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Is it possible to predict the early post-transplant allograft function using 20-HETE measurements? A preliminary report

Barbara Dołęgowska,[1] Wojciech Błogowski[2] and Leszek Domański[3]

1 Department of Biochemistry and Medical Chemistry, Pomeranian Medical University, Szczecin, Poland
2 Department of Laboratory Diagnostics and Molecular Medicine, Pomeranian Medical University, Szczecin, Poland
3 Department of Nephrology, Transplantology and Internal Medicine, Pomeranian Medical University, Szczecin, Poland

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Correspondence
Wojciech Błogowski, Department of Laboratory Diagnostics and Molecular Medicine, Pomeranian Medical University, Al. Powstancow Wielkopolskich 72, 70-111 Szczecin, Poland. Tel.: +48 91 466 1490; fax: +48 91 466 1492; e-mail: drannab@wp.pl

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Summary

20-HydroxyEicosaTetraEnoic (20-HETE) acid is an arachidonic acid metabolite that is generated via cytochrome P450 enzymes, and according to the findings from recent studies, may be involved in the pathogenesis of ischemia–reperfusion injury. The aim of this study was to: examine the dynamics of 20-HETE changes during the first 5 min of allograft reperfusion, and analyze whether the observed changes are associated with post-transplant graft function. Sixty-nine renal transplant recipients were divided, according to their outcome, into early, slow and delayed graft function (EGF, SGF, DGF) group. Blood samples were collected directly before and during the first 5 min of allograft reperfusion. 20-HETE concentrations were measured using ELISA. The results demonstrated significant differences in the concentrations and in the dynamics of 20-HETE changes between patients with immediate graft function, and individuals with allograft activation problems. The sensitivity, specificity, positive and negative predictive value of 20-HETEΔ(5-0) parameter in discriminating EGF and SGF from DGF were 69%, 54%, 74% and 48% respectively. Therefore, our results demonstrated that the dynamics of 20-HETE changes, which occurs during early phase of allograft reperfusion, is associated with early post-transplant graft function and also highlighted 20-HETE as a novel clinical marker of post-transplant allograft function.

Introduction

Ischemia–reperfusion injury (I/R) is an unfavorable and unavoidable process that exerts a profound effect on both, early and long-term outcome of the transplanted kidney. Although for the last 20 years, much effort has been put into understanding its pathophysiology, still the precise mechanisms responsible for this phenomenon remain enigmatic. However, what is already well known is that several molecular mechanisms, i.e. activation of inflammatory response, formation of reactive oxygen species, duration of dialysis treatment pretransplantation and of cold ischemia, microcirculatory disturbances, as well as, activation of cellular protective and apoptotic genes contribute to its plausible scenario. Moreover, the involvement of various mediators, such as TNF-α, endothelin, and active metabolites of arachidonic acid (AA) has been suggested [1–8].

Arachidonic acid is a component of cellular membranes that may be metabolized in three different pathways – via cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 enzymes (CYP450). The active products of AA metabolism, eicosanoids, play a pivotal role in the regulation of renal homeostasis, as their action significantly influences renal blood flow, glomerular filtration rate, vascular tone, ion transport, and severity of inflammation process [9]. However, eicosanoids' action should also be considered as a double-edged sword, as various

AA derivatives may modulate completely antagonistic processes i.e. COX-derived thromboxanes potentiate vasoconstriction, whereas simultaneously other COX products – prostaglandins stimulate vasodilatation. Most of these regulatory functions are possible, as AA metabolites act only locally in an autocrine or paracrine manner because of their unstable nature and short half-life [10].

The discovery of the 'third' pathway of AA metabolism (via CYP450 enzymes) has uncovered novel arachidonate metabolites that possess myriads of potent biologic activities. Primary products of AA CYP450 pathway are 20-HydroxyEicosaTetraEnoic acid (20-HETE), and epoxyeicosatrienoic acids. So far, it is apparent that these eicosanoids also play an important role in the regulation of renal vascular tone and tubular function. 20-HETE possesses potent vasoconstrictive properties, as it activates L-type Ca^{2+} channels leading to vasoconstriction of renal afferent arterioles, as well as, inhibits Na^+–K^+–ATPase activity in the proximal tubule by enhancing protein kinase C-induced phosphorylation of the Na^+–K^+–ATPase's α-subunit [11,12]. Moreover, 20-HETE modulates transport in key nephron segments [13], and is a second messenger, accounting for many of the diverse actions of peptide hormones as mitogens, secretagogues, vasoactive agents, and regulators of volume and composition of body fluids [14,15].

