GIN

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Il *Giornale Italiano di Nefrologia* è la rivista bimestrale di educazione continua della Società Italiana di Nefrologia. Tra i suoi principali obiettivi sono l'aggiornamento, la pubblicazione di linee guida e la comunicazione intra- e interdisciplinare. Il GIN pertanto offre la più aggiornata informazione medico-scientifica rivolta al nefrologo sotto forma di rassegne, rubriche tematiche, casi clinici e articoli originali.

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Raccogliere un'eredità e aprire nuove prospettive

Editoriali

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Caro Gaetano, cari Membri dell'Editorial Board, cari Lettori,

raccolgo con profonda emozione e sincera gratitudine le parole di Gaetano, e desidero esprimere il mio più sentito ringraziamento per il significativo contributo offerto nel corso dei suoi otto anni alla guida del *Giornale Italiano di Nefrologia*, che hanno rappresentato un periodo di crescita solida, coerente e lungimirante.

Grazie alla sua guida, il GIN ha saputo rafforzare la propria identità scientifica, ampliare il proprio orizzonte internazionale e consolidare il legame con la comunità nefrologica italiana con un progressivo rafforzamento della qualità scientifica.

I risultati raggiunti – dall'avvio del processo di indicizzazione ai sistemi di archiviazione, dall'adozione dei DOI, all'adozione di standard editoriali avanzati e alla valorizzazione della dimensione digitale – testimoniano una visione editoriale attenta, rigorosa e orientata al futuro, con una costante attenzione alla qualità.

A Gaetano va il mio più sincero riconoscimento per la competenza, la dedizione e il senso di responsabilità con cui ha svolto il proprio incarico, contribuendo in modo determinante al consolidamento del ruolo del GIN nel panorama scientifico nazionale e internazionale.

Desidero ringraziare anche l'Editorial Board, gli autori, i revisori e i lettori, che rappresentano l'anima viva del Giornale. È grazie al loro contributo quotidiano se il GIN continua a essere uno spazio di confronto, crescita e condivisione scientifica.

Assumo questo incarico con profonda consapevolezza dell'importante lavoro svolto e con l'impegno a proseguire nel solco tracciato, valorizzando i risultati raggiunti e promuovendo ulteriormente lo sviluppo scientifico ed editoriale del GIN.

Il mio impegno sarà quello di proseguire lungo la direzione già intrapresa, valorizzando quanto costruito e affrontando con determinazione le nuove sfide che attendono la nostra disciplina, in un momento di grande rivoluzione e innovazione terapeutica.

Tra gli obiettivi prioritari rientrano il perseguimento dell'Impact Factor, il rafforzamento dell'internazionalizzazione, l'attenzione all'innovazione editoriale e l'uso responsabile delle nuove tecnologie. In questa prospettiva la nostra forza è rappresentata in larga parte dai giovani e a loro vorrei dedicare ampio spazio nel comitato editoriale e nelle pubblicazioni.

Viviamo una fase di profonde trasformazioni nella nefrologia, nella ricerca e nella pratica clinica. In questo contesto, il *Giornale Italiano di Nefrologia* è chiamato a confermare il proprio ruolo come un punto di riferimento autorevole, capace di coniugare rigore scientifico, apertura al cambiamento, trasparenza e radicamento nella realtà italiana.

Con questo spirito, intendo svolgere il mio mandato in un'ottica di continuità, dialogo e collaborazione, nella convinzione che solo attraverso un impegno condiviso sarà possibile consolidare ulteriormente il prestigio della rivista.

Grazie, Gaetano, per l'esempio che ci lasci.

Grazie a tutti per la fiducia.

Con stima e impegno,

Laura Cosmai

Tempistica e Durata delle Visite Nefrologiche in Italia

Documenti di indirizzo: la voce del GIN

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Premessa

L'Organizzazione Mondiale della Sanità il 23 maggio 2025 ha aggiunto la malattia renale cronica (MRC) alla lista delle malattie cronico-degenerative da essa riconosciute quali priorità per la salute pubblica [1]. La MRC colpisce il 10-15% della popolazione mondiale, più di 850 milioni di persone; di questi, il 5% ha bisogno di trattamento renale sostitutivo. Il numero totale di pazienti nefropatici nel mondo è il doppio dei pazienti con diabete mellito, venti volte maggiore dei pazienti con neoplasia, superando anche per mortalità e spesa sanitaria le altre malattie cronico-degenerative: il costo complessivo della MRC è oggi considerato "catastrofico" [2]. In Italia l'epidemiologia della MRC è stata stimata dallo studio CARHES (principale Health Examination Survey europea sulla MRC). La survey nazionale, eseguita da ISS-ANMCO-SIN su campione di 7546 adulti provenienti da tutte le Regioni Italiane ha evidenziato per il 2010 una prevalenza di MRC di circa il 7%, con dati sovrapponibili ed omogenei nei due sessi e nell'intero territorio; la prevalenza aumenta progressivamente con l'età (17% negli ultrasettantenni) [3].

Questi dati sono verosimilmente sottostimati poiché nell'ultima decade la MRC ha presentato un incremento della prevalenza in tutto il mondo.

Le dimensioni della patologia MRC in Italia sono descritte in Tabella 1 [3–5].

L'intervento del nefrologo nelle fasi precoci della malattia renale è essenziale per permettere di rallentarne la progressione; attraverso la corretta pianificazione diagnostica-terapeutica ed il ricorso a trattamenti dietetici e farmacologici personalizzati, si garantisce un miglioramento della prognosi *quoad vitam* e della qualità di vita dei pazienti e di conseguenza anche una riduzione della spesa sanitaria correlata alla MRC, come indicato dalle nuove Linee Guida Internazionali sulla MRC [6]. Il nefrologo ha anche il compito di disegnare il miglior percorso di cura negli stadi avanzati di malattia guidando il paziente verso il trattamento sostitutivo più

indicato (trapianto, dialisi peritoneale, emodialisi, terapia conservativa) e di favorire la prossimità e domiciliazione delle cure.

MRC in fase non dialitica: 4-5 milioni
MRC associata a rischio CV, ospedalizzazioni e minore implementazione di trattamenti salvavita (malattie infettive, cardiologiche, oncologiche)
Pazienti ESKD: 45.000 in trattamento dialitico sostitutivo (6.000 nuovi/anno), 28.000 con trapianto di rene (2.000 nuovi/anno)
Mortalità annua ESKD: 17% Emodialisi, 12% Peritoneale, 4% Trapianto
Costo medio dell'emodialisi ospedaliera: 40.000/50.000 euro/anno per paziente (il SSN spende circa 2.5 miliardi euro/anno per lo 0.08% della popolazione)
MRC avanzata e ESKD determinano perdita di produttività (giornate lavorative del paziente e/o caregiver)

Tabella 1. Il "peso" della Malattia Renale Cronica in Italia.

Razionale clinico-organizzativo

Per la numerosità attuale e futura della popolazione affetta da MRC, e per un'ottimizzazione del trattamento ed omogeneità nell'accesso alle cure di tutti i pazienti, è fondamentale definire una standardizzazione dei percorsi e una corretta e uniforme pianificazione dell'organizzazione ed erogazione delle cure, al fine di eliminare le differenze qualitative e quantitative oggi esistenti tra le diverse regioni e strutture, in termini di offerta nefrologica.

In questo contesto l'organizzazione dell'attività ambulatoriale e della presa in carico rappresentano un elemento fondamentale per la corretta gestione ospedale-territorio della persona affetta da MRC. Definire la cadenza dei controlli e la tempistica delle prestazioni ambulatoriali (prime visite e controlli) è indispensabile per un'adeguata gestione delle agende ambulatoriali specialistiche, per la riduzione delle liste d'attesa e per l'ottimizzazione delle risorse umane e della spesa sanitaria. La complessità intrinseca della MRC, le notevoli differenze evolutive delle diverse patologie renali e la frequente comorbidità, condizionano ulteriormente i percorsi di cura e la presa in carico della persona affetta da MRC.

Questi importanti aspetti sono oggi declinati non solo dalle ultime Linee Guida internazionali sulla MRC [6], ma anche dal Percorso Preventivo Diagnostico Terapeutico Assistenziale (PPDTA) della MRC pubblicato dalla SIN e dal Ministero della Salute e inviato a tutte le Regioni Italiane ad Aprile 2025 [5].

La Società Italiana di Nefrologia (SIN) ritiene essenziale definire ed uniformare sul territorio nazionale l'organizzazione ed i tempi adeguati di tutta l'attività ambulatoriale finalizzata alla identificazione e valutazione del paziente nefropatico e alla pianificazione di un piano di cura personalizzato, per garantire qualità, tempestività ed equità di cura.

Obiettivi del documento

Il documento SIN si pone quale obiettivo generale una corretta e adeguata pianificazione dell'attività ambulatoriale nefrologica per l'identificazione e gestione della MRC sul territorio nazionale, offrendo un riferimento uniforme da adottare nei sistemi di prenotazione (CUP, Call Center) e nei piani organizzativi aziendali al fine di allineare gli standard nazionali di appropriatezza e qualità dell'assistenza.

In particolare:

A. Definire i criteri minimi per un riferimento "on time" al nefrologo **[Allegato A]**
B. Definire in primis la durata minima raccomandata per lo svolgimento delle prime visite nefrologiche e dei controlli (follow-up) **[Allegato B]**
C. Fornire indicazioni per le tempistiche di invio al nefrologo per le prime visite, in relazione al

rischio di progressione della patologia di base e allo stadio di avanzamento della malattia renale, nel rispetto delle tabelle dei codici RAO [7] **[Allegato C]**

D. Fornire indicazioni di massima sulla più adeguata e corretta presa in carico del paziente sul territorio (medicina di base; case di comunità), in condivisione territorio-ospedale o prevalentemente in ambito ospedaliero (specialista nefrologo), sulla base delle caratteristiche della malattia e del suo stadio evolutivo **[Allegato D]**

PROPOSTA ALLE ISTITUZIONI

La SIN propone al Ministero della Salute, AGENAS ed Assessorati alla Salute Regionali di:

1. Recepire i contenuti della proposta e adottarli come standard nazionali.
2. Uniformare le agende CUP e le schede prestazionali delle visite ambulatoriali sulla base delle tempistiche indicate e dei codici RAO.
3. Monitorarne l'applicazione tramite indicatori (durata media, numero visite per sessione, aderenza agli standard).

Conclusioni

Definire tempi standard per prime visite e controlli nefrologici rappresenta un passo cruciale per assicurare qualità assistenziale, equità di accesso e una efficiente programmazione delle risorse sanitarie destinate alla principale malattia cronico-degenerativa.

