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

Investigation of novel vascular biomarkers in end-stage renal patients before and after transplantation

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The Examination takes place at the Meeting Room of Building A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen
Debrecen, April 9, 2025. at 11:30 AM

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The PhD Defense takes place at the Lecture Hall of Building A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen
Debrecen, April 9, 2025. at 1 PM

Introduction

Patients who have undergone kidney transplantation, similar to those with end-stage renal disease (ESRD), experience higher mortality and morbidity rates. Cardiovascular diseases occur significantly more frequently in both groups compared to the general population and are the primary cause of death, largely due to atherosclerotic vascular diseases. Despite this, kidney transplantation remains the gold standard treatment for ESRD, as it significantly reduces mortality and the incidence of cardiovascular events compared to regular dialysis, while also improving the quality of life. The increased atherogenesis observed after transplantation is mostly associated with traditional risk factors such as hypertension, diabetes, smoking, and dyslipidemia. Dyslipidemia is particularly common after kidney transplantation, partly due to the effects of corticosteroids, cyclosporine, tacrolimus, and mammalian target of rapamycin (mTOR) inhibitors. The significant role of oxidation in the pathogenesis of atherosclerosis is well-established. These findings suggest that oxidative stress can induce the oxidation of lipoproteins, including low-density lipoprotein (LDL), which is the first step in the process of atherosclerosis. Moreover, oxidative stress is a well-known mediator of adverse complications following transplantation.

In addition to traditional cardiovascular risk factors, recent observations have demonstrated the involvement of various antiangiogenic factors in the pathogenesis of kidney failure and cardiovascular complications in patients with renal disease. Pigment epithelium-derived factor (PEDF) is a multifunctional, pleiotropic glycoprotein that inhibits angiogenesis and is produced by various human tissues. Recently, PEDF has been recognized as a protective protein against cardiovascular disease risk factors due to its antioxidant, anti-inflammatory, antifibrotic, and insulin-sensitizing effects. The C-type natriuretic peptide (NT-pro-CNP), known for its anti-atherogenic properties, is a vasoprotective protein with antiproliferative, anti-inflammatory, and antithrombotic functions. Plasma NT-proCNP levels have been shown to correlate closely with kidney

function. Although the aforementioned data suggest that NT-proCNP reflects vascular and renal integrity, its serum concentration in ESRD and kidney transplant patients has not yet been investigated.

Given the increased cardiovascular risk observed in this patient population, there is a crucial need to identify additional markers that could help in identifying high-risk patients and exploring further therapeutic options within this group.

The significance of chronic kidney disease

The number of individuals suffering from chronic kidney disease (CKD) is rapidly increasing, affecting over 500 million people worldwide. In more than 120 countries, over 1.5 million patients are currently receiving renal replacement therapy. The most common causes of end-stage renal disease are diabetes, prediabetes, and hypertension. The life expectancy of patients with kidney disease is often determined not by their underlying condition itself, but by the complications that arise as a result of the primary disease. In this patient group, atherosclerosis progresses more rapidly, and the associated cardiovascular diseases occur significantly more frequently than in the general population, despite the considerable advancements in dialysis techniques over the past few decades.

Literature review

Dyslipidemia in chronic kidney disease

In patients with end-stage renal disease (ESRD), the development of dyslipidemia is significantly influenced by the reduced activity of lipoprotein lipase and hepatic triglyceride lipase. Consequently, triglyceride-rich lipoproteins containing apolipoprotein B are not adequately processed by the liver and continue to circulate in peripheral tissues. Some studies have observed a loss of lecithin-cholesterol acyltransferase (LCAT), an enzyme crucial for cholesterol esterification, high-density lipoprotein (HDL) metabolism, and reverse cholesterol transport, through the kidneys. The activation of lipoprotein lipase

is diminished in kidney disease patients, leading to an accumulation of triglyceride-rich lipoproteins such as very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL) in the plasma. Chronic kidney disease (CKD) patients often exhibit decreased HDL levels, with a shift in HDL distribution towards smaller HDL3 particles due to impaired HDL maturation, lower apolipoprotein A1 (ApoA1) concentration, and reduced LCAT activity. As a result, HDL in CKD not only has lower cholesterol levels but also displays diminished antioxidant and anti-inflammatory functions. Although LDL cholesterol (LDL-C) is typically not elevated in CKD patients, the LDL particles are generally smaller, denser, and more atherogenic. The levels of oxidized LDL (ox-LDL) and IDL, both of which are considered highly atherogenic, are elevated. Due to the significantly altered lipid subfractions, the residence time of lipoproteins in circulation is prolonged. Consequently, these lipoproteins are at increased risk for post-translational modifications, including glycation, oxidation, and carbamylation. These modified lipoproteins have reduced affinity for classical LDL receptors and are more likely to be taken up by scavenger receptors, which are increased in uremia, on the surface of macrophages. The high affinity of these lipoproteins for macrophages results in cholesterol accumulation and the formation of foam cells in the arterial walls, eventually leading to the development of atherosclerotic plaques.

Oxidative stress in chronic kidney disease

Oxidative stress occurs when there is an imbalance between the production and breakdown of reactive oxygen species (ROS) in the body. Excessive ROS levels can cause cellular damage by interacting with biomolecules such as proteins, lipids, and nucleic acids, thereby negatively impacting tissue structure and function. Since the kidneys are a major source of antioxidant enzymes, the gradual decline in kidney function leads to increased levels of pro-oxidant substances. Therefore, oxidative stress is common in ESRD and contributes to the progression of kidney damage by promoting renal ischemia, glomerular injury, and chronic inflammation. In uremic patients, renal

dysfunction is associated with oxidative stress, manifesting as elevated levels of various uremic toxins and oxidized proteins in the plasma. Hemodialysis patients have shown increased oxidative stress and lipid peroxidation due to several factors, including the activation of neutrophil granulocytes, which produce large amounts of superoxide anion. Anemia, uremia, and malnutrition also contribute to the increased oxidative stress, while the antioxidant system, both enzymatic and non-enzymatic, becomes less effective. Previous research has demonstrated that HDL can protect other lipoproteins and cells from oxidative damage by removing and inactivating lipid hydroperoxides from other lipoproteins and cells. Human paraoxonase-1 (PON1) is likely the most important antioxidant enzyme associated with HDL, catalyzing the hydrolysis of lipid peroxides. HDL also exhibits lipolactonase, paraoxonase, and arylesterase activities. Furthermore, PON1 may exert indirect antioxidant effects by inhibiting myeloperoxidase (MPO) activity.

