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Hypertension or Something More? Rethinking Hypertensive Kidney Disease in ESRD Populations

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Abstract

Introduction. Hypertension is a significant contributor to end-stage renal disease (ESRD) in Macedonia, representing 25.8% of incident cases requiring renal replacement therapy (RRT). This study aimed to investigate the association between uncontrolled hypertension and hypertensive kidney disease, as well as the presence of nephroarteriosclerosis on renal biopsies.
Methods. This study utilized two data sources from the University Clinic of Nephrology in Skopje. Firstly, we conducted a record analysis linking data from a prior study on hypertension risk factors with patient records for hypertensive chronic kidney disease (CKD) at the Clinic over the past eight years. Secondly, we analyzed histopathological data from renal biopsies performed at the same Clinic.
Results. The analysis of hypertension risk factors revealed that 74% of patients in the study of risk factors had uncontrolled hypertension. Of these, only 1.7% had consulted the University Clinic of Nephrology for hypertensive kidney disease within the last eight years. In the analysis of renal biopsies (2017-2024) from 478 cases, nephroarteriosclerosis was confirmed in 2.5% of samples. Furthermore, clinical criteria for hypertensive kidney disease (Shlesinger criteria) were met by 17% of patients, with a similar proportion (17%) exhibiting uncontrolled hypertension.
Conclusion. By combining more precise diagnostic criteria, better clinical and pathological characterization, and improved data collection and registry management, the reliability of hypertensive nephrosclerosis statistics will meaningfully improve.

Keywords: end stage renal disease, hypertensive kidney disease, nephroarteriosclerosis, renal biopsy, renal replacement therapy, uncontrolled hypertension

Introduction

Hypertension is one of the leading causes of end-stage renal disease (ESRD) in Macedonia, accounting for around 25.8% of incident ESRD patients requiring renal replacement therapy (RRT) depending on the year and dataset [1]. There is a growing belief that the term "hypertensive nephropathy" (HN) should be abandoned, in favor of "hypertensive kidney disease" (HKD) [2]. This perspective is supported by the evidence that nephroarteriosclerosis, a key morphological feature, is not exclusive for hypertension and can be observed in various chronic nephropathies [3]. Furthermore, research indicates that hypertension may contribute to CKD progression rather than being the primary cause in many instances. The precise prevalence of HKD remains a subject of debate, compounded by diagnostic challenges arising from non-uniform criteria and infrequent biopsy confirmation [4].
The diagnosis of HKD should rely on clinical and morphological criteria [2]. Clinical, Schlesinger criteria involve family history of hypertension, evidence of longstanding arterial hypertension predating CKD and proteinuria <1g/d, typically elevated blood pressure (systolic BP >155 mm Hg based on newer optimized criteria), age >75 years, absence of diabetes mellitus and signs of hypertensive end-organ damage (hypertensive retinopathy, left ventricular hypertrophy and ultrasonographically small kidneys).
The sensitivity and specificity of the clinical criteria are suboptimal, underscoring the need for renal biopsy confirmation. Histopathologically, hallmarks of hypertensive nephrosclerosis involve changes in medium and small renal arteries, afferent/efferent glomerular arterioles, accompanied by medial hypertrophy of arterioles, duplication of internal elastic lamina, glomerular lesions like generalized sclerosis and focal segmental glomerulosclerosis, and interstitial fibrosis, tubular atrophy, and inflammatory cell infiltrates [5]. Kidney biopsy remains crucial for definitive diagnosis, especially in atypical cases or when proteinuria is significant. Unfortunately, renal biopsies are rarely performed in patients with hypertension and thus the diagnosis of HKD leading to CKD and RRT may not be accurate. There is a growing concern among nephrologists that hypertensive nephrosclerosis diagnosis often reflect incomplete diagnostic workups, where other ca-