Allegato A

Criteri "minimi" di invio a prima visita nefrologica

Fattori di rischio	Indagini necessarie	Invio al nefrologo
Almeno una tra: – Familiarità – Ipertensione – Diabete – Malattia CV – Obesità	Creatininemia (eGFR) Albuminuria (ACR) Esame delle urine, se microematuria, con sedimento e morfologico emazie Emoglobina	IN PRESENZA DI Almeno una tra: – eGFR<45 ml/min o perdita di eGFR> 3 ml/min/anno – ACR>200 mg/g – Anemia (hb <11) in presenza di eGFR patologico – Ematuria di origine glomerulare e/o albuminuria indipendentemente dal valore di eGFR

Allegato B

Proposta di tempario delle visite nefrologiche

Prestazione	Durata minima	Contenuti principali		Note
Prima visita	45 minuti	– anamnesi completa	(15 min)	Le tempistiche possono essere aumentate in caso di pazienti con plurime comorbidità e primo accesso nefrologico tardivo. La prima visita nutrizionale deve essere separata dalla prima visita nefrologia e richiede 45 minuti.
		– valutazione esami	(10 min)	
		– esame obiettivo	(10 min)	
		– stratificazione del rischio e attività burocratica (esenzioni, piani terapeutici)	(10 min)	
Visita di controllo (follow-up)	30 minuti	– revisione anamnesi	(10 min)	Le tempistiche aumentano a 45 m in caso di rivalutazione/counseling nutrizionale
		– valutazione esami	(5 min)	
		– esame obiettivo	(5 min)	
		– ricognizione terapia	(5 min)	
		– counseling ed adeguamento del piano assistenziale	(5 min)	
Tele visita	15-20 minuti	– valutazione parametri clinici/laboratoristici già disponibili	(10 min)	Destinato a pazienti in stadi iniziali e/o stabili di malattia con esami già caricati su piattaforma digitale
		– counseling terapeutico e verifica aderenza	(5-10 min)	
Tele-prescrizione per rinnovo piano terapeutico	10 minuti	– valutazione parametri laboratoristici finalizzati alla prescrizione	(5 min)	–
		– prescrizione telematica	(5 min)	

Allegato C

Criteri di urgenza per prestazioni ambulatoriali: Manuale RAO

Il Manuale RAO (Raggruppamenti di Attesa Omogenea), redatto da AGENAS e aggiornato dalla Commissione Salute della Conferenza delle Regioni e Province Autonome il 16 dicembre 2020, rappresenta lo strumento ufficiale per la definizione di criteri clinici e codici di priorità con relativi tempi massimi di attesa (Tempa) per le prestazioni specialistiche ambulatoriali previste dal Nomenclatore nazionale ai sensi del DPCM 12 gennaio 2017, e costituisce un riferimento fondamentale per il Piano Nazionale di Governo delle Liste di Attesa (PNGLA 2019–2021) [7].

Per migliorare l'appropriatezza è auspicabile la revisione del Manuale RAO in merito ad alcune indicazioni alla valutazione nefrologica, declinate nei vari gradi di urgenza, rispetto a quanto tuttora definito nelle tabelle del manuale stesso.

Si richiede ad Agenas l'accettazione delle modifiche proposte al Manuale:

CLASS_RAO 037	PRIMA VISITA NEFROLOGICA – Codice 89.7B.5 Incluso: stesura del piano di trattamento conservativo (dietetico e farmacologico), sostitutivo (dialisi extracorporea o peritoneale) o per trapianto	
CLASSE DI PRIORITÀ	**TEMPO MASSIMO DI ATTESA**	**INDICAZIONI CLINICHE RACCOMANDATE DAL GRUPPO DI LAVORO**
EMERGENZA***	INVIO AL PS	1. Anuria in soggetto con insufficienza renale già nota **o trapianto di rene** 2. Crisi ipertensiva in paziente già in terapia farmacologica **in presenza di IRC** 3. Disionie gravi: ipokaliemia < 2,5 mEq/L; iperpotassiemia > 6,5 mEq/L; sodiemia < 125 mEq/L o > 150 mEq/L; grave acidosi metabolica (bicarbonati < 17 mmol/L) **ipercalcemia >12,5 mg/dl** 4. Edema polmonare in paziente con nefropatia già nota **o in trattamento dialitico** 5. Grave deficit o peggioramento acuto della funzione renale con oliguria 6. Iperazotemia di recente insorgenza (> 250 mg/dL) o meno se ingravescente 7. Sospetta pielonefrite acuta **se presente addominalgie in dialisi peritoneale o febbre in trapianto renale**
EMERGENZA*** (PEDIATRIA)	INVIO AL PS	1. Anuria/sovraccarico idrico in soggetto con sospetta insufficienza renale acuta 2. Diarrea emorragica con sospetto interessamento renale 3. Disionie o alterazioni acido base sintomatiche 4. Edemi con proteinuria o ematuria 5. Febbre in trapianto renale o paziente nefropatico in terapia immunosoppressiva 6. Ipertensione sintomatica 7. Macroematuria se esclusa causa urologica 8. Poliuria e disidratazione (sospetta tubulopatia sintomatica) 9. Urosepsi e/o sospetta pielonefrite acuta

CLASS_RAO 037	PRIMA VISITA NEFROLOGICA – Codice 89.7B.5 Incluso: stesura del piano di trattamento conservativo (dietetico e farmacologico), sostitutivo (dialisi extracorporea o peritoneale) o per trapianto	
CLASSE DI PRIORITÀ	**TEMPO MASSIMO DI ATTESA**	**INDICAZIONI CLINICHE RACCOMANDATE DAL GRUPPO DI LAVORO**
U	72h	1. Grave sovraccarico idrico (edemi o PA > 180/100) in paziente con nefropatia già nota 2. Insufficienza renale acuta (aumento creatinina del doppio rispetto alla precedente o ≤ classe 3 se non conosciuta la precedente) non oligurica in paziente con comorbidità (es. diabete), in situazioni di disidratazione associate a terapie potenzialmente tossiche 3. Ipertensione arteriosa in gravidanza e/o riscontro de novo di proteinuria al 3° trimestre 4. Malattia renale cronica stadio 5 (VFG < 15 ml/min) di primo riscontro 5. Patologie intercorrenti in trapiantato renale 6. Potassiemia tra 2,5-3 mEq/L o tra 6-6,5 mEq/L in paziente già in terapia con ACE-inibitori o sartani e/o anti-aldosteronici 7. Altro (10%)**
U (PEDIATRIA)	72h	1. Poliuria con ritardo di crescita 2. Proteinuria > +++ o > 0,5 mg/mg di primo riscontro senza edemi, ipertensione, insufficienza renale, oligoanuria 3. Recidiva di macroematuria 4. Riscontro di insufficienza renale (eGFR < 60 ml/min/1,73m^2 sec formula di Schwartz) 5. Altro (10%)**
B	10 gg	1. Edemi e proteinuria > 3 g 2. Insufficienza renale cronica al IV stadio di primo riscontro 3. Ipertensione di difficile controllo in paziente già in trattamento con ≥ 3 farmaci anti-ipertensivi 4. Macroematuria escluse cause urologiche 5. Rapido peggioramento della funzione renale in nefropatia cronica nota (aumento creatinina > 15% in 3 mesi) 6. Riscontro di nefropatia de novo in paziente con malattia sistemica (es. LES) 7. Sospetta neoplasia renale **non compete al nefrologo**
B (PEDIATRIA)	10 gg	1. Ipertensione arteriosa sintomatica 2. Insufficienza renale di primo riscontro (eGFR 60-90 ml/min/1,73m^2 sec formula di Schwartz) 3. Proteinuria persistente < +++ o < 0,5 mg/mg con o senza microematuria in patologia sistemica 4. Altro (10%)**

CLASS_RAO 037	PRIMA VISITA NEFROLOGICA – Codice 89.7B.5 Incluso: stesura del piano di trattamento conservativo (dietetico e farmacologico), sostitutivo (dialisi extracorporea o peritoneale) o per trapianto	
CLASSE DI PRIORITÀ	**TEMPO MASSIMO DI ATTESA**	**INDICAZIONI CLINICHE RACCOMANDATE DAL GRUPPO DI LAVORO**
D	30 gg	1. Anemia (**Hb < 10**) in o da IRC (prescrizione per farmaci soggetti a piano terapeutico) 2. Infezioni urinarie recidivanti 3. Insufficienza renale cronica III stadio di primo riscontro 4. Microematuria escluse cause urologiche 5. Proteinuria (< 3 g/24h) 6. Nefropatia diabetica 7. Altro (10%) **
D (PEDIATRIA)	30 gg	1. Agenesia renale in paziente < 6 mesi 2. Idroureteronefrosi con o senza RVU non complicata 3. Cisti renali multiple di primo riscontro 4. Infezioni urinarie recidivanti 5. Proteinuria persistente < +++ o < 0,5 mg/mg con o senza microematuria 6. Urolitiasi di primo riscontro asintomatica 7. Altro (10%) **
P	120 gg	1. Anomalie ecografiche renali asintomatiche (escluse sospette neoplasie) 2. Cisti renali multiple 3. Insufficienza renale cronica I–II stadio di primo riscontro 4. Microematuria o proteinuria non accompagnata da dolore né da alterazioni funzionali renali 5. Malattia renale cronica (III stadio) 6. **Calcolosi renale non chirurgica** 7. Altro (10%) **
P (PEDIATRIA)	120 gg	1. Anomalie ecografiche renali asintomatiche (escluse sospette neoplasie) 2. Enuresi in paziente > 5 anni 1. Microematuria isolata persistente 2. Altro (10%) **

Tabella riassuntiva Codici RAO e Tempi Massimi di Attesa

Codice RAO	Descrizione	Tempo massimo di attesa
U	**Urgente** – prestazione da eseguire rapidamente per condizioni cliniche a rischio	Entro 72 ore
B	**Breve** – condizioni che richiedono valutazione rapida ma non immediata	Entro 10 giorni
D	**Differibile** – prestazioni programmabili in tempi medi	Entro 30 giorni
P / D	**Programmabile** – prestazioni non urgenti, da eseguire in tempi più lunghi	Entro 90 giorni o oltre

Allegato D

Presa in carico del paziente affetto da MRC

La numerosità crescente della popolazione affetta da MRC rende obbligatoria una pianificazione della presa in carico del paziente nelle differenti realtà assistenziali sanitarie (territorio-ospedale) a seguito di una prima valutazione di pertinenza esclusivamente nefrologica.

In base al differente stadio di malattia renale cronica, ma anche alla differente tipologia di malattia di base e alla sua prevedibile evolutività, possono essere ipotizzati i seguenti scenari di presa in carico del paziente.

