POSSIBLE ROLE OF MICROVASCULAR FUNCTION IN CARDIOVASCULAR RISK PREDICTION IN CHRONIC KIDNEY DISEASE

Orsolya Cseprekál[1], József Egresits[1,2], János Nemcsik[3], Jan Kielstein[4], Philipp Kümpers[5], Alexander Lukasz[5], Ádám Tabák[1], Adrienn Marton[6], Zsófia Németh[6], Katalin Farkas[7], Zoltán Járai[8], István Kiss[9], András Tislér[1]

[1]Semmelweis University, Ist. Department of Internal Medicine, Budapest, HUNGARY [2]University Hospital Regensburg, Department of Internal Medizine II. Regensburg, GERMANY, [3]Semmelweis University, Department of Family Medicine, Budapest, HUNGARY, [4]Hannover Medical School, Department of Medicine/Division of Nephrology and Hypertension, Hannover, GERMANY, [5]University Hospital Münster, Department of Medicine D, Division of General Internal Medicine, Nephrology and Rheumatology, Münster, GERMANY, [6]Uzsoki Teaching Hospital, Nephrology Division, Budapest, HUNGARY, [7]St Imre University Teaching Hospital, Angiology Division, Budapest, HUNGARY, [8]St Imre University Teaching Hospital, Department of Cardiology, Budapest, HUNGARY, [9]St Imre University Teaching Hospital, Department of Nephrology and Hypertension, Budapest, HUNGARY

Background

- The role of biochemical and functional markers of microvascular dysfunction to predict cardiovascular (CV) outcome and all-cause mortality in non-dialyzed chronic kidney disease (CKD) remains unclear
- Laser Doppler Flowmetry (LDF) allows non-invasive assessment of microvascular reactivity, however, literature data on the predictive value of the measurable parameters are limited. (1,2)

Aims

- To evaluate correlations between LDF parameters and to identify their associations with biochemical markers
- To study the prognostic role of LDF parameters and biochemical markers in CV risk prediction

Study population

- Prospective cohort study of 105 CKD stage 2-5 (nondialysed – ND) patients (65±13.1ys, 51 males, eGFR 35.8 (23.8-49.9) ml/min/1.73m²)

Conclusions

- Among the functional and biochemical microvascular parameters, **PORH$_{HA}$** seems to be the one that best **predicts CV events** in CKD.
- The robustness of **traditional risk factors seems to outweigh the predictive role of microvascular biomarkers on all-cause mortality and incidence of CV events.**

Protocol and Methods

- **baseline** clinical assessment, laboratory data, LDF parameters (Laser Doppler Flowmetry (Periflux 5001) and a micropharmacology system (Perilont), Iontophoresis (Acethylcolin-Ach, Sodium nitroprussid-SNP), postocclusive reactive hyperaemia (PORH$_{HA}$) (3,4)
- **follow-up** for a median of 2026 (1211-2446) days; 67 (40-81) months
- **Hard end points -first events n=50 (second events n= 12)**
  - **Cardiovascular death: 16** (ACS 4, stroke 3, HF 8, PAD 1)
  - **Cardiovascular events: 34** (ACS 8, stroke 6, HF13, PAD 7)
- **Non-cardiovascular cause of death: 12** (dementia 5, pneumonia 2, accidents 2, cancer 2, pancreatitis 1)

Results

Spearman correlation analysis (p)

	ADMA	SDMA	Ang2	ACh	SNP	PORH$_{HA}$
ADMA	1 (0.0)	**0.308 (0.002)**	**0.292 (0.003)**	-0.045 (0.683)	-0.153 (0.164)	0.015 (0.883)
SDMA		1 (0.0)	**0.332 (0.001)**	-0.112 (0.31)	-0.038 (0.734)	0.112 (0.283)
Ang2			1 (0.0)	-0.161 (0.145)	-0.17 (0.122)	0.114 (0.273)
ACh				1 (0.0)	**0.498 (0.001)**	**0.28 (0.01)**
SNP					1 (0.0)	**0.233 (0.033)**
PORH$_{HA}$						1 (0.0)

