Renal denervation improves metabolic disturbances and inflammation with positive impact on kidney function in patients with resistant and difficult-to-control hypertension in long-term follow up

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This article was submitted to RAD CASA - Medical Sciences as the original article

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 2 November 2025
Accepted: 15 December 2025
Published: 28 December 2025

Citation:
Barisic K, Jelakovic A, Simunovic L, Perkov D, Josipovic J, Prkacin I, Zivko M, Zeljkovic Vrkic T, Domislovic M, Gellineo L, Kos J, Vukovic Brinar I, Ivandic E, Lovric M, Pecin I, Jelakovic B. Renal denervation improves metabolic disturbances and inflammation with positive impact on kidney function in patients with resistant and difficult-to-control hypertension in long-term follow up
569=72-73 (2025): 16-25
DOI: 10.21857/moxpjh72jm

Abstract

Introduction: The aim of this study was to examine the effects of catheter renal denervation (RDN) on blood pressure (BP), inflammatory and metabolic biomarkers and kidney function in patients with resistant and difficult-to-control hypertension during an average 33-month follow-up.

Materials and Methods: The analysis included 27 out of 125 patients from the Croatian Registry for RDN. Office BP and ABPM were performed before and during the follow-up period. In addition to classic metabolic parameters and determination of kidney function, evaluation of new biomarkers was performed (neutrophil-to-lymphocyte ratio (NLR), triglyceride-to-glucose index (TyGi) and triglyceride-to-HDL cholesterol ratio (TG/HDL)).

Results: A significant reduction in BP was observed after RDN which was accompanied by significant decrease in total and LDL cholesterol, triglycerides and fasting blood glucose, as well as with the improvement of kidney function. In addition, there was a significant decrease in NLR (p=0.037), TyGi (p=0.006) and TG/HDL (p=0.068). A decrease in these biomarkers indicates an improvement in systemic inflammation and metabolic profile.

Conclusions: RDN significantly reduces BP and has a favorable effect on biomarkers of inflammation and metabolic risk as well as on kidney function in patients with resistant and difficult-to-control hypertension. These results indicate that RDN may contribute to overall cardiovascular risk reduction independent of effect on BP.

Keywords: Renal denervation; hypertension; dyslipidemia; biomarkers

Sažetak:

Renalna denervacija poboljšava metaboličke poremećaje i upalu s pozitivnim utjecajem na funkciju bubrega kod pacijenata s rezistentnom i teško kontroliranom hipertenzijom u dugotrajnom praćenju

Uvod: Cilj ove studije bio je ispitati učinke kateterske bubrežne denervacije (RDN) na krvni tlak (KT), upalne i metaboličke biomarkere te funkciju bubrega kod pacijenata s rezistentnom i teško kontroliranom hipertenzijom tijekom prosječnog praćenja od 33 mjeseca.

Materijali i metode: Analiza je obuhvatila 27 od 125 pacijenata iz Hrvatskog registra za RDN. Prije i tijekom razdoblja praćenja provedeni su ordinacijski krvni tlak i ABPM. Uz klasične metaboličke parametre i određivanje funkcije bubrega, provedena je evaluacija novih biomarkera (omjer neutrofila i limfocita (NLR), indeks triglicerida i glukoze (TyGi) i omjer triglicerida i HDL kolesterola (TG/HDL)).

Rezultati: Uočeno je značajno smanjenje krvnog tlaka nakon RDN-a, što je bilo popraćeno značajnim smanjenjem ukupnog i LDL kolesterola, triglicerida i glukoze u krvi natašte, kao i poboljšanjem funkcije bubrega. Osim toga, došlo je do značajnog smanjenja NLR-a (p=0,037), TyGi (p=0,006) i TG/HDL-a (p=0,068). Smanjenje ovih biomarkera ukazuje na poboljšanje sistemske upale i metaboličkog profila.

Zaključci: RDN značajno smanjuje krvni tlak i ima povoljan učinak na biomarkere upale i metaboličkog rizika, kao i na funkciju bubrega u bolesnika s rezistentnom i teško kontroliranom hipertenzijom. Ovi rezultati ukazuju na to da RDN može doprinijeti ukupnom smanjenju kardiovaskularnog rizika neovisno o učinku na krvni tlak.