Stadio di MRC	Setting di presa in carico	Follow-up nefrologico
1 e 2	territorio	Se aggravamento
3a (no proteinuria)	territorio	Se aggravamento/proteinuria
3a (con proteinuria)	nefrologo/territorio	Ogni 8-12 mesi
3b	nefrologo/territorio	Ogni 6 mesi
4	nefrologo	Ogni 3-4 mesi
5	nefrologo	Ogni 2-3 mesi

Condizioni particolari di patologia: riferimento e intervalli visite

Patologie autoimmuni:	nefrologo/territorio	ogni 3-6 mesi*
Malattia policistica:	nefrologo/territorio	ogni 4-6 mesi**
Rapida progressione MRC:	nefrologo	ogni mese
Transizione / rifiuto dialisi:	nefrologo	ogni mese
Trapianto di rene:	nefrologo/territorio	ogni 1-12 mesi***
Trattamento dialitico:	nefrologo	secondo quadro clinico

*in base alla attività di malattia o a terapia immunosoppressiva in fase acuta o stabile
**in base a presenza di terapia specifica o secondo gravità di funzione renale
***secondo le tempistiche legate al progredire del follow up post-intervento

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IgA-Dominant Idiopathic Membranoproliferative Glomerulonephritis: Insights into Clinicopathological Characteristics and Kidney Outcomes in a Developing Country

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ABSTRACT

Background. IgA-dominant idiopathic membranoproliferative glomerulonephritis (MPGN) is a rare and understudied renal condition that overlaps morphologically with atypical IgA nephropathy (IgAN) and infection-related glomerulonephritis (IRGN). Its unique presentation and limited literature necessitate a deeper examination of its clinical features and outcomes.

Methods. This retrospective study analyzed 10 biopsy-confirmed cases of IgA-dominant idiopathic MPGN diagnosed between 1999 and 2019 at the Sindh Institute of Urology and Transplantation (SIUT), Karachi. All patients were followed post-biopsy, and secondary causes, including infections and systemic illnesses, were excluded.

Results. Patients had a median age of 22 years (range: 15–30), with 60% being male. Common clinical manifestations included nephrotic-range proteinuria, hematuria, and renal insufficiency. Median estimated glomerular filtration rate (eGFR) at presentation was 29 mL/min/1.73 m². Complement levels were normal, and serological tests were negative. Hypertension was noted in 40% of cases, all of whom required kidney replacement therapy (KRT). Immunosuppressive therapy was administered to 60% of patients. At 3-year follow-up, 80% had progressed to end-stage kidney disease (ESKD), one patient died (10%), and two achieved partial remission (20%) but were subsequently lost to follow-up.

Conclusion. IgA-dominant idiopathic MPGN exhibits an aggressive course with poor renal outcomes compared to typical IgAN. The absence of identifiable secondary causes and high progression to ESKD highlight its severity and the urgent need for targeted research to better understand its pathogenesis and refine treatment approaches.

KEYWORDS: Immunoglobulin A (IgA), membranoproliferative glomerulonephritis (MPGN), IgA nephropathy (IgAN), end-stage kidney disease (ESKD), kidney replacement therapy (KRT).

Key points

- IgA-dominant idiopathic MPGN is increasingly recognized as a rare and distinct kidney disorder with specific pathological and immunological characteristics, differentiating it from conventional IgA nephropathy.
- Despite its clinical relevance, this variant remains underexplored in the literature. This study aimed to delineate the clinicopathological features and treatment outcomes of this rare entity.
- Due to its unfavorable prognosis, deeper investigation is essential to clarify its mechanisms and develop effective therapies.

Introduction

Membranoproliferative glomerulonephritis (MPGN), also referred to as mesangiocapillary glomerulonephritis (MCGN), represents a unique and intricate pattern of immune or non-immune mediated kidney injury. This condition mostly arises as a result of the deposition of immune complexes or complement fragments within the glomeruli, leading to inflammation and structural alterations. Immune-mediated MPGN can be further classified based on findings obtained through immunofluorescence (IF) microscopy, distinguishing between immune complex (IC)-mediated and complement (C)-mediated MPGN subtypes [1].

Among the IC-mediated variants lies a rare and complex entity known as Immunoglobulin A (IgA)-dominant MPGN. This condition accounts for a small proportion, estimated at only 0.2% to 0.3%, of the native kidney biopsy cases [2]. It is defined by its distinctive histological features observed under light microscopy (LM), characterized by a membranoproliferative pattern of injury coupled with dominant or codominant IgA staining detected on IF. Notably, this rare kidney pathology differs significantly from IgA nephropathy (IgAN) [3] as well as from IgA-dominant infection-related glomerulonephritis (IRGN) [4–6]. The unique morphological features of IgA-dominant MPGN include frequent subendothelial immune complex deposition, remodeling of the glomerular basement membrane in peripheral capillary loops, and the scarcity of exudative changes. Furthermore, cases exhibit infrequent subepithelial deposits and lack definitive correlation with infectious etiologies.

Despite the identification of IgA-dominant MPGN, there remains a paucity of detailed literature regarding its idiopathic variant, which poses significant challenges for clinicians and researchers alike. Existing documentation comprises isolated case reports describing this disease in diverse contexts, including pediatric patients [7, 8], children with cirrhosis and portal hypertension [9], individuals with alcoholic cirrhosis [10], patients suffering from cirrhosis prior to the identification of the hepatitis C virus (HCV) [11, 12], and adults experiencing urinary tract infections [13]. However, these reports are sporadic and leave considerable gaps in understanding the broader implications and mechanisms of this disease.

Kidney outcomes in patients diagnosed with idiopathic MPGN vary depending on numerous factors, including disease severity, the patient's response to therapeutic interventions, and associated underlying conditions [14]. While poor kidney outcomes have been documented among patients with infection-related IgA-dominant MPGN [4], the clinical trajectory and prognosis of IgA-dominant idiopathic MPGN remain largely unknown. Nonetheless, limited research highlights its tendency toward progressive kidney damage, with one particular study suggesting that the kidney survival rate in IgA-dominant idiopathic MPGN might be inferior to both IgAN and aggressive variants of IgAN [2].

Given the significant knowledge gap concerning IgA-dominant idiopathic MPGN, a focused study has been conducted to shed light on its clinicopathological characteristics. This investigation aimed to provide a comprehensive understanding of the disease's clinical presentations and long-term kidney outcomes. By deepening insights into this unique morphologic finding, the study aspires to address unanswered questions and enhance approaches to diagnosis and management.

Materials and Methods

Ethics Statement

This study received approval from the Institutional Review Board of the Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan (approval number: SIUT-ERC-2025/A-551). All research activities were conducted in strict adherence to the ethical principles outlined in the Declaration of Helsinki.

Study population

This study retrospectively analyzed the medical records of patients aged 15 years and older who were referred to the Kidney Division of the SIUT, Karachi, Pakistan. These referrals spanned from January 1999 to December 2019, specifically for native kidney biopsies. Eligible patients were those with a histopathological diagnosis of idiopathic MPGN who had been monitored at the kidney clinic following their kidney biopsy. Patients who reached the study endpoint within 12 months were included regardless of follow-up duration, while others were followed for a minimum of 12 months. Among the reviewed cases, only 10 patients were identified with dominant or co-dominant IgA deposition on IF and an absence of exudative features.

The diagnosis of idiopathic MPGN was established clinically, adhering to the algorithm outlined in UpToDate 2024 [15], after rigorously excluding all secondary causes. These excluded causes encompassed infections, autoimmune diseases, plasma cell dyscrasias, lymphoproliferative disorders, and cryoglobulinemia. Special attention was given to excluding secondary causes in MPGN cases with C1q positivity on IF, using viral and autoimmune serology. Furthermore, patients presenting with Henoch-Schönlein purpura (HSP), hemolytic uremic syndrome (HUS), segmental or focal MPGN features, exudative characteristics, monoclonal Ig deposition diseases with κ and λ staining, or those previously treated with corticosteroids or other immunosuppressive agents were excluded from the study.

Data Collection

Patient medical records were thoroughly examined, encompassing clinical, biochemical, serological, and histopathological findings both at the time of biopsy and during subsequent follow-ups. Clinical data included factors such as age, gender, biopsy indications, presence of hypertension, administered treatment protocols, the necessity for kidney replacement therapy (KRT), and follow-up details. Laboratory investigations recorded serum creatinine and albumin levels upon admission and at subsequent intervals, along with complement levels (C3 and C4) categorized as either normal or reduced. Additionally, a comprehensive urinalysis was conducted, including the urine protein-to-creatinine ratio (PCR) at baseline and during follow-ups, as well as 24-hour urinary protein measurements, where available. The estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Collaboration (CKD-EPI) creatinine formula [16].

Histopathology

The histopathological assessment comprised a detailed analysis of the total number of glomeruli, including those exhibiting sclerosis. It also evaluated the proportion of glomeruli displaying crescents categorized as cellular, fibrocellular, or fibrous, along with mesangial and endocapillary hypercellularity, which was noted as either diffuse or focal. Additional features such as capillary wall double contours and the extent of interstitial fibrosis and tubular atrophy (IFTA) were graded into four categories: none (0–5%), mild (6–25%), moderate (26–50%), or severe (>50%). Immunofluorescence (IF) results demonstrated positivity for IgA, IgG, IgM, C3, C1q, κ, and λ, with staining patterns and intensities rated on a scale ranging from 0 to 3+ (Figure 1). Pathological variables were scored using the 2016 revised Oxford Classification MEST-C criteria, [17] encompassing mesangial hypercellularity (M0/M1), endocapillary hypercellularity (E0/E1), segmental glomerulosclerosis (S0/S1), tubular atrophy/interstitial fibrosis (T0/T1/T2), and crescents (C).

All cases initially diagnosed as idiopathic MPGN through LM were reclassified using IF-based criteria as either IC-MPGN or C-MPGN. This reevaluation was conducted by two renal pathologists with significant experience, one with over 20 years and the other with 10 years, who performed independent analyses followed by collaborative review in cases of disagreement. Both pathologists were blinded to patient outcomes. IgA-dominant MPGN was characterized by IgA deposition at a level of ≥2+, accompanied by C3 and/or non-dominant IgG staining at ≥1+, with the IgG intensity lower or equal to IgA. Additional criteria included the presence of negligible (<+1) C1q staining and the absence of significant exudative features (such as glomerular neutrophilic infiltration) or extraglomerular deposits. Electron microscopy (EM) was not universally performed in all cases.

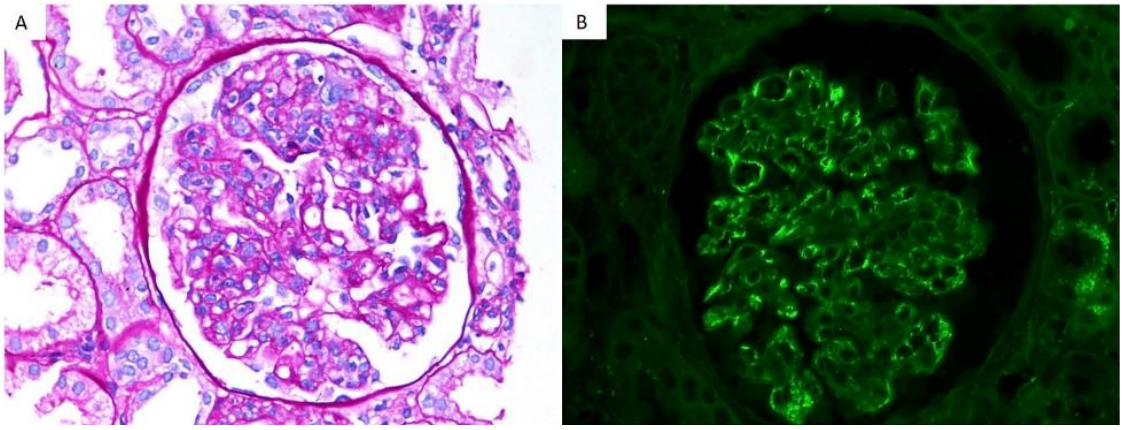

Figure 1. Histopathological features of IgA-dominant membranoproliferative GN. A) Membranoproliferative pattern of injury with lobular accentuation, mesangial proliferation, endocapillary hypercellularity, and segmental duplication of the glomerular basement membranes (PAS stain, ×400). B) Granular staining for IgA (2+) in peripheral capillary loops and some mesangial regions by immunofluorescence (IF) (IgA by IF, ×400).

