Lencovsky *et al. Artery Research* (2023) 29:73–78
https://doi.org/10.1007/s44200-023-00034-4

Artery Research

RESEARCH ARTICLE

Open Access

Patients with CKD Secondary to Glomerular Disorders have Lower Arterial Stiffness, as Compared to Hypertensive and Diabetic CKD

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Abstract

Background Chronic kidney disease (CKD) manifested as reduced GFR and/or albuminuria, has been known to accelerate arterial stiffness and early vascular aging (EVA). Diabetes, hypertension, and glomerular disorders are the leading causes of CKD and renal failure.

The question which etiology contributes more to this vascular phenomenon-hypertensive and diabetic CKD or CKD secondary to immune-mediated glomerulonephritis—remained unclear.

Objective To compare pulse wave velocity (PWV), a marker of arterial stiffness, between CKD patients of different etiologies: hypertensive and diabetic nephrosclerosis. vs. CKD secondary to glomerular disorders.

Methods Clinical data were collected on 56 patients followed at the Nephrology and Hypertension Institute in Samson Assuta Ashdod University Hospital. All patients had at least one visit at our Nephrology clinics prior to recruitment. All patients with a glomerular disorder had a clinical-pathological diagnosis based on a recent kidney biopsy.

Pulse wave velocity (PWV) was measured using a validated Sphygmocor XCEL® device. Univariate and multivariate analyses were performed to compare PWV between hypertensive/diabetic CKD and CKD secondary to glomerular disorders.

Results PWV was significantly higher in the hypertensive/diabetic CKD group, compared to the CKD-GN group, with an average of. 12.2 m/s vs 8.3 m/s, respectively ($p < 0.001$).

In a multivariate linear regression model, having CKD secondary to glomerulonephritis was associated with a significantly lower PWV ($B = -3.262$, $p < 0.001$), compared with CKD secondary to hypertension and diabetes, with adjustment of age, creatinine, and comorbidities.

Conclusion CKD Patients secondary to glomerulonephritis, have lower PWV when compared to CKD patients with diabetes and/or hypertension, even after adjusting for age, renal function, and the presence of comorbidities. It is intriguing to further study the possible protective role of immunosuppression on the arterial properties of CKD patients.

Keywords CKD, Glomerulonephritis, Pulse wave velocity, Aortic stiffness, Inflammation

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1 Introduction

Arterial stiffness refers to a pathological process in which continuous and intermittent distention of the aorta with each heartbeat and during lifespan causes fatigue and fracture of the elastin fibers, and accumulation of collagen, leading to increased stiffening and decreased elasticity of the aorta's wall [1]. The stiffer the artery, the higher the pressure wave speed, which results in increased pulse wave velocity (PWV) [2].

Aging (normal or accelerated) as well as high blood pressure (BP) [3] are the main determinants of the decline in arterial wall elasticity. Additional associated contributors are hyperlipidemia, diabetes mellitus (DM) and chronic kidney disease (CKD) [4–6].

During the development and progression of CKD, the aortic compliance decreases, reducing systolic volume (SV) buffering capacity, resulting in an exaggerated increase of the systolic blood pressure (SBP) and a drop in diastolic blood pressure (DBP) [6].

The most common causes of CKD leading to renal failure are poorly controlled diabetes, uncontrolled hypertension, and a variety of glomerular disorders [7]. While the effect of hypertension and diabetes on arterial stiffness is quite established, autoimmune dysregulation, underlying most glomerulopathies, was not considered, until recently, as an accelerator of early vascular aging (EVA). However, a recent association was found between increased arterial stiffness and chronic inflammatory states such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), psoriatic arthritis, Crohn's disease etc. [8, 9].

CKD secondary to glomerular disorders (CKD-GN), due to the known natural course of the diseases, is characterized by immune dysregulation, treatment with different immunosuppressive drugs, and a relapsing and remitting course [10]. It is quite different from the low grade, persistent inflammatory milieu of diabetic and hypertensive CKD. The effects of these unique characteristics on arterial wall remodeling were not fully studied.

