study offers unique opportunities assessing the frequency of occurrence of unfavourable outcomes following donation and allows determining risk factors associated to them. More specifically, we are particularly interested increasing our understanding of the long term effect of donation on renal function, the risk to develop hypertension or abuminuria and to explore 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 critical parameters of kidney function or general health change for the worse.

An overview of the existing evidence

In the eighties and early nineties many interesting papers were already available [2-7 11-19]. 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 and incompletely. The percent of missed donors ranges from 21% [2 3] to 31% [4], to 42% [5 6] up to 77% [7]. Prospective long-term follow-up of living donors has not been regarded generally as a necessity.

Today, kidney donation is now generally accepted as a relatively safe procedure based on additional retrospectively collected long-term data that are still quite incomplete [20-23]. Several methods of endoscopic (including robotic assisted) nephrectomy have been introduced and have shown to be relatively safe[24-34]. Single centre reports are mainly defending their own used technology [26 29-32]. Bottom line however, countrywide prospective cohorts allowing a

comparison of various surgical procedures are yet unavailable or in an early phase comparing no more than two methods [28].

The question whether kidney donation increases the risk for hypertension, which was already on debate in the eighties [4 12 18], is still unsettled due to limited studies [25]. We think that the results of this large national wide prospective cohort study will answer many still open questions concerning living kidney donor outcome.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors participated in study design; GT drafted the protocol. All the authors read and approved the final manuscript.

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

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		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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 and set-up of this cohort.

Methods/Design All kidney donors in Switzerland are registered and examined before donation and biennially after donation starting in the first year after nephrectomy. In the lead-up of a follow-up visit, the study centre sends a little parcel to the kidney donor containing the health questionnaire, blood and urine tubes and a pre-paid envelope for sending the samples to the central laboratory. The donor makes an appointment with his family physician, who examines the donor and reports findings such as pain and other complains, blood pressure, creatinine, albumin and all major health events and the state of mental and social wellbeing to the study centre. All data are centrally managed. All abnormal findings in the follow-up of individual donors are regularly discussed with the principle investigator and all necessary measures are taken. Any intervention is stored in the database. The health-insurance of the organ-recipient covers all costs of the donor-follow-up. Main outcomes are the occurrence of albuminuria, hypertension and renal insufficiency. Secondary outcomes are major somatic and social events such as death, cardiovascular disease, stroke and depression.

Discussion This prospective cohort offers unique opportunities assessing the risks of living kidney donation and allows examining risk differences for all available methods used for nephrectomy in Switzerland (various forms of open surgery and endoscopic nephrectomy). Moreover, the prospective collection of all clinically relevant data and the monitoring of participants on a regular basis allow timely interventions at an early stage before critical parameters of kidney function or general health problems occur.

BACKGROUND

Living kidney donors were used in Switzerland since 1967 but at a low rate. This, however, changed in the early nineties. Rapid expansion of live kidney transplantation took place especially in one large Swiss transplant centre, where live kidney was formerly strictly disapproved over two decades because of ethical reasons. But the rising number of live donor transplantation was not well accepted from all sides. 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 percent of donors without follow up data ranged from 21% [2 3] to 31% [4], to 42% [5 6]up to 77% [7]. Given the available evidence, any fair counselling of potential living donors seems difficult.

Since living donor transplantation was mainly propagated by the Basel transplant centre, we felt obliged to offer a long-time 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 SOL-DHR (Swiss Organ Living Donor Health Registry) was initiated in April 1993.

This paper describes the rationale and set-up of this prospective cohort study aiming at assessing the prevalence of complications of living kidney donation and aiming at identifying risk profiles associated with unfavourable outcomes. In particular the study is designed to prospectively quantify the risks to donors after living kidney donation such as the development of hypertension, albuminuria, renal failure and psychological diseases and to assist in the management of individual donors at an early stage if such complications occur.

METHODS / DESIGN

Prospective cohort study: There was an a priori consensus among the founding members that health state of all consenting eligible living kidney donors should be assessed life-long at regular time intervals in the context of a prospective cohort study. The protocol and the 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 lifelong follow-up of living donor's health state is required by the Swiss Transplant Law and as long as data are analysed anonymously. However, to assure compliance to 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 quit their participation by simply ignoring the invitation from SOL-DHR to visit their family physician.

Donors from all six kidney transplant centres are included in the SOL-DHR. 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 and Zurich n=360).

Main objectives

- Gaining prospective outcome data from living kidney donors in Switzerland
- Assess and quantify the risks for early and late complications due to organ removal
- Improve the information given to potential donors before agreeing to donate a kidney
- Install a system of timely intervention in case of deterioration in state of health
- Compare the consequences of different methods of organ removal on state of health
- Provide a neutral platform, where donors can express complains and receive help

Data collection principles

Study inclusion and a first medical examination before kidney donation is done by the transplant centre (see basic medical questionnaire below). A second questionnaire (early complication questionnaire) is collected from the transplant centre at the time of discharge after nephrectomy. 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. In the lead-up of a follow-up visit, the SOL-DHR centre sends a little parcel to the kidney donor asking the donor to make an appointment with the present family physician of his choice. The parcel contains the brief information for the donor and the family physician, a health questionnaire, tubes for blood and urine samples and a pre-paid envelope for sending the samples at room temperature to the central laboratory (Viollier AG Basel). The basic biennial follow up questionnaire is filled in by the family physician. Every five years the donor fills in the additional SF8 and social status questionnaire (see below).