Hercule and Oyekan [16] have recently demonstrated that 20-HETE may be involved in the pathomechanisms of I/R injury in rat experimental model. Therefore, in this study, we wanted to verify whether this observation also applies to human I/R injury, which occurs during renal transplantation. Our aims were to measure the perioperative 20-HETE levels in renal transplant recipients and (i) examine whether the prereperfusion 20-HETE levels are associated with post-transplant creatinine and diuresis levels, (ii) examine the dynamics of 20-HETE changes, which occurs during the first 5 min of kidney allograft reperfusion, (iii) analyze whether the observed changes in the concentrations and direction of 20-HETE changes are associated with post-transplant graft function, and (iv) determine whether perioperative measurements of 20-HETE levels may serve as a novel marker of post-transplant graft function.

Materials and methods

Patients

The study included 69 patients, who were divided into three groups depending on graft activation: early (immediate), slow and delayed graft function (EGF, SGF, and DGF respectively) group according to the previously published criteria [17,18]. A general characteristic of the donors and recipients is summarized in Table 1. The patients with immediate activation of the graft, defined by serum creatinine levels below 3 mg/dl on the fifth postoperative day, were included in the EGF group. The patients with graft activation problems were divided into SGF (creatinine level higher than 3 mg/dl on the fifth postoperative day, however, no dialysis treatment required) and DGF group (need for dialysis in the first week after transplantation). The cross-matching status was determined using microcytotoxic test, complement-dependent cytotoxicity. All patients were transplanted for the first time and were receiving standard immunosuppressive protocol with triple drug therapy including cyclosporine A, azathioprine, and steroids. Renal allografts were received from patients, who died because of craniocerebral trauma ($n = 25$), subarachnoid hemorrhage

Table 1. General characteristics of donors and recipients (means ± SD).

	EGF	SGF	DGF
Donors			
Age (years)	50.07 ± 13.48	49.85 ± 14.46	51.30 ± 12.55
Gender (M/F)	(12/12)	(15/6)	(15/9)
Terminal creatinine (mg/dl)	1.38 ± 0.71	1.28 ± 0.86	1.26 ± 0.75
Recipients			
Number of patients	24	21	24
Age (years)	46.67 ± 13.08	48.19 ± 13.28	43.88 ± 11.13
Gender (M/F)	(10/14)	(17/4)	(15/9)
Cold ischemia time (min)	1311.0 ± 550.8	1221.6 ± 388.8	1577.4 ± 656.4
Warm ischemia time (min)	4.23 ± 0.55	4.29 ± 0.42	4.27 ± 0.63
Surgical revascularization (min)	21.35 ± 4.06	23.20 ± 5.64	24.08 ± 5.72
Mismatch (%)			
HLA-A	49.80	49.28	50.92
HLA-B	48.83	47.02	46.33
HLA-DR	46.12	46.02	46.08
Panel reactive antibodies (%)	0	0	0

EGF, early graft function group; SGF, slow graft function group; DGF, delayed graft function group.

($n = 11$), intracerebral hemorrhage ($n = 19$), stroke ($n = 5$), brain tumor ($n = 4$), neuroinfection ($n = 2$) or committed suicide ($n = 3$). Grafts were cold-stored and perfused with EuroCollins preservation solutions.

Methods

The [0] blood sample was taken from the iliac vein before anastomosing the kidney vessels with recipient's iliac vessels. Next, the renal vein of the graft was cannulated and blood samples [1], [3], [5] were taken at the first, third and fifth minute of reperfusion (respectively). The reperfusion of the transplanted kidney was measured precisely with ThermaCAM SC500 (AGEMA; Infrared System AB, Danderyd, Sweden) thermovision camera, which detects infrared radiation, and records digital images presenting surface temperature distribution of tested objects. The process of total reperfusion was completed, when the scans from thermovision camera demonstrated the whole organ filled with recipient's blood. Sample [1] was taken from the inserted catheter after total tissue reperfusion had been observed on the scan monitor. Blood samples [3] and [5] were taken 2 and 4 min after blood sample [1].