Outcomes

In the absence of established guidelines for determining remission in MPGN, we applied criteria typically used for proliferative lupus nephritis (LN) and classified patients into three distinct groups [18]:

- **Complete Remission (CR)**: characterized by a normal urinalysis, indicated by a dipstick result that is either negative or shows trace amounts of protein and blood, serum albumin levels >3.5 g/dl, along with an eGFR > 90 mL/min/1.73 m².

- **Partial Remission (PR)**: denoted by an abnormal urinalysis, which may reveal as microscopic hematuria or proteinuria ≥1, serum albumin levels < 3.5 g/dl, and the eGFR within the range of 60 to 90 mL/min/1.73 m².
- **No Remission (NR)**: defined as persistent proteinuria > 3 g/day or a progressive decline in kidney function.
- **Kidney Survival**: refers to the duration from the initial kidney biopsy to the earliest instance of initiating dialysis, undergoing a kidney transplant, or a reduction in eGFR to <15 mL/min/1.73 m², with no subsequent recovery to levels above 15 mL/min/1.73 m² during the follow-up period.
- **Kidney Flare**: describes a recurrence or exacerbation, evidenced by a dipstick result turning positive after previously being negative, or an increase in proteinuria identified either through dipstick analysis or elevated PCR levels in patients previously achieving CR or PR [19].

Study endpoints

- The **primary endpoint** was defined as kidney survival without the onset of ESKD or death.
- The **secondary endpoint** focused on the proportion of patients achieving CR or PR during the follow-up period.

Statistical Analysis

The statistical analysis was performed using version 25.0 of the Statistical Package for the Social Sciences (SPSS) software (IBM Corp, Armonk, NY, USA). Continuous variables were presented as either mean ± standard deviation (SD) or median with interquartile range (IQR). Categorical data were reported as frequencies and percentages, while discrete variables were expressed in terms of proportions. Kaplan–Meier methodology was employed to construct the overall survival curve. A p-value below 0.05 was regarded as indicative of statistical significance.

Results

Between 1999 and 2019, a total of 10 patients were diagnosed with biopsy-confirmed IgA-dominant MPGN.

Patient Demographics and Clinical Characteristics at Presentation

Table 1 summarizes the demographic, clinical, and serological attributes of individuals with IgA-dominant idiopathic MPGN. The median age at diagnosis was 22 years (range: 15–30 years), with the cohort comprising 6 males (60%) and 4 females (40%). Upon presentation, all patients exhibited edema alongside nephrotic-range proteinuria and/or nephrotic syndrome accompanied by microscopic hematuria. Hypertension was noted in 4 patients (40%), while none displayed macroscopic hematuria. Additionally, complement levels were found to be within normal ranges across all cases at the time of presentation. The median serum creatinine concentration was recorded at 3.2 mg/dl (range: 1.0–8.9 mg/dl), whereas the median eGFR was 29 ml/min/1.73 m² (range: 6.75–78.75 ml/min/1.73 m²). Furthermore, 4 patients (40%) required KRT upon admission.

	n=10
Age at biopsy (years), median (IQR)	22 (15-30)
Gender: Male, n (%) Female, n (%)	 6 (60) 4 (40)
Weight (Kg), mean ± SD	66.8 ± 9.1
HTN, n (%)	4 (40)
Presence of Edema, n (%)	10 (100)
Evidence of recent infection, n (%)	0
Asymptomatic, n (%) Urinary abnormality Abnormal creatinine Newly diagnosed HTN Symptomatic Nephrotic syndrome Nephritic syndrome Gross hematuria	 0 0 0 10 (100) 0 0
Proteinuria (Dipstick), n (%) Trace +1 +2 +3 +4	 0 0 0 9 (90) 1 (10)
Microscopic hematuria, n (%) Trace +1 +2 +3 +4	 1 (10) 3 (30) 0 5 (50) 1 (10)
Serum Creatinine (mg/dl), median (IQR)	3.2 (1.0-8.9)
eGFR (ml/min/1.73^2), median (IQR)	29 (6.75-78.75)
Serum albumin (g/dl), median (IQR)	2.8 (2.07- 3.15)
24-hr Urinary protein (g/day), median (IQR)	4.2 (3.7-9.2)
Serum C3 levels, n (%) Low (< 80 mg/dL) Normal (>80 mg/dL)	 0 10 (100)
Serum C4 levels, n (%) Low (< 16 mg/dL) Normal (>16 mg/dL)	 0 10 (100)
Required KRT (%)	4 (40)
Median follow-up in months (IQR)	12 (3.0- 27)

Table 1. Baseline Demographic and Clinical Characteristics of Patients IgA-dominant MPGN. IgA: Immunoglobulin A; MPGN: membranoproliferative glomerulonephritis; SD: standard deviation; IQR: interquartile range; kg: kilogram; HTN: hypertension; eGFR: estimated glomerular filtration rate; KRT: kidney replacement therapy.

Kidney Histopathological Characteristics

The histopathological features of the kidneys in patients with IgA-dominant idiopathic MPGN are summarized in Table 2. The median number of glomeruli observed was 14 (range: 8.7–27.5). A diffuse and global MPGN pattern of injury was noted in all cases. Segmental glomerular sclerosis was evident in 2 out of 10 patients (20%), while the median percentage of globally sclerotic glomeruli was 3 (range: 1–6). Extracellular crescentic proliferation was a prominent feature, present in 9 patients (90%). Furthermore, tubular atrophy was noted in 7 patients (70%) as mild to moderate and in 1 patient (10%) as severe. All patients demonstrated a MEST-C score of 3 or higher. IgA emerged as the dominant immunoglobulin in all cases, with staining intensities of 2+ or above. In half of the biopsy samples (50%), IgG coexisted with a staining intensity of 1+ or trace levels. Nearly all cases exhibited positive C3 staining, with 60% showing intensities of 2+ or greater. C1q staining was either trace or absent, and both lambda and kappa light chains were detected in all cases.

	n = 10
Total glomeruli, median (IQR)	14 (8.7-27.5)
Globally sclerosed, median (IQR)	3 (1.0-6)
Mesangiocapillary proliferation, n (%)	
Focal	0
Diffuse	10 (100)
Segmental glomerular sclerosis, n (%)	
S0	8 (80)
S1	2 (20)
Tubular atrophy / interstitial fibrosis, n (%)	
T0	2 (20)
T1	7 (70)
T2	1 (10)
Cellular crescents, n (%)	
C0	1 (10)
C1	5 (50)
C2	4 (40)
MEST-C Score	
1	0
2	0
3	1 (10)
4	5 (50)
5	3 (30)
6	1 (10)
Immunofluorescence results	
Ig A, n (%)	
Negative	0
Trace	0
+1	0
+2	4 (40)
+3	6 (60)
Ig G, n (%)	
Negative	5 (50)
Trace	4 (40)
+1	1 (10)
+2	0
+3	0
Ig M, n (%)	
Negative	3 (30)
Trace	0
+1	4 (40)
+2	3 (30)
+3	0
C3, n (%)	
Negative	0
Trace	3 (30)
+1	1 (10)
+2	3 (30)
+3	3 (30)
C1q, n (%)	
Negative	6 (60)
Trace	4 (40)
+1	0
+2	0
+3	0

Table 2. Histopathological Characteristic in patients with IgA-dominant MPGN. IgA: Immunoglobulin A; MPGN: membranoproliferative glomerulonephritis; SD: standard deviation; IQR: interquartile range; IF/TA: interstitial fibrosis/ tubular atrophy; MEST C Score: mesangial hypercellularity, endocapillary hypercellularity, segmental sclerosis, tubular atrophy, and interstitial fibrosis, crescents.

Treatment and Outcomes

Table 3 provides an overview of the therapeutic interventions and kidney outcomes in patients diagnosed with IgA-dominant MPGN. At a median follow-up or study endpoint post-kidney biopsy (range: 12–27 months), 6 out of 10 patients (60%) had undergone immunosuppressive therapy. Of these, three received steroid monotherapy at a dose of 1 mg/kg for a total of 6 months, while the remaining three were treated with combination therapy consisting of steroids (1 mg/kg for 6 months) and cyclophosphamide (CYC) at 1.5 mg/kg for 3 months. One of these patients was subsequently maintained on azathioprine (AZA) for an additional 6 months. One patient received antiproteinuric treatment alone, whereas three individuals did not receive any therapeutic intervention due to advanced disease progression. PR was achieved in 2 patients (20%) at 12 and 24 months, respectively; however, both patients were subsequently lost to follow-up. The remaining 8 patients (80%) exhibited progression to ESKD by 36 months, with one patient succumbing to sepsis. Kaplan-Meier survival analysis was employed, encompassing the interval from treatment initiation to either the conclusion of follow-up or mortality. At 36 months, renal survival among the cohort was nonexistent, as all surviving patients were reliant on dialysis (Figure 2).

Case no:	Age (yrs)	Sex	24-hr Urinary protein (g/day) on admission	eGFR (ml/min/1.73^2) at presentation	MEST-C Score	Treatment	Outcomes	Follow-up (months)
1	21	M	4.28	19	4	Prednisolone, CYC, AZA	ESKD	24
2	22	M	3.45	95	3	Prednisolone	PR with proteinuria of 2.5g/day, lost to follow-up	12
3	28	F	3.8	14	5	Prednisolone, CYC	ESKD	12
4	19	M	8.3	13	6	No IS	ESKD, listed for transplant	03
5	17	M	3.1	8	4	No IS	ESKD, listed for transplant	02
6	15	F	12.2	84	5	Prednisolone, CYC	ESKD	36
7	20	M	4.17	47	4	Prednisolone	ESKD	36
8	30	F	3.85	77	5	ACE inhibitor	PR, lost to follow-up	24
9	25	M	N/A	07	4	No IS	ESKD-Mortality	03
10	23	F	4.2	39	4	Prednisolone	ESKD	12

Table 3. Clinical course of IgA-dominant MPGN patients. IgA: Immunoglobulin A; MPGN: membranoproliferative glomerulonephritis; M: male; F: female; eGFR: estimated glomerular filtration rate; MEST C Score: mesangial hypercellularity, endocapillary hypercellularity, segmental sclerosis, tubular atrophy, and interstitial fibrosis, crescents; PR: partial remission; CYC: cyclophosphamide; AZA: azathioprine; ESKD: end stage kidney disease: IS: immunosuppressive; ACE: angiotensin-converting enzyme inhibitor; N/A: not available.

