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Kynurenine pathway – a new link between endothelial dysfunction and carotid atherosclerosis in chronic kidney disease patients

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ABSTRACT

Purpose: The endothelium dysfunction is an important component of atherosclertic cardiovascular disease. It has been also suggested that kynurenine pathway activation may be involved in the pathogenesis of this disease.
Material/Methods: This is a cross-sectional study in chronic kidney disease (CKD) patients (n=106; 60 Males). The plasma markers of endothelial dysfunction and kynurenine (KYN), 3-hydroxykynurenine (3-HKYN), kynurenic acid (KYNA), anthranilic acid (AA) and quinolinic acid (QA) were measured in relation to an early indicator of the systemic atherosclerosis - intima-media thickness (IMT).
Results: Kynurenines, von Willebrand factor (vWF), thrombomodulin (TM), soluble adhesion molecules (sICAM-1, sVCAM-1) and IMT in each uraemic group were significantly higher than in healthy people. In contrast, no significant differences in sE-selectin and sP-selectin concentrations were observed between CKD patients and controls. Kynurenines were positively associated with vWF, TM, sICAM-1 and sVCAM-1, whereas sP-selectin was inversely associated with the most of kynurenines. IMT was positively correlated both with kynurenines: KYN, 3-HKYN, QA as well as with endothelial markers: TM, vWF, sICAM-1 and sVCAM-1 (all $p<0.01$). Finally, multiple regression analysis identified age, vWF, sVCAM-1 and QA levels as the independent variables significantly associated with increased IMT in this population (adjusted $r^2 = 0.51$).
Conclusions: This study suggests a relationship between kynurenine pathway activation, endothelial dysfunction and the progression of atherosclerosis in CKD patients. It opens a new idea that the inhibition of kynurenine pathway may provide an effective strategy to slow down endothelial dysfunction and thereby the prevalence of atherosclerosis in this population.

Key words: atherosclerosis, chronic kidney disease, endothelial dysfunction, kynurenines

INTRODUCTION

Atherosclerotic cardiovascular disease (CVD) remains the leading cause of increased morbidity and mortality observed in chronic kidney disease (CKD) patients [1] and there is consistent evidence of a particular association between an endothelial dysfunction and the atherosclerotic process in uraemia [2-4]. Endothelial dysfunction, which is one of the earliest steps of atherogenesis, results in increased adhesiveness and permeability of endothelium for leukocytes [5]. Binding and recruitment of circulating leukocytes to the vascular endothelium and their further migration into the subendothelial spaces are mediated through a diverse family of cellular adhesion molecules (CAM) [5]. E-selectin and P-selectin mediate initial rolling of leukocytes along the endothelium and intercellular adhesion molecule -1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1) play important roles in the firm attachment and transendothelial migration of leukocytes [6]. Moreover, the endothelium is pivotal in the control of hemostasis and thrombosis because it is primary source of many of the major hemostatic regulatory molecules, such as von Willebrand factor (vWF) or thrombomodulin

Table 1. **Demographic and biochemical characteristics of healthy controls and chronic kidney disease patients.**

