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QUESTIONNAIRE-BASED SCREENING FOR PRIMARY HYPEROXALURIA IN HEMODIALYSIS PATIENTS: CLINICAL IMPLICATIONS AND A PRACTICAL PERSPECTIVE

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Abstract

Primary hyperoxaluria (PH) is a rare inherited metabolic disorder that is frequently underrecognized in adult patients, particularly those undergoing chronic hemodialysis. Diagnostic challenges arise from the reduced reliability of biochemical markers in advanced kidney failure, often leading to delayed or missed diagnosis and the development of systemic oxalosis. Recent studies have proposed a simple clinical prediction model based on readily available “red flags” for identifying patients at increased risk of PH1 in dialysis populations. Building on this approach, we propose implementing a questionnaire-based screening strategy adapted for routine clinical use. The potential applicability of this strategy in North Macedonia is further outlined, as a significant proportion of patients receiving kidney replacement therapy have an unknown primary renal disease. Given the existing dialysis care

system, systematic screening using a simple questionnaire could be feasibly integrated into clinical practice. Such an approach may facilitate earlier identification of high-risk patients, enable targeted genetic testing, and improve clinical outcomes.

Keywords**:** *Hemodialysis; Primary Hyperoxaluria; Surveys; Questionnaires.*

Introduction

Primary hyperoxaluria (PH) is a group of rare autosomal recessive disorders of glyoxylate metabolism characterized by excessive endogenous oxalate production. Three types of PH have been described (PH1, PH2 and PH3), caused by defects in specific hepatic enzymes: alanine–glyoxylate aminotransferase (AGT, encoded by AGXT gene) in PH1, glyoxylate reductase/hydroxypyruvate reductase (GRHPR) in PH2, and 4-hydroxy-2-oxoglutarate aldolase (HOGA1) in PH3 (1). The pathophysiology of kidney injury in PH is driven by hepatic overproduction of oxalate, which is primarily excreted by the kidneys. Persistent hyperoxaluria leads to calcium oxalate supersaturation, resulting in recurrent nephrolithiasis, nephrocalcinosis, and progressive tubulointerstitial damage. As kidney function declines, plasma oxalate levels rise, exceeding renal clearance and leading to systemic oxalosis with multi-organ involvement (1,2).

Despite this well-established pathophysiology, PH remains underdiagnosed, particularly in adult patients. Clinical heterogeneity and often subtle early manifestations contribute to delayed recognition. Diagnostic delay is substantial, with reports suggesting a median delay of 3–5 years from symptom onset to diagnosis, and a significant proportion of patients being diagnosed only after progression to advanced chronic kidney disease or end-stage kidney disease (ESKD) (3,4). Our real-world experience further illustrates this challenge. A case

from North Macedonia demonstrated that PH may remain unrecognized until after kidney transplantation, when early graft failure led to the diagnosis, following detection of calcium oxalate deposition on graft biopsy (5). Such cases highlight the critical implications of missed diagnosis, particularly given that isolated kidney transplantation without correction of the underlying metabolic defect is associated with rapid disease recurrence and graft loss. Moreover, a subset of patients undergoing chronic hemodialysis with presumed unknown etiology of kidney failure may, in fact, have unrecognized PH or clinically significant hyperoxaluria. Although the exact prevalence remains uncertain, prediction models suggest that a substantial proportion of dialysis patients exhibit clinical "red flags" for PH, underscoring the need for simple and accessible PH screening strategies in this high-risk population (3). Recently published national evidence-based guidelines for primary hyperoxaluria (2025) provide a structured framework for disease management; however, they do not specifically address systematic screening of patients undergoing chronic hemodialysis (6).

Clinical Importance of Identifying PH in Dialysis Patients

Recognition of PH in patients undergoing chronic dialysis remains critically important despite the presence of advanced kidney failure. Ongoing hepatic overproduction of oxalate persists even in the absence of renal function, leading to progressive systemic oxalosis with deposition of calcium oxalate in multiple organs, including bone, myocardium, retina, and vascular tissues, resulting in significant morbidity and mortality (2,4). Establishing the diagnosis of PH in dialysis patients directly influences dialysis management strategies in HD units. Current recommendations by ERKNet and OxalEurope emphasize the need for intensified and individualized dialysis regimens in patients with PH, as conventional

schedules are insufficient to control the oxalate burden. This includes the use of high-flux hemodialysis with maximal blood flow, as well as increased dialysis sessions frequency, tailored to plasma oxalate levels and clinical manifestations of systemic oxalosis in order to improve patients' survival (2).