Systemic inflammatory processes in chronic kidney disease

Several factors contribute to the chronic inflammatory state observed in CKD, including increased production of proinflammatory cytokines, oxidative stress, acidosis, chronic and recurrent infections, gut dysbiosis, and altered adipose tissue metabolism. In CKD, the clearance of cytokines and inflammatory mediators is impaired due to reduced renal clearance. Previous studies have shown that proinflammatory cytokines, such as IL-6, IL-1, and TNF-α, positively correlate with the severity of CKD. These cytokines are produced by dysfunctional adipose tissue, which, in the context of CKD, overexpresses mRNA for pro-inflammatory cytokines. Among these markers, IL-6 contributes to the development of atherosclerosis through metabolic, endothelial, and procoagulant mechanisms. In addition to traditional risk factors, TNF-α has been associated with an increased risk of heart failure in CKD, and elevated TNF-α levels have been linked with markers of malnutrition and inflammation, predicting an increased risk of mortality.

Endothelial dysfunction in chronic kidney disease

Endothelial dysfunction and the development of atherosclerosis are common in kidney failure, as are cardiovascular complications. Kidney failure, hypertension, thrombosis, and atherosclerosis are all associated with endothelial injury and may contribute to the accelerated atherosclerosis observed in patients with chronic kidney disease. However, traditional risk factors alone do not fully explain the high prevalence and incidence of cardiovascular disease in CKD, leading to increased investigation into non-traditional risk factors such as endothelial dysfunction, oxidative stress, and insulin resistance. On the one hand, chronic kidney disease may be part of a subclinical, generalized atherothrombosis; on the other hand, impaired kidney function may contribute to the development of an atherogenic milieu. The retention of vasotoxic substances and/or metabolic changes can lead to increased oxidative stress or a low-grade inflammatory state. In humans, declining kidney function can also influence the levels of other inflammatory molecules, such as CRP, IL-6, and hyaluronic acid, which have been shown to inversely correlate with creatinine clearance. These changes result in endothelial dysfunction in CKD patients. Additionally, the retention of uremic toxins, dyslipidemia, hypertension, and secondary hyperparathyroidism contribute to endothelial cell damage. Measuring circulating E-selectin, which is located on endothelial cells, may be useful in assessing endothelial cell activation or damage. In a study by Bonomini et al., elevated E-selectin levels were found in non-dialyzed, hemodialyzed, and peritoneally dialyzed patients.

The importance of kidney transplantation

In recent decades, two main methods have been used to replace kidney function in patients with chronic kidney failure: hemodialysis and peritoneal dialysis. However, kidney transplantation, which is increasingly available, is considered the gold standard treatment for kidney failure. From the outset, it has been evident that this treatment option provides

a better quality of life for eligible patients. Later studies have shown that the feasibility of transplantation is limited by comorbidities. It is important to note, however, that although cardiovascular mortality is reduced in kidney transplant recipients compared to those on dialysis, the risk of cardiovascular mortality in this patient group remains 4-5 times higher than that of the general population.

Increased risk of atherosclerosis following kidney transplantation

Dyslipidemia after kidney transplantation

After kidney transplantation, an increase in serum total cholesterol levels, particularly in LDL-C levels, has been observed. In many cases, there is also an increase in VLDL cholesterol and triglyceride levels. The changes in HDL-C levels are less clear-cut. Some studies report a decrease in the HDL-2 subfraction, which is protective against atherosclerosis, while others describe a decrease in HDL3 levels. These lipid abnormalities typically become detectable within 3-6 months post-transplantation, with some cases showing persistent dyslipidemia while others exhibit improvement, likely due to the reduction or discontinuation of immunosuppressive therapy. Post-transplantation, the transplanted kidney normalizes renal function, resolving the metabolic conditions that previously sustained lipid abnormalities in renal failure. However, hyperlipidemia is a well-known metabolic complication in organ transplant recipients, including kidney transplant patients. Factors contributing to its development include patient age, smoking, hypertension, insulin resistance, renal function, and the immunosuppressive treatment regimen. While post-transplant hyperlipidemia is dose-dependently associated with immunosuppressive therapy, this relationship is most significant in the early post-transplant period. It is believed that other factors, beyond immunosuppressive therapy, are responsible for persistent lipid abnormalities in the late post-transplant period.

Oxidative stress following kidney transplantation

The effects of kidney transplantation on oxidative status are contradictory. Post-transplant oxidative stress is primarily driven by reactive oxygen species (ROS) generated during end-stage renal disease, ischemia-reperfusion injury, and the use of immunosuppressive therapy. As renal function improves, previously impaired antioxidant systems are reactivated, and the excretion of toxins that promote ROS formation is enhanced. However, new factors that increase oxidative stress emerge after transplantation. One such factor is ischemia-reperfusion injury, which occurs following kidney transplantation. Evidence suggests that NADPH oxidase is activated during ischemia-reperfusion injury and plays a potential role in the resulting renal damage. The extent of this damage is naturally dependent on the duration of the ischemic period. During the reperfusion stage, tissue damage worsens due to the release of oxygen free radicals, which enhance lipid peroxidation. The degree of reperfusion and oxidative damage is correlated with long-term graft survival and influences the recovery of renal function post-transplantation. Additionally, the immune response against donor cells contributes to the increase in oxidative stress. Various immunosuppressive agents contribute to oxidative stress to varying degrees. Post-transplant oxidative phenomena, such as endothelial dysfunction, inflammation, and atherosclerosis, are responsible for graft damage, cardiovascular complications, and are a leading cause of mortality in transplant recipients.

