ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Cardiac Autonomous Functions in Patients with Chronic Glomerulonephritis

Kronik Glomerülonefrit Hastalarında Kardiyak Otonom Fonksiyonların Değerlendirilmesi

Burcu Cakir[1], Gokay Taylan[2], Ilhan Kurultak[3], Sedat Ustundag[3]

[1]Cardiology Department, Turhal State Hospital, Tokat; [2]Department of Cardiology; [3]Department of Nephrology, Trakya University Hospital, Edirne, Türkiye

ABSTRACT

Aim: *Our study aims to investigate the presence of autonomic dysfunction, which is one of the important causes of cardiovascular mortality, by evaluating heart rate variability and heart rate turbulence in patients with chronic glomerulonephritis*

Material and Methods: *In this case-control study, 42 individuals with chronic glomerulonephritis classified as stage 1–3 chronic kidney disease and 102 age- and sex-matched healthy subjects were compared in terms of heart rate variability and heart rate turbulence. Subgroup analyses were performed by dividing the patient group into nephrotic and nephritic syndrome subgroups. p<0.05 was accepted as significant.*

Results: *In the glomerulonephritis group, significant decreases were observed in heart rate variability parameters, indicating that cardiac autonomic functions changed in favor of sympathetic activation. When subgroup analysis was performed, it was observed that the decrease in the parameters representing parasympathetic activation of heart rate variability continued in the nephritic syndrome group.*

Conclusions: *This study demonstrated that autonomic dysfunction characterized by parasympathetic suppression and sympathetic activation is present in patients with chronic glomerulonephritis, even in the early stages of chronic kidney disease.*

Key words: *glomerulonephritis, cardiac autonomic function, heart rate variability, heart rate turbulence*

ÖZET

Amaç: *Çalışmamızın amacı, kronik glomerülonefrit hastalarında, kalp hızı değişkenliği (KHD) ve kalp hızı türbülansı (KHT) değerlendirmesiyle, kardiyovasküler mortalitenin önemli nedenlerinden birisi olan otonom disfonksiyon varlığının araştırılmasıdır.*

Gereç ve Yöntem: *Bu vaka-kontrol çalışmasında evre 1–3 kronik böbrek hastalığı (KBH) olarak sınıflandırılan 42 kronik glomerülonefritli birey ile yaş ve cinsiyet açısından eşleştirilmiş 102 sağlıklı birey KHT ve KHD açısından karşılaştırıldı. Hasta grubu nefrotik ve nefritik sendrom alt gruplarına ayrılarak alt grup analizleri yapıldı. p<0,05 anlamlı kabul edildi.*

Bulgular: *Glomerülonefrit grubunda, KHD'nin önemli parametreleri olan SDNN, SDNN endeks, rMSSD, pNN50 ve HF değerlerinde kontrol grubuyla karşılaştırıldığında anlamlı düşüş gözlendi (p=0,046, p=0,031, p=0,019, p=0,013, p=0,032, sırasıyla). Subgrup analizi yapıldığında nefritik sendrom grubunda rMSSD ve pNN50 değerlerinde istatistiksel olarak anlamlı azalmanın devam ettiği görüldü. (sırasıyla p=0,049, p=0,032)*

Sonuç: *Bu çalışma ile kronik glomerülonefritli hastalarda KBH'nin erken evrelerinde dahi parasempatik baskılanma ve sempatik aktivite ile karakterize otonomik disfonksiyonun var olduğu gösterilmiştir.*

Anahtar kelimeler: *glomerülonefrit; kardiyak otonom fonksiyon; kalp hızı değişkenliği; kalp hızı türbülansı*

Introduction

Glomerulonephritis is a group of diseases characterized by immune damage and cell proliferation in the glomerular capillaries. Although it typically follows a chronic course, it can occasionally present with acute clinical manifestations such as rapidly progressive glomerulonephritis or acute nephritic syndrome. Glomerulonephritis is classified into nephritic and nephrotic syndromes based on its pathogenesis, histopathological appearance and clinical presentation[1]. Nephritic syndrome is characterized by the presence of antigen-antibody deposits on an inflammatory basis, and its clinical manifestations include hematuria, hypertension and edema. In nephrotic syndrome, proteinuria, hypoalbuminemia, hyperlipidemia and edema occur due to non-inflammatory immune-mediated

İletişim/Contact: *Burcu Çakır, Tokat Turhal State Hospital, Cardiology Department, Tokat, Türkiye* • ***Tel:*** *0532 580 97 73* • ***E-mail:*** *burcu_cakir2@hotmail.com* • ***Geliş/Received:*** *05.01.2025* • ***Kabul/Accepted:*** *18.03.2025*

ORCID: *Burcu Çakır: 0000-0002-0190-7670 • Gökay Taylan: 0000-0002-7015-4537 • İlhan Kurultak: 0000-0001-5607-1375 • Sedat Üstündağ: 0000-0002-8502-9181*

damage where immune cells do not infiltrate the glomeruli[2,3]. Patients with chronic glomerulonephritis (CGN) –often accompanied by risk factors such as hypertension, hyperlipidemia and renal dysfunction– are considered to be at high risk for cardiovascular (CV) events[4].