If no response from the donor is received within 2 months, SOL-DHR initiates a search for the donor and attempts collecting possible data on donor death and its reason by contacting the recipient, the donor's health insurance and the public registries.

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

Participation of family physicians

Whereas kidney recipients live usually in the area of the transplant centre, kidney donors often do not. Asking donors to travel lifelong biennially to the distant transplant centre for

control has little chance to be followed, particularly since travel expenses are not covered. Follow-up controls done by the family physician working in the vicinity of the donor improve donor's willingness to participate manifold. Family physicians as well as young medical assistants at the transplant centre follow the protocols provided by the study centre.

Collected data

Laboratory data

We quantify creatinine in blood and urine, albumin and protein in urine. The method used to quantify creatinine in blood changed over the years: 1993 -1996 Jaffee, 1997 -2003 enzymatic assay (Roche), 2004 – 2005 "Jaffe compensated" (Roche), 2006 – 2007 "Jaffe corrected" (Siemens). Since September 2007 enzymatic assay (Siemens). In order to avoid systematic errors due to different assays prior to the data base entry all values are converted to values traceable to isotope dilution mass spectrometry (IDMS) as recommended by the KDIGO 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 Diagnostics).

Whenever during a follow-up a laboratory results (creatinine or albumin/creatinine ratio) exceeds the expected range in an individual donor, the sampling and the laboratory analysis is repeated.

Definitions

Estimation of the glomerular filtration rate (GFR)

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

eGFR (mL/min/1.73 m2) =

$175 \times (Scr/88.4)^{-1.154} \times (Age)^{-0.203} \times (0.742^{*}) \times (1.212^{+})$ * If female + If African

Micro-albuminuria (= high albumin excretion)

We assume a daily urinary excretion of 10 mmol Creatinin/24h as being normal for donors (mean value for both genders taken together, - underestimating it for males, overestimating for females). Data on albuminuria will be presented based on cut-off points 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 albumin excretion to be called micro-albuminuria or high albumin excretion is set to > 30 mg albumine / g creatinine corresponding to ≥ 3.3 mg albumin / mmol creatinine. For clarity reasons we will use the term micro-albuminuria which is commonly used in Europe rather than the term "high albumin excretion" used in North America. For the definition of macro-albuminuria or very high albumine excretion at cut-off point of >300 mg albumin / g creatinine corresponding to 33.9 mg albumin / mmol creatinine is used.

Hypertension

Donors having a systolic pressure above 140 mm Hg or diastolic above 90 mmHg or both or taking any antihypertensive drug are classified as hypertensive. In any case of new onset hypertension, we ask the family physician to perform a 24h pressure recording. If hypertension is confirmed, we recommend antihypertensive treatment with ACEI or an Angiotensin receptor antagonist (ARA).

Health state data

At each visit, the family physician is asked to measure the actual weight, height and blood pressure (3 times in sitting position). Moreover he is requested to examine the bare abdomen of the donor in an upright posture in order to look for an incisional hernia or abdominal wall bulging caused by the nephrectomy. When the donor is complaining about pain at any specific place (i.e. lumbar back pain), it should be examined and evaluated, whether it is or could be causally related to nephrectomy. New complains, disease or any problems (somatic, mental, social) need to be mentioned carefully in a separate line of the form.

Questionnaires

- The basic medical questionnaire to be collected before donation:

  The basic medical questionnaire collects information on body weight, sitting blood pressure (3 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 realize 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 is collecting 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 do 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 1 =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 as compared to the simple sum of observed complications per donor score. The two sums have different interpretations. For a given (sub) population of donors, i.e. older than 60 years, the "mean sum of complications" shows the frequency of early complications seen in elderly donors, the mean Clavien sum" however, their severity.

- The basic biennial follow up questionnaire

The family physician is requested to measure body weight, sitting blood pressure (3 times), examine the nephrectomy scare and to ask the donor all questions necessary to file-out the medical questionnaire including questions about pain and all serious health problems including major events such as stroke, cardiovascular events, diabetes or malignancies since the last examination. Back-pain is considered as nephrectomy related only if specified by the donor or his physician as being clearly more intensive than before donation as pain related to nephrectomy can be caused by instability of the abdominal wall after large lumbar incision with partial muscular palsy. Furthermore the family physician is asked to note all drugs currently taken; make a dip-stick examination of the urine and finally fill a blood and a urine tube and send both tubes to the central laboratory. If the urinary dip stick turns out to be positive for blood, protein, white blood cells and other abnormalities, the doctor has to make an additional microscopic examination of the urinary sediment. All clinical data, including the health state questionnaire, are sent to the study centre SOL-DHR.