Systemic inflammatory processes following kidney transplantation

Previous studies have shown that in cases where acute rejection did not occur following kidney transplantation, inflammatory markers increased immediately after transplantation and returned to baseline within the following week. Cueto-Manzano and colleagues, in an 18-month follow-up study, found that chronic systemic inflammation persisted even one year post-transplantation in stable patients. This study indicated that while CRP, IL-6, and TNF-α levels returned to normal by the 6th month post-transplantation, IL-6 and

TNF-α levels rose again between the 12th and 18th months, leading to sustained low-grade systemic inflammation. This may be due to an immune response against the allograft, which manifests systemically. Inflammation observed in early post-transplant biopsies has been associated with the progression of interstitial fibrosis, reduced graft function, and the development of de novo donor-specific antibodies (dnDSA). Following kidney transplantation, the risk of various opportunistic infections increases due to immunosuppressive therapy, which also contributes to the maintenance of systemic inflammation in these patients.

Endothelial dysfunction following kidney transplantation

Following kidney transplantation, the elimination of uremic toxins improves endothelial function. Several studies have examined changes in endothelial dysfunction post-transplantation. Kanbay and colleagues conducted a meta-analysis of nine studies and found that all four parameters used to assess endothelial function (FMD, nitroglycerin-mediated dilation (NMD), CRP, adiponectin) showed improvement following kidney transplantation. Given the link between endothelial dysfunction and the pathogenesis of various diseases, including atherosclerosis and coronary artery disease, the studies they reviewed support the growing body of literature indicating that kidney transplantation helps reduce inflammation and cardiovascular risk. Despite the restoration of renal function, endothelial function typically does not normalize to levels observed in healthy kidneys. Sharma and colleagues observed that even three months after transplantation, FMD levels in CKD patients were still lower than those in healthy individuals. The failure to fully normalize endothelial function may be one reason why cardiovascular mortality remains the leading cause of death among transplant recipients.

Pigment epithelium-derived factor (PEDF)

PEDF is an adipokine and glycoprotein that belongs to the serine protease inhibitor family. Discovered in 1980 by Joyce Tombran-Tink and Lincoln Johnson, PEDF is

predominantly produced by adipose tissue and the liver but is also expressed in inflammatory and vascular cells. It has multiple effects, including anti-angiogenic, antithrombotic, anti-inflammatory, antioxidant, neurotrophic, antifibrotic, and tumor-suppressive properties. PEDF inhibits endothelial damage induced by cytokines and growth factors, platelet aggregation, and T-cell activation. Recently, more data has been published regarding circulating PEDF levels in kidney disease, but these findings are quite contradictory. PEDF levels in HD-treated ESRD patients are significantly higher than in healthy controls. Furthermore, higher serum PEDF levels have been significantly associated with renal dysfunction in stages 3 or 4 CKD. However, lower pre-dialysis PEDF levels in HD patients have been linked to an increased risk of mortality, suggesting that PEDF expression may be a response to the inflammatory and oxidative processes associated with CKD. The mechanism of PEDF clearance remains unclear. Motomiya and colleagues investigated PEDF levels in ESRD patients and found that serum PEDF levels were significantly higher in this patient group compared to healthy controls, with blood urea nitrogen being the sole independent determinant. However, elevated PEDF levels could not be solely attributed to reduced renal clearance of the protein. It was also shown that ESRD patients with lower PEDF levels had a higher risk of mortality. The exact pathophysiological role of PEDF in chronic kidney disease and kidney transplant patients has yet to be fully elucidated.

N-terminal pro C-type natriuretic peptide (NT-proCNP)

C-type natriuretic peptide (CNP) is a paracrine growth factor identified in 1990 by Sudoh and colleagues as the oldest member of the natriuretic peptide family. CNP is expressed in various tissues, including vascular endothelium. Its expression is primarily induced by vascular inflammation, mainly through tumor necrosis factor-α released by macrophages. CNP is produced as a propeptide, which is then cleaved into the biologically active C-terminal hormone and the more stable amino-terminal fragment, the latter being suitable as a surrogate for measuring serum CNP levels. CNP is considered a vasoprotective protein with antiproliferative, anti-inflammatory, and antithrombotic functions.

Moreover, CNP has been shown to protect against atherogenesis in humans by inhibiting fibroblast proliferation and collagen production and promoting endothelial cell regeneration. Due to increased production and possibly decreased renal function, plasma natriuretic peptide levels are generally elevated in patients with renal insufficiency. However, several studies have found a negative correlation between NT-proCNP and eGFR. It is believed that CNP clearance from circulation occurs primarily through renal-independent pathways: it can be hydrolyzed by endopeptidases or internalized and degraded after binding to natriuretic peptide receptor-C. It is hypothesized that in addition to decreased NT-proCNP clearance and increased tubular reabsorption, increased C-type natriuretic peptide expression in the kidney in response to tubular injury may also contribute to the higher circulating levels of proCNP and its derivatives observed in chronic kidney disease.

Objectives

In the first part of our work, our objectives were to examine in patients with end-stage renal disease (ESRD):

- The changes in NT-proCNP levels and lipoprotein subfractions before transplantation and at 1 and 6 months post-transplantation.
- The relationship between NT-proCNP and the structure and function of HDL.

In the second part of our work, we aimed to:

- Investigate PEDF levels before transplantation and at 1 and 6 months post-transplantation in ESRD patients and in a matched healthy control population.
- Examine the relationship between PEDF and LDL and HDL subfractions.

Patients and methods

Study population

We included seventy kidney transplant patients (47 males and 23 females, mean age: 51.7±12.4 years, body mass index (BMI): 26.3±4.1 kg/m²) from the Transplantation

Department of the Surgical Institute at the University of Debrecen. Before transplantation, the patients had undergone hemodialysis treatment for an average of 60.68±52.24 months. In accordance with international guidelines, we regularly monitored the hydration status of our HD patients using whole-body impedance spectroscopy (BCM), a validated tool for accurately measuring body volume compartments (Fresenius Medical Care, Bod Hamburg, Germany; BCM Body Composition Monitor software version: 3.3.0.1637). Patients with overhydration exceeding 1.5-2.0 liters were excluded from our study. With the exception of three patients who received live-donor transplants, all patients underwent cadaveric organ transplantation. Prior to transplantation, we assessed the main comorbidities and medications of the kidney transplant patients based on data available in the patient documentation system. We also included 34 healthy volunteers (14 males and 20 females, mean age: 42.5±6.4 years, BMI: 24.8±2.1 kg/m²) from the General Outpatient Clinic of the Internal Medicine Department at the University of Debrecen. All participants provided written informed consent. The study protocol was approved by both local and national ethics committees (RKEB/IKEB:4739/2017, approval date: 20/02/2017, and ETT/TUKEB 7324-9/2017/EÜIG). The study was conducted in accordance with the Declaration of Helsinki. Exclusion criteria included liver disease, endocrine disorders (thyroid and parathyroid diseases, pituitary and adrenal disorders, etc.), acute infectious and autoimmune diseases, and elevated liver enzyme levels. Additional exclusion criteria were pregnancy, breastfeeding, current smoking, alcoholism, and drug addiction. Fourteen transplant patients (20%) were diagnosed with type 2 diabetes mellitus. The main immunosuppressive regimen consisted of tacrolimus, mycophenolate mofetil, and methylprednisolone.

