Clinica Chimica Acta 447 (2015) 55–58

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Glycocalyx injury in adults with nephrotic syndrome: Association with endothelial function

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ARTICLE INFO

Article history:
Received 4 February 2015
Received in revised form 21 May 2015
Accepted 22 May 2015
Available online 28 May 2015

Keywords:
Glomerulopathy
Endothelium
Syndecan-1

ABSTRACT

Background: Glomerulopathy is a group of diseases that affect mainly young adults. Endothelial dysfunction, atherosclerosis, and increased cardiac mortality can complicate the evolution of such patients. However, there is no study evaluating endothelial glycocalyx in this pathology.
Methods: This cross-sectional study included 49 patients with untreated primary nephrotic syndrome that were otherwise healthy. In addition to routine laboratory measurements, syndecan-1, intercellular adhesion molecule-1 (ICAM-1), and e-selectin were measured. Moreover, flow-mediated dilation (FMD) was used as the main endothelial function surrogate.
Results: Of the 49 patients with nephrotic syndrome, 25 (51.0%) were females. The mean age of patients was 39.0 ± 12.1 y. FMD was reduced in nephrotic patients in comparison with controls (3.7 ± 1.7 vs. 6.6 ± 1.1%, $p < 0.001$). Nephrotic patients had higher levels of ICAM-1 (616.6 ± 219.7 vs. 356.9 ± 102.0 ng/ml, $p < 0.001$) and syndecan-1 (180.3 ± 64.1 vs. 28.2 ± 9.8 ng/ml, $p < 0.001$). No significant difference was observed regarding e-selectin (129.9 ± 54.2 vs. 120.2 ± 61.5 ng/ml, $p = 0.489$). After adjusting for age and glomerular filtration rate, syndecan-1 was significantly associated with 24-h urinary protein excretion, LDL-cholesterol, HDL-cholesterol, and triglycerides. While age, LDL-cholesterol, and 24-h urinary protein excretion were associated with FMD in the multivariate analysis, when syndecan-1, ICAM-1, and e-selectin were added to the model, only syndecan-1 was independently associated with FMD.
Conclusions: We demonstrated that syndecan-1, a marker of endothelial glycocalyx damage, is increased in patients with nephrotic syndrome and near-normal renal function. Moreover, we determined its association with nephrotic syndrome features and suggest it can have a role in the endothelial dysfunction of these patients.
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1. Introduction

Glomerulopathy is a group of diseases that affect mainly young adults between 20 and 40 y. Patients with nephrotic syndrome generally present with important edema, lipid alterations, hypoalbuminemia, and possible loss of renal function [1]. The primary alteration in nephrotic syndrome is a loss of the glomerular filtration barrier (consisting of glomerular endothelium, glomerular basement membrane, and podocytes). One major damaged component of filtration barrier in nephrotic syndrome is the podocyte. Podocytes are highly differentiated epithelial cells that form a complex molecular network known as the slit diaphragm. It is pivotal for maintaining the size-selective nature of the glomerular filtration barrier [2].

Nephrotic patients have increased relative risk of cardiovascular infarction, resulting in an almost threefold increase in cardiac mortality [3]. It is a widely held view that impaired endothelial function is the initial step in atherogenesis, which is largely responsible for ischemic heart disease and thrombotic strokes occurring decades later [4]. Additionally, endothelial dysfunction has been recognized in adult nephrotic patients [5]. Moreover, the endothelial dysfunction in these patients was correlated with levels of low-density lipoprotein (LDL) cholesterol, which improved after statin therapy [6].

Glycocalyx, an approximately 1-μm-thick carbohydrate-rich structure with antiadhesive and anticoagulant properties that protects the endothelium and maintains vascular barrier function [7], has never been studied in nephrotic patients. The roles of glycocalyx include maintenance of the vascular permeability barrier, mediation of shear-stress-dependent nitric oxide production, and housing vascular protective enzymes (for example, superoxide dismutase), as well as housing a wide array of coagulation inhibition factors, such as antithrombin, the protein C system, and tissue factor pathway inhibitor [8]. Glycocalyx also modulates the inflammatory response by preventing leukocyte adhesion and by binding to several ligands, including chemokines, cytokines, and growth factor [9, 10].

Although not clearly evaluated, some authors postulate that glycocalyx injury can be the first step in endothelial dysfunction and

http://dx.doi.org/10.1016/j.cca.2015.05.013
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subsequent atherothrombotic process [11]. Syndecan-1 is a member of a conserved family of 4 heparan- and chondroitin-sulfate–containing transmembrane HSPGs (syndecans 1 to 4), being expressed on epithelial cells, endothelial cells, and leukocytes and seems to play a role in tumorigenesis [12]. Also, a previous study demonstrated that podocytes can produce syndecan-1 [13]. Because of its expression in the endothelial and podocyte components of the filtration barrier, syndecan-1 has a role in nephrotic syndrome, as demonstrated in animal studies [13].

When measured in the blood plasma, syndecan-1 is a biomarker of endothelial glycocalyx damage, and it is increased in patients with marked reduction in glomerular filtration rate (GFR), correlating with markers of endothelial dysfunction [14]. However, its role as a biomarker in nephrotic patients is unknown. Additionally, there is no study evaluating whether glycocalyx damage correlates with endothelial dysfunction in nephrotic syndrome.

2. Methods

2.1. Subjects

This is a cross-sectional study performed from January through August 2014. Adult patients (age > 18 y) with nephrotic syndrome and renal biopsy indication by the assistant physician were included. Nephrotic syndrome diagnosis was performed when patients had 24-h urinary protein excretion >3.5 g/24 h/1.73 m^2, edema, hypoalbuminemia, and elevated serum lipids. Patients with significant reduction in renal function (glomerular filtration rate <60 ml/min) were not included. GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [15].