Ključne riječi: Biomarkeri, dislipidemija, hipertenzija, renalna denervacija

Introduction

Clinical trials have shown that catheter-based renal denervation (RDN) can safely and effectively lower blood pressure (BP) [1,2]. Recent guidelines include RDN as a complementary therapeutic option in the management of resistant hypertension and difficult-to-control hypertension [3]. In the Consensus Statement on RDN, the Croatian Hypertension League, the indications and algorithm for diagnosis and follow-up are more detailed, presented, and elaborated [4]. Results obtained in several studies found RDN to be associated with a decrease in target organ damage such as albuminuria [5]. In addition to BP reduction, Mahfoud et al. observed a significant improvement in insulin sensitivity and glucose metabolism after RDN in patients with resistant hypertension [6]. In contrast, despite a statistically significant reduction in 24-hour systolic BP, other authors failed to find a reduction in metabolic parameters, i.e. fasting blood glucose (FBG), Hemoglobin A1c (HbA1c) and cholesterol [7]. However, there was a decrease in the average values of triglycerides and an improvement in the levels of High-Density Lipoprotein (HDL) cholesterol [8]. The most important issue is whether RDN reduces total cardiovascular (CV) risk. Multi-year analyses revealed that RDN can effectively reduce CV risk and CV mortality in high-risk patients in the long term [9]. In the last several years, new biomarkers and predictors of CV events, easily applicable in clinical work, have been investigated. The neutrophil-to-lymphocyte ratio (NLR), a simple marker of inflammation, was found to be a significant predictor of CV diseases and all-cause mortality [10]. It was concluded that NLR could serve as a useful biomarker for assessing overall CV risk [11]. The neutrophil-to-HDL-cholesterol ratio (NHR) has shown a high predictive value for CV events, including myocardial infarction [12]. In the general population, the triglyceride-glucose index (TyGi) and triglycerides and HDL-cholesterol ratio (TG/HDL) independently predict the risk of CV disease, with the effect partially mediated by hypertension, dyslipidemia and diabetes [13]. TyGi showed a greater predictive value for cardiometabolic outcomes compared to TG/HDL, including 5-year mortality in patients with heart failure [14].

In this study, we aimed to analyze the effect of RDN on these new biomarkers of cardio-metabolic risk and kidney function beyond effects on BP in follow-up period of average thirty-three months.

Materials and methods

In this study, we included patients with resistant and difficult-to-control hypertension from the Croatian Registry on RDN [4]. Exclusion criteria for RDN were white coat hypertension, pregnancy or lactation, anatomically inadequate renal arteries, secondary forms of hypertension and unsigned informed consent, age younger than 18 years, RDN done with Flex catheter, follow-up less than 18 months, patients not examined and followed according to the consensus algorithm. Out of 125 patients included in the Croatian Registry on RDN, 27 fulfilled inclusion/exclusion criteria (flow chart Figure 1). Chronic kidney disease (CKD) was not an exclusion criterion and in three