Since the 1970 s, many studies have shown that impaired cardiac autonomic function in various diseases is associated with CV mortality[5–8]. In this context, studies investigating CV mortality in renal diseases have demonstrated that individuals with advanced chronic kidney disease (CKD) –including those with glomerulonephritis as the underlying etiology– exhibit impaired cardiac autonomic function[9]. However, this pathology remains unclear due to the limited number of studies focusing on patients with glomerulonephritis in the early stages of CKD.

With current technology, the most objective tests for assessing cardiac autonomic functions are heart rate variability (HRV) and heart rate turbulence (HRT). It has been shown that a reduction in these parameters plays a role in sudden cardiac death (SCD) and CV mortality[6–8], whereas an increase is beneficial for predicting atrial fibrillation[10]. Heart rate variability measures the variability in R-R intervals, which persist under controlled conditions. Time-domain indices of HRV include the standard deviation of normal to normal (NN) intervals (SDNN), standard deviations of all normal sinus NN intervals in 5-minute segments (SDNN index), the root mean square of differences between successive NN intervals (rMSSD) and percentage of adjacent NN intervals differing by more than 50 ms divided by the total number of NN intervals (pNN50). These measures are particularly useful for evaluating parasympathetic activity[11]. In contrast, frequency-domain analysis examines different spectral components: the high-frequency (HF) band reflects parasympathetic influences, while the low-frequency (LF) band includes both sympathetic and parasympathetic effects, with LF primarily serving as an indicator of sympathetic activity. The LF/HF ratio is commonly used to evaluate the balance between these two autonomic components[12]. Heart rate turbulence analyzes the autonomic modulatory response of the sinus node to a ventricular extrasystole (VES). It is assumed to consist of a combination of two neural reflexes: a baroreceptor-related increase in heart rate after a hemodynamically inefficient ventricular contraction (called TO; turbulence onset, which corresponds to the first RR interval shortening) and a reflex bradycardia resulting from increased ventricular filling which elevates arterial pressure after a compensatory pause (called TS; turbulence slope, which reflects the subsequent prolongation period)[13]. Heart rate variability and HRT are known to be the most important predictors of cardiac mortality in patients with acute myocardial infarction[7].

In this study, we aimed to investigate the presence of autonomic dysfunction, which is one of the important causes of CV mortality, in patients with CGN, which is classified within the early stages of CKD, using HRV and HRT parameters from 24-hour electrocardiographic (ECG) Holter monitoring.

Material and Methods

The study was conducted among patients who presented to the university hospital's cardiology and nephrology outpatient clinics between December 2019 and July 2022. Before the study, ethical approval was obtained from the local ethics committee (dated 28.09.2020, decision number 15/32, TÜTF-BAEK 2020/341 protocol document). The patient group (42 subjects) was selected from individuals with CGN who were followed in the nephrology outpatient clinic and had a definitive diagnosis confirmed by renal biopsy (8 patients with immunoglobulin A nephropathy, 2 with lupus nephritis, 6 with vasculitic nephropathy, 9 with membranous nephropathy, 14 with focal segmental glomerulosclerosis, and 3 with minimal change disease). Within the patient group, 16 patients were classified as having nephritic syndrome and 26 as having nephrotic syndrome, as determined in the subgroup analysis. The control group (102 subjects) was selected from individuals who attended the cardiology clinic, underwent 24-hour ECG Holter and transthoracic echocardiography (TTE) examinations, and were demographically matched to the patient group. Acute glomerulonephritis was excluded from the study due to its clinical course, which could affect hemodynamics and the autonomic nervous system (ANS). Since previous studies have shown cardiac autonomic dysfunction in coronary artery disease, diabetes mellitus, and stage 4–5 CKD, individuals with these conditions were excluded from the study. Additionally, individuals with pacemakers, those taking antiarrhythmic drugs or medications that affect ANS, and those with structural heart disease due to an increased risk of arrhythmia were also excluded.