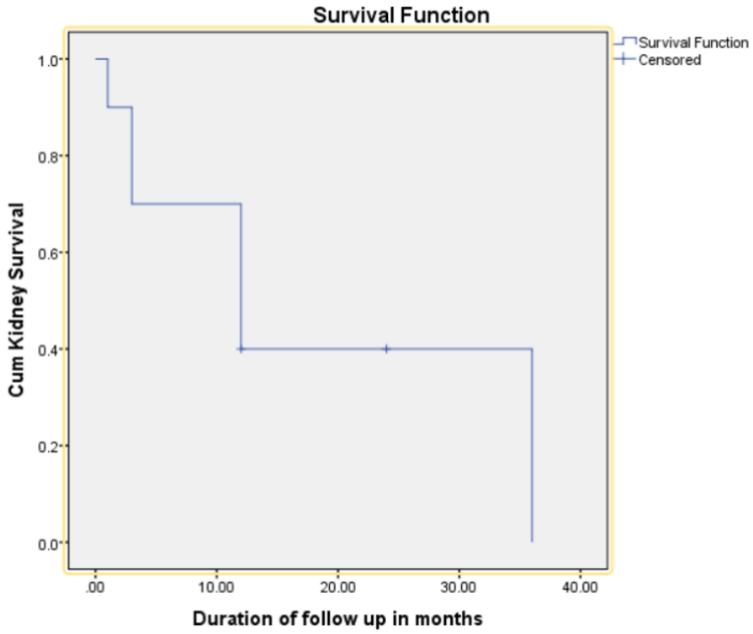

Figure 2. Kaplan-Meier survival analysis of IgA-dominant membranoproliferative GN patients.

Discussion

This study presents an in-depth analysis of the clinical, biochemical, serological, and histopathological characteristics, alongside kidney and patient outcomes, in individuals diagnosed with idiopathic IgA-dominant glomerulonephritis displaying a membranoproliferative pattern of injury. This condition is characterized by a predominantly diffuse MPGN injury pattern observed under LM, devoid of exudative features. IF reveals IgA-dominant or co-dominant staining, with prominent deposits along the peripheral capillary walls and within the mesangium. Although the findings are based on a single-center study, this work holds significant importance, as it stands among the first to explore this distinctive clinicopathological entity in Asia and offers a representative glimpse into the Pakistani population.

A novel insight of this study lies in its observation that patients with this disease exhibit distinct pathological characteristics and a clinical progression that sets it apart from other conditions within its differential diagnosis spectrum, including IgAN [3], IgA-dominant IRGN [4–6], IgA-proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) [20], and LN. The clinical features bear similarities to IgAN, including male predominance, early age of onset, and normal serum complement levels. However, a key distinction from IgAN is the rapid deterioration of kidney function, in contrast to the 50% ESKD rate observed over 30 years in a large IgAN cohort [21]. Additionally, among the 244 IgAN cases reported by Haas M, none displayed MPGN-like histological features [3]. Instead, it closely resembles other forms of IC-MPGN. These findings suggest that IgA-dominant idiopathic MPGN may constitute either a unique clinicopathological entity or an aggressive variant of IgAN.

The long-term prognosis for kidney survival in patients diagnosed with IgA-dominant idiopathic MPGN remains inadequately defined, primarily due to the limited availability of data. Current knowledge is derived from a handful of case reports and a single cohort study, both of which exhibit variability in their associations and outcomes. Cases of IgA-dominant MPGN have been documented in the pediatric population, including isolated instances involving an infant [8] and two children [7].

These pediatric cases were largely asymptomatic and were identified incidentally through routine screening processes. Among them, only one child exhibited clinical symptoms, specifically a history of fever accompanied by gross hematuria, sterile cultures, and nephrotic-range proteinuria with preserved kidney function. These children responded well to immunosuppressive therapy, demonstrating favorable outcomes. In contrast, adult cases of this condition have been reported predominantly in association with underlying factors such as infections, systemic diseases, cirrhosis, vaccination, malignancy, or severe injuries like burns [10–13, 22–24]. Adults typically presented with advanced uremia and, in many instances, required KRT. Despite treatment, the kidney outcomes in this demographic have been generally poor. This divergence highlights the variability in disease presentation and outcomes between pediatric and adult patients. The findings of the current study underscore the overlapping clinical characteristics between children and adults. While the patients in this cohort were relatively young and presented with nephrotic-range proteinuria, a feature more akin to the pediatric population [7–8], the majority also exhibited moderate to severe kidney impairment. This level of kidney dysfunction necessitated KRT in many cases, mirroring the unfavorable outcomes observed in adult populations [2]. These observations align with the findings of Andeen et al. [2], the only existing study to detail poor outcomes in primary IgA-dominant MPGN, which included 15 adult patients.

The rarity of this condition poses significant challenges in fully comprehending its natural progression and treatment response. Anecdotal reports from nephrologists treating such cases suggest that patients often exhibit a positive response to intensified immunosuppressive therapies. Notably, a recent adult case demonstrated favorable outcomes with a combination of steroids and cyclosporine treatment [25], lending credence to the hypothesis of the disease's intrinsically aggressive nature. Furthermore, three individuals from the current study cohort presented with an eGFR below 15 mL/min/1.73 m^2 at diagnosis and did not receive immunosuppressive therapy because of advanced disease, highlighting the severity and aggressive clinical manifestation of this condition at the time of presentation.

Strengths and limitations of the study

The study boasts several notable strengths. Foremost among these is its distinction as the pioneering research to examine adult cohorts of biopsy-confirmed IgA-dominant MPGN cases originating from a developing South Asian nation. Given the rarity of this condition and the scarcity of existing data, this study fills a significant knowledge gap, marking the first published dataset on patient outcomes related to this rare entity in Pakistan. Furthermore, the patients involved were diligently monitored up to the study's endpoint, enabling individualized assessments of treatment efficacy. Another notable contribution of this study is its presentation of data concerning ESKD and mortality rates, adding invaluable insights into the prognosis of this disease. However, the study is not without limitations. Firstly, as a retrospective investigation, certain missing data may have influenced the robustness of the final analysis. Moreover, the inherent constraints of a retrospective study design make it challenging to account comprehensively for all potential confounding variables. Secondly, the single-center nature of the research restricts the generalizability of the findings, as the results may not fully reflect the broader population of the country. Thirdly, EM studies were not conducted for all cases, which may have limited the depth of pathological insights. Lastly, the lack of standardization in treatment regimens introduces variability in patient outcomes, potentially obscuring clearer interpretations of therapeutic effectiveness.

Conclusion

IgA-dominant idiopathic MPGN represents a unique clinicopathological condition, distinguished by its severe progression and significantly worse outcomes relative to IgAN or even its more aggressive subtypes. The unfavorable prognosis highlights an urgent need for in-depth investigations to unravel its underlying mechanisms and develop more effective treatment approaches to prevent the development of histological sclerotic lesions characteristic of MPGN.

Acknowledgments

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Data Availability

The datasets generated and/or analyzed during this study are available upon reasonable request from the corresponding author.

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Efficacy of Automatic Dynamic Ultrafiltration Compared to Constant Ultrafiltration Methods on Hypovolemic Intradialytic Symptoms: A Single-center Experience

Articoli originali

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ABSTRACT

Background. Hypovolemic intradialytic complications, including cramps, fatigue, and hypotension, are common in hemodialysis patients. Bioimpedance spectroscopy is the gold standard for fluid assessment, but it is not available in all dialysis centers. Ultrasound techniques can help clinicians, but they are operator-dependent and time-consuming. Ultrafiltration control (UF-control), a newer technology, allows for continuous monitoring of real-time blood volume changes (RBV%) and it adjusts ultrafiltration rates optimizing plasma refilling. This study aims to evaluate UF-control’s effectiveness in reducing hypovolemia-related events and post-dialysis weight adjustments in chronic dialysis patients.

Methods. We enrolled 21 chronic hemodialysis patients, each undergoing 3 treatments with standard constant UF and 3 treatments with UF-control modalities. Hypovolemia-related events were recorded both individually and as a composite outcome. An individualized “critical RBV%” was determined for each patient, with UF-control programmed to avoid dropping below this threshold. Data were analyzed using the Wilcoxon signed-rank test and generalized linear mixed models (GLMM), adjusted for interdialytic weight gain (IDWG) and the difference between prescribed and effective ultrafiltration.

Results. Hypovolemia-related symptoms were reduced from 32% in the constant UF setting to 7% in UF-control setting ($p = 0.007$). Similarly, intradialytic hypotension decreased from 18% to 4% ($p = 0.022$). GLMM analysis confirmed UF-control’s significant effect (adj-OR: 0.12, 95% CI: 0.06–0.26, $p = 0.004$). UF-control also enabled dynamic adjustments to post-HD weight in most patients, with no signs of fluid overload observed.

Conclusions. UF-control seems to actually reduce hypovolemic events in dialysis patients and provides a valuable tool for personalized fluid management. This technology can optimize patient tolerance and facilitate precise, session-by-session, dry weight adjustments.

KEYWORDS: Dry weight, Hemodialysis, Water control, UF-control

Introduction

Intradialytic cramps, fatigue, and hypotension are common clinical manifestations in patients experiencing hypovolemia. These symptoms may manifest in the context of absolute or effective hypovolemia, the latter occurring when plasma refilling is slower than the ultrafiltration rate. Accurate assessment and management of volume status is crucial for the safety and quality of dialysis treatments [1].

Bioimpedance spectroscopy represents the gold standard for assessing fluid status in dialysis patients, but it is not available in all dialysis centers. Some ultrasound-based techniques, such as the detection of B-lines, lung comet-tail artefacts, or the more recently introduced Venous Excess Ultrasound Score (VExUS score), can help clinicians. However, they are operator-dependent and entail a considerable expenditure of clinical time and professional resources, limiting their practical use in daily clinical workflows. Furthermore, these tools are likewise not available across all dialysis centers [2].

Recent advances in dialysis technology introduced Ultrafiltration control (UF-control), which operates by continuously monitoring the real-time change in blood volume, computing the relative blood volume percentage (RBV%), and instantaneously regulating the ultrafiltration (UF) rates based on this feedback [3]. By adjusting ultrafiltration in response to hemoconcentration changes, UF-control aims to optimize plasma refilling and reduce hypovolemia-related symptoms.

The objective of our study was to evaluate the clinical effectiveness of UF-control in reducing hypovolemia-related events in a sample of chronic dialysis patients in a real-world clinical setting, where Bioimpedance spectroscopy is not available. In addition, we aimed to assess how UF-control may facilitate adjustments to a patient's post-HD weight and to analyze the discrepancies between prescribed and actual fluid removal.

