SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Arterial stiffness investigations in kidney transplanted patients

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The Examination takes place at the Library of Building C, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, December 6, 2017, 11 AM

Head of the Defense Committee: Prof. József Balla, MD, PhD, DSc
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The PhD Defense takes place in the Lecture Hall of Auguszta Center, Faculty of Medicine, University of Debrecen, December 6, 2017, 1 PM
Atherosclerosis in patients with end stage kidney disease and after kidney transplantation
Chronic kidney disease is one of the main risk factors of cardiovascular disease. In chronic kidney disease cardiovascular risk is much higher than the healthy population. Development of atherosclerosis is accelerated in end stage renal failure patients. Overall vascular system is more or less affected by the age related accelerated atherosclerosis. Kidney vascular disorders have negative impact on metabolism. Impaired functions aggravates more the atherosclerosis process. However kidney transplantation positive impacts reason of patients’ mortality with well-functioning graft remains mainly cardiovascular. Assessment of cardiovascular is has a high importance from the aspect of early diagnosis and proper intervention during waiting list management, right before and during surgery, and the short and long term follow up. Non-invasive techniques may have a high importance in cardiovascular risk assessment.
Patients with kidney transplantation are under a regular lifelong general check-up. Graft function, immunosuppressant drug serum levels regularly monitored and general risk assessment and intervention are performed during the long term follow up.
Evaluation of arterial stiffness is a widely used non-invasive method, for the early diagnosis and follow-up of atherosclerosis and evaluation of endothel dysfunction. Changing of these parameters can predict the risk of cardiovascular disease. The correlation with other parameters is important for the clinical practice in the prevention of high mortality risk cardiovascular disease. Impaired electrolyte metabolism elevated blood pressure secretion and excretion disorders contributes to the accelerated atherosclerosis.
**Arterial stiffness measure**
Early diagnosis of asymptomatic atherosclerosis has remarkable importance from the aspect of proper treatment and complication prevention of vascular diseases. Early complex treatment may reduce or regress the disorder progression.
Several studies found that the peripheral and central vascular disease co-morbidity occurs very often together such as peripheral arterial disease, coronary sclerosis, carotid artery stenosis and occlusion. Patients with peripheral vascular disease have higher morbidity and mortality due to cerebral and cardiac reasons. Ankle/brachial index (ABI) widespread applied non-invasive risk assessment method a ratio of blood pressure measured on low extremity and upper arm. Score below 0.9 show significant arterial occlusion.
Ongoing studies are aimed to develop clinical marker to predict disorders at the early phase in an easy, fast and well-reproducible way. Recently, investigations focused on arterial stiffness assessment. Augmentation index (Aix) and pulse wave velocity (PWV) are widely used stiffness parameters. Previous studies proved that progression in stiffness, namely elevation of Aix and PWV are precede the manifestation of atherosclerosis. These parameters are independent risk factors of cardiovascular disorders based on atherosclerosis. These parameters are appropriate methods for prevention, early diagnosis and follow up.

**Objectives**
1. Cross section study
   Investigation of the correlation between arterial functional parameters (stiffness assessed by Arteriograph, ankle/brachial index) applied for cardiovascular risk evaluation and traditional cardiovascular risk parameters (laboratory parameters, CV disorders, mortality and morbidity). The correlation with other
parameters is important for the clinical practice in the prevention of high mortality risk cardiovascular disease.

2. Longitudinal study
   A. Longitudinal study with 24 patients on a 3 year long follow up Analysis of stiffness parameters progression.
   B. Longitudinal study with 41 patients on a 3 year long follow up Analysis of stiffness parameters progression and correlation analysis with overall cardiovascular morbidity.

3. Arterial stiffness study during the perioperative term.
   Direct changes had been observed during the perioperative term due to kidney transplantation.

**Patients and Methods**

Clinical studies were performed at the University of Debrecen Surgical Institute Transplantation Department in cooperation with the Institute for Internal Medicine Department for Angiology. Approved by the Ethical Committee with the ‘DE RKEB/IKEB 4804-2017’ ethical permission.