Assays of 20-HETE concentrations

For the quantitative assessment of changes in the metabolism of 20-HETE, 5 ml of blood was collected and mixed with 109 mM trisodium citrate (9:1; v/v). Afterwards, blood was centrifuged (10 min; 20 °C; 106 *g*), platelet-rich plasma was obtained, transferred to another test tube, and then re-centrifuged (10 min; 20 °C; 3824 *g*). Platelet-poor plasma (PPP) was transferred to a fresh test tube and stored at −80 °C until the assays were performed.

The total content of 20-HETE in the PPP samples was determined using the ELISA method (20-HETE Assay Kit; Detroit R&D Inc, Detroit, Michigan, USA).

Analysis of changes related to 20-HETE dynamics

To determine the differences in the direction of 20-HETE changes following parameters were calculated:

1 20-HETEΔ(1-0) – the difference between 20-HETE levels stated in the first minute of allograft reperfusion and directly before reperfusion.
2 20-HETEΔ(3-1) – the difference between 20-HETE levels stated in the third and first minute of allograft reperfusion.
3 20-HETEΔ(5-3) – the difference between 20-HETE levels stated in the fifth and third minute of allograft reperfusion.
4 20-HETEΔ(5-0) – the difference between 20-HETE levels stated in the fifth minute of reperfusion and directly before allograft reperfusion.

Clinical parameters of allograft function

Creatinine, diuresis, and GFR levels were measured in the first, fifth and 10th post-transplant days in order to determine the early allograft function. GFR values were calculated according to the Cockroft–Gault formula.

Clinical predictive value of 20-HETEΔ(5-0) parameter values in discriminating early and slow graft function from delayed graft function

Application of cut-off limits permitted classification of the patients into four categories: true positive (a), true negative (b), false positive (c), and false negative (d). The sensitivity, specificity, positive and negative predictive values were calculated according to the following equations:

$$\text{Sensitivity} = [a/(a+d)] \times 100$$

$$\text{Specificity} = [b/(b+c)] \times 100$$

$$\text{Positive predictive value} = [a/(a+c)] \times 100$$

$$\text{Negative predictive value} = [b/(b+d)] \times 100$$

Statistical analysis

To check the normality of distribution of variables Shapiro–Wilk's test was used. The differences between 20-HETE concentrations in the subsequent samples during reperfusion were assessed by Friedman's ANOVA test. For comparison of mean values of parameters between examined groups Student's t-test was used (for normally distributed variables). Non-normally distributed variables were log-transformed. If a normal distribution was achieved, values were also compared using Student's t-test. However, if the transformation did not have normal distribution, Mann–Whitney's test was performed. Correlations between various parameters were calculated analogically using Pearson's test (for normally distributed variables) and Spearman's test (for non-normally distributed variables). In order to conduct the multivariate assessment of the degree of dependence between the parameters tested, the linear multiple regression model was used. Statistical analysis was performed using SPSS statistical analysis software. Statistical significance was defined when P-values less than 0.05 were stated.

The study protocol was approved by the Bioethics Committee of the Pomeranian Medical University in

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Szczecin. The study subjects submitted their informed written consent for participation.

Results

Mean 20-HETE levels, stated directly before, and in consecutive minutes of kidney allograft reperfusion, as well as, their statistical comparison between the groups, are presented in Table 2.

The results demonstrated that, during first 5 min of allograft reperfusion, significant changes in the concentrations of 20-HETE occur only in EGF and DGF patients, and the 'direction' of these changes is completely in opposite directions, in other words in EGF individuals a significant elevation in the eicosanoid levels was observed ($P = 0.00007$), in DGF patients 20-HETE concentrations significantly decreased ($P = 0.038$), whereas in SGF group no statistically significant differences were detected ($P = 0.26$). Moreover, the analysis revealed, that throughout the reperfusion period, 20-HETE concentrations were significantly lower in EGF group comparing to DGF individuals, and no statistically significant differences between SGF and DGF individuals, in relation to the concentrations of 20-HETE, were determined.