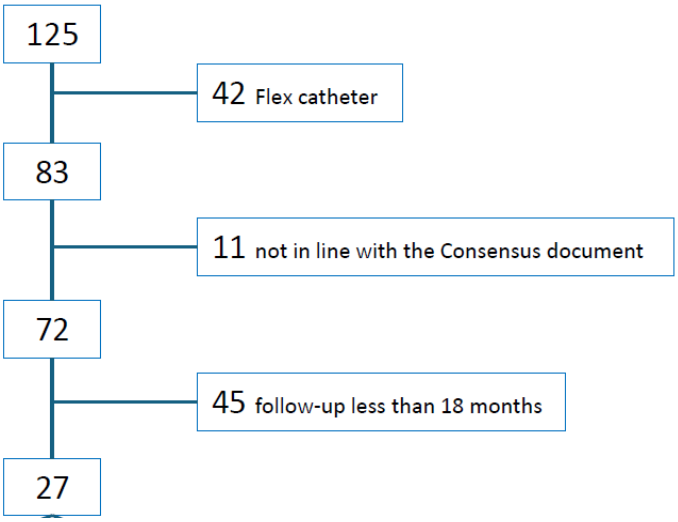

Figure 1. Flow chart of the study

patients we conducted RDN with CO2 angiography. All patients were discussed at regular monthly meetings of the multidisciplinary team of the Croatian Hypertension League and European Society of Hypertension (ESH) Excellence Center, who determined their suitability for RDN. The final decision on RDN was made together with the patient. In addition to mandatory tests, we determined serum uric acid, FBG, HbA1c, total cholesterol, Low-Density Lipoprotein (LDL) cholesterol, HDL cholesterol and triglycerides [4]. For the purposes of this study, the following inflammatory and metabolic biomarkers/ratios were determined: (i) NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count; (ii) NHR was obtained by dividing the absolute neutrophil count by the HDL-cholesterol; (iii) the TG/HDL was obtained by dividing the triglyceride concentration by the HDL concentration; (iv) TyGi, triglyceride and glucose concentrations in mmol/L were previously converted to mg/dL using standard conversion factors, and, the TyGi index was calculated (TyG\ index=ln(Triglycerides\ (mg/dL)\ timesGlucose\ (mg/dL)/2)). Reference values of NLR range from 0.78 to 3.53, and elevated values indicate an increased inflammatory response and higher CV risk [15]. TyGi, with a cutoff value of 9.03, has been identified as optimal for predicting CV events [16]. TG/HDL has cutoff values of 2.967 for men and 2.237 for women for predicting metabolic syndrome [17]. Also, NHR greater than 11.28 was associated with an increased risk of adverse CV events in-hospital [18]. Before RDN and in follow-up visits, we measured BP with an ABPM device (Mobilograph PWA; IEM, Stolberg, Germany). CKD stages and albuminuria were assessed and defined according to the KDIGO guidelines [19]. Body mass index (BMI) was calculated using the standard formula: BMI = weight (kg) / height² (m²). Body surface area (BSA) was estimated using the Mosteller equation: BSA (m²) = [(height(cm) × weight(kg)) / 3600]. Absolute glomerular filtration rate (GFR) was calculated using the formula: (BSA x estimated GFR according to CKD-EPI equation)/1.73m2. Total daily salt intake was calculated based on 24-hour urinary sodium excretion. A comprehensive list of antihypertensive, antidiabetic, and antilipemic drugs was obtained for each patient. All RDN procedures were performed in the ESH Excellence Center Zagreb by the same physician (D.P.) using the Medtronic Simplicity Spiral system following the recommendation of the Croatian consensus document [4]. This research was approved by the Ethics Committee of University Hospital Center Zagreb (class: 8.1-21/277-2, number: 02/21 AG).

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA). The level of significance was set at $p < 0.05$ for all tests. Descriptive statistics were calculated for continuous variables and presented as mean ± standard deviation (SD) or median and interquartile range (IQR), depending on the distribution. Categorical variables were summarized as frequencies and percentages. The normality of data was assessed using the Shapiro–Wilk test and inspection of histograms and Q-Q plots. Categorical data were compared using Chi-square or Fisher's exact test, as appropriate. To assess the effect of RDN on inflammatory and metabolic biomarkers, as well as changes in 24-hour systolic ABPM (ΔABPM24hSyst), we calculated delta values as the difference between baseline (pre-intervention) and follow-up measurements taken two or more years post-RDN (Δ= baseline – follow-up). These delta values were then used as inputs in regression analyses to identify predictors of response to RDN. A multiple linear regression analysis was employed to explore the association between changes in biomarkers and the change in ΔABPMSyst24 as the dependent variable. All delta biomarker variables were initially considered for inclusion. However, due to the risk of multicollinearity and overfitting in models with a large number of predictors and a small sample size, a stepwise backward elimination method was applied using a removal criterion of $p \geq 0.10$. Variance inflation factors (VIF) and tolerance statistics were used to assess multicollinearity. Variables with VIF > 10 were considered highly collinear and were reviewed in a separate principal component analysis (PCA) to identify those most responsible for redundancy. Based on PCA loadings, variables contributing most to collinearity were excluded from the final models. Multicollinearity diagnostics (VIF and tolerance) were reported for all predictors in the final models. Model fit was evaluated using R^2 and adjusted R^2 values, as well as ANOVA F-statistics. The residuals were assessed to ensure homoscedasticity and linearity assumptions were met.