Subjects with cardiovascular disease, diabetes, hypothyroidism, liver disease, alcoholism, postural hypotension, concurrent diseases, and significant psychiatric disorders were excluded. Also, patients receiving statin therapy were excluded. Patients receiving angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, diuretics, or any other antihypertensive drugs were not excluded, as these constitute the best clinical practice. All renal biopsies were indicated after consultation with an independent nephrologist.

Because some biomarkers do not have an established normal range, a control group was included. The control group comprised subjects with no renal disease or significant comorbidity that were recruited from the community. Subjects were studied while off lipid-lowering drugs and aspirin.

Blood samples and vascular function studies of the brachial artery and forearm microcirculation were carried out in the morning after a 12-h fasting from food and beverages and after resting in the supine position for at least 15 min. Smoking was not allowed on the day of the test. The Institutional Ethical Committee approved this study, and patients signed the informed consent term prior to enrollment.

2.2. Flow-mediated dilatation

Flow-mediated dilation (FMD) was assessed in all subjects noninvasively by B-mode high-resolution ultrasound imaging (Medison CO Ltd.) according to current guidelines [16]. Briefly, each patient remained in a quiet, temperature-controlled room and rested for 20 min before any measurement was performed. A 7.0-MHz linear array transducer was used to measure the diameter of the right brachial artery at end-diastole using electronic calipers. After a baseline measurement, a cuff fitted distally to the brachial artery was inflated, altering arterial flow for 5 min. The brachial artery was scanned continuously for 60–90 sec after cuff deflation and the vessel's maximal diameter was defined (diameter during reactive hyperemia). FMD was calculated as the percent of change in the artery's diameter. Intra-observer variability for brachial diameter measurements for the researcher was 0.05 ± 0.12 mm. At the end of the protocol, images were obtained again 4 min after sublingual nitroglycerin (0.4 mg) for measurement of endothelium-independent dilatation.

2.3. Laboratory measurements

Blood samples were collected into tubes containing ethylenediaminetetraacetic acid (EDTA). These samples were immediately processed and frozen at −80 °C for later measurement of syndecan-1, intercellular adhesion molecule-1 (ICAM-1), and e-selectin. Syndecan-1 was measured as a biomarker of endothelial glycocalyx damage a using commercially available enzyme-linked immunosorbent assay kit (Abcam). Intercellular adhesion molecule-1 (ICAM-1), a marker of endothelial cell activation, was measured using a commercially available enzyme-linked immunosorbent assay kit (Life Technologies). Moreover, e-selectin was measured using a commercially available enzyme-linked immunosorbent assay kit (Abcam).

Moreover, medical records were retrieved to assess laboratory data at the time of the kidney biopsy and the last evaluation prior to study inclusion. Laboratory data included an assessment of serum creatinine, serum urea, serum albumin, total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein (HDL) cholesterol, triglycerides, and 24-h urinary protein excretion rate.

2.4. Statistical analysis

Descriptive statistics are expressed as mean ± SD or absolute numbers as appropriate. All variables were tested for normal distribution using the Kolmogorov–Smirnov test. Student's *t*-test was applied to compare means of continuous variables and normal distribution data between patients and the control group.

Partial Pearson's correlation coefficients (r) were used to determine adjusted correlations between the analyzed variables. Subsequent multiple linear regression modeling was used to determine which variables that were significant in the univariate analysis were independently associated with FMD. Two models for FMD were determined separately. In the second model, we added all endothelial and glycocalyx biomarkers: ICAM-1, e-selectin, and syndecan-1. Backwards elimination was performed, and variables (interaction terms and predictors) that

Table 1
Clinical and biomarker characteristics of control subjects and patients.

	Glomerulopathy patients (n = 49)	Controls (n = 25)	p
Age (years)	39.0 ± 12.1	38.5 ± 9.6	NS
Gender (M/F)	24/25	11/14	NS
Renal biopsy diagnosis			
FSGS/ML	23	–	–
MN	09	–	–
IgAN	06	–	–
MPGN	03	–	–
Others	08	–	–
Serum creatinine (mg/dl)	1.1 ± 0.3	0.82 ± 0.1	<0.001
Serum urea (mg/dl)	62.8 ± 28.0	36.2 ± 11.2	<0.001
GFR (ml/min/1.73 m^2)	72.3 ± 13.4	107.4 ± 9.6	<0.001
Serum albumin (g/dl)	2.69 ± 0.86	4.06 ± 0.32	<0.001
Total cholesterol (mg/dl)	286.1 ± 98.4	183.4 ± 26.7	<0.001
LDL-cholesterol (mg/dl)	180.2 ± 80.9	86.0 ± 16.5	<0.001
HDL-cholesterol (mg/dl)	67.3 ± 20.6	50.6 ± 9.5	<0.001
Triglycerides (mg/dl)	254.4 ± 114.2	134.7 ± 27.0	<0.001
24-h urinary protein excretion (g/1.73 m^2)	5.5 ± 2.4	0.09 ± 0.01[a]	<0.001
Flow-mediated dilatation (%)	3.7 ± 1.7	6.6 ± 1.1	<0.001
ICAM-1 (ng/ml)	616.6 ± 219.7	356.9 ± 102.0	<0.001
e-selectin (ng/ml)	129.9 ± 54.2	120.2 ± 61.5	NS
Syndecan-1 (ng/ml)	180.3 ± 64.1	28.2 ± 9.8	<0.001

FSGS: focal and segmental glomerulosclerosis; ML: minimal lesions; MN: membranous nephropathy; IgAN: IgA nephropathy; MPGN: membranoproliferative glomerulonephritis.
[a] n = 13 for control group.

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