In this study, we measured pulse wave velocity (PWV, m/sec), a validated marker of arterial stiffness, in CKD secondary to glomerular disorders (CKD-GN) compared with that of CKD secondary to hypertension or diabetes (CKD- HTN/DM).

2 Methods

Fifty-six patients were enrolled in our study. According to the definition of CKD, all patients recruited had either estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 or urinary albumin to creatinine ratio (uACR) ≥ 30 mg/gram, persistent over more than 3 months [7].

We compared CKD due to hypertension and/or diabetes (CKD-HTN/DM) with CKD secondary to glomerulopathies (CKD-GN). All patients had at least one visit at our Nephrology clinics prior to recruitment. CKD (GN) patients had a clinico-pathological diagnosis based on a kidney biopsy done at our institute within 3 years prior to study recruitment. Patients in this group had multiple glomerular disorders as the etiology for their CKD. Patients with HTN or DM-related CKD had been formally diagnosed by a nephrologist with a clinical diagnosis of essential hypertension, hypertensive nephrosclerosis, benign nephrosclerosis, diabetic nephropathy, or diabetic kidney disease. They were excluded if they were found to have an accompanying glomerular disease. Biopsy was not mandatory in the CKD-HTN/DM group. The CKD-GN could have hypertension or diabetes, as long as their nephropathy was clearly due to the immune mediated glomerulonephritis.

Patients with end-stage renal disease (ESRD) who were either on renal replacement therapy or had a renal transplant were excluded, as well as patients under the age of 18, and pregnant women. Patients with immune disorders, whose primary disease was extra-renal (skin, joints, intestine, nerves) were also excluded.

Data was collected from patients' EMRs (electronic medical records). Data included demographic details, comorbidities, year of diagnosis, chronic medications, updated blood and urine test results etc. Each patient underwent a full physical examination, brachial blood pressure measurement by an automated oscillometric device, and a non-invasive central (aortic) blood pressure measurement (PWA—Pulse Wave Analysis) using applanation tonometry based Sphygmocor® XCEL device (Atcor Medical, Sydney, Australia).

Patients were supine at rest. Three brachial blood pressure measurements were automatically recorded, and the average brachial value was reported as well as the central blood pressure. To determine the carotid–femoral PWV, the pulse wave was recorded simultaneously at the femoral artery (using a unique BP cuff over the thigh) and at the carotid artery by a tonometer probe. The distance between the neck (at the palpated carotid pulse) and the upper edge of the thigh cuff was measured and 80% of this distance was automatically reported (direct measurement) [11].

The study was approved by Samson Assuta Ashdod Hospital's IRB, and all patients signed an informed consent.

2.1 Statistical Analysis

The dependent variable was PWV measured by meter/sec. Univariate analysis was performed to compare the groups' background characteristics and laboratory

findings (patients with CKD-GN vs. patients with CKD- HTN/DM). All categorical variables are presented as numbers and frequencies (%). Most continuous variables were not normally distributed and therefore presented as median (IQR). The distribution of PWV in both groups was normal. We used the Mann–Whitney U test to examine the relationship between quantitative independent variables and glomerular disease. We used the chi-square test to examine the relationship between nominal independent variables and glomerular disease (no corrections were needed). A univariate linear regression model was used to determine the effect of independent parameters associated with glomerular disease on PWV. Parameters were then selected for the multivariate analysis based on their level of significance (p-value < 0.2), their clinical significance, and the confounding potential of the main comparison in the study.

3 Results

The study included fifty-six patients, thirty-one of whom were in the CKD-GN group and 25 in the CKD-HTN/DM group (Table 1).

Figure 1 presents the different etiologies in the CKD-GN group, the most common being IgA nephropathy 52%) and membranous nephropathy (19%).