Measurement of routine laboratory parameters

All venous blood samples were collected in Vacutainer® tubes before transplantation and at 1 and 6 months post-transplantation. Serum and plasma samples were separated by centrifugation at 3500 g for 10 minutes at +4 °C. Routine laboratory parameters—including high-sensitivity C-reactive protein (hsCRP), procalcitonin, total cholesterol,

triglycerides, HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), glucose, creatinine, glomerular filtration rate (GFR), and urea levels—were determined on the day of blood collection at the Laboratory Medicine Institute of the University of Debrecen using a Cobas 6000 analyzer (Roche Ltd, Mannheim, Germany). Samples were stored at -70°C in approximately 0.5 ml aliquots for subsequent enzyme-linked immunosorbent assay (ELISA) measurements and lipoprotein subfraction analyses.

Measurement of donor-specific antibodies (DSA)

The additional assessment of human leukocyte antigen (HLA) antibodies against class I and class II DSA was performed using a Luminex®-based single-bead assay.

Analysis of lipoprotein subfractions

HDL subfractions were determined using the Lipoprint® system (Quantimetrix Corp., Redondo Beach, CA, USA) according to the manufacturer's instructions. HDL subfractions were separated by size using non-gradient polyacrylamide gel electrophoresis. We applied 25 µl of serum to the upper portion of tubes pre-filled with acrylamide for HDL subfraction separation, then added a liquid gel containing Sudan Black dye to detect lipoproteins in the samples. After photopolymerization, the tubes were placed in an electrophoresis tank filled with a buffer solution containing Tris and boric acid. The samples were electrophoresed at a current of 3 mA/tube and a voltage of 500 V for 50 minutes. In each electrophoresis tank, we ran the manufacturer's quality control (Liposure Serum Lipoprotein Control, Quantimetrix Corporation, Redondo Beach, CA, USA). After electrophoresis, HDL subfractions were separated into 10 bands between the VLDL+LDL and albumin bands, which were categorized into three main classes: large (HDL1-HDL3), medium (HDL4-HDL7), and small (HDL8-HDL10) HDL subfractions (Figure 8). The cholesterol concentration of HDL particles was calculated using Lipoware software (Quantimetrix Corp., CA, USA) by multiplying the total HDL-C concentration of the samples by the relative area under the curve (AUC%) of the subfraction bands.

LDL subfractions were also determined using the Lipoprint® system (Quantimetrix Corp., Redondo Beach, CA, USA). For each polyacrylamide gel tube, 25 μl of serum and 200 μl of liquid gel containing Sudan Black dye were added. The subsequent steps were identical to those for the HDL subfraction analysis. Up to seven LDL subfractions can be identified between the VLDL and HDL peaks. The proportion of large LDL (large LDL%) was determined as the sum of LDL1 and LDL2, while the proportion of small dense LDL (small dense LDL%) was determined as the sum of LDL3-LDL7 (Figure 9). The cholesterol concentration of LDL subfractions was determined by multiplying the relative AUC of the subfractions by the total cholesterol concentration. The calculated total LDL-C was the sum of cholesterol in the mid-bands from C to A (consisting mainly of IDL) and LDL subfractions (LDL1-LDL7). The calculated LDL-C correlated with directly measured LDL-C (Lipoprint LDL: 130.8 ± 30.14 mg/dl vs. β-Quant LDL: 130.0 ± 30.42 mg/dl, r2 = 0.887). The average LDL size was also determined using the Lipoware software.

Measurement of oxidized LDL (oxLDL) concentration

The oxidized LDL level was determined using an ELISA kit (Mercodia AB, Uppsala, Sweden, cat. no. 10-1143-01) according to the manufacturer's instructions. The intra-assay and inter-assay coefficient of variation (CV) were 5.5-7.3% and 4.0-6.2%, respectively.

Measurement of PON1 paraoxonase and arylesterase activities

Serum PON1 paraoxonase and NaCl-stimulated activities were measured in a microtiter plate using a kinetic, semi-automated method with paraoxon (O,O-diethyl-O-p-nitrophenyl phosphate, Sigma Aldrich, Budapest, Hungary) as the substrate. The hydrolysis of paraoxon was monitored at 405 nm at room temperature. Serum PON1 arylesterase activity was assessed using phenyl acetate substrate (Sigma Aldrich,

Budapest, Hungary), and the hydrolysis of phenyl acetate was monitored at 270 nm at room temperature, as previously described.

Determination of serum PEDF levels

Human PEDF concentration was determined using a commercially available ELISA kit (BioVendor, Brno, Czech Republic, cat. no. RD191114200R) according to the manufacturer's instructions. The intra-assay and inter-assay CVs were 3.6% and 5.9%, respectively.

Determination of NT-proCNP

Human NT-proCNP was measured using a commercially available ELISA kit (Biomedica GmBH, Vienna, Austria, Cat.No. BI-20812) according to the manufacturer's instructions. The intra-assay and inter-assay coefficients of variation (CV) were 2-6% and 2-7%, respectively.

Statistical analyses

Statistical analyses were performed using Statistica 13.5.0.17 software (TIBCO Software Inc., USA) and GraphPad Prism 6.01 (GraphPad Prism Software Inc., USA). The normality of data distribution was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Data are presented as mean ± standard deviation (SD) for normally distributed variables or as median (interquartile range - IQR) for skewed distributions. Comparisons of data from transplanted patients during follow-up were made using repeated measures analysis of variance (ANOVA) with Fisher's LSD post-hoc test or the Kruskal-Wallis H test.