Results

The basic demographic and clinical characteristics of enrolled subjects are shown in Table 1. Their average age was 51.9 ±10.8 years, and there were 20 men. Most of the patients were overweight and obese, with an average BMI of 30.9 ± 0.9 kg/m2. All enrolled patients had resistant or difficult-to-control hypertension. The average number of antihypertensive drugs was 6.1±1.3. The most significant changes were observed in systolic ABPM values, which were obtained despite very high salt intake (Table 2 and Table 3). A reduction in the number of antihypertensive drugs was achieved. Estimated glomerular filtration rate (eGFR) remained preserved during the follow-up period and albuminuria showed a decreasing trend, which both could be considered as a signs of kidney protection. A decrease in FBG and significant improvements in the lipid profile were also recorded. A significant decrease in NLR, TyGi and TG/HDL was observed, which may indicate a decrease in systemic inflammation and insulin resistance, further confirming the favourable metabolic effect of RDN (table 3). Aiming to determine predictors of change in BP, we constructed several regression models (Table 4). In the final multiple linear regression model, three significant predictors of ΔABPM24hSyst were identified: ΔNLR, ΔNHR, and ΔACR. An increase in the ΔNRL by one unit was associated with an average decrease in systolic BP of 12.65 mmHg, suggesting that a more pronounced anti-inflammatory shift (i.e., reduction in inflammatory activity) contributes to a greater therapeutic effect. Furthermore, an increase in the ΔNHR by one unit was associated with an average increase in systolic BP of 5.77 mmHg. Finally, a decrease in ΔACR by one unit was associated with a decrease in systolic BP of 0.19 mmHg, which is in line with beneficial effects not only on the kidney but also on endothelial function. This model explained approximately 43% of the variance in systolic BP change (R^2 = 0.430), with moderate multicollinearity among predictors (all VIF < 2). Additional univariable linear regression models were performed to explore the potential reverse associations between changes in BP and biological markers further. In these models, ΔABPM24hSyst was used as a predictor variable, while the individual delta biomarkers were treated as dependent variables. In the models with ΔABPM24hSyst as the predictor, none of the tested biomarkers showed a statistically significant association with changes in systolic BP (all p > 0.05). Overall, these univariable regression models did not confirm a robust reverse association between changes in BP and most of the analyzed inflammatory or metabolic biomarkers. This further reinforces the notion that the multiple regression model with ΔABPM24hSyst as the dependent variable and selected biomarkers as predictors offers a more comprehensive and statistically reliable insight into the mechanisms underlying BP response to intervention.

Tables

Table 1. Basic clinical characteristics of enrolled patients before renal denervation

Variable	Mean ± SD	Median	IQR
Age (years)	51.9 ± 10.8	53	44–61
Height (cm)	172.9 ± 8.5	174	165–180
Weight (kg)	92.6 ± 17.0	93	83–105
Waist circumference (cm)	107.3 ± 14.4	107	96–118
BMI (kg/m²)	30.9 ± 4.9	32	27.2–34
BSA (m²)	2.1 ± 0.2	2.1	2–2.3
Number of denervated spots right	21.6 ± 4.6	20	19.8–23.3
Number of denervated spots left	17.6 ± 3.6	18	15–20
BMI = body mass index; BSA = body surface area. Values are presented as mean ± standard deviation (SD).			