Failure to establish the diagnosis of PH prior to kidney transplantation carries major clinical consequences. Isolated kidney transplantation in undiagnosed PH is associated with a high risk of early graft failure due to rapid oxalate deposition in the allograft, as demonstrated in clinical reports (4,5). Importantly, identification of PH has implications beyond the individual patient. Given the autosomal recessive inheritance pattern, early diagnosis enables targeted family screening and detection of affected carrier relatives, allowing timely intervention and prevention of disease progression in other family members (2,7). In addition, the emergence of novel disease-modifying therapies, including RNA interference–based treatments that reduce hepatic oxalate production, further emphasizes the value of early and accurate diagnosis even in advanced disease stages (2).

Taken as a whole, these considerations highlight that diagnosing PH in dialysis patients is not merely of academic interest, but has direct implications for prognosis, transplant strategy, family counseling and therapeutic decision-making.

From Diagnostic Challenges to Practical Solutions: Questionnaire-Based Screening

The biochemical diagnosis of PH in patients on dialysis is limited by several fundamental pathophysiological and analytical constraints. In advanced kidney failure, urinary oxalate excretion is no longer a reliable marker, as reduced glomerular filtration leads to decreased urinary elimination despite ongoing hepatic overproduction of oxalate (4,8,9). In this setting,

plasma oxalate becomes the principal marker; however, its diagnostic specificity is significantly reduced. Plasma oxalate levels increase in all patients with kidney failure due to reduced clearance, and values may overlap between PH and non-PH populations. Importantly, plasma oxalate levels exceeding the supersaturation threshold of approximately 30–50 μmol/L are associated with systemic oxalosis, but this threshold may be reached in both primary and secondary hyperoxaluria in dialysis patients (9,10). Moreover, plasma oxalate concentrations are highly dependent on dialysis-related factors, including dialysis modality, frequency, membrane type, and timing of sampling relative to dialysis sessions. Post-dialysis measurements may underestimate total body oxalate burden, whereas pre-dialysis levels may vary considerably, further complicating interpretation (2). These diagnostic limitations are further illustrated by reported cases of delayed diagnosis in dialysis patients, where PH remained unrecognized for years despite ongoing treatment. In one such case, the diagnosis was established only after the development of systemic oxalosis with severe multisystem involvement, highlighting the consequences of relying solely on conventional diagnostic approaches (11).

Differentiating primary from secondary hyperoxaluria represents an additional challenge in this population. Secondary causes, including increased intestinal absorption or dietary factors, may also lead to elevated plasma oxalate levels in patients with kidney failure, thereby reducing the specificity of biochemical markers alone (4,10) Although adjunctive markers such as plasma glycolate may support the diagnosis of PH1, their limited availability restricts their routine use. At the same time, pre-analytical issues, including oxalate precipitation in urine samples and strict requirements for plasma handling, further reduce the reliability of biochemical testing (9,10). Consequently, reliance on biochemical markers alone is insufficient for accurate diagnosis in dialysis populations. Importantly, the recently

adopted national evidence-based guidelines for primary hyperoxaluria (2025) primarily focus on diagnostic and therapeutic strategies following established clinical suspicion, without addressing systematic screening in dialysis populations (6). Given that a significant proportion of dialysis patients have an unknown primary renal disease, this represents a clinically relevant gap. The questionnaire-based screening approach proposed in this study may serve as a practical and implementable strategy to bridge this gap by enabling early identification of high-risk patients. In this context, current expert recommendations emphasize genetic testing in patients with high clinical suspicion; however, given its cost and limited accessibility, initial patient selection using simple clinical tools, such as questionnaire-based screening, may represent a necessary and pragmatic first step (4,12).

Clinical Prediction Model and Questionnaire-Based Screening

A clinical prediction model for PH1 in adult dialysis patients has recently been developed based on five readily available clinical "red flags": active nephrolithiasis or nephrocalcinosis, prior graft loss, early initiation of hemodialysis (before 40 years of age), and family history of chronic kidney disease (3). Using these variables, a scoring system ("PH score") was developed, demonstrating excellent diagnostic performance, with strong discrimination ability (AUC 0.93 in the training cohort and 0.85 in validation). The score ranges from 0 to 3, with higher values indicating a greater probability of PH1. Importantly, even a low threshold (≥1 positive criterion) provides high sensitivity (up to 91%), supporting its role as an initial screening tool in dialysis populations (3).