Comparisons between control and transplanted patient data were made using unpaired t-tests or Mann-Whitney U tests. Correlations between continuous variables were assessed using linear regression analysis with Pearson tests. For variables with skewed distributions, logarithmic values were used in the correlation analyses. Based on the

Pearson test results, we selected variables that significantly correlated with NT-proCNP and PEDF concentrations, then conducted multiple regression analyses to identify the variables that best predicted NT-proCNP and PEDF levels. Results were considered significant at $P<0.05$.

Results

Clinical parameters and main drug treatments for transplant patients

Seventy TX patients (47 males and 23 females) were included in our study, with an average duration of dialysis of 60.69±52.24 months. Mean age was 51.7±12.4 years and mean BMI was 26.3±4.1 kg/m^2. The DSA positivity rate among patients was 27.1% and 10% before transplantation. Of TX patients, 20% had type 2 diabetes mellitus, 10% coronary artery disease, 4.3% peripheral artery disease, 10% cerebral artery disease, 21.4% cardiomyopathy and 90% hypertension.

Laboratory parameters and lipoprotein subfractions in controls and ESRD Patients before and after transplantation (1 and 6 months post-transplantation)

During the follow-up, total cholesterol, HDL-C, LDL-C, oxLDL, GFR, and average LDL size increased significantly, while serum creatinine and serum urea decreased significantly 1 and 6 months after kidney transplantation. The hsCRP measured at 6 months was significantly lower than at baseline and 1 month after transplantation. We also compared our results with those of the healthy control group. We found that transplant patients had significantly higher serum oxLDL, triglyceride, creatinine, urea, hsCRP, and glucose levels compared to controls, while HDL-C, LDL-C, and GFR were significantly lower. The proportion and absolute amount of VLDL and small dense LDL subfractions were significantly lower, while the proportion and amount of IDL subfraction were higher in healthy controls compared to pre-transplantation patients. One month after transplantation, the percentage and amount of small dense LDL subfraction decreased, while the percentage and amount of large LDL subfraction increased in patients after 6 months of follow-up. Similar to total HDL-C, the amount of medium and

small HDL subfractions was significantly higher in controls than in patients before transplantation. During follow-up, these subfractions increased significantly in patients, reaching levels comparable to those of healthy controls.

Changes in NT-proCNP levels and correlation with laboratory parameters in ESRD patients before and after transplantation (1 and 6 months post-transplantation)

The average NT-proCNP level in patients decreased significantly 1 and 6 months after transplantation (Pre-TX: 45.8±21.9 pmol/l; 1 month post-TX: 5.3±2.5 pmol/l; 6 months post-TX: 7.7±4.9 pmol/l; P<0,001; Figure 10a). During the 6-month follow-up, the HDL-associated antioxidant enzyme PON1 showed improved arylesterase, paraoxonase, and salt-stimulated activity compared to pre-transplantation levels, both 1 month and 6 months after transplantation. Before transplantation, there was a strong positive correlation between NT-proCNP and procalcitonin (r=0.61, P<0.001). Additionally, serum creatinine and NT-proCNP were positively correlated at all three time points (Baseline: r=0.70, P<0.001; 1 month: r=0.38, P<0.01; 6 months: r=0.59, P<0.001), while circulating NT-proCNP showed a strong negative correlation with GFR (Baseline: r=-0.60, P<0.001; 1 month: r=-0.32, P=0.02; 6 months: r=-0.46, P<0.001). Pre-transplantation, LDL-C and large LDL were negatively correlated with NT-proCNP. Serum NT-proCNP was negatively correlated with HDL-C and with medium and small HDL at both baseline and during follow-up. There was also a negative correlation between serum NT-proCNP and PON1 arylesterase activity (r=-0.32, P=0.046) and a marginal negative correlation between serum NT-proCNP and PON1 paraoxonase (r=-0.27, P=0.063) and salt-stimulated activity (r=-0.27; P=0.056) at baseline. These correlations were not observed 1 and 6 months after transplantation.

We performed a multiple, backward stepwise multivariate analysis to determine which variable(s) best predicted NT-proCNP levels in pre-transplant patients. The model included procalcitonin, creatinine, GFR, PON1 arylesterase activity, large HDL (mmol/l), medium HDL (mmol/l), small HDL (mmol/l), and large LDL (mmol/l). According to the

analysis, the best independent predictors of pre-transplant NT-proCNP in ESRD patients were procalcitonin (β=0.367, P<0.001), creatinine (β=-0.538, P<0.001), and PON1 arylesterase activity (β=-0.32; P<0.001).

Changes in PEDF concentration in ESRD patients before and after transplantation, and correlation of PEDF with lipid subfractions and PON1 enzyme activities

Before transplantation, PEDF levels were significantly higher in patients compared to controls (23.88±4.2 μg/ml vs. 14.68±3.7 μg/ml; p<0.001). One month after transplantation, PEDF levels in patients significantly decreased, reaching the levels of healthy controls (14.9±3.6 μg/ml), and this low level persisted throughout the 6-month follow-up period (13.9±2.8 μg/ml). There was no difference in PEDF levels between males and females in either the transplant (p=0.52) or control group (p=0.28). The PEDF/creatinine ratio was 80% lower in pre-transplant cases compared to controls, and although this ratio significantly increased after one month, it remained only 50% of the control values. In the DSA-positive group, pre-transplant PEDF levels were significantly lower compared to DSA-negative patients (21.8±0.5 vs. 24.6±1.3 μg/ml; p=0.03). A positive correlation was found between PEDF levels and BMI in transplant patients (r=0.37; p=0.004), while age showed no correlation with PEDF concentration (controls: p=0.64; transplant patients: p=0.56).

Before transplantation, only average LDL size, triglycerides, VLDL percentage, and large and medium HDL subfractions correlated with PEDF levels. During follow-up, more lipid parameters showed a correlation with PEDF concentration.

Six months after transplantation, oxLDL levels positively correlated with PEDF levels, while average LDL size showed a significant negative correlation with PEDF levels both before and six months after transplantation.