Written informed consent was obtained from all patients. All TTE evaluations were performed using a 2.5–3.5 MHz transducer on the 'Vivid s70N, General Electric Health Care, Horten/Norway' echocardiography device. Data on age, gender, chronic diseases, and medications used were collected. Hypertension was defined as either a history of hypertension with a blood pressure of 140/90 or higher or the use of antihypertensive medication. Hyperlipidemia was defined as either receiving lipid-lowering treatment or meeting the criteria for such treatment according to the guidelines. Chronic glomerulonephritis patients were divided into nephrotic and nephritic syndrome groups for subgroup analysis based on the clinical presentation matching their histopathological findings. Based on histopathological findings, patients with proteinuria >3.5 g/day/1.73 m^2, hypoalbuminemia, and edema were classified as having nephrotic syndrome; those with hematuria, non-nephrotic proteinuria (<3.5 g/day/1.73 m^2), hypertension, edema and renal dysfunction were classified as having the nephritic syndrome. Patients who did not strictly meet the aforementioned hypertension criteria but exhibited elevated blood pressure and other clinical features more consistent with nephritic syndrome were included in the nephritic syndrome subgroup.

Electrocardiographic Holter evaluation: 24-hour Holter monitoring of all patients was performed with a 3-channel ECG recorder (DMS Holter Recorder, Biomedical Instruments Co. LTD., Beijing/China). These recordings obtained 24-hour average heart rate, RR variability and sinusoidal response to VES data. The recordings were visually inspected, and noisy regions were excluded from the analysis. The computer analyzed HRV and HRT parameters (Biomedical Instruments Co. LTD., Holter Software, China software). The power spectrum analysis of the frequency parameters of HRV was performed by the "Fast Fourier" transform. According to power spectrum analysis, 0.16–0.40 was considered high frequency (HF; high frequency), 0.04–0.15 as low frequency (LF; low frequency). Normalized (nu) values of low-frequency and high-frequency parameters calculated according to the formula below were used: LF (nu)=LF (100/ Total Power), HF (nu)=HF (100/ Total Power). Heart rate variability parameters were evaluated according to the North American Battery and Electrophysiological Society guidelines and the European Society of Cardiology[14].

When HRT analysis was first introduced, taking at least 5 appropriate VESs for accurate calculation in HRT evaluation was recommended since the reliability of measurements would decrease in patients with few VESs due to factors such as sinus arrhythmia and parasites[15]. However, later studies reported that a single appropriate VES may be sufficient for baroreflex assessment[16]. In this study, to perform more HRT evaluation in patients, all records were scanned and beats with arrhythmia, interference or misclassification in 5 sinus beats before VES and 15 sinus beats after compensatory pause were excluded from the analysis. Thus, HRT measurements were performed in patients with one or more VESs. Schmidt criteria were used in the calculation of TO and TS[7]. Calculation of turbulence initial value; $T0=[(RR_1+RR_2)-(RR_{-2}+RR_{-1})] / (RR_{-2}+RR_{-1}) \times 100$. This study considered TO ≥%0 and TS ≥2.5 ms/RR value pathological.

Statistical analysis: The normality condition for continuous variables was checked using the Shapiro-Wilk test. Normally distributed data were compared between two groups with Student's t-test and between three or more groups with One-way analysis of variance (Post-Hoc: Tukey HSD and Fisher's LSD test). When the data were not normally distributed, the Mann-Whitney U test and Kruskal Wallis H test (Post-Hoc: Dunn test) were used instead of these tests. Pearson's Chi-square test and Fisher's Exact test examined the relationship between two categorical variables. The Kaplan-Meier method examined Glomerulonephritis durations according to microalbuminuria groups in 24-hour urine (<30 mg/day, 30–300 mg/day and >300 mg/day). The Mantel-Cox Log Rank test was used to investigate whether there was any significance between the groups. The Kaplan Meier method used the RStudio (survival v. 3.4 and survminer v. 0.4.9 packages) program. IBM Statistical Package for Social Sciences (SPSS) program version 23 (IBM Inc., Armonk, NY) was used for all other analyses. The significance level was determined as $p < 0.05$.

Results

A total of 144 patients participated in the study. Of these, 42 were in the patient group (16 with nephritic syndrome and 26 with nephrotic syndrome), and 102 were in the control group. The patient and healthy groups were similar concerning demographic characteristics and echocardiographic findings. When laboratory values were compared to those of healthy subjects,

patients with glomerulonephritis showed lower *modification of diet in renal disease glomerular filtration rate* (MDRD-GFR), total protein and albumin levels, as well as higher urea, creatinine, uric acid, potassium, phosphorus (all p<0.05) (Table 1). C-reactive protein (CRP) was lower in the patient group. However, this may not reflect the true situation due to variations in CRP kits and reference ranges during the study period.

In the 24-hour ECG Holter evaluation, all HRV values were lower in the patient group compared to the healthy group, and the LF/HF ratio was higher in the patient group, correlating with these results. Low SDNN, SDNN-index, rMSSD, pNN50 and HF values showed statistical significance (p=0.046, p=0.031, p=0.019, p=0.013, p=0.032, respectively). No significant differences regarding HRT parameters were found between the patient and healthy groups (Table 2).