- SF-8 questionnaire to be collected every 5 years after donation (since 2002).

  The validated SF-8 multiple choice questionnaire was used to calculate the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

  The questionnaire was supplemented by the three following multiple choice questions: 1) In comparison to the last year how would you describe your actual health? 2) How has your emotional relation to the kidney recipient changed since donation? 3) Would you donate a kidney again, if you still had two kidneys?. The answers to these questions are analysed separately from the 8 SF-8 questions.

- Social status questionnaire (since 2002).

  This instrument has been developed by SOL-DHR and contains multiple choice questions about the actual professional activity, working capacity, efficiency, and physical fitness and two open questions: 1) draw backs because of donation (e.g. financial, insurance, pension fund or professional disadvantages) and 2) donor's suggestion on possible improvement for the SOL-DHR activity (What can SOL-DHR do better for you?)

Data monitoring and quality assurance

All incoming data are checked by cohort staff for completeness and plausibility, and are entered thereafter into an electronic database. In case of lacking information, staff calls to the office of the family physician and tries to receive any missing data. All cases with an abnormality are discussed with the principle investigator once or twice a month. 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 do not only observe our cohort, but we also intervene actively, as soon as any potential danger is turning

up. Interventions are planned to be provided by the family physician based on the recommendation of the study leaders. Recommendations my include performing a diagnostic procedure like the 24h blood-pressure measurement in order to confirm hypertension or to perform a sonongraphy of the remaining kidney or simply 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 are provided on a volunteer base by GT since 1993 and 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 to pay the dialysis costs if no living donation had taken place. Coverage includes all costs including those of late complications of the donor that are causally related to the donation. Hence, the Swiss transplant law requires the health insurances of the kidney recipients to cover the bills from the family physicians for biennial donor follow-up as long as the recipient stays alive with an official pay scale. After recipients death the bills for the donor follow-up are covered by SNO. The bills for the donor follow-up examination are sent to the SOL-DHR headquarter, which forwards the bill to the health insurance of the kidney recipient. The costs for the chemical analysis in blood and urine of donors are covered by the Violliers AG Basel. Cost for drugs required by the donor are paid by the compulsory health insurance of the donor independently whether the drug treatment is related to donation or not.

Handling missing responses

If within 2 months no response is received after invitation (neither a filled out questionnaire from the donor nor the family physician or laboratory) SOL-DHR staff calls the donor. If the donor declares, that he does not longer want to participate he or she will be marked "inactive" in the cohort database and follow-up is suspended. If the donor, however, changes his or her mind, and gets in touch with us again (i.e. after moving back to Switzerland) the status is changed back to "active" immediately at any time.

Control population

To control for the risk of developing hypertension we plan using two different reference groups. First, we will compare the frequency of occurrence of hypertension in our cohort to that of the MONICA-study with data from a normal Swiss population. [12-14]Second, since living donors are a positive selection out of 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 is used to analyse the outcome of this positively selected donor population after donation.

Statistical Considerations

Epidemiologic data and patients' descriptives available on continuous scales will be presented with medians, interquartile ranges or means and standard deviations as appropriate. Categorical data will be presented as rates and percentages. Association of individual (independent) variables on 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 multivariate modelling. Assessment of causal associations will be performed using multivariate 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 1 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 survival time on the control treatment is 5 years. If the true median survival times on the control and experimental 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 (pre-surgery) 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 and set-up of a lifelong prospective cohort study of living kidney donors in Switzerland. This study offers unique opportunities assessing the frequency of occurrence of unfavourable outcomes following donation and allows determining risk factors associated to them. More specifically, we are particularly interested increasing our understanding of the long term effect of donation on renal function, the risk to develop hypertension or abuminuria and to explore 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 critical parameters of kidney function or general health change for the worse.

An overview of the existing evidence

In the eighties and early nineties 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 data are prone to selection bias. Based on these retrospective studies kidney donation is now generally accepted as a relatively safe procedure but long-term data that are still quite incomplete [24-27].

Up to now prospective long-term follow-up of living donors has not been regarded generally as a necessity. The advantage of a prospective long-term follow-up study of living donors as set out in the present protocol is not only likely to improve the quality of the data sets regarding the short term safety of living kidney donation but allows also for a timely intervention if an individual donor experience a potential problem. This will provide important data to clarify the potential need and requirements of long-term donor follow-up.

In addition, new questions such as the effect of various surgical techniques have risen recently. Several methods of endoscopic (including robotic assisted) nephrectomy have been introduced and have shown to be relatively safe[28-38]. Single centre reports are mainly defending their own used technology [30 33-36]. Bottom line however, countrywide prospective cohorts allowing a comparison of various surgical procedures are yet unavailable or in an early phase comparing no more than two methods [32].

The question whether kidney donation increases the risk for hypertension, which was already on debate in the eighties [4 16 22], is still unsettled due to limited studies [29]. We think that the results of this large national wide prospective cohort study will answer many still open questions concerning living kidney donor outcome.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Professor Thiel was involved in the conception and design of the study, drafted the protocol, supervised the revisions and approved the final manuscript. Dr. Tsinalis was involved in conception and design of this study, revised the draft critically for intellectual content and approved the final revised manuscript. Ms Nolte was involved in the conception of the study, revised the draft critically for intellectual content and approved the final manuscript.