Twenty-one of the 56 subjects (37.5%) were females. The median age was 52.5 (IQR 37–67). The CKD-GN group patients were younger than the CKD-HTN/DM patients (41 vs. 67 years old, p < 0.001) and had fewer comorbidities (Table 1).

Both groups had similar diastolic BP values, both brachial and central (p value = 0.95). Patients in the CKD-HTN/DM group had an elevated brachial systolic BP compared to CKD-GN-147 mmHg vs. 123 mmHg (p = 0.0011) (Table 2). Interestingly, central (aortic) BP as measured by Pulse Wave Analysis (PWA) was not significantly different between groups (132 mmHg vs 119 mmHg, p = 0.23).

Table 1 Epidemiological characteristics in the study group and the control group

	All subjects (n = 56, 100%)	CKD-GN (n = 31, 55.4%)	CKD-HTN/DM (n = 25, 44.6%)	p value
Age (years) median (IQR)	52.5 (37–67)	41 (28–52)	67 (58.5–75)	< 0.001[a]
Gender (female) n (%)	35 (62.5%)	20 (64.5%)	15 (60%)	0.729[b]
BMI (KG/M2) median (IQR)	27.8 (25.3–30.6)	26.9 (22.3–28.4)	30.5 (28.1–32.5)	< 0.001[a]
Glucose (MG/DL) median (IQR)	102 (94–123)	96 (89–103)	118.5 (102–146.9)	< 0.001[a]
HBA1C (%) median (IQR)	5.6 (5.3–6.4)	5.4 (5.2–5.6)	6.2 (5.6–7.2)	0.003[a]
LDL (MG/DL) median (IQR)	94.5 (75.5–135.5)	128.4 (94.5–150.3)	82.6 (71–106.5)	0.003[a]
Triglycerides (MG/DL) median (IQR)	126 (90.5–190)	105 (78.8–136.5)	155 (109–234)	0.002[a]
Albumin (MG/DL) median (IQR)	3.9 (3.7–4.3)	3.9 (3.6–4.3)	4 (3.8–4.4)	0.367[a]
Hemoglobin level (MG/DL) median (IQR)	12.7 (11.1–13.7)	12.9 (11.4–13.7)	12.6 (10.5–14.2)	0.936[a]
Creatinine (MG/DL) median (IQR)	1.26 (0.9–1.6)	1.1 (0.9–1.4)	1.4 (1.2–1.7)	0.056[a]
GFR median (IQR)	50 (38.2–90)	86 (45.8–106.8)	42 (37–53)	0.002[a]
Urine protein-creatinine ratio (PCR) MEDIAN (IQR)	653.1 (193.5–1104)	733.7 (416–1227.8)	345.1 (131.2–759.5)	0.119[a]
Urine albumin-creatinine ratio (ACR) median (IQR)	94.1 (26.4–300)	137.1 (34.9–316.8)	94.1 (22.8–225.8)	0.314[a]
Urine protein median (IQR)	300.7 (177.3–852.9)	277.5 (176.8–870.3)	337.7 (155.6–856)	0.975[a]
Smoking n (%)	12 (22.6%)	4 (13.3%)	8 (34.8%)	0.064[b]
Diabetes mellitus n (%)	17 (30.4%)	2 (6.5%)	15 (60%)	< 0.001[b]
Hypertension n (%)	30 (60%)	10 (38.5%)	20 (83.3%)	0.001[b]
Raas inhibitors n (%)	34 (69.4%)	18 (72%)	16 (66.7%)	0.686[b]
Calcium channel blockers n (%)	15 (30.6%)	4 (16%)	11 (45.8%)	0.024[b]
Beta blockers n (%)	17 (34.7%)	3 (12%)	14 (58.3%)	0.001[b]
Diuretics n (%)	14 (28.6%)	2 (8%)	12 (50%)	0.001[b]
Alpha blockers n (%)	8 (16.3%)	2 (8%)	6 (25%)	0.108[b]
Statins n (%)	27 (55.1%)	8 (32%)	19 (79.2%)	0.001[b]
Drug treatment for diabetes n (%)	16 (32.7%)	2 (8%)	14 (58.3%)	< 0.001[b]
Treatment for dyslipidemia n (%)	24 (51.1%)	11 (47.8%)	13 (54.2%)	0.664[b]