Table 2. Blood pressure and heart rate values (office and ABPM) of enrolled patients before and at the end of follow up period

Variable	Mean Baseline ± SD	Mean Follow-up ± SD	Mean Difference	p-value
24-h ABPM systolic BP*	140 (131-149)	125 (119-136)	-15.0	<0.001
24-h ABPM diastolic BP	88.4 ± 10.0	78.6 ± 8.8	-9.8	<0.001
24-h heart rate (bpm)	75.8 ± 10.4	76.1 ± 8.4	0.3	0.897
Daytime ABPM systolic BP*	142 (136-152)	132 (118-139)	-10.0	<0.001
Daytime ABPM diastolic BP	92.0 ± 10.9	82.5 ± 8.8	-9.5	<0.001
Daytime heart rate (bpm)	79.9 ± 10.0	78.9 ± 8.7	-1.0	0.633
Nighttime ABPM systolic BP	129.9 ± 17.5	117.6 ± 12.0	-12.3	0.004
Nighttime ABPM diastolic BP	80.3 ± 10.1	70.9 ± 9.1	-9.3	<0.001
Nighttime heart rate (bpm) 66.9 ± 7.1 65.7 ± 9.4 -1.1				0.392
Office systolic BP	150.4 ± 22.5	145.3 ± 20.7	-5.0	0.444
Office diastolic BP	93.8 ± 9.8	85.8 ± 11.3	-8.0	0.017
Office heart rate (bpm)	77.6 ± 14.1	72.1 ± 12.3	-5.5	0.160
ABPM = ambulatory blood pressure monitoring; BP = blood pressure (mmHg), bpm= beat per minute, SD = standard deviation. Values are presented as mean ± SD and for those indicated with * as median and interquartile range.				

Table 3. Laboratory data and new biomarkers of enrolled patients before and at the end of follow up period

Variable	Mean Baseline ± SD	Mean Follow-up ± SD	Mean Difference	p-value
Neutrophils (×10⁹/L)	4.8 ± 1.49	4.7 ± 1.5	-0.14	0.61
Lymphocytes (×10⁹/L)	1.8 ± 0.53	1.9 ± 0.4	0.17	0.19
Glucose (mmol/L) *	6.5 (5.3-9.1)	5.9 (5 5.2-6.8)	-0.6	0.05
HbA1c (%) *	6.4 (5.9-7.0)	6.0 (5.6-6.8)	-0.4	0.29
HDL cholesterol (mmol/L) *	1.1 (0.9-1.2)	1.1 (0.9-1.3)	0	0.28
Triglycerides (mmol/L) *	1.5 (1.2-2.7)	1.3 (0.8-2.2)	-0.2	0.02
LDL cholesterol (mmol/L)	2.7 ± 1.1	2.2 ± 1.0	-0.48	0.03
Total cholesterol (mmol/L)	4.7 ± 1.28	4.1 ± 1.1	-0.62	0.01
24-hour albuminuria (mg/dU) *	22.5 (10.0-105.0)	17.0 (5.0-38.0)	-6.5	0.28
ACR (mg/mmol) *	1.4 (0.7-7)	0.9 (0.4-2.5)	-0.5	0.47
eGFR (mL/min/1.73m²)	77.2 ± 24.7	75.9 ± 23.5	-1.28	0.56
GFR absolute (mL/min)	95.6 ± 33.9	93.6 ± 32.3	-1.96	0.44
Potassium (mmol/L) 4.2 ± 0.56 4.2 ± 0.5 -0.05 0.64				
Sodium (mmol/L)	140.0 ± 2.3	140.3 ± 2.5	-0.26	0.69
Uric acid (mmol/L)	397.3 ± 104.8	367.0 ± 83.8	-30.31	0.07
Daily salt intake (g)	12.64 ± 20	12.22+20	-0.42	0.76
Sodium in daily urine (mmol/dU)	219.8 ± 97.5	212.4 ± 88.2	-7.35	0.76
Potassium in daily urine (mmol/dU)	81.8 ± 29.5	74.0 ± 22.24	-7.77	0.26
Number of antihypertensive drugs	6.0 ± 1.3	5.1 ± 1.47	-0.89	0.07
NLR	2.85 ± 1.0	2.41 ± 0.62	-0.44	0.01
NHR	4.67 ± 2.1	4.36 ± 2.04	-0.31	0.40
TyGi	9.18 ± 0.73	8.81 ± 0.71	-0.36	0.003
TG/HDL	1.94 ± 1.35	1.48 ± 0.98	-0.46	0.03
ACR = albumin-to-creatine ratio; dU = daily urine; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; HbA1c = Hemoglobin A1c; HDL = High-Density Lipoprotein; LDL = Low-Density Lipoprotein; NHR = neutrophil-to-HDL ratio; NLR = neutrophil-to-lymphocyte ratio; SD = standard deviation; TG/HDL = triglyceride-to-HDL ratio; TyGi = triglyceride-glucose index. Values are presented as mean ± SD and for those indicated with * as median and interquartile range.				