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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 pre-paid envelope for sending the samples to the central laboratory. The donor makes an appointment with his family physician, who examines the donor and reports findings such as pain and other complains, blood pressure, creatinine, albumin and 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 pre-paid 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. Main outcomes are the occurrence of albuminuria, hypertension and renal insufficiency. 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 general health problems occur.

BACKGROUND

Living kidney donors have been used in Switzerland since 1967 but at a low rate. This, however, changed in the early nineties. Rapid expansion of live kidney transplantation took place especially in the large transplant centre in Basel that had for the two previous decades rejected live donation 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 percent 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-time 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 SOL-DHR (Swiss Organ Living Donor Health Registry) 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 an a priori consensus among the founding members that health state of all consenting eligible living kidney donors should be assessed life-long at regular time intervals in the context of a prospective cohort study. The protocol and the 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 lifelong follow up of 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 assure compliance to 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 and Zurich n = 360).

Main objectives

- Obtain prospective outcome data from consecutive living kidney donors in Switzerland
- Quantify the risks for early and late complications due to nephrectomy
- Improve the information given to future potential donors before agreeing to donate a kidney and to produce standardized 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 his or her choice. This contains the brief information for the donor and the family physician, a health questionnaire, tubes for blood and urine samples and a pre-paid envelope for sending the samples at room temperature to the central laboratory (Viollier AG Basel). The basic biannual follow-up questionnaire is filled in by the family physician. Every 5 years the donor fills in the additional SF8 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 live usually in the area of the transplant centre, kidney donors often do not. Donors are not likely to adhere to a recommendation to travel lifelong biannually to a distant transplant centre for follow up; particularly since travel expenses are not covered. We believe that adherence will be much greater if 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 analyze 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), 2004 – 2005 "Jaffe compensated" (Roche), 2006 – August 2007 "Jaffe corrected" (Siemens), and since September 2007 an enzymatic assay (Siemens). In order to avoid systematic errors due to different assays prior to the data base entry all values are converted to values traceable to isotope dilution mass spectrometry (IDMS) as recommended by the KDIGO 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 Diagnostics).

Whenever during a follow up a laboratory results (creatinine or albumin/creatinine ratio) exceeds the expected range in an individual donor, the sampling and the laboratory analysis is repeated.

Definitions

Estimation of the glomerular filtration rate (GFR)

To estimate GFR, we use the MDRD equation for IDMS-traceable creatinine values (9)

eGFR (mL/min/1.73 m2) =

$175 \times (Scr/88.4)^{-1.154} \times (Age)^{-0.203} \times (0.742^{*}) \times (1.212^{+})$ * If female + If African

Micro-albuminuria (= 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 points defined by the report of the scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. (10) The cut- point for microalbuminuria or high albumin excretion is > 30 mg/g ($\geq$ 3.3 mg/mmol). For clarity reasons 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-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 above 90 mmHg 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-hour 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 (3 times in 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 at any specific place (e.g., 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

- The basic medical questionnaire to be collected before donation:

  The basic medical questionnaire collects information on body weight, sitting blood pressure (3 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 realize 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 post-operatively 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 do 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, eg, older than 60 years, the mean simple sum of complications shows the frequency of early complications seen in elderly donors, whereas the mean Clavien sum shows their severity.

- The basic biannual follow up questionnaire

We ask the family physician to measure body weight, sitting blood pressure (3 times), examine the nephrectomy scar and to 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 his 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 and fills blood and urine vials and send both vials 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 (PCS) and the Mental Component Summary (MCS).
  We ask three supplementary multiple choice questions, which are analysed separately: 1) In comparison to one 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) draw backs 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 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 do not only observe our cohort, but we 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 like the 24-hour 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 are provided on a volunteer basis by G.T. since 1993 and D.T. 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 biannual 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 are covered by the Viollier AG Basel since 1993. Cost for drugs required by

the donor are 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 (neither a filled out questionnaire from the donor nor the family physician or laboratory) SOL-DHR staff call the donor. If the donor declines to participate further, he or she will be marked "inactive" in the cohort database and follow up is suspended. If the donor later changes his or her 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 using two different reference groups. First, we will compare the incidence and prevalence of hypertension in our cohort with that of the MONICA 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) is 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 1 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 (pre-surgery) 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 organization 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 determining risk factors associated to them. More specifically, we are particularly interested in increasing our understanding of the long term effect of donation on renal function, 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.

An overview of the existing evidence

In the eighties and early nineties 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 are 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. Prospective long-term follow-up study of living donors as set out in the present protocol is not only 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 robotic 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 was already debated in the eighties (4, 16, 22), is still unsettled due to limited studies (29). We think that the results of this large national wide prospective cohort study will address many important unanswered questions about outcomes in living kidney donors.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Professor Thiel was involved in the conception and design of the study, drafted the protocol, supervised the revisions and approved the final manuscript. Dr Tsinalis was involved in conception and design of this study, revised the draft critically for intellectual content and approved the final revised manuscript. Ms Nolte was involved in the conception of the study, revised the draft critically for intellectual content and approved the final manuscript.

