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ORIGINAL ARTICLE

BEYOND LIVING DONOR KIDNEY TRANSPLANTATION IN COL4 NEPHROPATHY - A REAL-WORLD CLINICAL DILEMMA IN LIGHT OF CURRENT GUIDELINES

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ABSTRACT

Kidney transplantation is the best choose of modality for treatment of the patients with end-stage kidney disease (ESKD). However, hereditary conditions like COL4 nephropathy introduce significant obstacles in living kidney donor selection. This review presents a real-world clinical dilemma involving a 24-year-old male with autosomal recessive COL4 nephropathy (Alport syndrome) and his 51-year-old mother, a heterozygous carrier. We analyzed the clinical spectrum of COL4 nephropathy in North Macedonia, where 92 patients have been identified via next-generation sequencing (NGS), and COL4A5 mutations were the most prevalent at 67.4%. Because current the kidney disease improving global outcomes (KDIGO) recommendations for living kidney donor evaluation are general and offer scarce guidance for hereditary conditions, we evaluated the recent 2025 ERK Net/ERA/ESPN criteria. These updated guidelines suggest that while donation is generally avoided in carriers, it may be considered in highly selected individuals over 40 years of age with preserved kidney function and no subclinical kidney damage on biopsy. Careful and individualized evaluation of potential living donors from affected families is essential. This approach is particularly important in settings with persistent organ shortages and limited access to deceased-donor transplantation.

INTRODUCTION

Kidney transplantation remains the optimal treatment modality for patients with end-stage kidney disease (ESKD), regardless of the underlying etiology [1]. However, in hereditary kidney diseases such as COL4 nephropathy, the evaluation of potential living kidney donors poses unique clinical and ethical challenges [2].

This dilemma is well illustrated by a real-life clinical scenario: a 24-year-old male with genetically confirmed autosomal recessive COL4 nephropathy (Alport syndrome) who progressed to ESKD and has been treated with hemodialysis (HD) for one year. Despite being listed for deceased-donor kidney transplantation for almost two years, no suitable organ has become available. His 51-year-old mother, a heterozygous carrier of the pathogenic COL4A3 mutation, presents with isolated persistent microhematuria, normal kidney function, and no proteinuria. The key clinical question arises: ***can she be considered a safe living kidney donor?***

This case reflects a growing challenge in the management of COL4 nephropathy in the context of organ shortage and highlights the need for clearly defined, evidence-based criteria for living donor evaluation.

METHODS AND MATERIALS

In this narrative review we performed a comprehensive analysis by reviewing clinical data and international recommendations for living kidney donation in COL4 nephropathy. A literature search was conducted, using PubMed and the ERA Registry [3]. Selection was prioritized based on the 2017 KDIGO and latest 2025 ERK Net/ERA/ESPN guidelines [4,5]. Population-specific data were sourced from the North Macedonian National Registry for Genetic Diseases and the registries under the umbrella of Ministry of Health of North Macedonia.

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COL4 nephropathy: definition and clinical spectrum

COL4 nephropathy is a hereditary disorder of the glomerular basement membrane caused by mutations in the COL4A3, COL4A4, or COL4A5 genes, characterized by persistent hematuria and often progressing to chronic kidney disease (CKD) or kidney failure (KF) [6]. The classical forms include X-linked Alport syndrome (XLAS), autosomal recessive Alport syndrome (ARAS), and autosomal dominant Alport syndrome (ADAS), each associated with variable renal and extrarenal manifestations such as sensorineural hearing loss and ocular abnormalities[6].

COL4 nephropathy in North Macedonia

Over the past decade, 92 patients with genetically confirmed COL4 nephropathy using next-generation sequencing (NGS) have been identified in North Macedonia, including 49 males (53.3%), with a mean age at diagnosis of 24 years. Nearly half (45.7%) were diagnosed before the age of 14, while 5.4% were older than 60 years. Mutations in COL4A3, COL4A4, and COL4A5 were detected in 6.5%, 26.1%, and 67.4% of patients, respectively. All patients presented with microhematuria, and 67.4% had a positive family history. Extrarenal manifestations included sensorineural deafness in 22.8% and ocular abnormalities in 12.0%. Importantly, ocular abnormalities and hearing loss were significantly associated with earlier initiation of kidney replacement therapy (KRT) compared to patients without these abnormalities ($p < 0.05$) [7].The mean age at CKD diagnosis was 18.2 years, and 14 patients (15.2%) required KRT. All patients requiring KRT were treated with HD at some point; one received peritoneal dialysis (PD), and eight underwent kidney transplantation. The mean age at initiation of KRT was 33.1 years [7].

Kidney transplantation outcomes in COL4 nephropathy

National transplant registries do not routinely report annual transplant numbers specifically for COL4 nephropathy. In a large cohort by *Mallet et al.*, 296 patients with COL4 nephropathy were identified among 58,422 individuals initiating KRT (approximately 0.5%) [8]. Similarly, ERA-EDTA Registry data showed that between 1990 and 2009, 408 male patients with COL4 nephropathy underwent kidney transplantation, accounting for less than 1% of all transplants [8,9]. Patients transplanted due to COL4 nephropathy demonstrate excellent long-term outcomes, with graft survival rates of 75–80% at 10 years and over 45% at 20 years [10]. This favorable prognosis is attributed to the absence of disease recurrence and the younger age of recipients, reinforcing kidney transplantation as the preferred treatment option for these patients[10].