During subgroup analysis, when the patients were divided into nephrotic and nephritic syndrome groups and compared with healthy subjects, no significant differences were observed in demographic and echocardiographic values. MDRD-GFR remained significantly lower in the nephritic syndrome group than in the healthy group subjects, whereas the decrease in the nephrotic syndrome group did not reach statistical significance. Total protein and albumin were significantly lower in both nephritic and nephrotic syndrome groups than in healthy subjects (Table 3).

Table 1. *Demographic characteristics, echocardiographic findings and laboratory values of the patient and healthy group*

	Patient group (n=42)	Healthy group (n=102)	p
Age, year	48.45±12.30	47.76±11.99	0.757*
Gender			
Female	13 (30.95)	35 (34.31)	0.697
Male	29 (69.05)	67 (65.69)	
Hypertension			
No	22 (52.38)	69 (67.65)	0.084
Yes	20 (47.62)	33 (32.35)	
Hyperlipidemia			
No	29 (69.05)	66 (64.71)	0.617
Yes	13 (30.95)	36 (35.29)	
Echocardiography			
LVEF, %	64.5 (61.75–67.25)	63 (60–66)	0.168
LVEDD	47.67±3.45	47.23±3.92	0.527*
LVESD	30 (27–31,25)	30 (26–33)	0.841
IVS	10 (9–11)	10 (9–11)	0.578
PWT	10 (9–11)	10 (9–11)	0.481
Laboratory			
MDRD-GFR	82.5 (50.25–110)	99 (89–108,25)	**0.006**
Urea, mg/dL	45 (29.75–67.25)	29 (24–34.25)	**<0.001**
Creatinine, mg/dL	1.05 (0.8–1.52)	0.8 (0.69–0.9)	**<0.001**
Uric acid, mg/dL	6.1 (5.18–7.05)	5 (3.9–5.6)	**<0.001**
Fasting blood sugar, mg/dL	95.5 (89.75–105.5)	98 (92–103)	0.671
Sodium, mmol/L	140 (138–142.25)	140 (139–141)	0.714
Potassium, mmol/L	4.57±0.43	4.41±0.33	**0.017***
Chlorine, mmol/L	104 (102–105.25)	104 (102–106)	0.945
Total calcium, mg/dL	9.5 (9.1–9.7)	9.5 (9.28–9.8)	0.161
Phosphorus, mg/dL	3.67±0.51	3.38±0.54	**0.004***
Magnesium, mg/dL	2 (1.9–2.2)	2 (1.9–2.1)	0.705
Total protein, g/dL	6.7 (6.28–7.13)	7.2 (6.9–7.5)	**<0.001**
Albumin, g/dL	4.15 (3.7–4.4)	4.4 (4.1–4.6)	**<0.001**
CRP, mg/L	0.38 (0.3–1.23)	3 (1.3–4.7)	**<0.001**
HCT, %	41.35 (37.65–45.65)	42.5 (39.18–44.93)	0.416
TSH, ulU/mL	1.6 (0.9–3.03)	1.66 (1.17–2.35)	0.718

CRP; C-reactive protein, HCT; hematocrit, IVS; interventricular septum, LVEDD; left ventricular end-diastolic diameter, LVEF; left ventricular ejection fraction, LVESD; left ventricular end-systolic diameter, MDRD-GFR; Modification of Diet in Renal Disease-Glomerular Filtration Rate, PWT; posterior wall thickness, TSH; thyroid-stimulating hormone.

Table 2. *24-Hour ECG Holter results of the patient and healthy group*

	Patient group (n=42)	Healthy group (n=102)	p
SDNN, msn	125 (105.25–149.25)	140.5 (110.75–172)	**0.046**
SDNN-index	51.5 (41.75–60.75)	58 (48–69.5)	**0.031**
rMSSD, msn	23 (18.5–34)	29 (23–38)	**0.019**
pNN50, %	3.5 (1.75–10)	7 (4–13)	**0.013**
HF	118 (62.13–290)	208.5 (115.5–346.75)	**0.032**
LF	447.5 (263.5–637.75)	522.5 (333.75–747.75)	0.067
LF/HF	2.91 (1.7–4.55)	2.32 (1.55–4.15)	0.414
VLF	881.88±319.35	1008.76±415.95	0.079*
TO‡	-2.5 (-1.63-{-3.57})	-2.95 (-1.56-{-4.88})	0.546
TS‡	14.8 (8.59–26.7)	13.67 (8.59–22.19)	0.641

HF; high frequency, LF; low frequency, pNN50; percentage of differences between adjacent NN intervals >50 ms, rMSSD; root mean square of the successive differences, SDANN; standard deviation of 5 min averaged NN intervals, SDNN; standard deviation of all NN intervals, TO; turbulence onset, TS; turbulence slope, VLF; very low frequency. Data are shown as median (25th to 75th percentile) or mean ± standard deviation. Mann-Whitney U test, *: Student t test. ‡: Patient group: n=19, Healthy group: TO n=41, TS n=43.