Multivariate regression analysis

dependent variable: lnACh			model R²=0.096
explanatory variable	*estimate*	*p*	*partial R²*
diabetes	-0.5662	0.005	0.096

dependent variable: lnSNP			model R²=0.128
explanatory variable	*estimate*	*p*	*partial R²*
diabetes	-0.5978	0.001	0.128

dependent variable: lnPORH$_{HA}$			model R²=0.174
explanatory variable	*estimate*	*p*	*partial R²*
brachial PP	-0.0334	<0.001	0.128
age	0.0186	0.031	0.045

dependent variable: lnAng2			model R²=0.361
explanatory variable	*estimate*	*p*	*partial R²*
lnFGF23	0.1561	<0.001	0.150
chol	-0.1728	<0.001	0.099
lnCRP	0.1549	0.004	0.061
lnAlb_cr	0.0529	0.007	0.050

dependent variable: lnADMA			model R²=0.168
explanatory variable	*estimate*	*p*	*partial R²*
age	0.0047	0.001	0.078
heart rate	0.0047	0.002	0.055
PO$_4$	0.1571	0.049	0.034

dependent variable: lnSDMA			model R²=0.749
explanatory variable	*estimate*	*p*	*partial R²*
eGFR	-0.0128	<0.001	0.635
lnFGF23	0.1337	<0.001	0.045
lnAlb_cr	0.0439	0.003	0.029
albumin	0.0132	0.027	0.015
heart rate	0.0041	0.041	0.012
diabetes	-0.1198	0.049	0.011

Multiple failure time Univariate Cox Regression analysis

	CV mortality +CV events			All cause mortality +CV events		
	HR	CI 95%	p	HR	CI 95%	p
CCI	**1.27**	**1.13-1.427**	**0.001**	**1.244**	**1.114-1.364**	**0.0001**
CVD	**2.492**	**1.208-5.138**	**0.013**	**2.728**	**1.427-5.214**	**0.002**
DM	**3.231**	**1.715-6.084**	**0.0001**	**2.589**	**1.526-4.397**	**0.0001**
Smoke	0.521	0.175-1.557	NS	0.679	0.31-1.487	NS
Age (ys)	**1.022**	**1-1.045**	**0.048**	**1.028**	**1.007-1.049**	**0.009**
Gender	0.765	0.439-1.329	NS	0.847	0.515-1.389	NS
BMI (kg/m²)	1.054	0.999-1.113	NS	1.033	0.985-1.084	NS
eGFR (ml/min/1.73m²)	0.984	0.969-1	NS	**0.982**	**0.967-0.996**	**0.015**
Hgb (g/L)	0.994	0.9771.012	NS	**0.981**	**0.965-0.997**	**0.019**
Chol (mmol/l)	0.859	0.686-1.075	NS	0.842	0.678-1.046	NS
ln CRP	1.326	0.981-1.794	NS	**1.381**	**1.058-1.803**	**0.018**
Alb (g/l)	1.032	0.959-1.111	NS	1.012	0.952-1.076	NS
ln ACR	1.041	0.905-1.198	NS	1.038	0.916-1.177	NS
BPP (mmHg)	**1.028**	**1.005-1.051**	**0.013**	**1.031**	**1.012-1.05**	**0.001**
SBP (mmHg)	1.017	0.997-1.037	NS	1.017	0.999-1.035	NS
HR (1/min)	1.017	0.995-1.039	NS	1.018	0.997-1.038	NS
ln Ach	0.791	0.592-1.056	NS	0.863	0.644-1.154	NS
ln SNP	0.939	0.592-1.489	NS	1.029	0.676-1.567	NS
ln PORH	**0.634**	**0.423-0.95**	**0.027**	**0.648**	**0.452-0.929**	**0.018**
ln PORH$_{HA}$	**0.698**	**0.577-0.843**	**0.001**	**0.755**	**0.619-0.921**	**0.005**
ln FGF23	1.195	0.851-1.677	NS	1.387	0.996-1.932	0.053
ln iPTH	1.209	0.866-1.689	NS	1.111	0.817-1.511	NS
ln Ang2	**1.998**	**1.251-3.191**	**0.004**	**2.029**	**1.314-3.134**	**0.001**
ln Arg	0.506	0.187-1.369	NS	0.648	0.262-1.598	NS
ln SDMA	1.257	0.642-2.463	NS	1.51	0.834-2.736	NS
ln ADMA	1.038	0.236-4.566	NS	1.598	0.417-6.123	NS