IQR interquartile range, *BMI* body mass index, *HbA1C* hemoglobin A1C, *LDL* low-density lipoprotein cholesterol, *GFR* glomerular filtration rate, *RAAS* renin–angiotensin–aldosterone system

[a] Mann–Whitney test U

[b] χ^2 test

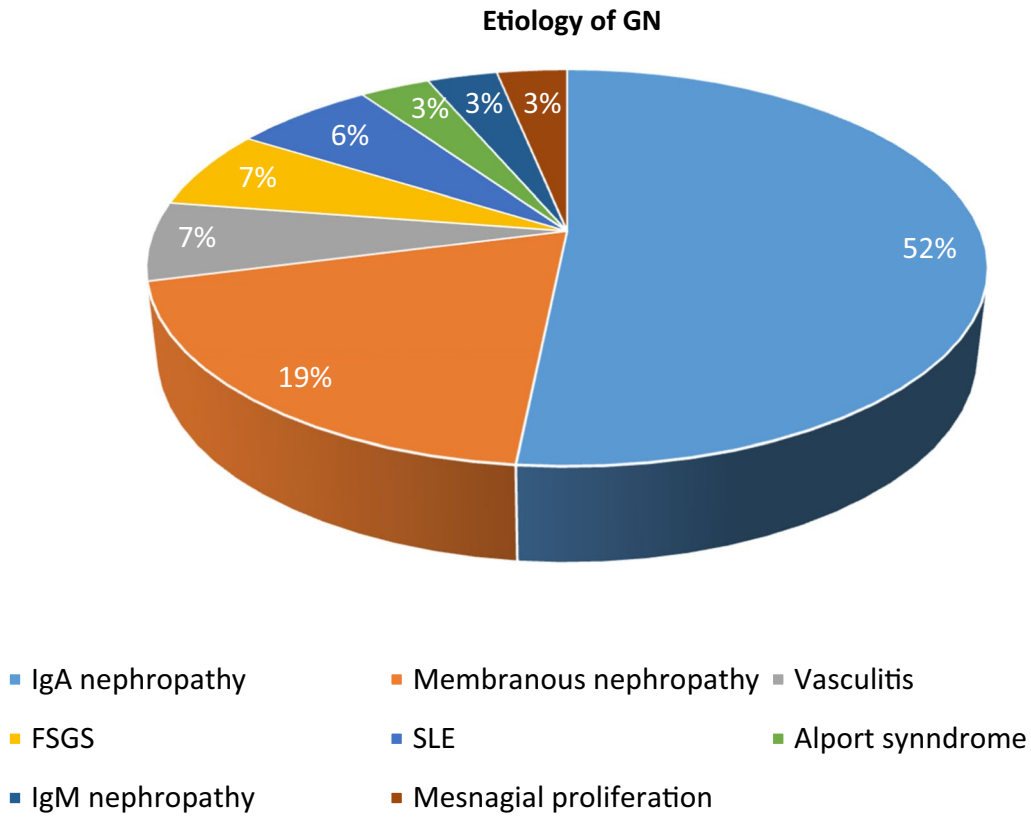

Fig. 1 Etiologies of Glomerulonephritis. This pie chart describes the frequency (by percentages) of the different etiologies of glomerulonephritis in the CKD-GN group. *FSGS* focal segmental glomerulosclerosis, *SLE* systemic lupus erythematosus

Table 2 Brachial blood pressure, Central (Aortic) blood pressure and Pulse Wave Velocity (PWV) in both CKD-GN and CKD-HTN/DM groups