Table 4. Univariable linear regression analysis of biomarkers in relation to changes in systolic 24-hour ambulatory blood pressure

Dependent Variable	B	S.E.	Beta (Std.)	t	p
Δ NLR	0.005	0.012	0.082	0.387	0.70
Δ NHR	0.033	0.02	0.33	1.641	0.11
Δ TyGi	0.009	0.007	0.257	1.332	0.19
Δ TG/HDL	0.018	0.014	0.258	1.338	0.19
Δ daily salt intake	0.092	0.079	0.264	1.161	0.26
Δ ACR	0.715	0.723	0.24	0.99	0.33
Predictor: Δ ABPM 24-hour systolic blood pressure					
ACR = albumin/creatinine ratio; NHR = neutrophil-to-HDL ratio; NLR = neutrophil-to-lymphocyte ratio; TG/HDL = triglyceride-to-HDL ratio; TyGi = triglyceride-glucose index.					

Discussion

Our results are in line with previous reports which found that significant reduction in BP was sustained after RDN for a long period of time [1,2]. The BP reduction was achieved regardless of the average very high daily salt intake, indicating the effectiveness of RDN in this very frequent real-life situation. In most of patients an improvement in BP control was achieved with a lower antihypertensive pharmacological burden. We also confirmed the results of others who found improvement in several metabolic parameters [6,8]. In our group, total cholesterol, LDL cholesterol, triglycerides and FBG were significantly lower two years after RDN without introducing antilipemic or antidiabetic drugs. As far as we know, this is the first study which demonstrated statistically significant improvements in TyGi, TG/HDL and NLR, biomarkers of metabolic syndrome, inflammation, atherosclerosis and total CV risk after RDN. TyGi and TG/HDL are proven indicators of insulin resistance [20]. An analysis conducted on a large cohort showed that people with the highest TyG index values had twice the risk of developing major CV events compared to the lowest quartile, regardless of traditional risk factors [21]. Early pilot studies have indicated that RDN can improve glycoregulation. Mahfoud et al. recorded a significant decrease in FBG, insulin and HOMA-IR index three months after RDN in patients with resistant hypertension [6]. Other authors reported improved glycemic control in patients with type 2 diabetes and resistant hypertension after RDN [22]. Some studies have not consistently confirmed these findings [23,24]. In the DREAMS study, which included patients with metabolic syndrome, there was no significant improvement in insulin resistance twelve months after RDN [23]. A meta-analysis showed no significant changes in FBG, insulin, HbA1c, total cholesterol and LDL cholesterol after RDN, while there were improvements in triglyceride and HDL cholesterol levels [24]. In our study, we found significant improvement in FBG, total cholesterol, LDL cholesterol and triglycerides without changes in the HDL cholesterol two years after RDN. Furthermore, we observed a significant reduction in TG/HDL. Statistically significant reductions in TG/HDL indicate improvement in general cardiometabolic health. High TG/HDL is known as an indicator of insulin resistance and is closely associated with metabolic syndrome [25]. Subjects with higher TG/HDL were more likely to have a metabolic syndrome and tend to have more of its components [26]. TG/HDL also correlated with the severity of atherosclerosis, with more plaques and was considered a part of the "atherogenic" lipid profile [25,26]. We have also found a statistically significant decrease in the TyGi, which is in line with observations that reduced sympathetic tone after RDN resulted in improved insulin sensitivity without specific antidiabetic interventions [6]. A decrease in the TyGi after RDN, indicating reduced insulin resistance, could decrease the risk for diabetes. In addition to improving metabolic balance, RDN also affects immunological and inflammatory mechanisms. Increased sympathetic activity in hypertension is associated with sub-clinical chronic inflammation and mobilization of leukocytes, especially monocytes and neutrophils, through the activation of adrenergic receptors on immune system cells [27]. Conversely, RDN attenuates systemic inflammation. In one study, RDN reduced monocyte activation and monocyte-platelet aggregate formation, suggesting a reversal of inflammatory activity. Another study confirmed that RDN can modulate BP and inflammatory changes in monocytes in hypertensive patients [28]. Our results are in line with these data. We observed a significant decrease in monocyte numbers more than two years after intervention. Furthermore, we obtained interesting and important results with the NLR. It was reported that elevated NLR was associated with an increased risk of coronary artery disease and the development of more severe coronary lesions, CV and all-cause mortality [11,15,29]. In the NHANES

