Metabolic failure and energy depletion in kidney transplantation

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Primary Objective: -To compare metabolic activity and efficiency directly after transplantation in living and deceased donor kidney grafts. Secondary Objective(s): -To assess whether the contribution of aerobic and anaerobic metabolism differs...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal disorders (excl nephropathies)
Study type	Observational invasive

Summary

ID

NL-OMON39126

Source
ToetsingOnline

Brief title
Metabolic failure and energy depletion in kidney transplantation

Condition

- Renal disorders (excl nephropathies)
- Renal and urinary tract therapeutic procedures

Synonym
Ischemia/reperfusion injury. Graft failure after transplantation.

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Ischemia/reperfusion injury, Kidney transplantation, Metabolomics

Outcome measures

Primary outcome

Metabolic activity of the kidney as measured by pO2, pCO2, lactate, glucose and full lipid profile. The respiratory quotients (RQ) for every time-point will be calculated.

Secondary outcome

Kidney biopsies taken before (routine clinical biopsy) and after reperfusion (this study) will be collected in all patients. Biopsy specimens will be snap frozen and processed to make it suitable for NMR. By NMR different intermediates of the citric acid cycle will be quantified, to be able to estimate activity of aerobic metabolism and more accurately to define where potential problems are.

Since measurements are dependent on flow kinetics and perfusion of the kidney, flow in the renal artery and microvascular perfusion will be measured as well. Both will be compared between living and cadaveric donor kidneys. Measurements of metabolism will be related to microvascular perfusion
We will also measure renal blood flow in the living donor and compare this to the renal blood flow through the same kidney after transplantation.

Study description

Background summary

Kidney transplantation is the treatment of choice for patients with end-stage renal disease and is accepted as the most advanced form of renal replacement therapy. As a consequence of organ shortage and long waiting lists, more marginal donors are accepted. Graft survival for living unrelated donation is superior compared to grafts from brain dead donors, even though the average human leukocyte antigen (HLA) matching is worse in living unrelated donation.1 Therefore, the poor graft survival from deceased donors cannot be exclusively attributed to differences in immunogenicity.

Already during the process of transplantation the graft is exposed to various events, which may in turn lead to functional deterioration.
Ischemia/reperfusion (I/R) injury is the exacerbation of tissue damage upon reestablishment of circulation after a period of ischemia. I/R injury is an inevitable consequence of organ transplantation, and a major determinant of patient and graft survival. The pathophysiology of I/R injury is complex and incompletely understood. This complexity in the identified mechanisms leading to I/R injury may have been one of the reasons why clinical trials inhibiting specific factors such as complement or cytokines have failed thus far.2,3

This stimulated us to step back and try to assess basic differences between living and deceased donor kidney transplantation. Preliminary results indicated an involvement of metabolic activity.

Not much is known on metabolic re-activation after transplantation. Oxygen is needed for a normal aerobic metabolism, and hypoxia will switch metabolism from aerobic to anaerobic pathways. Although organs that are preserved for transplantation are preferentially cooled to 4 ºC, metabolic activity is never completely diminished. Anaerobic metabolism will result in insufficient ATP production, deprivation of glycogen reserve and production of toxic metabolic products, such as lactate. Loss of ATP primarily causes disturbance of cellular functions such as maintenance of homeostasis and capability of apoptosis. Later consequences of ATP shortage are insufficient Na/K pump activity and intracellular accumulation of metabolic products which lead to hyperosmolarity. Both can cause cell edema in ischemic tissue, which will eventually lead to loss of cell function or even cell death.

Study objective

Primary Objective:
-To compare metabolic activity and efficiency directly after transplantation in living and deceased donor kidney grafts.

Secondary Objective(s):
-To assess whether the contribution of aerobic and anaerobic metabolism differs

between living and deceased donor kidney grafts after reperfusion.
-To assess differences between living and deceased donor kidneys in renal perfusion after transplantation.
-To follow up the renal blood flow from the kidney in the donor and after transplantation in the recipient and to analyze whether this correlates with graft function and survival.
-To form a control group by 1 arteriovenous measurement over the donor kidney, before donation in the living donor.

Study design

In 10 consecutive patients undergoing living donor kidney transplantation and 10 patients undergoing deceased donor kidney transplantation, per-operative arteriovenous blood samples will be collected. By cannulating the renal artery and vein, paired arterial en venous blood samples will be collected and immediately measured on pO2, pCO2, lactate, glucose and full lipid profile. The respiratory quotients (RQ) for every time-point will be analyzed and uptake of glucose and release of lactate will be compared between the groups. Since measurements are dependent on flow kinetics and perfusion of the kidney, flow in the renal artery and microvascular perfusion will be measured during reperfusion as well. (Before living donor procedures, renal blood flow will be measured in the donor, for that there will be a follow up by the flow measurement in the recipient). Paired kidney biopsies will be collected before and after reperfusion to assess metabolites of the citric acid cycle in renal tissue.
Thereby we want to ad a control group of 4 living donors, by performing 1 arteriovenous measurement over the donor kidney, before donation, so we can validate the measurements over transplantated kidneys.

Study burden and risks

Risks associated with participation can be considered negligible since limited amounts of blood will be sampled and a very small biopsy will be taken after reperfusion. We are experienced with the biopsy method and have performed it safely for many times now, without ever experiencing complications. Since all samples are collected during the transplantation, the burden for the patient can be considered minimal.

The renal blood flow measurement in the donor is non-invasive, it does not increase hospitalization and it is a short measurement. Therefore, we assume that it is not a great burden.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Recipients of a kidney graft by kidney tranplantation. (20 recipients)
Living donors (10 donors for a pre-surgical measurement of bloodflow in the a.renalis, non-invasive by echo-doppler).4 of these living donors for 1 arterio and 1 venous sample as control measurement during surgery.

Exclusion criteria

Increased risk of bleeding.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-10-2012
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	02-08-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	21-05-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL40612.058.12