	All subjects (n = 56, 100%)	CKD-GN (n = 31, 55.4%)	CKD- HTN/DM (n = 25, 44.6%)	p value[a]
Arterial stiffness (PWV), (ms) Median (IQR)	10 (7.9–12.1)	8.3 (7.2–10)	12.2 (10.5–13.6)	**< 0.0011**
Systolic brachial BP, (mmHg) Median (IQR)	134 (121–152)	123 (118–131)	147.5 (134.3–163)	0.0011
Diastolic brachial BP, (mmHg) Median (IQR)	76 (67–85)	76 (67–83)	75.5 (66.8–87.3)	0.9581
Central systolic BP, (mmHg) Median (IQR)	127.5 (107–148.5)	119 (103–146)	132 (116.5–151)	0.2281
Central diastolic BP, (mmHg) Median (IQR)	76 (70–87)	76 (71–84)	76 (68.5–88.5)	0.9491

PWV pulse wave velocity, *IQR* interquartile range, *BP* blood pressure

[a] Mann-Whitney U test

P < 0.05 in bold

Patients with CKD- GN were found to have a significantly lower PWV as compared with CKD-HTN/DM patients—8.3 m/s vs. 12.2 m/s, respectively (p < 0.0001, Table 2).

The univariate linear regression models are summarized in Table S1. Variables that had the most noticeable effects on PWV were age (B = 0.111, 95%CI = 0.069–0.152, p < 0.001), presence of diabetes mellitus (B = 3.058, 95%CI = 1.201–4.915, p = 0.002) and eGFR (B = − 0.048, 95%CI = − 0.077–0.018, p = 0.002).

In a multivariate model adjusted for age, comorbidities (diabetes, hypertension), and creatinine levels—only the presence of CKD-GN and age were found to be significant variables (p = 0.006 and p = 0.039 accordingly;

Table 3 A multivariate linear regression analysis—factors associated with PWV ($P < 0.05$ in bold)

Variable	B	Beta	P value	95%CI	
Glomerular disease	− 3.262	− 0.489	**0.006**	− 5.531	− 0.993
Age (years)	0.063	0.351	**0.039**	0.003	0.123
Diabetes	− 0.379	− 0.054	0.689	− 2.331	1.574
Hypertension	− 1.435	− 0.211	0.131	− 3.313	0.443
Creatinine (mg/dl)	0.775	0.210	0.083	− 0.106	1.656

Table 3). No collinearity was found between the independent variables (using Spearman correlation with a cutoff of $r < 0.6$). No interactions between the independent variables were detected. According to this model, CKD-GN was associated with lower PWV compared with CKD- HTN/DM (B = − 3.262, 95% CI − 5.531 to − 0.993, $p < 0.001$).

4 Discussion

In this study, we found that patients with CKD secondary to glomerular disorders have a PWV which is far less than that of CKD of diabetic/hypertensive origin (8.3 m/s vs. 12.2 m/s).

Laurent et al. and The Reference Values for Arterial Stiffness' Collaboration published reference values of PWV stratified by age and blood pressure categories [12, 13]. People at an age range of 60–69 years and stage I hypertension (thus comparable to our CKD-HTN/DM group) had a median PWV of 10.7 m/sec. A median value of 12.2 m/sec, as in our hypertensive and diabetic CKD group is significantly higher.

In the CKD-GN group (median age 41, median brachial systolic BP 123 mmHg) we have measured a median PWV of 8.3 m/sec, somewhat higher than that of age and BP matched reference values of 7.4 m/sec [13], but still significantly lower than the arterial stiffness observed in our CKD-HTN/DM group.

Being a marker of arterial stiffness, our study confirms the well-known connection between CKD and early vascular aging [13]. Moreover, our study demonstrates, regarding the effects on large arteries, that not all CKD is the same; When assessing CKD of different etiologies and their impact on vascular structure and function, CKD secondary to diabetes and hypertension is a very low-grade, chronic inflammatory state leading to the aforementioned changes in the vascular structure of the great arteries and slow gradient increase in the arterial stiffness [14].