study, hypertensive patients with NLR values >3.5 had a twice as high risk of death from CV events than patients with NLR values <3.5 [29]. The average value of NLR in our group was 2.85 before RDN, which was in the upper normal range, according to most authors [11,15,29]. The observed decreasing trend in NRL after RDN might be considered a biomarker of reduced total CV risk, potentially through a decrease in systemic low-grade inflammation beyond BP reduction. Kidney function after RDN is also of utmost interest. The procedure proved to be safe, but discussion about whether RDN could improve kidney function is going on. Several authors have shown that RDN can lower albuminuria and proteinuria, especially in patients with resistant hypertension and normal kidney function. This benefit was usually linked to a stronger drop in BP [30]. Sousa et al. observed a statistically significant decrease in the ACR after a twelve-month follow-up period without a significant change in eGFR [9]. We found that a decrease in ACR by one unit was associated with a decrease in systolic BP of 0.19 mmHg. There were no changes in eGFR, regardless of which equation was used. Thus, RDN resulted in a slower yearly eGFR decline than expected for high-risk hypertensive patients.

Our study has several important strengths. This is the first study which observed a long period of follow-up improvements in subclinical inflammation and metabolism after RDN using new and simple biomarkers. When these results are confirmed in larger groups of patients, these biomarkers could be suggested as markers of effects beyond lowering BP after RDN. Secondly, we used a very strict procedure for selecting and follow-up of our patients, making our group very homogenous. Third, all RDN procedures were done by one very experienced interventional radiologist, and in all patients, the number of denervated spots was high and in line with recommendations. We included only patients who were denervated using Simplicity catheters and who were followed up for longer than two years. This study has a few limitations. Firstly, the small sample size of the cohort reduces the strength of the statistical analyses and limits the ability to generalize the findings to other populations of patients with resistant and difficult-to-control hypertension. An important methodological limitation is the absence of a control group, which makes it impossible to distinguish with complete certainty the effects of RDN from spontaneous changes or other factors that could influence the outcomes. Therefore, the results of the study should be interpreted with caution, and future research should include larger samples, control groups, and systematic monitoring of adherence and lifestyle habits to more clearly define the role of RDN in the modification of metabolic and inflammatory parameters.

We can conclude that our results indicate that RDN has a favourable effect beyond significantly lowering BP on metabolism and subclinical inflammation. Among these, NLR and TyGi stand out as potential surrogate endpoints for systemic improvement post-RDN. We also observed an improvement in albuminuria and stable eGFR, which contributes to a lower total CV risk. New reliable, simple, and cheap biomarkers of subclinical inflammation and insulin resistance could be suggested for follow-up on the effects of RDN beyond BP lowering. However, future studies with larger samples and independent validation cohorts are warranted to confirm these findings and to better define which patients derive multi-systemic benefits from RDN. Nevertheless, our findings imply that RDN may confer pleiotropic benefits, most notably anti-inflammatory and metabolic effects, that are not solely dependent on BP response. This aligns with emerging evidence suggesting RDN may modulate sympathetic tone and vascular function in broader ways.

Acknowledgment

We are thankful to all patients who agreed to participate in this study and to be included in the Croatian registry on renal denervation. We are grateful to all other members of Working group on renal denervation of the Croatian Society for Hypertension. This study was supported by the research grant of the Croatian Hypertension League.

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