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uses of CKD, including genetic kidney diseases, primary glomerular diseases, renovascular disease, or other nephropathies, are not excluded [6].
Despite these challenges, hypertension is acknowledged as a significant factor in the pathogenesis of CKD. The kidneys themselves play a crucial role in regulating blood pressure through hormonal mechanisms, and conversely, high blood pressure impacts the kidneys [7]. The understanding of the mechanisms of kidney damage in hypertension involves the loss of autoregulatory properties of renal microcirculation, leading to increased intraglomerular pressure, and adaptive reactions like arteriolar hypertrophy [8]. Genetic factors, such as variations in the MYH9 and APOL1 genes, are also being investigated for their role in predisposing individuals to kidney damage from hypertension, particularly in populations of African descent [9].

Material and methods

This study involved analysis of two types of data, available from the University clinic of Nephrology in Skopje.
The first type of data is record based analysis. Data from a 2003 study on hypertension risk factors in 2,367 patients from Macedonia with normal renal function, who were controlled in primary healthcare settings, were linked with clinical records from the "Moj Termin" system at the University Clinic of Nephrology over the last eight years. Patients were categorized based on their hypertension control status as Group 1 (controlled hypertension) and Group 2 (uncontrolled hypertension), among those undergoing antihypertensive treatment. This analysis included office blood pressure measurements, age, sex, and evidence of target organ damage as potential risk factors for uncontrolled hypertension. Patients with comorbidities or pre-existing CKD were excluded from this linkage.
For the second component of the study, we analyzed the histopathology of renal biopsies obtained at the University Clinic of Nephrology. This analysis aimed to determine the prevalence of nephroarteriosclerosis as a marker of HKD and to review the corresponding clinical characteristics of these patients.
Data were analyzed using SPSS version 26.0. Numerical variables were expressed as mean ± standard deviation (SD) and compared using Student's t-test. Categorical variables were analyzed with the chi-square test. The frequency of nephroarteriosclerosis on histopathological findings in renal biopsies was presented as percentages, and a risk ratio was calculated to evaluate associations.

Results

In a 2003 study investigating risk factors for hypertension, 74% of participants were found to have uncontrolled hypertension (Table 1). This subgroup was predominantly female (63%) with a mean age of 64.1±10 years. The average systolic blood pressure among patients with uncontrolled hypertension (N=1.749) was 166±15 mmHg, and the average diastolic pressure was 94±10 mmHg.

Table 1. Average blood pressure values, age and gender in the groups with controlled and uncontrolled blood pressure

N=2367	Controlled HT 618 pts (26%)	Uncontrolled HT 1749 (74%)	P
Women	357 (58%)	1111 (63%)	0.000
Mean age (years)	61 12	64 10	0.000
Average systolic blood pressure (SBP) in mmHg	1328	166 15	0.000
Average diastolic blood pressure (DBP) in mmHg	83 8	94 10	0.000

Among patients with uncontrolled hypertension, 1.7% sought consultation at the University Clinic of Nephrology over the last eight years for HKD and CKD (Table 2). There was no statistically significant difference compared to controls, with a risk ratio of 1.5. The analysis was limited by the absence of data on patients who died or migrated.

Table 2. The risk for check ups for hypertensive kidney disease and CKD

N=2367	Controlled HT- 618 pts (26%)	Uncontrolled HT -1749 (74%)	P	Risk ratio for future check ups for CKD among uncontrolled HT
Patients with future check ups for CKD	15/618(2.4%)	30/1749(1.7%)	0.17	1.5(95% CI 0.8-2.8)

The second dataset comprised an analysis of renal biopsies performed at the Clinic between 2017 and 2024. Among 478 biopsies, histopathological findings confirmed nephroarteriosclerosis in 2.5% of cases (Table 3). Of the patients diagnosed with nephroarteriosclerosis, 17% met clinical (Shlesinger) criteria for

HKD and had a history of uncontrolled hypertension. Proteinuria exceeding 1 g/day was observed in 58% of these patients. In 17% of cases, further evaluation-including review of medical history and genetic analysis -led to a confirmed diagnosis of Alport syndrome. Hemodialysis was initiated immediately following biopsy in 17% of patients and within four years in an additional 8.5%.