Methods

We conducted a prospective observational study involving 21 chronic hemodialysis patients, for a total of 126 dialyses. Each patient underwent dialysis sessions of 4 hours using two modalities: initially with standard constant UF settings, in which the post-HD weight was detected through classical methods, and subsequently with the UF-control module activated. Each patient underwent 3 treatments with constant UF setting and 3 treatments with UF-control. This study was approved by the government direction of our institution with protocol number I0049080 of April 28, 2025. All patients signed written informed consent.

Intradialytic hypotension, muscle cramps, and post-dialysis fatigue were systematically recorded as hypovolemic signs. Intradialytic hypotension was defined as systolic blood pressure <90 mmHg or a difference of more than 30 mmHg from baseline, while muscle cramps and post-dialysis fatigue were reported subjectively by patients. These were clustered into a composite outcome representing hypovolemia-related events.

UF-control works by decreasing ultrafiltration when hemoconcentration increases, which suggests inadequate refilling. Instead, low hemoconcentration reduction increases the UF when there is a sign of insufficient fluid removal. These adjustments are made automatically and instantaneously, optimizing the plasma refilling process and reducing hypovolemia-related manifestations. Furthermore, UF-control allows for small variations in dry weight that can be clinically imperceptible during individual treatments, enabling the dynamic modulation of a patient's post-HD weight on a session-by-session basis.

Before implementing UF-control, we determined an individualized "critical RBV%" for each patient over three dialysis sessions, used as a washout period. It is defined as the lowest RBV% reached

without the onset of hypovolemia-related symptoms. Once established, UF-control was programmed to avoid dropping below this critical RBV%, dynamically adjusting UF in real-time.
Data were collected on each session, both before and after the implementation of UF-control, recording if the composite outcome occurred and calculating the percentage of sessions affected by hypovolemia for each patient. The number of dialyses with UF-control was 50% of the total dialysis included in the analysis, with a temporal line of one month to reduce time-dependent bias. The Fresenius 5008S or Nipro monitor was used for the dialysis treatment. The first works with a variation of 500 g up or down the estimated UF, while Nipro works with an ultrafiltration up to 1.5 times the desired UF, as measured by various dialysis monitors.

Demographic and clinical variables, including age, sex, comorbidities, and interdialytic weight gain (IDWG), were also recorded. Data distribution was evaluated through the Kolmogorov-Smirnov test and graphical evaluation. The Wilcoxon signed-rank test for paired samples was used to compare the proportion of sessions with hypovolemia-related events before and after UF-control. The generalized linear mixed model (GLMM) was employed to assess the effect of UF-control on the composite outcome, with the patient ID as a random effect. Each GLM model was adjusted for IDWG and the difference between prescribed and effective ultrafiltration.

Overload was monthly detected through echographic VCI evaluation and pulmonary B-lines.

Results

A total of 21 patients were included in the analysis, with a median age of 73 [69-77] years. Thirteen were male (62%), and all had a history of hypertension pharmacologically treated, while heart failure was diagnosed in only one patient. In total, 126 dialysis sessions were analyzed (Table 1).

Implementation of UF-control resulted in a median increase in effective UF volume of 100 g for the session (interquartile range: –100 to +400 g). In detail, effective UF increased in 39 sessions and decreased in 22 sessions, compared to the corresponding prescribed UF.

Variable	
Age, year, median [IQR]	73 [69-77]
Sex, male n (%)	13 (62%)
BMI (kg/m^2), median [IQR]	25 [22-28.5]
Type 2 DM, n (%)	11 (52%)
Hypertension, n (%)	21 (100%)
Heart failure, n (%)	1 (5%)
IDWG, median [IQR]	2400 [1700-3000]

Table 1. Baseline features. DM: diabetes mellitus; IDWG: interdialytic weight gain.

During the four-month follow-up after UF-control implementation, post-dialysis weight adjustments were made in nearly all patients. In 11 patients, post-HD weight was reduced (range: –600 g to –2300 g), while in 6 patients it was increased (range: +600 g to +3000 g). In four patients, the weight remained unchanged.

The percentage of dialysis sessions manifesting hypovolemia-related symptoms declined from 32% during standard UF sessions to 7% with UF-control (p = 0.007) (Figure 1). Similarly, the incidence of intradialytic hypotension decreased from 18% to 4% (p = 0.022).

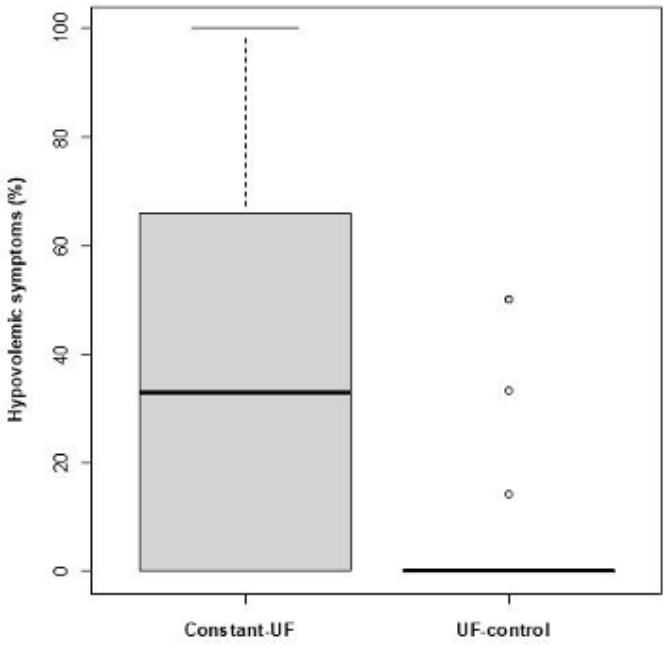

Figure 1. Comparison between Constant-UF and UF-control.

GLMM analysis confirmed a statistically significant effect of UF-control in reducing the risk of hypovolemia-related events (OR: 0.13, 95% CI: 0.07–0.24, p = 0.004). This association remained significant after adjusting for IDWG and the difference between prescribed and effective UF (adjusted OR: 0.12, 95% CI: 0.06–0.26, p = 0.004). Neither IDWG nor the difference between prescribed and effective UF had a statistically significant effect on outcomes (p = 0.53 and p = 0.58, respectively).

No signs of fluid overload were observed during the four-month follow-up, except one peritibial monolateral edema without echographic signs of hypervolemia. Indeed, Inferior Vena Cava collapsibility was higher than 30% and no B-lines were detected.

Discussion

Our study supports the clinical utility of UF-control modules in hemodialysis machines. UF-control seems to reduce hypovolemia-related symptoms, including fatigue, cramping, and intradialytic hypotension, by adapting the ultrafiltration rate based on real-time changes in blood volume. Furthermore, UF-control provides a novel and automated indicator to fine-tune a patient's post-HD weight, detecting subtle imbalances that may otherwise go unnoticed session-by-session.

This is particularly valuable considering that even minor discrepancies in dry weight estimation can accumulate over time, leading to chronic fluid imbalance or progressive cardiovascular strain. As fluid tolerance varies day-by-day, session-level optimization may prevent long-term complications [4].

Maintaining euvolemia is one of the greatest clinical challenges, both in elderly and comorbid patients, i.e. diabetes, heart failure, and autonomic dysfunction. Indeed, these conditions can exacerbate the difficulties in volume homeostasis and may increase the risk of intradialytic symptoms. In this setting, UF-control provides a practical tool for real-time and individualized fluid management based on intravascular dynamics and allows clinicians to identify early trends of fluid mismanagement [5].

The observed discrepancies between prescribed and actual fluid removal highlight the challenge of

accurately predicting fluid needs based on static clinical assessments. UF-control seems to minimize this gap, ensuring more precise volume management [6]. In this line, our analysis showed that UF-control is able to modulate the effective UF, either increasing or decreasing it. This demonstrates the UF-control's ability to personalize fluid removal to each session's intravascular response.

This is of particular importance, given that small fluctuations in fluid status are often undetectable by conventional clinical assessment but may significantly impact patient well-being [7]. These micro-adjustments are frequently influenced by external factors such as dietary salt intake, interdialytic weight gain, and vascular refill rates, which are not captured through conventional assessments. Therefore, automated volume-guided systems may act as a bridge between clinical observation and physiological variability [8].
In this light, UF-control supports a more personalized dialysis, reducing long-term cardiovascular events.

Potential limit of UF-control includes the determination of the individualized "critical RBV%". Indeed, incorrect critical RBV could cause fluid overload. Furthermore, a deep staff training is needed to correctly interact with the monitor's advice about the continuous changes in the intradialytic concentration.
Furthermore, intradialytic hypotension is strongly related to Cardiovascular events [9]. In detail, dialysis patients are characterised by high vascular stiffness with reduced ability of adapting to difference in arterial pressure. For this, intradialytic hypotension seems to be associated with impaired coronary perfusion [10, 11].
Although few small observational studies evaluated the efficacy of the UF-control on the hypovolemic manifestation [12], our analysis highlighted this effect, adjusting for the intrasubject variability with a model for repeated measures, UF targets and IDWG, enhancing internal validity. Furthermore, no other study enrolled patients without frequent hypotension. A key strength of our study, distinguishing it from previous observational data, is the inclusion of patients across a spectrum of intradialytic hypotension risk, including those at low risk. This strategy was employed to minimize selection bias and ensure that the observed effects of the UF-control module were not solely exaggerated by an enrollment limited to highly unstable individuals. Enrolling all patients, the external validity is increased due to the general hemodialysis population has been included in the analysis. A limitation of our study is the small and non-randomised sample. Indeed, as a pivotal study, we enrolled patients who perform dialysis in a single center. Furthermore, only Caucasian patients were included, and this reduced the generalizability of our results.

Conclusion

Our findings suggest that the implementation of UF-control in dialysis practice appears to improve patient tolerance and suggest that it could reduce the intradialytic complications. It can be useful mostly in the absence of advanced monitoring tools like bioimpedance or ultrasound. Future perspectives should be based on patient-reported outcomes (PROs), such as post-HD symptoms and the quality of recovery. Furthermore, larger and longitudinal studies, including bioimpedance as a comparator, with diversified populations will be performed to confirm the UF-control efficacy in a longer follow-up and advanced artificial intelligence can be implemented for better weight control.