To estimate the dynamics of 20-HETE changes, the differences among 20-HETE concentrations, stated in consecutive minutes of allograft reperfusion, were measured (Table 3). The analysis demonstrated that in the first 3 min of graft reperfusion 20-HETE levels in EGF group significantly increased and then decreased, whereas in patients with graft acceptance problems a completely different trend was noticed. Interesting is the fact that, in the group of individuals with SGF allografts, the changes in the 20-HETE dynamics initially resembled that observed in the individuals with DGF allograft; however, during 5 min of allograft reperfusion, the eicosanoid levels increased in a manner typical of patients with EGF allograft.

The next question we wanted to answer was whether the observed changes in the concentrations and in the dynamics of 20-HETE changes are related to early post-transplant renal allograft function. To realize this aim, 20-HETE concentrations were correlated with post-transplant creatinine and diuresis levels measured on the first, fifth, and 10th postoperative days (Table 4), as also a multivariate analysis of factors influencing creatinine and GFR values was performed (Tables 5–7). This analysis demonstrated, that 20-HETE concentrations, measured directly before and in the third and fifth min of reperfusion, positively correlate with post-transplant creatinine (Table 4) and negatively with diuresis levels measured on the 10th postoperative day ($r = -0.38$, $P = 0.002$; $r = -0.27$, $P < 0.05$ respectively). Interestingly, the parameters which did not differ between the groups, i.e. 20-HETE levels stated in the first minute of graft reperfusion, are not associated with post-transplant graft function. In addition, the observed differences in the dynamics of 20-HETE changes were also related to post-transplant graft

Table 2. 20-HETE values stated in consecutive minutes of graft reperfusion (means ± SD).

Parameter/min	0	1	3	5	ANOVA
20-HETE (pg/ml)					
EGF	3.04 ± 2.84*	3.91 ± 2.68	2.69 ± 2.39**†	3.39 ± 1.72*	0.00007
SGF	4.01 ± 2.72	3.47 ± 2.26	4.78 ± 3.34	4.58 ± 2.67	0.26
DGF	6.29 ± 4.49	3.83 ± 2.61	4.06 ± 1.86	5.28 ± 3.03	0.038

EGF, early graft function group; SGF, slow graft function group; DGF, delayed graft function group; HETE, hydroxyeicosatetraenoic acid.
*$P < 0.01$; **$P < 0.005$ – level of significance for differences between means (EGF versus DGF).
†$P < 0.01$, level of significance for differences between means (EGF versus SGF).

Table 3. Mean values of differences between 20-HETE concentrations measured in consecutive minutes of allograft reperfusion (means ± SD).

Parameter/min	Δ(1-0)	Δ(3-1)	Δ(5-3)	Δ(5-0)
Δ20-HETE (pg/ml)				
EGF	0.84 ± 3.09	−1.17 ± 2.51*	0.67 ± 2.49	0.34 ± 2.46†
SGF	−0.53 ± 2.92	1.31 ± 3.73	−0.20 ± 4.50	0.57 ± 1.93‡
DGF	−2.47 ± 5.14	0.24 ± 3.23	1.21 ± 2.02	−1.02 ± 2.10

EGF, early graft function group; SGF, slow graft function group; DGF, delayed graft function group; HETE, hydroxyeicosatetraenoic acid.
*$P < 0.01$ – level of significance for differences between means (EGF versus SGF).
†$P < 0.05$ – level of significance for differences between means (EGF versus DGF).
‡$P < 0.05$ – level of significance for differences between means (SGF versus DGF).

Table 4. Coefficients of correlations between 20-HETE values, stated in consecutive minutes of allograft reperfusion, and post-transplant creatinine levels stated on the first, fifth and 10th postoperative days.