Table 3. Findings of nephroarteriosclerosis on renal biopsies and frequency of clinical characteristics

Nr. of renal biopsies (2017-2024)	N=478
Nephroarteriosclerosis (NAS)	12/478(2.5%)
Uncontrolled HT in pts with NAS	2/12(17%)
Schlesinger criteria for hypertensive kidney disease in NAS	2/12(17%)
Proteinuria above 1 g/dU in NAS	7/12(58%)
GFR<60 ml/min in NAS	7/12(58%)
Further analysis showed Alport syndrome in NAS	2/12(17%)
Started HD immediately after biopsy (NAS)	2/12(17%)
Started HD after 4 years (NA	1/12(8,5%)

Discussion

The findings of this study demonstrate that among the high proportion of patients with uncontrolled hypertension identified in the 2003 cohort, only 1.7% subsequently presented to the University Clinic of Nephrology for evaluation of hypertensive CKD. The calculated risk ratio for developing hypertensive CKD was 1.5. A smaller proportion of uncontrolled HT patients had follow-ups compared to the controlled HT group (1.7% vs. 2.4%), which could suggest underreferral or lack of CKD awareness in patients with uncontrolled HT. The study design did not include continuous follow-up and did not account for patients who died, potentially underestimating the true burden of CKD in this population.

Few studies have quantified the risk of incident CKD attributable to hypertension. A meta-analysis by Weldegeorgis *et al*. reported that the relative risk (RR) of incident CKD or ESRD in individuals with hypertension, compared to those with optimal blood pressure, was 1.56 in women and 2.06 in men [10], indicating a notably higher risk in men.

A graded association between time-varying blood pressure and the development of CKD has been demonstrated, with increased CKD risk observed at systolic blood pressures (SBP) ≥130 mmHg and diastolic blood pressures (DBP) ≥90 mmHg [11-13]. Earlier studies have similarly shown a continuous, graded relationship between elevated blood pressure and the onset of kidney disease [14,15].

Uncontrolled hypertension is expected to exert long-term detrimental effects on renal function, and nephroarteriosclerosis is frequently identified in kidney biopsies performed in this context. In our cohort, nephroarteriosclerosis was confirmed in 2.5% of all renal biopsies, a finding consistent with previously published data [16,17]. These results support the argument for expanding the indications for renal biopsy to improve diagnostic accuracy.

A significant clinicopathological discordance was observed in cases of biopsy-confirmed nephrosclerosis. In approximately 50% of these cases, concomitant glomerular disease was identified [18]. Similarly, our findings revealed that only 17% of patients with nephroarteriosclerosis had uncontrolled hypertension and fulfilled the clinical criteria for hypertensive nephropathy. In contrast, a substantial proportion (58%) exhibited significant proteinuria (>1 g/day) and severely reduced renal function (eGFR <30 mL/min/1.73 m²).

Furthermore, in 17% of patients initially diagnosed with nephroarteriosclerosis, Alport syndrome was confirmed following further clinical evaluation. A significant number of these patients required initiation of hemodialysis shortly after the biopsy.

In summary, the current limitations in diagnostic precision-including the absence of specific diagnostic criteria, the predominance of exclusion-based approaches, the limited specificity of renal biopsy findings, and incomplete data capture in national registries-render existing statistics on hypertensive nephrosclerosis unreliable and not fully reflective of the true prevalence or disease burden. To improve diagnostic accuracy and epidemiological reporting, the development and implementation of more comprehensive diagnostic criteria and standardized biopsy protocols are strongly recommended.

Conclusion

By combining more precise diagnostic criteria, better clinical and pathological characterization, and improved data collection and registry management, the reliability of hypertensive nephrosclerosis statistics will meaningfully improve.

Conflict of interest statement. None declared.

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