

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

Arterial stiffness investigations in kidney transplanted patients

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UNIVERSITY OF DEBRECEN

DOCTORAL SCHOOL of Kálmán Laki

Debrecen, 2017.

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The PhD Defense takes place in the Lecture Hall of Augustza 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: $46,16 \pm 12,19$ year) stable kidney function (creatinine $<140 \mu\text{mol/l}$, 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.:posotperative 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.

ACKNOWLEDGMENTS

This thesis could not have been completed without the support of Prof.Dr.László Damjanovich head of the Surgical Institute University of Debrecen.

I would like to express my sincere gratitude to my supervisor Prof.Dr.Pál Soltész for the continuous support of my Ph.D study and related research, for his patience, motivation, and immense knowledge.

I would like to express my special gratitude to Dr. László Asztalos establishing head of Transplantation Department for the special surgical techniques and for continuous support of my Ph.D study

I will always remember with a great gratitude to Dr. Lajos Lócsey associate professor for the essential support of my Ph.D. study.

I also would like to express my gratitude Dr. Balázs Nemes head of Transplantation Department for the great support of my Ph.D study.

I would like to thank the all support of the nurses, doctors, coordinators of the Transplantation Department.

Thanks for Rita Porcsin assistant manager for the administrative help, and all support of the nurses, doctors of the Department for Angiology.

I am grateful to my wife and children who have provided me through moral and emotional support in my life. I am also grateful to all of my family members who have supported me along the way.



Registry number: DEENK/33/2017.PL
Subject: PhD Publikációs Lista

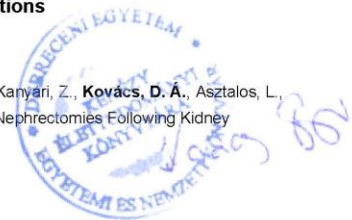
Candidate: Dávid Ágoston Kovács
Neptun ID: FZIF5J
Doctoral School: Kálmán Laki Doctoral School

List of publications related to the dissertation

1. **Kovács, D. Á.**, Lőcsey, L., Laczik, R., Szabó, L., Zsom, L., Kabai, K., Fedor, R., Nemes, B., Asztalos, L., Soltész, P.: Three-year longitudinal clinical trial of arterial function assessed by a oscillometric non-invasive method in comparison with carotid sclerosis and transferrin kidney-transplanted patients.
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Total IF of journals (all publications): 8,878

Total IF of journals (publications related to the dissertation): 2,971

The Candidate's publication data submitted to the IDEa Tudóstér have been validated by DEENK on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

27 February, 2017