Multiple failure time Multivariate Cox Regression analysis

	CV mortality +CV events			All cause mortality +CV events		
	HR	CI 95%	p	HR	CI 95%	p
ln AH	**0.663**	**0.494-0.891**	**0.006**			
bPP (mmHg)	-	-	-	**1.03**	**1.011-1.049**	**0.002**
Age (ys)	1.034	1.007-1.062	0.013	1.031	1.005-1.056	0.016
ln CRP	1.319	1.062-1.638	0.012			
DM	3.334	1.702-6.531	0.0001	3.016	1.733-5.246	0.0001

Backward: CVD. eGFR. BPP. Gender.

Baseline diagnosis

Baseline diagnosis	N (Yes/No)
Diabetes (DM)	47/58
CVD	65/40
Heart failure	19/86
PAD	54/51
Stroke *	24/81
Smoke (current) *	12/93
Hypertension *	103/2
* p<0.05	
Medication	
ACEi	93/12
ß inhibitor	57/48
Diuretics	78/27
CCB	56/49
Statin	65/40
TAG	52/53
EPO	38/67

Variables	All patients	eGFR >30 ml/min/1.73m²	eGFR ≤30 ml/min/1.73m²	p-value
N	105	53	52	
Age (years)	65 (13.1)	64.1	65.9	
male % (n)	49 (51)	52 (28)	44 (23)	
BMI (kg/m²)	28.2 (5.0)	27.8	28.7	
Smoke % (n)	11 (12)	11 (6)	11 (6)	
CVD % (n)	62 (65)	55 (29)	69 (36)	
DM % (n)	45 (47)	38 (20)	52 (27)	
Charlson comorbidity index (CCI)	3.7 (2.47)	3.0	4.38	0.009
eGFR (ml/min/1.73m²)	40.1 (21.7)	56.1	23.8	0.000
Hgb (g/L)	126 (14.4)	131	122	0.001
Chol (mmol/l)	4.88 (1.01)	4.90	4.84	
Ca (mmol/l)	2.36 (0.12)	2.35	2.37	
iP (mmol/l)	1.22 (0.24)	1.14	1.30	0.001
Albumin (g/l)	45.2 (4.21)	45.0	45.5	
CRP* (mg/l)	2.3 (0.9-4.5)	1.60 (0.7-3.1)	3.05 (1.20-6.25)	0.020
ACR* (mg/mmol)	7.2 (1.7-46)	4.6 (0.98-28.8)	16.7 (3.9-83.1)	0.010

variable	All patients	eGFR >30 ml/min/1.73m²	eGFR ≤30 ml/min/1.73m²	p-value
FGF23*	30.1 (21.0-55.3)	23.5 (19.1-34.8)	44.4 (28.3-68.2)	0.000
iPTH* (pg/ml)	56 (38-102)	45 (25-58)	92 (54-168)	0.000
Ang-2* (ng/ml)	3.1 (2.4-4.2)	2.9 (2.2-3.6)	3.4 (3-4.9)	0.009
Arg* (umol/l)	71 (58-80)	71.1 (61.4-79.8)	70.0 (56.7-81.4)	NS
ADMA* (umol/l)	0.597 (0.535-0.650)	0.565 (0.522-0.608)	0.622 (0.560-0.683)	0.009
SDMA* (umol/l)	0.941 (0.739-1.302)	0.754 (0.613-0.910)	1.272 (1.016-1.947)	0.000
SBP (mmHg)	134 (15.8)	135	134	NS
DBP (mmHg)	73 (9.7)	74	72	NS
bPP (mmHg)	61 (13.4)	61	62	NS
Heart rate (1/min)	66 (12.3)	65	68	NS
ACh*(%)	413 (244-614)	436 (276-610)	407 (202-691)	NS
SNP* (%)	454 (208-766)	602 (214-791)	372 (179-709)	NS
PORH* (%)	311 (178-484)	323 (192-498)	297 (172-470)	NS
PORH$_{HA}$*	592 (280-1047)	569 (266-1047)	690 (311-1069)	NS

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