Accumulation of advanced glycation end products (AGEs), due to increased production and decreased elimination occurs even in non-diabetic CKD. AGEs, together with high sodium load, uric acid, phosphate (and accompanying hormones such as PTH, fetuin-A, klotho and FGF23), angiotensin II, aldosterone, asymmetric dimethylarginine (ADMA), endothelin-1, increased sympathetic activity and baroreflex dysfunction- all cause an interplay of events leading to oxidative stress, endothelial dysfunction, increased vascular tone, inflammation and vascular calcification [15].

One might speculate, looking at our results, that among CKD patients with rheumatological and immunological disorders, this interplay of events is somewhat different.

Our group had previously published a study on colchicine-treated Familial Mediterranean Fever (FMF) patients. We have demonstrated that they had PWV values similar to healthy controls, suggesting a favorable outcome of intermittent, waxing and waning inflammation, as opposed to chronic, low-grade, inflammation. We also suggested that colchicine could have a protective role on arterial structure and function [16].

Similar findings were demonstrated in a study that compared patients with IgA nephropathy, the most common type of glomerulonephritis (GN), to polycystic kidney disease (PKD) and controls. In this study, arterial stiffness in both groups was higher than in the control group. However, a pre-specified subgroup analysis demonstrated IgA nephropathy patients to have lower PWV than the PKD group [17].

IgA nephropathy, just like FMF, is a disease with intermittent inflammation rather than the classical chronic low-grade inflammatory state of diabetic or hypertensive CKD. And it is therefore safe to assume that PWV should act in a similar way [18].

In a study by Karras et al. on 161 consecutive renal transplant patients, mean PWV decreased from 10.8 m/sec in the third month post-transplant to 10.1 m/sec after 12 months ($p < 0.001$), interestingly there was no relation between vascular function improvement and GFR [19].

It is possible that immunosuppressive treatment (prednisone, colchicine, post-transplant immunosuppression) interferes with the inflammatory milieu in CKD, which is the cornerstone of arterial stiffening. Since patients in our GN group had previously been on different immunomodulatory drugs, it can possibly explain the low values of PWV seen in our CKD-GN group.

Our study's main limitations are a small sample size as well as baseline differences between groups. For that reason, we used a multivariate regression model, that took into account the main possible confounders (age, presence of diabetes, presence of hypertension and CKD severity). Still, residual confounders are always a possibility. Another limitation is the lack of accurate data on multiple immunomodulatory and immunosuppressive treatments given to our CKD-GN patients during the course of their disease. Pulse was not documented during

measurements and therefore we could not address the possible SBP amplification.

The strengths of our study are the accurate histological diagnosis of our GN patients, which had recent kidney biopsies done at our institute, as well as comprehensive clinical and laboratory data on all patients.

In conclusion, our study suggests that CKD secondary to immune-mediated GN carries a lower risk of early vascular aging and stiffening, as compared to CKD related to hypertension and diabetes. Since cardiovascular morbidity and mortality are the main burden of disease in CKD patients, further study is needed to delineate the exact mechanisms underlying such vascular protection.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s44200-023-00034-4.

Below is the link to the electronic supplementary material.Supplementary file1 (DOCX 21 KB)

Author Contributions

OL: author of the article, AAA: Scientific editing, EG: Data collection. RTBI: Statistical analysis, MA: patients' enrollment and data collection, OK: patients enrollment and data collection, AL: Head of the nephrology department in Assuta Ashdod, scientific editing, statistical analysis.

Funding

No funding was provided.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflicts of Interest

The authors have no conflicts of interest to declare.

Ethical Approval and Consent to Participate

The study was approved by Samson Assuta Ashdod Hospital's IRB, and all patients signed an informed consent.

Consent for Publication

Not applicable.

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Received: 17 April 2023 Accepted: 23 May 2023
Published online: 6 June 2023

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