	Controls	Non-dialysed CKD	CAPD	HD
Sex, M/F	11/9	20/12	25/24	15/10
Age, years	50.94±6.50	53.19±14.52	51.92±12.56	59.28±13.28
BMI, kg/m2	26.05±3.73	25.21±3.55	25.18±4.16	24.04±3.43
Hematocrit, %	42.07±3.04	32.46±6.32***	36.71±4.73***††	32.98±4.46***^
White blood cells, x109/L	5.86±1.01	6.59±2.27	6.54±2.05	5.43±1.28
Total cholesterol, mmol/L	4.79±7.04	5.49±1.41	5.48±1.16	4.63±1.23
HDL-cholesterol, mmol/L	1.44±0.32	1.39±0.38	1.41±0.45	1.25±0.31
LDL-cholesterol, mmol/L	2.93±0.66	2.76±0.58	3.37±0.98	2.74±1.14
Triglycerides, mmol/L	0.81 (0.43-1.68)	2.38 (0.68-6.80)***	1.77 (0.69-3.3)***†	1.15 (0.40-2.40)###
Total protein, g/l	70.2±4.9	62.4±11.4	65.0±5.9	68.2±4.6###^
Albumin, µmol/l	644.8±136.2	454.9±84.0***	498.5±71.0***	546.3±50.7*##
Creatinine, µmol/L	95.5± 17.7	402.2± 209.5***	516.3± 342.1***†	752.3±205.9 ***###^^
Hs CRP, µg/ml	0.75 (0.1-10.89)	4.49 (0.1-47.0)***	3.28 (0.1-46.0)**	7.56 (0.1-68.0)***^
SBP, mmHg	126.22±10.18	135.53±11.51	130.27±20.28	134.80±24.29
DBP, mmHg	80.83±6.24	85.86±5.86	82.27±13.05	82.80±12.08
Smokers,%	12	28	25	32
Cardiovascular disease, %		38	49	52
Angiotensin-converting enzyme inhibitors, %		54	49	44
Calcium channel antagonists, %		63	43	66
β-blockers, %		55	41	42
α-blockers, %		9	8	16
EPO treatment, %		-	59	80
EPO, U/kg body weight/week		-	61.81±38.67	96.54±37.08^^

*p<0.05, **p<0.01, ***p<0.001 controls versus patients; ^p<0.05, ^^p<0.01 CAPD versus HD; †p<0.05, ††p<0.01 CAPD versus non-dialysed CKD; #p<0.05, ###p<0.001 HD versus non-dialysed CKD

Data are shown as mean±SD or median (range) depending on their normal or skewed distribution. BMI = Body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, EPO = erythropoietin, Hs CRP = high sensitivity C-reactive protein

(TM) [7]. The plasma levels of these factors are increased in ESRD patients [4,8,9] and are associated with a marker of preclinical atherosclerosis – carotid intima-media thickness (IMT) in hemodialysed (HD) patients [4].

Recently, it has been postulated that proinflammatory cytokine – interferon γ may be crucially involved in the pathogenesis of atherosclerosis and CVD in general population. Interferon-γ, which is released by activated T-lymphocytes, can stimulate the activity of indoleamine 2.3-dioxygenase (IDO) [10]. This enzyme, by degradation of tryptophan to kynurenine (KYN) [11], induces the kynurenine pathway activation and the production of different metabolites *(Fig. 1)*. Our previous studies demonstrated the accumulation of plasma KYN pathway metabolites both in experimental chronic renal failure [12,13] and in uraemic patients [14]. However, their contribution to vascular physiology and pathology both in general population and in uraemia was still not recognized. More recently, we demonstrated for the first time that some KYN metabolites, particularly 3-hydroxykynurenine (3-HKYN) and quinolinic acid (QA), are associated with increased oxidative stress, inflammation, cardiovascular disease (CVD) prevalence and atherosclerosis in end-stage renal disease patients [15,16]. However, to our knowledge, there are no data concerning KYN pathway activation, endothelial dysfunction and the carotid atherosclerosis in CKD patients.

The aim of the present study was therefore to examine the plasma levels of kynurenines; circulating forms of CAM, vWF and TM concentrations which have been implicated as markers of endothelial cell dysfunction and intima-media thickness (IMT), an early reflection of the systemic atherosclerosis in the population of 32 patients with CKD on conservative treatment (non-dialysed CKD), 49 patients on continuous ambulatory peritoneal dialysis (CAPD) and 25 on maintenance hemodialysis (HD).

MATERIAL AND METHODS

Subjects

One hundred six patients were enrolled in the study *(Tab. 1)*. All patients were clinically stable and free of active infections and autoimmune diseases. None of the patients received immunosuppressive treatment, lipid-lowering agents, non-