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Apolipoprotein L1 (APOL1) and Nephropathy

Articoli originali

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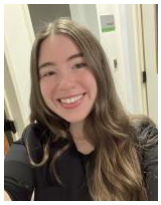
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ABSTRACT

Introduction. End-stage renal disease exhibits a disproportionate prevalence among Black individuals and older adults within the United States and worldwide. A significant genetic contributor to this disparity is the Apolipoprotein L1 (APOL1) gene, found exclusively in populations of African ancestry.
Materials and Method. We aim to perform a narrative review regarding the current understanding of APOL1 and its complex role in kidney disease pathogenesis.
Results. The G1 and G2 APOL1 risk alleles are strongly associated with an elevated risk for non-diabetic chronic kidney disease (CKD), including hypertensive nephropathy, focal segmental glomerulosclerosis, and HIV-associated nephropathy, in individuals who are homozygous or compound heterozygous for these variants. While 10-15% of African Americans carry two APOL1 risk alleles, approximately 80% remain disease-free, suggesting incomplete penetrance and the involvement of additional risk factors. In this condition, renal damage could be induced through different mechanisms such as altered cellular ion transport, mitochondrial dysfunction, and the requirement for additional stressors or "second hits".
Conclusion. The increased susceptibility to end-stage renal disease (ESRD) in individuals of African ancestry is influenced by variations in the APOL1 gene.

KEYWORDS: Apolipoprotein L1, kidney diseases, genetics

Introduction

Studies in the United States have revealed that the risk of developing end-stage renal disease (ESRD) is significantly higher in Black individuals and older adults. Specifically, Black individuals are almost three times more likely to develop this condition compared to White individuals, and those aged 75 and older are almost three times more likely to develop it compared to those aged 45 to 64 [1, 2].

Apolipoprotein L1 (APOL1) is a gene observed exclusively within populations of African ancestry. The APOL1 risk alleles, G1 and G2, which are characterized by two linked single nucleotide polymorphisms (G1) and a deletion (G2), respectively, are strongly associated with an elevated risk for non-diabetic chronic kidney disease in homozygous or compound heterozygous individuals, following an autosomal recessive inheritance pattern [3–12].

In African Americans, 50% carry at least one G1 or G2 allele, while 10-15% are homozygous or compound heterozygous for these risk alleles. Despite a significant risk of chronic kidney disease associated with G1 and G2 APOL1 variants, approximately 80% of individuals with two risk alleles will remain disease-free [8].

It is worth mentioning that Chen et al. found that even though the prevalence of hypertension, coronary heart disease, atrial fibrillation/flutter, stroke, and heart failure was similar between Black individuals with high-risk and low-risk APOL1 genotypes, significant disparities emerged when comparing Black and White participants. Black participants, regardless of APOL1 genotype (high or low risk), exhibited a higher prevalence of hypertension, diabetes mellitus, and overall cardiovascular disease compared to White participants. Moreover, APOL1 risk variants were identified as risk factors for end-stage renal disease, but not for mortality, and this association remained consistent across different age groups [1].

APOL1

APOL1, a recently evolved gene present only in humans and certain primates, circulates as part of high-density lipoprotein and protects against *Trypanosoma brucei rhodesiense*, the causative agent of African sleeping sickness, by inducing lysosomal swelling and lysis of the parasite [8].

The APOL1 gene is located at chromosome 22, and encodes apolipoprotein L1, a protein expressed across a range of tissues and cell types [1, 3, 10]. The APOL1 messenger RNA is expressed in various tissues, including liver, lung, placenta, and endothelial cells, with weaker expression in heart and pancreas, and potential expression in macrophages [4]. The majority of APOL1 present in human plasma is secreted by the liver, and circulates as part of high-density lipoprotein class 3, specifically the dense subclass 3a, and is largely absent from other HDL classes [5, 8]. Beyond its well-established association with kidney disease, APOL1 plays a key role in lipid metabolism, particularly as a structural component of high-density lipoprotein (HDL) particles. APOL1 is primarily secreted by the liver and circulates in HDL subclass 3a, where it participates in the reverse cholesterol transport (RCT) pathway, promoting cholesterol efflux from macrophages and peripheral tissues toward the liver for excretion. Variants in APOL1 (G1 and G2), although evolutionarily selected for their protective role against Trypanosoma brucei rhodesiense, may alter HDL composition and function, leading to reduced anti-atherogenic capacity.

This dysfunction could contribute to endothelial injury, vascular inflammation, and accelerated atherosclerosis in carriers of APOL1 risk alleles, potentially linking renal and cardiovascular pathogenesis within the same genetic framework. While findings remain partially inconsistent – some studies not demonstrating a direct causal link – emerging evidence supports that APOL1

variants may impair HDL-mediated cholesterol trafficking and anti-inflammatory functions, offering a unifying explanation for the increased cardiovascular and renal risk in individuals of African ancestry. Understanding this dual role of APOL1 in both lipid handling and kidney injury may help nephrologists interpret the broader systemic implications of APOL1 genotypes and design integrated approaches to patient care (Figure 1) [15].

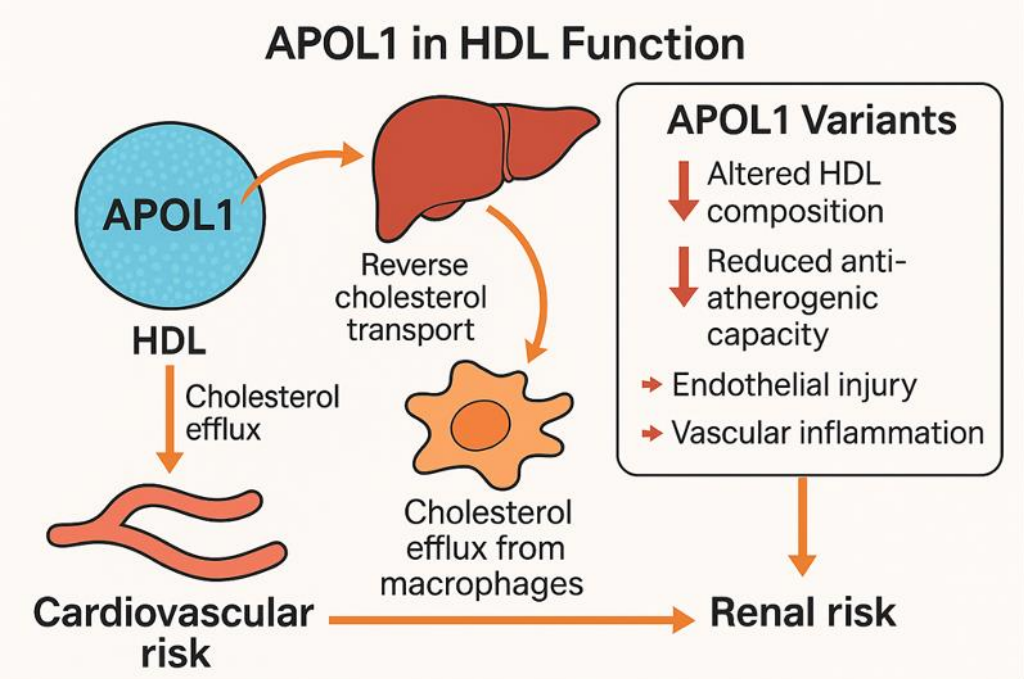

Figure 1. Schematic representation of the role of APOL1 in high-density lipoprotein (HDL) metabolism and reverse cholesterol transport. APOL1, primarily secreted by the liver, is incorporated into HDL3a particles that mediate cholesterol efflux from macrophages to the liver. APOL1 risk variants (G1, G2) may alter HDL composition, impair cholesterol trafficking, and reduce its anti-atherogenic capacity, contributing to endothelial injury, vascular inflammation, and increased cardio-renal risk.

The APOL1 protective effect against *Trypanosoma brucei rhodesiense* explains the high frequency of APOL1 risk variants in sub-Saharan Africa [4, 8, 10]. Thomson et al. found that the G1 variant of the APOL1 gene was most prevalent in West Africa, while the G2 variant was distributed more evenly across the globe [3, 5]. Genetic variation in the APOL1 gene is a major contributor to the disparity in non-diabetic kidney disease rates between African Americans and European Americans. Approximately 30% of African Americans chromosomes carry either the G1 or G2 APOL1 allele, which are mutually exclusive on single chromosomes. Around 10-12% of African Americans inherit two APOL1 risk alleles, while 49% lack any risk variants. In contrast, these risk variants are infrequent in European Americans, with roughly 0.3% carrying the G1 allele and 0.1% carrying the G2 allele [4].

The G1 allele was found in approximately 40% of Yoruba (West Africa) chromosomes but was absent in European, Japanese, and Chinese individuals. Similarly, G2 was detected in only three Yoruba subjects and not in the other groups [6]. North American studies have reported APOL1 allele frequencies between 20% and 39%, while Asian and some Latin American studies have shown considerably lower frequencies, ranging from 1.9% to 9.4% (Figure 2) [3].

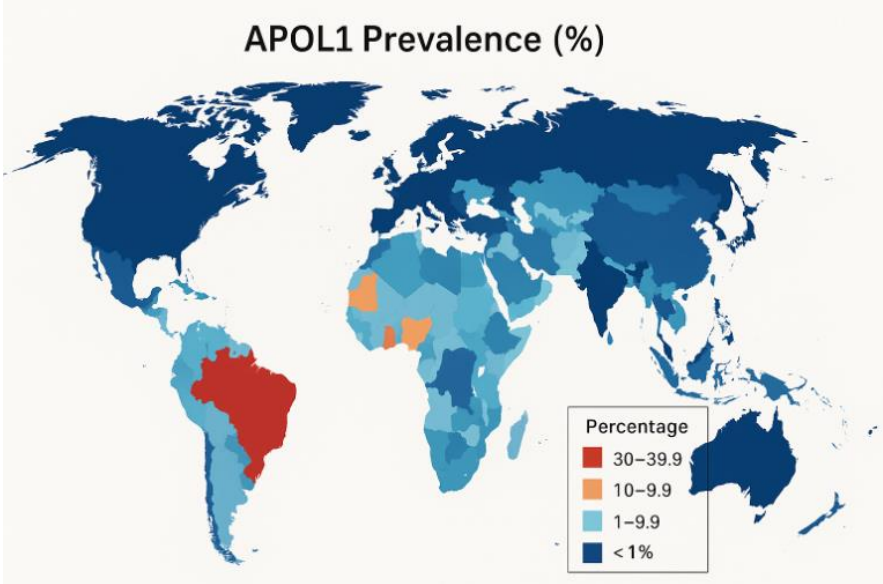

Figure 2. Global prevalence of APOL1 risk variants (G1 and G2). The map illustrates regional differences in APOL1 allele frequencies: dark red (>30%) in Sub-Saharan Africa, orange (10-30%) in North America and Afro-descendant regions, yellow (1-9%) in some Latin American populations, and light grey (<1%) in Europe, Asia, and Oceania. This distribution reflects the evolutionary pressure exerted by Trypanosoma brucei rhodesiense exposure.

APOL1 and kidney disease

APOL1 gene variants in African Americans significantly increase the risk of hypertensive kidney disease, lupus nephritis, sickle cell nephropathy, focal segmental and global glomerulosclerosis, characterized by interstitial scarring and arteriolar changes, and HIV-associated collapsing glomerulosclerosis [3–12]. In Afro-descendant patients with chronic kidney disease, the prevalence of APOL1 gene mutations is 20-22% for the G1 variant and 13-15% for the G2 variant [3].