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Main Sponsors:

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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 implentation 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 pre-paid envelope for sending the samples to the central laboratory. The donor makes an appointment with his family physician, who examines the donor and reports findings such as pain and other complains, blood pressure, creatinine, albumin and 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 pre-paid 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. Main outcomes are the occurrence of albuminuria, hypertension and renal insufficiency. 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 donorswill allow timely interventions at early stages before serious kidney general health problems occur.

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BACKGROUND

Living kidney donors have been used in Switzerland since 1967 but at a low rate. This, however, changed in the early nineties. Rapid expansion of live kidney transplantation took place especially in the large transplant centre in Basel that had for the two previous decades rejected live donation 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 percent 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-time 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 SOL-DHR (Swiss Organ Living Donor Health Registry) 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.

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METHODS

Prospective cohort study: There was an a priori consensus among the founding members that health state of all consenting eligible living kidney donors should be assessed life-long at regular time intervals in the context of a prospective cohort study. The protocol and the 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 lifelong follow up of 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 assure compliance to 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 and Zurich n = 360).

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Main objectives

- Obtain prospective outcome data from consecutive living kidney donors in Switzerland
- Quantify the risks for early and late complications due to nephrectomy
- Improve the information given to future potential donors before agreeing to donate a kidney and to produce standardized evidence based educational materials

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- 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

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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 his or her choice. This contains the brief information for the donor and the family physician, a health questionnaire, tubes for blood and urine samples and a pre-paid envelope for sending the samples at room temperature to the central laboratory (Viollier AG Basel). The basic biannual follow-up questionnaire is filled in by the family physician. Every 5 years the donor fills in the additional SF8 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.

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

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Collected data

Laboratory data

We analyze 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), 2004 – 2005 "Jaffe compensated" (Roche), 2006 – August 2007 "Jaffe corrected" (Siemens), and since September 2007 an enzymatic assay (Siemens). In order to avoid systematic errors due to different assays prior to the data base entry all values are converted to values traceable to isotope dilution mass spectrometry (IDMS) as recommended by the KDIGO 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 Diagnostics).

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Whenever during a follow up a laboratory results (creatinine or albumin/creatinine ratio) exceeds the expected range in an individual donor, the sampling and the laboratory analysis is repeated.

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Definitions

Estimation of the glomerular filtration rate (GFR)

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

eGFR (mL/min/1.73 m2) =

$175 \times (Scr/88.4)^{-1.154} \times (Age)^{-0.203} \times (0.742^{*}) \times (1.212^{+})$ * If female + If African

Micro-albuminuria (= 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 points defined by the report of the scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. [10] The cut- point for microalbuminuria or high albumin excretion is > 30 mg/g (> 3.3 mg/mmol). For clarity reasons 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-point for macroalbuminuria 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 above 90 mmHg 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-hour ambulatory blood pressure recording. If hypertension is confirmed, we recommend antihypertensive treatment with and ACE inhibitor or an angiotensin receptor blocker.

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Health status data

At each visit, the family physician is asked to measure the actual weight, height and blood pressure (3 times in 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 at 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 symptomscomorbidities or other problems (somatic, mental, social).

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Questionnaires

- The basic medical questionnaire to be collected before donation:

  The basic medical questionnaire collects information on body weight, sitting blood pressure (3 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 realize 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 post-operatively 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

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pain do 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, eg, older than 60 years, the mean simple sum of complications shows the frequency of early complications seen in elderly donors, whereas the mean Clavien sum shows their severity.

- The basic biannual follow up questionnaire

We ask the family physician to measure body weight, sitting blood pressure (3 times), examine the nephrectomy scar and to 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 his 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 and fills blood and urine vials and send both vials 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.

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- 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 (PCS) and the Mental Component Summary (MCS).

  We ask three supplementary multiple choice questions, which are analysed separately: 1) In comparison to one 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) draw backs 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?)

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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 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 do not only observe our cohort, but we 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

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diagnostic procedure like the 24-hour 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 are provided on a volunteer basis by G.T. since 1993 and D.T. 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 biannual 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 are covered by the Viollier AG Basel since 1993. Cost for drugs required by the donor are paid by the compulsory health insurance of the donor, whether the drug treatment is related to donation or not.

Handling missing responses

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If no response is received by 2 months after an invitation has been sent (neither a filled out questionnaire from the donor nor the family physician or laboratory) SOL-DHR staff call the donor. If the donor declines to participate further, he or she will be marked "inactive" in the cohort database and follow up is suspended. If the donor later changes his or her mind, and gets in touch with us again (eg, after moving back to Switzerland) the status is changed back to "active" immediately.

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Control population

To control for the risk of developing hypertension we plan using two different reference groups. First, we will compare the incidence and prevalence of hypertension in our cohort with that of the MONICA 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) is used to analyse the outcome of this positively-selected donor population after donation.

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Statistical considerations

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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.