Table 3. *Demographic characteristics, echocardiographic findings and laboratory values of nephritic syndrome, nephrotic syndrome and healthy group*

	Nephritic syndrome group (n=16)	Nephrotic syndrome group (n=26)	Healthy group (n=102)	p
Age, year	46.25±12.64	49.81±12.14	47.76±11.99	0.622*
Gender				
Female	6 (37.5)	7 (26.92)	35 (34.31)	0.723
Male	10 (62.5)	19 (73.08)	67 (65.69)	
Hypertension				
No	9 (56.25)	13 (50)	69 (67.65)	0.207
Yes	7 (43.75)	13 (50)	33 (32.35)	
Hyperlipidemia				
No	13 (81.25)	16 (61.54)	66 (64.71)	0.375
Yes	3 (18.75)	10 (38.46)	36 (35.29)	
Echocardiography				
LVEF	64.5 (62–66)	64.5 (60.75–68)	63 (60–66)	0.385
LVESD	48.06±3.94	47.42±3.16	47.23±3.92	0.712*
LVEDD	30 (27.25–32.75)	29.5 (27–30.25)	30 (26–33)	0.813
IVS	10 (9–11)	10 (9–11.25)	10 (9–11)	0.738
PWT	10 (9–11)	10 (9–11)	10 (9–11)	0.776
Laboratory				
MDRD-GFR	67 (50–107.25)[b]	89.5 (65.6–113.5)[a,b]	99 (89–108.25)[a]	**0.009**
Urea, mg/dL	62.5 (33.5–76.75)[a]	37.5 (27–57)[a]	29 (24–34.25)[b]	**<0.001**
Creatinine, mg/dL	1.38 (0.83–2.02)[a]	0.91 (0.79–1.33)[a]	0.8 (0.69–0.9)[b]	**<0.001**
Uric acid, mg/dL	6 (5.13–7.25)[a]	6.2 (5.13–7.05)[a]	5 (3.9–5.6)[b]	**<0.001**
Fasting blood sugar, mg/dL	95 (87.25–99.75)	98 (91.5–109)	98 (92–103)	0.365
Sodium, mmol/L	140 (138–141.75)	140 (138–143)	140 (139–141)	0.896
Potassium, mmol/L	4.56±0.42	4.57±0.45	4.41±0.33	0.057*
Chlorine, mmol/L	103.5 (102.2–105.7)	104 (102–105.25)	104 (102–106)	0.991
Total calcium, mg/dL	9.45 (8.95–9.8)	9.5 (9.1–9.63)	9.5 (9.28–9.8)	0.374
Phosphorus, mg/dL	3.77±0.51[a]	3.62±0.52[a,b]	3.38±0.54[b]	**0.010***
Magnesium, mg/dL	2.1 (2–2.2)[a]	2 (1.8–2.03)[b]	2 (1.9–2.1)[a,b]	**0.022**
Total protein, g/dL	6.55 (6.2–7.28)[b]	6.75 (6.3–7.1)[b]	7.2 (6.9–7.5)[a]	**<0.001**
Albumin, g/dL	4 (3.8–4.48)[b]	4.2 (3.68–4.33)[b]	4.4 (4.1–4.6)[a]	**<0.001**
CRP, mg/L	0.35 (0.2–1.48)[b]	0.38 (0.3–1.25)[b]	3 (1.3–4.7)[a]	**<0.001**
HCT, %	40.5 (34.38–43.88)	42 (38.75–47)	42.5(39.18–44.93)	0.317
TSH, ulU/mL	1.45 (0.66–2.53)	1.95 (1.15–3.6)	1.66 (1.17–2.35)	0.246

CRP; C-reactive protein, HCT; hematocrit, IVS; interventricular septum, LVEDD; left ventricular end-diastolic diameter, LVEF; left ventricular ejection fraction, LVESD; left ventricular end-systolic diameter, MDRD-GFR; Modification of Diet in Renal Disease-Glomerular Filtration Rate, PWT; posterior wall thickness, TSH; thyroid-stimulating hormone.