Transplantation practice in North Macedonia

In North Macedonia, a country with approximately 1.83 million inhabitants, the prevalence of patients on KRT in 2022 was 945 per million population (pmp). Of these, 85.3% were treated with HD/hemodiafiltration (HDF), 0.8% with PD, and 13.9% had a functioning kidney transplant, with 54.5% from living donors and 45.5% from deceased donors [3,11]. However, according to the latest analysis from the ERA Registry, North Macedonia has the lowest and most stable KRT prevalence growth in the region, with an average annual percent change (AAPC) of +2.2% (95% CI: +1.7 to +2.0) during 2010–2019, comparable to neighboring countries such as Serbia (+3.4%), Bulgaria (+3.3%), and Albania (+10.3%) [12].

During the last decade, eight patients with COL4 nephropathy underwent kidney transplantation: three received deceased-donor grafts with stable function after a mean follow-up of 3.5 years, while five received living-related donor grafts from non-carriers of COL4 mutations. Two of these grafts were lost due to chronic allograft nephropathy and graft malignancy, respectively, while the remaining recipients maintain stable graft function.

Due to the difficulty in identifying genetically safe living-related donors, deceased-donor transplantation is often preferred in patients with COL4 nephropathy. Currently, three patients with genetically confirmed COL4 nephropathy are listed for deceased-donor kidney transplantation in North Macedonia.

Living kidney donation: challenges and evolving recommendations

The shortage of organs highlights the need to optimize living donation in COL4 nephropathy through precise criteria defining when and under what conditions mutation carriers may safely serve as donors. According to the *kidney disease: improving global outcomes* (KDIGO) guidelines, the evaluation of living kidney donors is general and not disease-specific, and individuals with genetically confirmed kidney diseases should not be considered as donors [4]. These recommendations adopt a deliberately conservative approach, prioritizing donor safety in the context of limited long-term outcome data. The KDIGO guidelines do not provide specific criteria for evaluating carriers of COL4 nephropathies because outcome data in heterozygous donors are scarce, leaving much of the decision-making to the clinical judgment of individual transplant centers [4]. This uncertainty reflects the broad phenotypic variability of COL4-related disorders and the difficulty in predicting long-term renal outcomes in asymptomatic or mildly affected carriers [13]. Although KDIGO recommends careful interpretation of clinical findings, detailed family history assessment, genetic testing, consideration of alternative donors, and attention to donor age, it does not define age thresholds as clearly as the most recent ERK Net, ERA, and ESPN initiative [4,5]. As a result, clinical practice varies considerably between transplant centers, particularly in regions with limited access to deceased-donor transplantation.

Driven by these challenges, a joint initiative by ERK Net, ERA, and ESPN, in collaboration with patient advocacy groups, published updated guidelines in mid-2025 addressing the diagnosis, management, and treatment of COL4 nephropathy [5]. With regard to the assessment of potential living kidney donors in affected families, these guidelines strongly recommend genetic testing and precise genotype determination (COL4A3, COL4A4, and COL4A5), as clinically unaffected relatives may still carry pathogenic variants [5]. Current evidence indicates that the risk of developing kidney failure in heterozygous COL4A3 or COL4A4 variant carriers is less than 3% by the age of 60 years and slightly above 3% by the age of 80 years, whereas females with X-linked Alport syndrome have an estimated risk of approximately 20% by the age of 60 years [5,14]. In light of these data, living kidney donation is generally not advisable in heterozygous ARAS carriers and XLAS females, unless no alternative donor options exist, given the potential additive risk imposed by nephrectomy on an already vulnerable glomerular basement membrane.

Heterozygous carriers under 40 years of age with functional or structural kidney abnormalities such as: albuminuria, reduced estimated glomerular filtration rate, unexplained hematuria, or histological evidence of interstitial fibrosis and tubular atrophy on kidney biopsy are not considered suitable candidates for donation. However, in carefully selected carriers older than 40 years, with preserved kidney function, absence of proteinuria, and no evidence of subclinical kidney damage on renal biopsy, living kidney donation may be considered when the anticipated benefits outweigh the potential long-term risks to the donor and the well-being of the family as a whole [5]. Lifelong post-donation monitoring is strongly recommended, and renin-angiotensin system blockade should be initiated if microalbuminuria or hypertension develops, aiming to mitigate secondary renal injury and preserve long-term kidney function in donors. Audiometric evaluation is advised only in individuals reporting hearing impairment, while routine ophthalmologic screening is not recommended due to the rarity of ocular involvement in heterozygous carriers [5].

Individualized decision-making and clinical implications

To date, several case reports and small series of living-related kidney transplantation in COL4 nephropathy have been published, describing both favorable and unfavorable outcomes for donors and recipients [15-17]. Collectively, these reports demonstrate that no single clinical or genetic criterion can universally define donor suitability and consistently emphasize the necessity of an individualized approach, supported by comprehensive counseling and shared decision-making.

The clinical scenario of a heterozygous mother with isolated microhematuria, preserved kidney function, and advanced age exemplifies this "*gray zone*," in which living kidney donation may be considered only under strict evaluation protocols and in the absence of viable alternative donors. In such circumstances, a personalized approach incorporating transparent discussion of potential risks and benefits for both donor and recipient and acknowledging the residual uncertainty inherent to living kidney donation is imperative for achieving a successful and ethically sound outcome[18].

CONCLUSION

In summary, kidney transplantation remains the best treatment for patients with ESKD, including those with COL4 nephropathy. Careful and individualized evaluation of potential living donors from affected families is essential, guided by the latest international recommendations. Implementing these measures is particularly important in settings with persistent organ shortages and limited access to deceased-donor transplantation.

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Competing interests:

The authors declare no competing interests and have no financial interests to declare.

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