Parameter/Creatinine	1	5	10
20-HETE (pg/ml)			
(0)	0.38**	0.39†	0.38**
(1)	NS	NS	NS
(3)	NS	0.38**	0.37**
(5)	0.30*	0.44‡	0.39†

HETE, hydroxyeicosatetraenoic acid; NS, not significant.
*$P < 0.05$; **$P < 0.005$; †$P < 0.001$; ‡$P < 0.0005$.

function, as several correlations between 20-HETEΔ(5-0) parameter and creatinine or diuresis levels were stated (Figs 1 and 2). Moreover, the multivariate analyses demonstrated that 20-HETE levels, together with other well known pre- and peritransplant factors such as duration of cold ischemia time or surgical revascularization, significantly influence post-transplant creatinine and GFR levels in all the examined groups.

Finally, we wanted to verify the clinical value of 20-HETE changes as a possible predictor of post-transplant graft function. As we wanted to simplify this test as much as possible (so that it could easily be used in clinical practice), we decided to suggest 20-HETE measurements only directly before and in the fifth min of allograft reperfusion, as in our research we observed that in the EGF and SGF groups, during 5 min of reperfusion, 20-HETE levels increased, whereas in DGF patients the same decreased, and 20-HETEΔ(5-0) parameter significantly differed DGF

Table 5. Multivariate linear regression models for the study EGF group.

Dependent variable	Independent variable	Standardized coefficients in the regression equation (β)	P	R^2	P
log GFR1	log 20-HETE(3)	+0.599	0.01	0.31	0.01
	log 20-HETE(3)	+0.792	0.01	0.60	0.024
	CIT	−0.776	0.02		
log GFR5	Recipient's age	−0.576	0.008	0.33	0.008
log creatinine 1	log20-HETE(3)	−0.598	0.01	0.36	0.01
	log 20-HETE(3)	−0.744	0.01	0.58	0.02
	CIT	+0.699	0.03		

GFR1 and GFR5, GFR levels measured during the first and fifth post-transplant days; 20-HETE(3), 20-HETE levels measured in the third minute of reperfusion; CIT, cold ischemia time; creatinine 1, creatinine level measured on the first post-transplant day.

Table 6. Multivariate linear regression models for the study SGF group.

Dependent variable	Independent variable	Standardized coefficients in the regression equation (β)	P	R^2	P
log GFR1	log 20-HETE(1)	+0.741	0.03	0.55	0.03
	log20-HETE(1)	+0.720	0.02	0.88	0.0001
	log HD-pre-Tx	−0.960	0.04		
log GFR5	Surgical revascularization	−0.928	0.0001	0.84	0.0001
log GFR10	log20-HETE(5)	−0.707	0.03	0.50	0.03
	log20-HETE(5)	−0.581	0.03	0.77	0.04
	Surgical revascularization	−0.532	0.04		
	log20-HETE(5)	−0.471	0.01	0.93	0.02
	Surgical revascularization	−0.648	0.004		
	log20-HETE(1)	−0.425	0.02		
log creatinine 1	log20-HETE(1)	−0.825	0.01	0.68	0.01
	log20-HETE(1)	−0.841	0.01	0.87	0.04
	log HD-pre-Tx	+0.960	0.04		
log creatinine 5	Surgical revascularization	+0.928	0.0001	0.86	0.0001
log creatinine 10	log20-HETE(5)	+0.804	0.0005	0.65	0.0005

GFR1, GFR5, GFR10 – GFR levels measured during the first, fifth, and 10th post-transplant days; 20-HETE(1), 20-HETE(5) – 20-HETE levels measured in the first and fifth minute of reperfusion; creatinine 1, 5, and 10 – creatinine levels measured in the first, fifth and 10th post-transplant days; HD-pre-Tx, duration of hemodialysis treatment prior to transplantation.

Table 7. Multivariate linear regression models for the study DGF group.

Dependent variable	Independent variable	Standardized coefficients in the regression equation (β)	P	R^2	P
log GFR1	CIT	−0.891	0.02	0.79	0.02
	CIT	−0.511	0.01	0.83	0.02
	log20-HETE(5)	−0.384	0.04		
log creatinine 1	CIT	+0.939	0.005	0.85	0.02
	CIT	+0.684	0.003	0.99	0.01
	log20-HETE(5)	+0.416	0.01		
log creatinine 5	Recipients' gender*	−0.75	0.02	0.56	0.02
	Recipients' gender*	−0.829	0.004	0.80	0.04
	Recipients' age	−0.489	0.04		
log creatinine 10	Recipients' age	−0.77	0.03	0.53	0.03
	Recipients' age	−1.12	0.004	0.83	0.05
	CIT	+0.599	0.05		

GFR1, GFR levels measured during the first post-transplant day; 20-HETE(5), 20-HETE levels measured in the fifth minute of reperfusion; creatinine 1, 5, and 10, creatinine levels measured in the first, fifth and 10th post-transplant days.
*Male and female gender was assigned 0 and 1 value respectively.