1. Cross sectional study 184 (77 female, 107 male; age: 46,16±12,19 year) stable kidney function (creatinine <140 μmol/l, within 3 month) kidney transplanted patients were enrolled. Correlation was analysed between stiffness parameters (PWV, Aix, PP) and:
   - laboratory parameters: creatinine, GFR, urea, uric acid, cholesterine, triglyceride, high density lipoprotein, low density lipoprotein, C-reactive protein, haemoglobin
   - immunosuppressant drugs and serum level
   - age, time since transplantation
   - ankle/brachial index (ABI)
   - rejection episodes
   - comorbidities (carotid stenosis, cardiac hypertrophy, obesity)
2.A. Longitudinal study with 24 patients on a 3 year long follow up (24 (14 female, 10 male; age: 45,64 year) primer cadaver kidney transplanted patients were enrolled. Analysis of stiffness parameters progression.

B. Longitudinal study with 41 patients on a 3 year long follow up
41 primer cadaver kidney transplanted patients were enrolled. (21 female, 20 male; age: 40,16 ± 12,56 year)
- Analysis of stiffness parameters progression and correlation analysis with overall cardiovascular morbidity.
- Correlation was analysed between stiffness parameters (PWV, Aix, PP) and: laboratory parameters: creatinine, GFR, urea, uric acid, cholesterine, triglyceride, high density lipoprotein, low density lipoprotein, C-reactive protein, haemoglobin
- Carotid artery stenosis progression and correlation with stiffness parameters

3. Arterial stiffness study during the perioperative term
18 end stage kidney disease patient (8 female, 10 male; 46,16 year ± 12,19 year). Measurements:
1.:preoperatively (>2 hour, <12 hour)
2.:first postoperatively day (>15 day, <24 day)
3.:postoperative 7th day
4.:postoperative 14th day

Parameters observed
stiffness parameters: pulse wave velocity (PWV)
augmentation index (Aix)
pulse pressure (PP)
laboratory parameters: creatinine, urea, GFR, CRP
Results
Cross sectional study
In our cross-sectional study, PWV was significantly correlated with patients’ age (p<0,0001, r=0,41), however, not with immunosuppressant type or dosage or number of previous kidney transplantations. We observed a significant negative correlation between augmentation index and GFR. There were no significant correlations between the other laboratory values: creatinine, uric acid, urea, cholesterol, triglyceride, HDL, LDL, CRP, and haemoglobin. There was a significant positive correlation between pulse pressure (PP) and PWV and Aix. Patients with abnormal PWV (>12 m/s) had significantly higher systolic blood pressure, body mass index, PP, and Aix compared to patients with PWV <12 m/s. There was a significant positive correlation between PWV and thickness of the septal wall as well as the percentage of carotid artery stenosis.

Longitudinal studies
Our 3-year longitudinal study revealed a significant elevation in PWV with the progression of renal failure and chronic rejection (p=0,0035). There was no significant correlation between PP and AI values over the 3-year period. There was simultaneous significant progression concerning PWV and carotid artery sclerosis in the 3-year follow-up. We also find positive significant correlation between serum level of transferrin and PWV (Pearson R= -0,29; p=0,025. There was no significant correlation between stiffness parameters and serum creatinine, urea, hemoglobin, albumin, cholesterine, triglycerides, uric acid, glomerular filtration rate, or C-reactive protein. There was no fatal cardiovascular event during the study period among our patients. All of our patients involved in this study are still alive.
Arterial stiffness study during the perioperative term
Pulse wave velocity (PWV; p= .0075) and (AIx; p= .013) improved significantly after transplantation. Creatinine (p= .0008) and C-reactive protein (CRP; p=.006) serum levels decreased and GFR increased significantly (p = .0005) in the perioperative period. There was no significant change in the ABI, and hemoglobin concentration. Serum urea levels, and pulse pressure improved slightly but not significantly.

New findings

1. Correlation was detected between transplanted graft degeneration and vascular disorder progression predicted by arterial stiffness.

2. Arterial stiffness assessment may be appropriate method for global cardiovascular risk evaluation since significant correlation was detected between stiffness parameters and left ventricular hypertrophy, carotid artery stenosis and ankle/brachial index.

3. Relative rapid improvement detected in the arterial function during the post-transplantation period in end stage kidney disease patients.

4. Similar progression detected in kidney transplanted patients in case of carotid artery stenosis and pulse wave velocity.
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List of other publications


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