The clinical applicability of this algorithm has also been demonstrated in a multicenter Italian cohort of adult dialysis patients with genetically confirmed PH1, in which at least one "red

flag" was present in 93% of patients, confirming the high sensitivity of the model in real-world settings (8). As shown in the results of this study, active nephrolithiasis was the most frequent feature (87%), followed by early dialysis initiation, nephrocalcinosis and family history of CKD, supporting the relevance of these variables for clinical screening.

Based on this model, we adapted a translated Macedonian version of the questionnaire suitable for routine clinical use, incorporating four key elements derived from the original "red flags": (1) history of active nephrolithiasis, defined as recurrent, early-onset (<25 years), bilateral, or familial stone disease; (2) early initiation of dialysis before 40 years of age, suggesting rapidly progressive kidney disease; (3) previous kidney graft loss without a clear alternative explanation; and (4) family history of chronic kidney disease, reflecting the inherited nature of the disorder. The original version of the questionnaire is available at https://qxmd.com/calculate/calculator_886/primary-hyperoxaluria-prediction-tool (3). Each positive response in the questionnaire contributes to a cumulative score, with the presence of at least one criterion indicating a high-risk profile that should prompt further diagnostic evaluation. Increasing number of positive responses is associated with higher PH specificity, reaching up to 100% when three criteria are present (3,8). The Macedonian version of the questionnaire is provided as supplementary material to this manuscript.

Implementation of a Questionnaire-Based Screening in North Macedonia

According to the ERA Registry Annual Report 2023, the prevalence of patients with the need for kidney replacement therapy (KRT) in North Macedonia is 974.1 per million population (pmp), corresponding to a total of 1,779 patients. Among them, 84.7% are treated with hemodialysis, 0.8% with peritoneal dialysis, and 14.5% have a functioning kidney

transplant. Notably, 87.1 pmp (8.9%) of prevalent patients on KRT have an unknown primary renal disease. In 2023, the incidence of patients on KRT was 254.9 pmp, with a mean age of 65.2 years and a male predominance (57%). Among incident patients, 18.1 pmp (7.8%) have an unknown underlying kidney disease (13).

The dialysis care structure in North Macedonia provides a favorable framework for the implementation of systematic screening. Currently, there are 23 dialysis centers distributed across the country, each staffed with physicians responsible for the longitudinal care of patients undergoing chronic hemodialysis, with full access to their medical history (14). Within this structure, the proposed questionnaire-based screening could be readily integrated into routine clinical practice. Screening may be particularly valuable when performed at the initiation of dialysis, as well as during pre-transplant evaluation, where identification of undiagnosed primary hyperoxaluria has direct implications for transplant strategy and graft survival. The questionnaire would be administered by the treating nephrologist at the dialysis center, who would subsequently calculate the PH score for each patient. Particular focus should be placed on patients with unknown primary renal disease, as well as those with clinical features suggestive of PH, including a history of nephrolithiasis, early-onset kidney failure, or family history of kidney disease. Patients identified as high risk, based on a positive PH score, should be referred to the University Clinic of Nephrology in Skopje for further evaluation, including genetic testing to confirm the diagnosis. Such a structured, stepwise approach would allow efficient allocation of resources by prioritizing high-risk individuals for advanced diagnostics, while maintaining feasibility within the existing healthcare system.

Conclusion

Primary hyperoxaluria remains an underrecognized cause of kidney failure in dialysis populations, largely due to diagnostic limitations and clinical heterogeneity. Questionnaire-based screening represents a simple, low-cost, and scalable approach for identifying high-risk patients, particularly in settings with limited access to advanced diagnostics. In North Macedonia, where a notable proportion of patients on kidney replacement therapy have an unknown primary renal disease, and dialysis care is centralized within a structured network of centers, the implementation of such a screening strategy is both feasible and clinically justified. Integrating questionnaire-based screening into routine dialysis practice may facilitate earlier diagnosis, enable targeted genetic testing, and ultimately improve patient outcomes.

Declarations

Ethics Approval and consent to participate: Ethical approval was not required for this narrative review article because no human participants, patient data, or experimental interventions were involved.

Informed consent: Not applicable.

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contributed through supervision, critical revisions, and important scientific guidance. All authors reviewed and approved the final version of the manuscript.

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