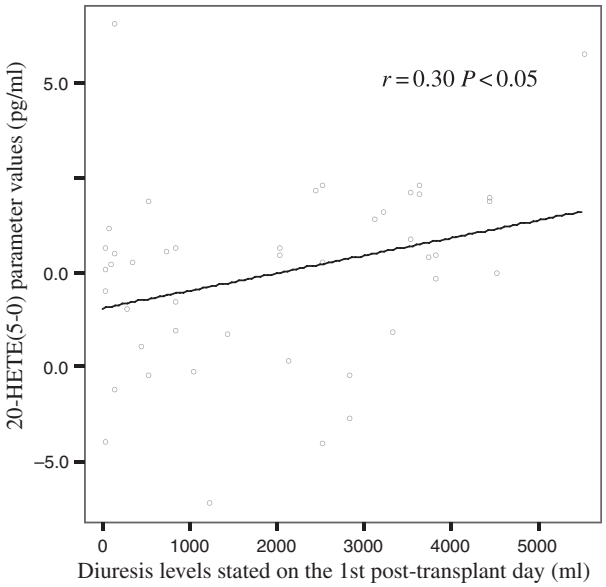

Figure 1 Correlation between 20-HydroxyEicosaTetraEnoic (20-HETE)Δ (5-0) parameter and post-transplant diuresis levels in all renal transplant recipients.

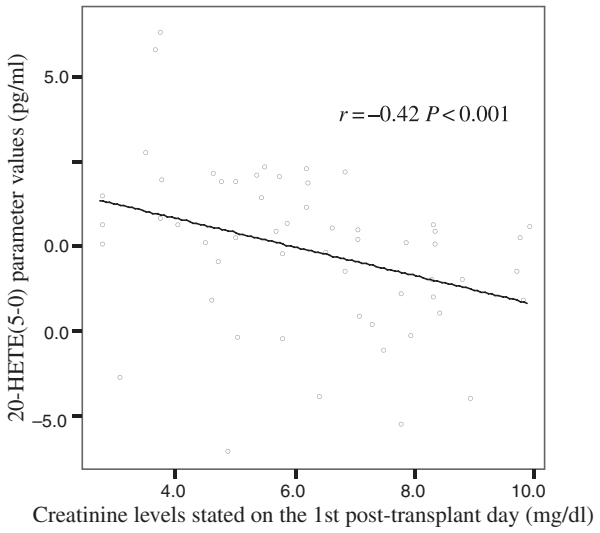

Figure 2 Correlation between 20-HydroxyEicosaTetraEnoic (20-HETE)Δ (5-0) parameter and post-transplant creatinine levels in all renal transplant recipients.

patients from EGF and SGF individuals. We assumed, that if the value of 20-HETEΔ(5-0) parameter is higher than 0, then it indicates immediate or slow graft activation, whereas 20-HETEΔ(5-0) values lower than 0 highlight severe graft activation problems and dialysis treatment requirement. The sensitivity, specificity, positive and negative predictive values of this test were computed and were 69%, 54%, 74% and 48% respectively.

Discussion

Ischemia–reperfusion injury exerts a profound effect on post-transplant outcome [19] and eicosanoids' influence on regulation of transplanted kidney functions seems to be of vital importance. Renal cells express significant levels of eicosanoid's receptors, as also possess enzymes of AA metabolism [20–22]. Interestingly, high expression of AA metabolizing enzymes was also found in liver, and at

lower levels was detected in the brain, heart and vasculature [23]. However, the specific activity of kidney's CYP450 is greater than that of the liver, and changes in the levels of monooxygenase activity and P450 isoforms in the rat kidney following I/R injury are faster than those in the liver [24,25]. During early phase of allograft reperfusion, transplanted kidney is exposed to various injurious stimuli, and the AA metabolism may not only protect the graft, but also reflect its response to all these unfavorable conditions [26], as CYP450 AA metabolism in the kidney is readily modifiable by hemodynamic and excretory function [27].