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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 1 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 survival time on the control treatment is 5 years. If the true median survival times on the control and experimental 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 (pre-surgery) survival curves are equal with probability (power) 80%. The Type I error probability associated with this test of this null hypothesis is 0.05.

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Discussion

This paper describes the rationale for and organization 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 determining risk factors associated to them. More specifically, we are particularly interested in increasing our understanding of the long term effect of donation on renal function, 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 function or general health change for the worse.

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An overview of the existing evidence

In the eighties and early nineties 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 are 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].

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Up to now prospective long-term follow-up of living donors has not been regarded generally as a necessity. Prospective long-term follow-up study of living donors as set out in the present protocol is not only 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

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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 robotic 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 was already debated in the eighties [4 16 22], is still unsettled due to limited studies [29]. We think that the results of this large national wide prospective cohort study will address many important unanswered questions about outcomes in living kidney donors.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Professor Thiel was involved in the conception and design of the study, drafted the protocol, supervised the revisions and approved the final manuscript. Dr Tsinalis was involved in conception and design of this study, revised the draft critically for intellectual content and approved the final revised manuscript. Ms Nolte was involved in the conception of the study, revised the draft critically for intellectual content and approved the final manuscript.

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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 and set-up of this cohort.

Methods/Design All kidney donors in Switzerland are registered and examined before donation and biennially after donation starting in the first year after nephrectomy. In the lead-up of a follow-up visit, the study centre sends a little parcel to the kidney donor containing the health questionnaire, blood and urine tubes and a pre-paid envelope for sending the samples to the central laboratory. The donor makes an appointment with his family physician, who examines the donor and reports findings such as pain and other complains, blood pressure, creatinine, albumin and all major health events and the state of mental and social wellbeing to the study centre. All data are centrally managed. All abnormal findings in the follow-up of individual donors are regularly discussed with the principle investigator and all necessary measures are taken. Any intervention is stored in the database. The health-insurance of the organ-recipient covers all costs of the donor-follow-up. Main outcomes are the occurrence of albuminuria, hypertension and renal insufficiency. Secondary outcomes are major somatic and social events such as death, cardiovascular disease, stroke and depression.

Discussion This prospective cohort offers unique opportunities assessing the risks of living kidney donation and allows examining risk differences for all available methods used for nephrectomy in Switzerland (various forms of open surgery and endoscopic nephrectomy). Moreover, the prospective collection of all clinically relevant data and the monitoring of participants on a regular basis allow timely interventions at an early stage before critical parameters of kidney function or general health problems occur.

BACKGROUND

Living kidney donors were used in Switzerland since 1967 but at a low rate. This, however, changed in the early nineties. Rapid expansion of live kidney transplantation took place especially in one large Swiss transplant centre, where live kidney was formerly strictly disapproved over two decades because of ethical reasons. But the rising number of live donor transplantation was not well accepted from all sides. 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 percent of donors without follow up data ranged from 21% [2 3] to 31% [4], to 42% [5 6]up to 77% [7]. Given the available evidence, any fair counselling of potential living donors seems difficult.

Since living donor transplantation was mainly propagated by the Basel transplant centre, we felt obliged to offer a long-time 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 SOL-DHR (Swiss Organ Living Donor Health Registry) was initiated in April 1993.

This paper describes the rationale and set-up of this prospective cohort study aiming at assessing the prevalence of complications of living kidney donation and aiming at identifying risk profiles associated with unfavourable outcomes. In particular the study is designed to prospectively quantify the risks to donors after living kidney donation such as the development of hypertension, albuminuria, renal failure and psychological diseases and to assist in the management of individual donors at an early stage if such complications occur.

METHODS / DESIGN

Prospective cohort study: There was an a priori consensus among the founding members that health state of all consenting eligible living kidney donors should be assessed life-long at regular time intervals in the context of a prospective cohort study. The protocol and the 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 lifelong follow-up of living donor's health state is required by the Swiss Transplant Law and as long as data are analysed anonymously. However, to assure compliance to 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 quit their participation by simply ignoring the invitation from SOL-DHR to visit their family physician.

Donors from all six kidney transplant centres are included in the SOL-DHR. 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 and Zurich n=360).

Main objectives

- Gaining prospective outcome data from living kidney donors in Switzerland
- Assess and quantify the risks for early and late complications due to organ removal
- Improve the information given to potential donors before agreeing to donate a kidney
- Install a system of timely intervention in case of deterioration in state of health
- Compare the consequences of different methods of organ removal on state of health
- Provide a neutral platform, where donors can express complains and receive help

Data collection principles

Study inclusion and a first medical examination before kidney donation is done by the transplant centre (see basic medical questionnaire below). A second questionnaire (early complication questionnaire) is collected from the transplant centre at the time of discharge after nephrectomy. 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. In the lead-up of a follow-up visit, the SOL-DHR centre sends a little parcel to the kidney donor asking the donor to make an appointment with the present family physician of his choice. The parcel contains the brief information for the donor and the family physician, a health questionnaire, tubes for blood and urine samples and a pre-paid envelope for sending the samples at room temperature to the central laboratory (Viollier AG Basel). The basic biennial follow up questionnaire is filled in by the family physician. Every five years the donor fills in the additional SF8 and social status questionnaire (see below).