Table 4. *24-hour ECG holter results in nephritic syndrome, nephrotic syndrome and healthy groups*

	Nephritic syndrome group (n=16)	Nephrotic syndrome group (n=26)	Healthy group (n=102)	p
SDNN, msn	127.5 (99.25–141.5)	124 (107.5–155.25)	140.5 (110.75–172)	0.133
SDNN-indeks	50.5 (38.75–58.75)	52 (44.25–68.5)	58 (48–69.5)	0.067
rMSSD, msn	22 (16.75–30.25)[b]	24.5 (18.5–38.25)[a,b]	29 (23–38)[a]	**0.049**
pNN50, %	3 (1–7)[b]	4 (2–13.25)[a,b]	7 (4–13)[a]	**0.032**
HF	118 (58–264.73)	118 (64.38–345)	208.5 (115.5–346.75)	0.082
LF	341 (211.23–620.5)	490 (372–670.75)	522.5 (333.75–747.75)	0.059
LF/HF	2.68 (1.54–3.92)	3.09 (1.9–4.76)	2.32 (1.55–4.15)	0.485
VLF	797.19±290.75	934±330.33	1008.76±415.95	0.117*
T0‡	-3.19 (-1.66-{-8.75})	-2.1 (-1.57-{-2.65})	-2.95 (-1.56-{-4.88})	0.116
TS‡	16.55 (11.69–36.3)	13.8 (8.2–19.35)	13.67 (8.59–22.19)	0.426

HF; high frequency, LF; low frequency, pNN50; percentage of differences between adjacent NN intervals >50 msn, rMSSD; root mean square of the successive differences, SDANN; standard deviation of 5 min averaged NN intervals, SDNN; standard deviation of all NN intervals, T0; turbulence onset, TS; turbulence slope, VLF; very-low frequency. Data are shown as median (25 th-75th percentile) or mean ± standard deviation. Kruskal Wallis test (Post-Hoc: Dunn test), *: One-way analysis of variance, a, b, c: same letters indicate no significant difference between the groups; p>0.05, different letters indicate significant difference between the groups; p<0.05. ‡: Nephritic syndrome group: n=10, Nephrotic syndrome group: n=9, Healthy group: T0 n=41, TS n=43.

Table 5. *Effect of duration of glomerulonephritis on SDNN and rMSSD according to microalbuminuria level in 24-hour urine*

		Microalbuminuria in 24-hour urine			
	Total	<30 mg/day	30–300 mg/day	>300 mg/day	p
Number of patients, n (%)	42 (100)	10 (23.8)	9 (21.4)	23 (54.8)	
SDNN					
SDNN <141 msn, n (%)	30 (71.4)	6 (60.0)	7 (77.8)	17 (73.9)	
Median duration (95% CI), month	80 (65.8–92.2)	80 (8.8–151.1)	69 (33.7–104.3)	71 (51–91)	0.597
rMSSD					
rMSSD <27 msn, n (%)	26 (61.9)	5 (50)	5 (55.6)	16 (69.6)	
Median duration, month	80 (67.3–92.6)	80 (0–198.5)	85 (0–182.9)	80 (65.4–94.6)	0.483

CI: Confidence interval, rMSSD; root mean square of the successive differences, SDNN; standard deviation of all NN intervals.
The median time is based on the time from the diagnosis of chronic glomerulonephritis to the evaluation.

Analysis of the 24-hour ECG Holter results revealed that pNN50 and rMSSD values were significantly lower in the nephritic syndrome group compared to healthy subjects (p=0.049, p=0.032, respectively). In contrast, the significant differences in SDNN, SDNN index and HF were no longer observed. In the nephrotic syndrome group, the decrease in HRV parameters did not reach statistical significance compared to the healthy group (Table 4).

Analysis with Kaplan Meier Method in patients: Microalbuminuria levels were evaluated using patients' 24-hour urine samples. Among the patients, 23.8% (n=10) had normal/mild microalbuminuria (<30 mg/day), 21.4% (n=9) had moderate microalbuminuria (30–300 mg/day), and 54.8% (n=23) had severe microalbuminuria (>300 mg/day). The time from diagnosis to evaluation was calculated to determine the duration of CGN in each patient.

Heart rate variability parameters were categorized using pre-defined cut-off values: SDNN was dichotomized at 141 msec (with 71.4% of patients, n=30, having SDNN values below 141 msec) and rMSSD at 27 msec (with 61.9% of patients, n=26, having rMSSD values below 27 msec). The median duration from the diagnosis of chronic glomerulonephritis to the point at which SDNN and rMSSD fell to risky levels was compared according to the microalbuminuria levels in 24-hour urine samples.

In the analysis, no significant difference was observed among the microalbuminuria groups (based on 24-hour urine samples) regarding the duration from CGN diagnosis to the point at which SDNN fell below 141 msec, and rMSSD fell below 27 msec (Table 5, Figure 1).