In our study, we have demonstrated that CYP450 AA metabolism, during early phase of renal allograft reperfusion, strongly differs between patients with immediate graft activation and individuals with allograft acceptance problems. In other words, in EGF patients, the 20-HETE levels significantly increased, however, although in DGF group the concentrations of this eicosanoid significantly decreased, still being significantly higher than that in EGF individuals. Moreover, the 'direction' of 20-HETE changes, throughout reperfusion period, was completely different in EGF patients when compared with the DGF individuals. Interesting also is the fact that in patients from SGF group 20-HETE levels did not significantly increase (resembling EGF patients), whereas 'DGF-type' of the dynamics was observed. Therefore, our results have not only confirmed, but also biochemically explained observations highlighted by others [17,18,28], that slow graft function after transplantation is an intermediate state, as it combines various elements typical for EGF and DGF states.

Paradoxically, although 20-HETE concentrations were negatively associated with post-transplant allograft function (positive correlation with creatinine levels), elevation in the concentration of this eicosanoid was observed only in patients that have not required dialysis treatment. At this stage of our research, it is very difficult to explain this phenomenon because of several reasons. First of all, according to recent studies, 20-HETE action is a double-edged sword. On the one hand, it is proved that exogenous administration of 20-HETE protects the glomerular permeability barrier *in vitro*, therefore 20-HETE may contribute to proteinuria limitation [29]. However, on the other hand, Benter *et al.* [30] have already associated elevation of 20-HETE levels with kidney and circulatory diseases, and suggested that administration of inhibitors of this eicosanoid's synthesis may be able to attenuate development of hypertension and end-organ damage. Second, 20-HETE synthesis is not the only mechanism of this eicosanoid generation in kidney. In other words, HETE, unlike prostaglandins, can be stored in tissue lipids, and rapidly 'released' in response to various stimuli, such as angiotensin II activity. In experimental models, it was proved that preformed HETE bound to lipids represent a significant reservoir in those tissues in which they have been generated [31,32]. In addition, CYP enzymes' inhibitors do not prevent release of preformed CYP AA products from lipid storage sites [32]. This sophisticated regulation may serve as a protective and adaptive mechanism, which, for example during I/R injury, preserves renal vasculature from excessive vasoconstriction [16]. Third, it is impossible to directly translate the results obtained in experimental models into clinical setting as 20-HETE formation in the rat and the human kidney strongly differs. Microsomes from human kidney cortex were found to convert AA to 20-HETE, but failed to perform AA epoxygenation and midchain hydroxylation, which is present in rats. Moreover, immunohistochemical analysis revealed that in humans the main CYP450 enzymes that synthesize 20-HETE are CYP4F2 and CYP4A11, which expression was demonstrated only in the S2 and S3 segments of proximal tubules in cortex and medulla, whereas in rats CYP4 expression was additionally observed in the preglomerular microvessel, glomerulus and the thick ascending limb. Finally, in humans no other CYP450 forms, such as CYP2C8, CYP2C9 nor CYP2E1, were detected [20,21].

It is also essential to highlight the clinical value of 20-HETE measurements. It seems very interesting that pretransplant 20-HETE levels are strongly associated with post-transplant graft function, and measuring the 20-HETEΔ(5-0) parameter may serve as a helpful clinical predictor of post-transplant graft function. This test can be easily used in clinical practice; however, in order to establish its predictive value further examinations on large cohorts of patients are needed.

In summary, our results demonstrated for the first time that 20-HETE levels are strongly associated with early post-transplant graft function in humans, and may, at least in part, contribute to early graft acceptance problems. The precise analysis of both – the dynamics of changes and 20-HETE concentrations, may serve as a helpful clinical predictor of post-transplant graft function.

Authorship

BD: designed and performed the study, reviewed the article. WB: data analysis, writing the paper. LD: samples collection, clinical aspects of the study.

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