If no response from the donor is received within 2 months, SOL-DHR initiates a search for the donor and attempts collecting possible data on donor death and its reason by contacting the recipient, the donor's health insurance and the public registries.

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

Participation of family physicians

Whereas kidney recipients live usually in the area of the transplant centre, kidney donors often do not. Asking donors to travel lifelong biennially to the distant transplant centre for

control has little chance to be followed, particularly since travel expenses are not covered. Follow-up controls done by the family physician working in the vicinity of the donor improve donor's willingness to participate manifold. Family physicians as well as young medical assistants at the transplant centre follow the protocols provided by the study centre.

Collected data

Laboratory data

We quantify creatinine in blood and urine, albumin and protein in urine. The method used to quantify creatinine in blood changed over the years: 1993 -1996 Jaffee, 1997 -2003 enzymatic assay (Roche), 2004 – 2005 "Jaffe compensated" (Roche), 2006 – 2007 "Jaffe corrected" (Siemens). Since September 2007 enzymatic assay (Siemens). In order to avoid systematic errors due to different assays prior to the data base entry all values are converted to values traceable to isotope dilution mass spectrometry (IDMS) as recommended by the KDIGO 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 Diagnostics).

Whenever during a follow-up a laboratory results (creatinine or albumin/creatinine ratio) exceeds the expected range in an individual donor, the sampling and the laboratory analysis is repeated.

Definitions

Estimation of the glomerular filtration rate (GFR)

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

eGFR (mL/min/1.73 m2) =

$175 \times (Scr/88.4)^{-1.154} \times (Age)^{-0.203} \times (0.742^{*}) \times (1.212^{+})$ * If female + If African

Micro-albuminuria (= high albumin excretion)

We assume a daily urinary excretion of 10 mmol Creatinin/24h as being normal for donors (mean value for both genders taken together, - underestimating it for males, overestimating for females). Data on albuminuria will be presented based on cut-off points 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 albumin excretion to be called micro-albuminuria or high albumin excretion is set to > 30 mg albumine / g creatinine corresponding to ≥ 3.3 mg albumin / mmol creatinine. For clarity reasons we will use the term micro-albuminuria which is commonly used in Europe rather than the term "high albumin excretion" used in North America. For the definition of macro-albuminuria or very high albumine excretion at cut-off point of >300 mg albumin / g creatinine corresponding to 33.9 mg albumin / mmol creatinine is used.

Hypertension

Donors having a systolic pressure above 140 mm Hg or diastolic above 90 mmHg or both or taking any antihypertensive drug are classified as hypertensive. In any case of new onset hypertension, we ask the family physician to perform a 24h pressure recording. If hypertension is confirmed, we recommend antihypertensive treatment with ACEI or an Angiotensin receptor antagonist (ARA).

Health state data

At each visit, the family physician is asked to measure the actual weight, height and blood pressure (3 times in sitting position). Moreover he is requested to examine the bare abdomen of the donor in an upright posture in order to look for an incisional hernia or abdominal wall bulging caused by the nephrectomy. When the donor is complaining about pain at any specific place (i.e. lumbar back pain), it should be examined and evaluated, whether it is or could be causally related to nephrectomy. New complains, disease or any problems (somatic, mental, social) need to be mentioned carefully in a separate line of the form.

Questionnaires

- The basic medical questionnaire to be collected before donation:

  The basic medical questionnaire collects information on body weight, sitting blood pressure (3 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 realize 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 is collecting 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 do 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 1 =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 as compared to the simple sum of observed complications per donor score. The two sums have different interpretations. For a given (sub) population of donors, i.e. older than 60 years, the "mean sum of complications" shows the frequency of early complications seen in elderly donors, the mean Clavien sum" however, their severity.

- The basic biennial follow up questionnaire

The family physician is requested to measure body weight, sitting blood pressure (3 times), examine the nephrectomy scare and to ask the donor all questions necessary to file-out the medical questionnaire including questions about pain and all serious health problems including major events such as stroke, cardiovascular events, diabetes or malignancies since the last examination. Back-pain is considered as nephrectomy related only if specified by the donor or his physician as being clearly more intensive than before donation as pain related to nephrectomy can be caused by instability of the abdominal wall after large lumbar incision with partial muscular palsy. Furthermore the family physician is asked to note all drugs currently taken; make a dip-stick examination of the urine and finally fill a blood and a urine tube and send both tubes to the central laboratory. If the urinary dip stick turns out to be positive for blood, protein, white blood cells and other abnormalities, the doctor has to make an additional microscopic examination of the urinary sediment. All clinical data, including the health state questionnaire, are sent to the study centre SOL-DHR.

- SF-8 questionnaire to be collected every 5 years after donation (since 2002).