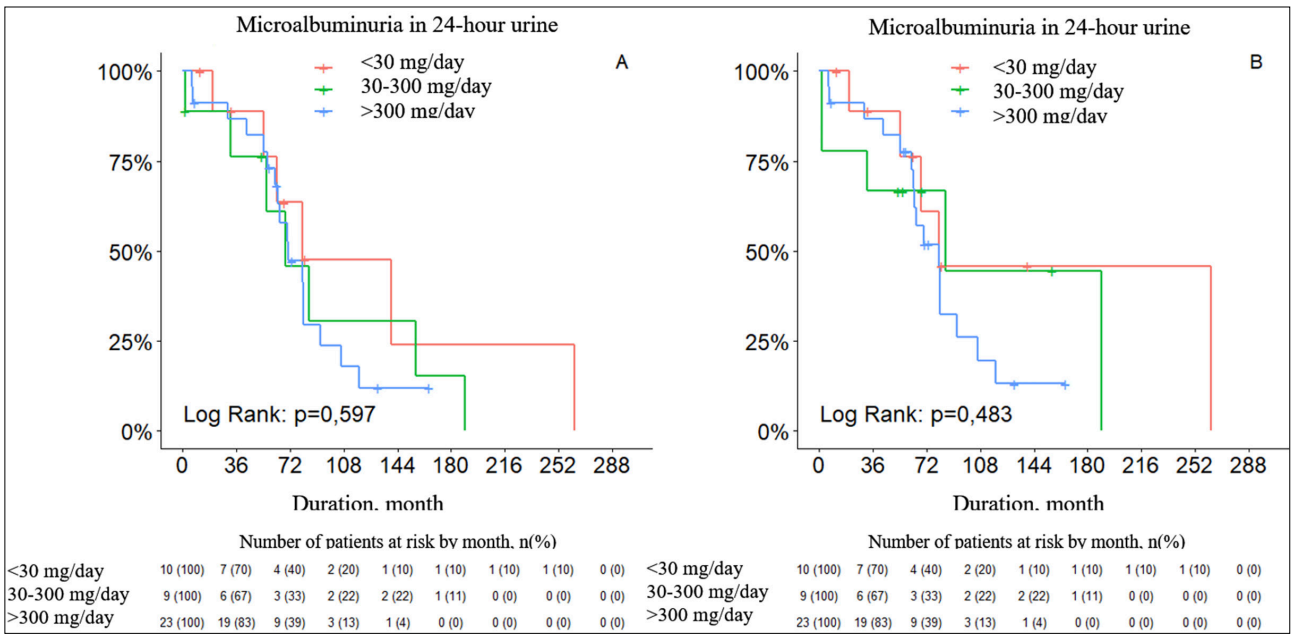

Figure 1. a,b. *Graphical presentation of the effect of glomerulonephritis duration on SDNN and rMSSD according to the microalbuminuria level in 24-hour urine.*

Discussion

This study evaluates cardiac autonomic function in the largest population of individuals with chronic glomerulonephritis before the onset of renal dysfunction. In this study, we found that the HRV parameters –SDNN, SDNN index, rMSSD, pNN50 and HF, which are important predictors of cardiac mortality– were significantly lower in the CGN group compared to the healthy group. These findings indicate the presence of autonomic dysfunction, marked by sympathetic activation and vagal suppression, even in CGN patients at the early stage. Since sympathetic-dominant autonomic dysfunction is associated with SCD, these results are crucial for the early prediction of CV risk and may guide timely intervention and treatment.

Our study found a statistically significant decrease in SDNN and the SDNN index in patients with CGN compared to control subjects (p=0.046 and p=0.031, respectively). In the study by Esposito et al.,[17] 21 patients with primary glomerulonephritis (without nephrotic syndrome) in the early stages of CKD were compared with 20 healthy subjects regarding time-domain HRV parameters. They found that SDNN was significantly lower in the patient group, which they interpreted as indicative of sympathetic hyperactivation and autonomic dysfunction. In this context, our findings regarding SDNN are consistent with those of Esposito et al. Moreover, the SDNN index –another parameter reflecting both short- and long-term influences on heart rate– was significantly lower in our patient group, further supporting the presence of sympathetic hyperactivation. However, when we divided the patient population into nephrotic and nephritic syndrome subgroups, the significant differences in SDNN and SDNN index observed in the overall patient group disappeared in both subgroups compared to the healthy group, contradicting the findings of Esposito et al., who evaluated CGN patients without nephrotic syndrome. This discrepancy may be due to the reduced sample size.