In analyzing the relationship between PEDF and HDL subfractions, we found a negative correlation between the percentage of large HDL and PEDF levels before and six months

after transplantation. Conversely, a positive correlation was observed between the percentage of small HDL subfraction and PEDF levels during the 6-month follow-up.

A multiple, backward stepwise multivariate analysis was conducted to identify the variables that best predicted PEDF levels in transplant patients six months after kidney transplantation. The model included BMI, oxLDL, average LDL size, cholesterol, triglycerides, VLDL, IDL, large LDL, small dense LDL, large HDL, and small HDL levels. The analysis indicated that the best predictor of PEDF levels was the level of large HDL (β=-0.58; $p<0.01$).

Summary of new findings

1. The average NT-proCNP levels in patients significantly decreased 1 and 6 months after transplantation (Pre-TX: 45.8±21.9 pmol/l; 1 month post-TX: 5.3±2.5 pmol/l; 6 months post-TX: 7.7±4.9 pmol/l; P<0.001).
2. Before transplantation, there was a strong positive correlation between NT-proCNP and procalcitonin (r=0.61, P<0.001).
3. NT-proCNP levels were positively correlated with serum creatinine at all three time points (Baseline: r=0.70, P<0.001; 1 month post-TX: r=0.38, P<0.01; 6 months post-TX: r=0.59, P<0.001), while a strong negative correlation was observed between NT-proCNP and GFR (Baseline: r=-0.60, P<0.001; 1 month post-TX: r=-0.32, P=0.02; 6 months post-TX: r=-0.46, P<0.001).
4. LDL-C and the amount of large LDL were negatively correlated with NT-proCNP before transplantation.
5. Serum NT-proCNP was negatively correlated with HDL-C, as well as with the amounts of medium and small HDL, both at baseline and during follow-up.
6. There was a negative correlation between serum NT-proCNP and PON1 arylesterase activity (r=-0.32, P=0.046) and a marginal negative correlation with PON1 paraoxonase (r=-0.27, P=0.063) and salt-stimulated activity (r=-0.27, P=0.056) at baseline.

7. A multiple backward stepwise multivariate analysis revealed that the best independent predictors of pre-transplant NT-proCNP in ESRD patients were procalcitonin (β=0.367, P<0.001), creatinine (β=-0.538, P<0.001), and PON1 arylesterase activity (β=-0.32; P<0.001).
8. Before transplantation, PEDF levels in patients were significantly higher than in controls (23.88±4.2 µg/ml vs. 14.68±3.7 µg/ml; P<0.001). One month after transplantation, PEDF levels in patients decreased significantly, reaching the levels observed in healthy controls (14.9±3.6 µg/ml), and this lower level persisted throughout the 6-month follow-up period (13.9±2.8 µg/ml).
9. In the DSA-positive group, PEDF levels were significantly lower before transplantation compared to DSA-negative patients (21.8±0.5 vs. 24.6±1.3 µg/ml; P=0.03).
10. A positive correlation was found between PEDF levels and BMI in transplant patients (r=0.37; P=0.004), while age showed no correlation with PEDF concentration (controls: P=0.64; transplant patients: P=0.56).
11. Before transplantation, only average LDL size, triglycerides, VLDL percentage, and the percentages of large and medium HDL subfractions correlated with PEDF levels. During follow-up, more lipid parameters showed correlations with PEDF concentration.
12. Six months after transplantation, oxLDL levels positively correlated with PEDF levels, while average LDL size showed a significant negative correlation with PEDF levels both before and six months after transplantation.
13. In analyzing the relationship between PEDF and HDL subfractions, a negative correlation was found between the percentage of large HDL and PEDF levels before and six months after transplantation, while a positive correlation was observed between the percentage of small HDL subfraction and PEDF levels during the 6-month follow-up.

14. A multiple backward stepwise multivariate analysis indicated that the best predictor of PEDF levels in transplant patients six months after kidney transplantation was the level of large HDL (β=-0.58; $P<0.01$).

Discussion

Our research group was the first to examine, in a long-term prospective study, the relationship between NT-proCNP and HDL structure and function in end-stage renal disease (ESRD) patients before and at 1 and 6 months after kidney transplantation. Since the kidney expresses numerous antioxidant enzymes, the gradual decline in renal function increases pro-oxidant levels. Consequently, oxidative stress is common in ESRD, contributing to the progression of kidney damage by promoting renal ischemia and glomerular injury, as well as exacerbating chronic inflammation. Several authors have reported increased oxidative modification of LDL in dialysis patients, one of the many qualitative changes in LDL. It is also known that PON1 hydrolyzes lipid peroxides, providing protection against LDL oxidation. However, oxidative modification of HDL inhibits PON1 expression. Indeed, reduced PON1 activity has been observed in ESRD in several previous studies, and our current findings are consistent with these earlier reports.

Numerous clinical studies have suggested a connection between oxidative stress and inflammation in ESRD patients. Our current findings also confirmed elevated concentrations of inflammatory markers, including hsCRP and procalcitonin, which may further influence PON1 activity.

CNP is expressed in the kidneys and the vascular system, particularly in the endothelium, where it induces vasodilation and acts as a paracrine endothelium-derived relaxing factor that enhances the effects of nitric oxide and prostacyclin. It has been shown that as renal function declines, NT-proCNP excretion through the kidneys decreases, while tubular reabsorption increases. It is also hypothesized that the rise in NT-proCNP levels is partly due to upregulation of renal C-type natriuretic peptide and increased renal expression of CNP proteins in response to tubular damage. Previously, serum NT-proCNP had not been

studied in ESRD patients. We found significantly elevated NT-proCNP levels in our ESRD patients before transplantation, reinforcing that impaired renal function is associated with increased NT-proCNP levels. Interestingly, serum NT-proCNP showed a significant negative correlation with PON1 arylesterase activity. We hypothesize that increased vascular inflammation induces NT-proCNP expression and reactive oxygen species (ROS) formation, which alters HDL structure and function, leading to impaired PON1 activity. Indeed, alongside creatinine, procalcitonin, and PON1 arylesterase activity were independent predictors of NT-proCNP, highlighting the close interaction between vascular function and HDL quality. Since PON1-associated arylesterase activity is known to protect lipoproteins from oxidation, the resulting decreased antioxidant capacity may lead to further oxidative damage and accelerated atherosclerosis in kidney patients.