  The validated SF-8 multiple choice questionnaire was used to calculate the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

  The questionnaire was supplemented by the three following multiple choice questions: 1) In comparison to the last year how would you describe your actual health? 2) How has your emotional relation to the kidney recipient changed since donation? 3) Would you donate a kidney again, if you still had two kidneys?. The answers to these questions are analysed separately from the 8 SF-8 questions.

- Social status questionnaire (since 2002).

  This instrument has been developed by SOL-DHR and contains multiple choice questions about the actual professional activity, working capacity, efficiency, and physical fitness and two open questions: 1) draw backs because of donation (e.g. financial, insurance, pension fund or professional disadvantages) and 2) donor's suggestion on possible improvement for the SOL-DHR activity (What can SOL-DHR do better for you?)

Data monitoring and quality assurance

All incoming data are checked by cohort staff for completeness and plausibility, and are entered thereafter into an electronic database. In case of lacking information, staff calls to the office of the family physician and tries to receive any missing data. All cases with an abnormality are discussed with the principle investigator once or twice a month. 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 do not only observe our cohort, but we also intervene actively, as soon as any potential danger is turning

up. Interventions are planned to be provided by the family physician based on the recommendation of the study leaders. Recommendations my include performing a diagnostic procedure like the 24h blood-pressure measurement in order to confirm hypertension or to perform a sonongraphy of the remaining kidney or simply 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 are provided on a volunteer base by GT since 1993 and 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 to pay the dialysis costs if no living donation had taken place. Coverage includes all costs including those of late complications of the donor that are causally related to the donation. Hence, the Swiss transplant law requires the health insurances of the kidney recipients to cover the bills from the family physicians for biennial donor follow-up as long as the recipient stays alive with an official pay scale. After recipients death the bills for the donor follow-up are covered by SNO. The bills for the donor follow-up examination are sent to the SOL-DHR headquarter, which forwards the bill to the health insurance of the kidney recipient. The costs for the chemical analysis in blood and urine of donors are covered by the Violliers AG Basel. Cost for drugs required by the donor are paid by the compulsory health insurance of the donor independently whether the drug treatment is related to donation or not.

Handling missing responses

If within 2 months no response is received after invitation (neither a filled out questionnaire from the donor nor the family physician or laboratory) SOL-DHR staff calls the donor. If the donor declares, that he does not longer want to participate he or she will be marked “inactive” in the cohort database and follow-up is suspended. If the donor, however, changes his or her mind, and gets in touch with us again (i.e. after moving back to Switzerland) the status is changed back to “active” immediately at any time.

Control population

To control for the risk of developing hypertension we plan using two different reference groups. First, we will compare the frequency of occurrence of hypertension in our cohort to that of the MONICA-study with data from a normal Swiss population. [12-14]Second, since living donors are a positive selection out of 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 is used to analyse the outcome of this positively selected donor population after donation.

Statistical Considerations

Epidemiologic data and patients' descriptives available on continuous scales will be presented with medians, interquartile ranges or means and standard deviations as appropriate. Categorical data will be presented as rates and percentages. Association of individual (independent) variables on 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 multivariate modelling. Assessment of causal associations will be performed using multivariate 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 1 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 survival time on the control treatment is 5 years. If the true median survival times on the control and experimental 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 (pre-surgery) 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 and set-up of a lifelong prospective cohort study of living kidney donors in Switzerland. This study offers unique opportunities assessing the frequency of occurrence of unfavourable outcomes following donation and allows determining risk factors associated to them. More specifically, we are particularly interested increasing our understanding of the long term effect of donation on renal function, the risk to develop hypertension or abuminuria and to explore 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 critical parameters of kidney function or general health change for the worse.

An overview of the existing evidence

In the eighties and early nineties 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 data are prone to selection bias. Based on these retrospective studies kidney donation is now generally accepted as a relatively safe procedure but long-term data that are still quite incomplete [24-27].

Up to now prospective long-term follow-up of living donors has not been regarded generally as a necessity. The advantage of a prospective long-term follow-up study of living donors as set out in the present protocol is not only likely to improve the quality of the data sets regarding the short term safety of living kidney donation but allows also for a timely intervention if an individual donor experience a potential problem. This will provide important data to clarify the potential need and requirements of long-term donor follow-up.

In addition, new questions such as the effect of various surgical techniques have risen recently. Several methods of endoscopic (including robotic assisted) nephrectomy have been introduced and have shown to be relatively safe[28-38]. Single centre reports are mainly defending their own used technology [30 33-36]. Bottom line however, countrywide prospective cohorts allowing a comparison of various surgical procedures are yet unavailable or in an early phase comparing no more than two methods [32].

The question whether kidney donation increases the risk for hypertension, which was already on debate in the eighties [4 16 22], is still unsettled due to limited studies [29]. We think that the results of this large national wide prospective cohort study will answer many still open questions concerning living kidney donor outcome.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Professor Thiel was involved in the conception and design of the study, drafted the protocol, supervised the revisions and approved the final manuscript. Dr. Tsinalis was involved in conception and design of this study, revised the draft critically for intellectual content and approved the final revised manuscript. Ms Nolte was involved in the conception of the study, revised the draft critically for intellectual content and approved the final manuscript.

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