Both rMSSD and pNN50 were lower in the patient group, with these differences reaching statistical significance (p=0.019 and p=0.013, respectively), indicating a reduction in parasympathetic tone. In the subgroup analysis, when patients were divided into nephrotic and nephritic syndrome groups, rMSSD and pNN50 were lower in both subgroups compared to healthy controls; however, statistical significance was maintained only in the nephritic syndrome group, while it was lost in the nephrotic syndrome group. Although this discrepancy may be partly attributable to the small sample size, the persistence of a statistically significant difference in the nephritic syndrome group –despite its smaller number of patients– suggests that other factors may be involved. It is known that the correlation between glomerular filtration rate (GFR) and autonomic function is curvilinear[18]. Glomerular filtration rate was significantly lower in the nephritic

syndrome group compared to healthy subjects, unlike in the nephrotic syndrome group; it is plausible that the decreases in rMSSD and pNN50 are related to reduced GFR. Furthermore, the nephritic syndrome is characterized by inflammation and immune complex deposition[19], and inflammatory markers have been shown to correlate negatively with HRV parameters, particularly pNN50[20]. Therefore, we propose that inflammation in nephritic syndrome patients may be one of the reasons for the observed statistically significant differences in pNN50 and rMSSD. Unfortunately, we were unable to quantitatively assess this relationship via CRP levels due to changes in the CRP assay during the study period.

In our study, a comparison between the patient and control groups revealed that patients exhibited decreases in both LF and HF, along with an increase in the LF/HF ratio, reflecting sympathetic activation and parasympathetic inhibition. A statistically significant difference was observed for HF (p=0.032), indicating reduced vagal tone in the patient group. Andoh et al.[21] investigated HRV via power spectral analysis in patients with nephrotic syndrome in the early stages of CKD to assess the role of sympathetic withdrawal in reducing sleep blood pressure. They found no significant differences between groups in HF and LF/HF ratios. Although they did not attribute the absence of a decrease in sleep blood pressure to a direct sympathetic effect– since no autonomic dysfunction was detected in the HRV analysis –they suggested that sympathetic activity might still play a role, as indicated by a higher heart rate during sleep in the patient group. In our study of CGN patients, overall, we observed reduced vagal tone and a shift toward sympathetic dominance. However, when the patient group was divided into nephrotic and nephritic syndrome subgroups, the significant difference in HF observed in the overall group was no longer evident. Our findings in the nephrotic syndrome subgroup are consistent with those of Andoh et al.

Andoh et al. reported a negative correlation between serum albumin concentration (SAC) and urinary protein excretion, suggesting that SAC may serve as a proxy marker for the severity of nephrotic syndrome. In our study, although both nephritic and nephrotic syndrome subgroups had significantly lower serum total protein and albumin levels than the healthy group, no significant differences in HRV parameters were observed in the nephrotic syndrome subgroup relative to healthy controls. In contrast, the nephritic syndrome subgroup showed a significant decrease in rMSSD and pNN50 values compared to healthy subjects. Subsequently, we examined the effect of proteinuria levels in 24-hour urine –a more quantitative measure– on HRV parameters. Using the Kaplan–Meier method, we analyzed the time from CGN diagnosis to the point at which SDNN and rMSSD reached significantly reduced levels, stratified by microalbuminuria. Our findings indicate that microalbuminuria level (mild, moderate, or severe) does not significantly affect the mean duration of disease at which HRV parameters deteriorate (p=0.597 for SDNN and p=0.483 for rMSSD). However, while no linear relationship was observed for SDNN, the proportion of patients with reduced rMSSD increased with higher microalbuminuria levels. This underscores the impact of microalbuminuria on rMSSD, an independent risk factor for mortality in CKD patients[22].

Time-domain measurements of HRV, such as rMSSD and pNN50, are closely related to frequency-domain measurements, particularly the HF parameter[11]. In our study, the significant and concordant reductions in HF, rMSSD, and pNN50 observed in the patient group reinforce the conclusion that vagal tone is diminished in these patients.

Suitable VES were detected for analysis in 19 individuals (45%) in the patient group and 41 individuals (40%) in the healthy group. Analysis of these VES revealed no significant differences between the patient and healthy groups regarding TO and TS. According to our findings, HRT parameters –used as mortality predictors– do not appear to be sensitive markers for determining risk in CGN patients in the early stages of CKD. The fact that suitable VES were observed in only 41% of the individuals included in the study may have influenced these HRT results.

This study has several limitations. The most important is its small sample size –a common issue in HRT studies– which makes it difficult to identify appropriate VES. Furthermore, because the echocardiographic data for the healthy volunteer group were obtained retrospectively, not all subjects were evaluated by the same individual, potentially introducing interobserver variability. Additionally, as the study was conducted in the post-COVID-19 period –and previous studies have demonstrated that HRV is increased in symptomatic individuals who have recovered from COVID-19[23]– the lack of assessment of COVID-19

history and symptoms means that their impact on the results remains unclear. Lastly, although this study involved a larger population than previous studies in this field, further investigations with larger sample sizes are needed to obtain definitive data.

Conclusion

As a result, the HRV parameters SDNN, SDNN index, rMSSD, pNN50, and HF were significantly lower in the patient group compared to the healthy group. Based on our findings, we conclude that these parameters are reliable, practical, and non-invasive tests that can predict cardiovascular autonomic dysfunction in chronic glomerulonephritis patients at the early stages of chronic kidney disease.

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