Although several metabolic disorders improve after kidney transplantation, oxidative processes associated with endothelial dysfunction, inflammation, and atherosclerosis intensify, contributing to both graft damage and cardiovascular complications, which remain a leading cause of mortality in transplant recipients. We observed a decrease in inflammatory markers 1 and 6 months after transplantation compared to pre-transplant levels, while oxLDL levels slightly increased, reflecting heightened oxidative stress.

We found that PON1 arylesterase activity, which correlates with enzyme protein concentration, significantly increased after kidney transplantation and remained elevated after 6 months of follow-up. PON1 paraoxonase activity, representing the enzyme's antioxidant capacity, and salt-stimulated PON1 activity, indicating maximal enzyme capacity, also increased significantly post-transplantation but did not change further during the follow-up period.

The impact of kidney transplantation on serum NT-proCNP had not been studied until now. In our study, we found a significant and sustained decrease in NT-proCNP after transplantation, which can be attributed to improved renal function, as previous studies

have reported a correlation between NT-proCNP and renal function. Additionally, the beneficial effects of transplantation on inflammatory processes may contribute to the reduction in NT-proCNP due to decreased CNP production. However, the correlations between arylesterase activity, procalcitonin, and NT-proCNP observed before transplantation were not evident after transplantation.

Our findings suggest that CNP-enhancing strategies, including CNP agonists, may contribute to vasculoprotection in kidney transplant recipients. Due to severe hypotensive side effects and short half-lives, recombinant natriuretic peptide drugs, such as nesiritide, carperitide, and ularitide, are not suitable for clinical use. Therefore, modified natriuretic peptides, developed by altering the genetic and amino acid sequences of natriuretic peptides, are currently under development. These hybrid peptides retain normal binding to natriuretic peptide receptors but are more resistant to degradation.

In summary, elevated serum NT-proCNP in ESRD patients correlates closely with renal function, procalcitonin levels, HDL subfraction distribution, and HDL antioxidant function, as characterized by PON1 activity. After kidney transplantation, serum NT-proCNP shows a significant and sustained decrease, primarily due to improved renal function and reduced inflammation. Our findings suggest that NT-proCNP could be a novel biomarker linking HDL dysfunction and vascular function impairment in ESRD. Further studies involving larger patient populations are needed to clarify the exact role of NT-proCNP in predicting cardiovascular risk in ESRD and after kidney transplantation.

In the second part of our study, we reported changes in serum PEDF levels in chronic kidney disease patients at 1 and 6 months after kidney transplantation, comparing these changes to PEDF levels in healthy controls. Consistent with previous reports, our patients had significantly higher PEDF levels than controls before transplantation. One month after transplantation, PEDF levels significantly decreased to levels observed in healthy controls, and this lower level persisted throughout the 6-month follow-up period. Given the anti-atherogenic effects of PEDF in chronic kidney disease, such a significant

decrease in circulating PEDF levels could be detrimental for our patients, potentially contributing to high cardiovascular morbidity and mortality. Our findings may suggest that PEDF could serve as a therapeutic target and/or agent after kidney transplantation. However, we found no significant correlation between PEDF and creatinine levels before or after transplantation, which may indicate an indirect relationship between PEDF levels and renal function.

The presence of small LDL particles is a known characteristic of uremic dyslipidemia, which is an important risk factor for cardiovascular diseases. This abnormality is not corrected by hemodialysis and persists after kidney transplantation. It has also been shown that HDL3a and HDL3b levels are significantly lower in kidney transplant recipients, while HDL2b levels are higher in males compared to control groups. Our results corroborate these findings. Small dense LDL subfractions were significantly higher in transplant patients before transplantation compared to healthy controls. One month after transplantation, the percentage and amount of small dense LDL subfractions decreased, while the percentage and amount of large LDL subfractions increased after 6 months of follow-up. The average LDL size showed a significant negative correlation with PEDF before and 6 months after transplantation. Additionally, the amount of intermediate and small HDL subfractions was significantly higher in controls compared to patients before transplantation.

During follow-up, these previously mentioned subfractions significantly increased in patients, reaching the levels observed in healthy controls. We found a negative correlation between the percentage of large HDL subfractions and PEDF levels before and 6 months after transplantation, while a positive correlation was observed between the percentage of small HDL subfractions and PEDF levels during the 6-month follow-up. To test whether the correlations identified in univariate analyses were independent of lipid parameters, we conducted multiple regression analyses with PEDF levels as the dependent variable. The backward stepwise analysis revealed that the best predictor of PEDF levels was the concentration of large HDL subfractions.

Several reports have suggested that PEDF can associate with HDL particles in both healthy individuals and ESRD patients before and after kidney transplantation. Furthermore, PEDF accumulation has been observed in the HDL proteome of ESRD patients compared to healthy controls. Additionally, PEDF enrichment in the transplant group was significantly reduced compared to ESRD patients, particularly in those with good graft function. Based on these findings, it was concluded that the restoration of renal function after kidney transplantation does not correct the impaired properties of uremic HDL. Our results align with these previous data. The significant correlations between PEDF levels and lipoprotein subfractions may shed light on the direct interaction between lipoproteins, metabolism, and endogenous anti-angiogenic mechanisms.

Kidney transplant recipients are prone to reperfusion injury, and ongoing oxidative stress can be detected in the early stages after transplantation. Findings from recipients of live-donor transplants suggest that oxidative stress parameters begin to improve immediately after kidney transplantation and continue to do so until day 28 post-transplantation. However, complete remission can only be achieved when renal function normalizes. The imbalance between prooxidant and antioxidant factors after kidney transplantation is well documented. Our findings indicate that transplant patients had significantly higher serum oxLDL levels compared to controls, while PON1 activity was significantly lower in the patient group compared to controls. Furthermore, oxLDL levels were significantly elevated both 1 and 6 months after transplantation. PON1 paraoxonase and arylesterase activities showed slight increases during the follow-up period after transplantation. We found a significant positive correlation between PEDF and oxLDL levels, while no correlation was found between PEDF levels and PON1 activity. The detailed mechanisms by which PEDF inhibits oxidative stress remain unclear. Our results suggest that PEDF may inhibit oxidative stress in transplant patients more by reducing oxidative stress itself rather than by inducing antioxidant capacity. We hypothesize that increased oxidative stress in both hemodialysis-treated and transplant patients may cause tissue damage, inflammation, and dysfunction, thereby inducing PEDF expression, which leads to

elevated serum PEDF levels despite the negative intracellular effects of reactive oxygen species on PEDF expression. However, this hypothesis requires further investigation.

We must also acknowledge some limitations of our study. Although we excluded patients with overhydration exceeding 1.5-2.0 liters, overhydration may still affect baseline serum PEDF levels, as reported by Liu and colleagues. Additionally, a larger sample size of transplant patients and control participants could increase the statistical power.

In our studies, we observed that elevated serum PEDF levels significantly decreased after kidney transplantation. The independent predictor of PEDF levels was the concentration of large HDL subfractions, highlighting the important role of HDL function in PEDF metabolism. Our findings suggest that the altered composition of HDL may directly contribute to increased atherosclerosis after kidney transplantation. Our data indicate that PEDF could be a potential therapeutic target for preventing vascular endothelial cell damage induced by oxLDL after transplantation. Further studies are needed to clarify the detailed pathophysiological role of PEDF.

Summary

C-type natriuretic peptide (CNP) is a paracrine growth factor expressed in various tissues, including vascular endothelium, where its expression is primarily induced by vascular inflammation. CNP is a vasoprotective protein with antiproliferative, anti-inflammatory, and antithrombotic functions. It is produced as a propeptide, which then cleaves into a biologically active C-terminal hormone and a more stable amino-terminal fragment, the latter serving as a surrogate marker for serum CNP levels. Elevated NT-proCNP levels have been documented in patients with renal insufficiency. It is hypothesized that the decline in renal function, along with reduced NT-proCNP excretion and increased tubular reabsorption, as well as upregulated renal expression of CNP in response to tubular damage, contribute to the higher circulating proCNP levels observed in chronic kidney disease.

We aimed to investigate the changes in NT-proCNP levels and lipoprotein subfractions in end-stage renal disease (ESRD) patients before and at 1 and 6 months after transplantation. Seventy kidney transplant patients from the Transplantation Department of the Surgical Institute at the University of Debrecen were included in our study. Human NT-proCNP levels were measured using a commercially available ELISA kit, and lipoprotein subfractions were separated by Lipoprint gel electrophoresis. PON1 paraoxonase and arylesterase activities were analyzed spectrophotometrically. In ESRD patients, elevated serum NT-proCNP correlated closely with renal function, procalcitonin levels, HDL subfraction distribution, and HDL antioxidant function, characterized by PON1 activity. Following kidney transplantation, we observed a significant and sustained decrease in serum NT-proCNP, primarily due to improved renal function and reduced inflammation. Our findings suggest that NT-proCNP may represent a novel link between HDL dysfunction and impaired vascular function in ESRD, which improves after kidney transplantation. Further studies with larger patient populations are needed to clarify the precise role of NT-proCNP in predicting cardiovascular risk in ESRD.

PEDF (Pigment Epithelium-Derived Factor) is an adipokine and glycoprotein belonging to the serine protease inhibitor family. It is predominantly produced by adipose tissue and the liver, but also by inflammatory and vascular cells. PEDF has multiple effects, including antiangiogenic, antithrombotic, anti-inflammatory, antioxidant, neurotrophic, antifibrotic, and tumor-suppressing properties. Elevated PEDF levels have been observed in patients with ESRD undergoing hemodialysis, and these elevated levels are often associated with lipid abnormalities, such as hypertriglyceridemia and lower HDL levels. The exact mechanism of PEDF clearance is not well understood. Previous studies have reported significantly higher serum PEDF levels in ESRD patients compared to healthy controls, although this elevation cannot be explained solely by reduced renal clearance of the protein. Lower PEDF levels have been associated with higher mortality risk in ESRD patients.

In the second part of our study, we examined PEDF levels before and at 1 and 6 months after kidney transplantation in ESRD patients and compared these changes to those in a matched healthy control group. PEDF concentrations were measured using a commercially available ELISA kit, and lipoprotein subfractions were separated by Lipoprint gel electrophoresis. We found that serum PEDF levels significantly decreased after kidney transplantation. The concentration of large HDL subfractions was the best predictor of serum PEDF levels, indicating the role of HDL composition in PEDF expression. These results suggest that the altered molecular composition of HDL after transplantation may directly contribute to increased atherogenesis, leading to early cardiovascular complications. Endothelial injury in the allograft macro- or microvasculature, especially if antibody-mediated, reduces graft survival. The pathophysiological role of PEDF level changes following transplantation warrants further investigation. These data suggest that PEDF may be a therapeutic target for mitigating vascular endothelial cell damage induced by ox-LDL after kidney transplantation.

Summary of new findings:

1. NT-proCNP predicts cardiovascular risk in chronic kidney disease patients

2. PEDF may be a potential therapeutic target for the prevention of oxidized LDL-induced vascular endothelial cell injury after kidney transplantation.

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Candidate: Réka Szentimrei
Doctoral School: Doctoral School of Health Sciences

List of publications related to the dissertation

1. **Szentimrei, R.**, Lőrincz, H., Szentpéteri, A., Varga, V. E., Seres, I., Varga, É., Nemes, B. Á., Harangi, M., Paragh, G.: Assessment of amino-terminal C-type natriuretic peptide serum level and its correlation with high-density lipoprotein structure and function in patients with end stage renal disease before and after kidney transplantation.
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2. **Szentimrei, R.**, Lőrincz, H., Szentpéteri, A., Varga, V. E., Harangi, M., Seres, I., P. Szabó, R., Nemes, B. Á., Paragh, G.: Changes in serum pigment epithelium-derived factor levels after kidney transplantation in patients with end-stage renal disease.
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List of other publications

3. Paragh, G., Zilahi, P., **Szentimrei, R.**, Lőrincz, H., Kolozsvári, L. R., Harangi, M.: Milyen kezelési lehetőségeink vannak a magas lipoprotein(a) csökkentésére?
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