In the population-based Dallas Heart Study, APOL1 risk variants were associated with an increased prevalence of microalbuminuria and a decreased glomerular filtration rate among African American participants. However, no statistically significant difference in proteinuria or estimated glomerular filtration rate was observed between individuals with two APOL1 nephropathy risk variants and those with less than two [7].

In kidney transplant patients, no significant difference in renal allograft survival was observed between recipients of kidneys from donors carrying one APOL1 nephropathy risk variant and those receiving kidneys from donors without such variants, while it was found significantly reduced renal allograft survival in recipients of deceased donor kidneys from African Americans with two APOL1 nephropathy risk variants compared to those receiving kidneys from African American donors with fewer than two risk variants [4]. Additionally, it has been suggested that APOL1 expression across podocytes, endothelial cells, and immune cells may independently or synergistically contribute to the complex pathogenic processes affecting renal allograft survival [12]. Recent evidence also suggests that APOL1 variants may influence cardiovascular risk beyond their established renal effects. As a structural component of high-density lipoproteins (HDL), APOL1 participates in reverse cholesterol transport, facilitating cholesterol efflux from peripheral macrophages to the liver. Alterations in APOL1 structure or expression could impair HDL function, potentially reducing its anti-atherogenic capacity. This dysfunctional HDL phenotype may contribute to endothelial injury, vascular inflammation, and accelerated atherosclerosis in APOL1 risk allele carriers. Although the

literature remains inconsistent – some studies failing to confirm a direct causal relationship – the possibility of a link between APOL1 variants, altered lipid metabolism, and cardiovascular disease warrants further investigation [13].

APOL1 damaging mechanisms

It has been hypothesized several potential mechanisms by which APOL1 variants may induce nephropathy in native kidneys:

- The APOL1 protein present in individuals homozygous for APOL1 risk alleles, may exhibit reduced HDL binding, leading to its filtration and reabsorption within the proximal nephron, culminating in kidney damage. In this sense, circulating APOL1 has been implicated in recurrent focal segmental glomerulosclerosis post-transplantation, a condition responsive to plasmapheresis [4].
- Abnormal HDL levels may contribute to renal microvascular disease, frequently observed in focal segmental glomerulosclerosis and hypertension-attributed end-stage renal disease [4].
- The requirement of two APOL1 risk alleles for phenotype development may be explained by a multimerization model. This model proposes that wild-type APOL1 interacts with an unknown factor to antagonize APOL1 toxicity. In the presence of a single APOL1 risk allele, the formation of APOL1 multimers containing at least one wild-type subunit is sufficient to maintain the inhibitory binding of the toxicity-blocking factor. Conversely, when two risk alleles are present, multimers predominantly lack wild-type APOL1, leading to the manifestation of toxicity [8].
- APOL1 podocyte expression may result in cellular dysfunction or injury. Given APOL1 structural and functional similarities to the Bcl2 family of apoptosis-related proteins, APOL1-induced podocyte apoptosis could lead to glomerulosclerosis. These pathways could contribute to subclinical APOL1-associated kidney disease in native kidneys, as well as to graft dysfunction post-donation in the context of cold ischemia and nephrotoxic agents, such as calcineurin inhibitors [4].
- Since nephropathy does not manifest in all individuals who present two APOL1 risk variants inheritance, this suggests that additional genetic and/or environmental factors (second hit) are necessary for developing this disease. This ‘second hit’ may interact with APOL1 risk variants, resulting in renal damage. For example, the presence of HIV infection (60-70% HIV-associated collapsing focal segmental glomerulosclerosis carry the high-risk APOL1 genotype) or variations within the podocin gene (NPHS2) may represent second hits [7]. Another potential ‘second hit’ is serum suPAR, a predictive biomarker for kidney disease in individuals with the high-risk APOL1 genotype, which could bind podocyte integrins and APOL1, potentially leading to renal damage [8].
- Interferon treatment in some individuals with this genotype has induced proteinuria and focal segmental glomerulosclerosis. These findings strongly suggest that viral infections, by an interferon-mediated mechanism, are a crucial second hit for kidney disease development. Interferon strongly induces APOL1 RNA and protein expression in cultured human podocytes and endothelial cells, due to multiple STAT-binding sites on APOL1 regulatory regions [8].
- It has been proposed that risk variant APOL1-induced toxicity is mediated by impaired late endosome-lysosome fusion (a VAMP8-mediated process), and subsequent disruption of autophagy flux [8].

- APOL1 variants mediate kidney disease pathogenesis by exerting ion channel activity, consequently resulting in the NLRP3 upregulated activation as cytotoxicity mediator and STING function as immune mediators inducer, both of which are nephropathy determinants (Figure 3) [12].

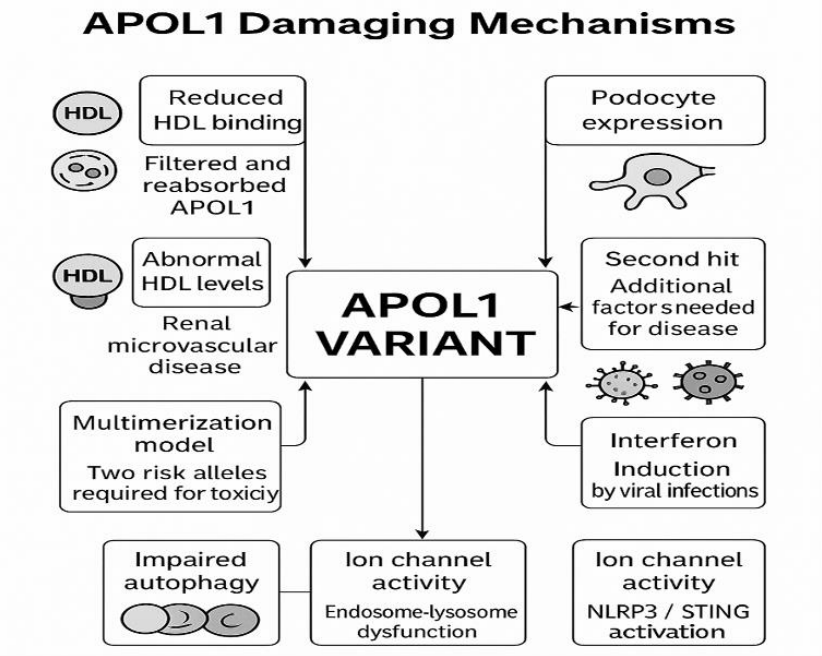

Figure 3. APOL1 Damaging Mechanisms.

APOL1 and pre-eclampsia

The life course of APOL1-related disease may begin in utero. In the CKiD and NEPTUNE cohorts, children carrying APOL1 risk variants (RVs) showed a higher likelihood of preterm birth. Although population studies do not confirm a general association between APOL1 and preterm delivery, fetal APOL1 RVs have been linked to an increased maternal risk of pre-eclampsia, particularly among U.S.-born women, suggesting that environmental factors may modulate this risk. Some evidence indicates an additive effect, where even a single maternal APOL1 RV increases susceptibility, but the highest risk occurs when the fetus carries a high-risk APOL1 genotype; mismatches between maternal and fetal genotypes may further influence outcomes. This association likely reflects the high placental expression of APOL1, as demonstrated in transgenic mice, where APOL1 expression in the placenta induced a pre-eclampsia-like phenotype – even in wild-type dams carrying APOL1-positive fetuses. Additionally, fetal APOL1 RVs have been associated with small-for-gestational-age infants in pre-eclamptic pregnancies. Collectively, these findings suggest that APOL1 genotyping could serve as a risk-stratification tool for pregnant women of African ancestry, and that pre-eclampsia or preterm birth might act as second hits predisposing to early-onset kidney disease in childhood [14].

APOL1 treatment

The growing understanding of the molecular basis of APOL1-mediated nephropathy has fostered the development of several targeted therapeutic strategies aimed at reducing APOL1 expression, inhibiting its cytotoxic function, and modulating downstream inflammatory pathways [10]. These interventions are grounded in the observation that APOL1-induced injury is driven by elevated

expression and aberrant channel activity of the high-risk G1 and G2 variants, which promote podocyte dysfunction, inflammation, and cell death. Therefore, reducing APOL1 levels or blocking its pore-forming activity is hypothesized to attenuate the initial pathogenic cascade. Among the most advanced compounds is Inaxaplin (VX-147), a small-molecule inhibitor designed to block APOL1 pore function and prevent cationic dysregulation within podocytes. In a Phase 2 study [15] treatment with Inaxaplin in patients carrying two APOL1 risk variants and focal segmental glomerulosclerosis resulted in a clinically meaningful reduction in proteinuria after 13 weeks, suggesting that selective inhibition of APOL1 function may slow the progression of nephropathy and potentially redefine the therapeutic approach for genetically determined glomerular disease. In parallel, antisense oligonucleotides (ASOs) targeting APOL1 mRNA have demonstrated preclinical efficacy by silencing APOL1 gene expression, thereby reducing the accumulation of toxic protein in podocytes and mitigating kidney injury [16]. This gene-specific strategy directly addresses the pathogenic source and may complement small-molecule inhibitors in patients with high-risk genotypes. Beyond direct APOL1 modulation, recent findings highlight the potential of downstream pathway inhibition. Wu et al. identified both the NLRP3 inflammasome and the STING (stimulator of interferon genes) signaling pathway as critical effectors operating downstream of APOL1 channel activity within podocytes. Inhibiting STING may represent a particularly promising strategy, given its role in amplifying interferon production, which in turn induces APOL1 overexpression and perpetuates cellular toxicity. STING blockade, therefore, could interrupt this pathogenic feedback loop and limit the inflammatory milieu driving APOL1-associated renal damage. Similarly, pharmacologic inhibition of NLRP3 inflammasome activation may attenuate pyroptosis and inflammatory cytokine release, thereby preserving podocyte viability [17].

Other approaches under investigation include JAK-STAT pathway inhibitors, such as baricitinib, which suppress cytokine-driven APOL1 transcription and have shown beneficial effects in experimental models of inflammatory podocytopathy. Collectively, these strategies reflect a multifaceted therapeutic paradigm – ranging from direct genetic and molecular inhibition of APOL1 to modulation of its downstream signaling effectors [18]. While most agents remain in early clinical or preclinical phases, these emerging data collectively underscore a paradigm shift in the management of APOL1-associated kidney diseases – from non-specific immunosuppression toward precision nephrology, grounded in genetic stratification and mechanistic understanding (Table 1). The integration of APOL1 genotyping into clinical practice will be crucial for patient selection and for guiding the application of these novel therapies, ultimately improving renal outcomes and addressing long-standing health disparities in populations of African ancestry.

Agent	Mechanism/Target	Development Phase	Key Reference(s)
Inaxaplin (VX-147)	Small-molecule APOL1 function/pore inhibitor; reduces proteinuria	Phase 2/3	Egbuna et al., N Engl J Med 2023
APOL1 Antisense Oligonucleotide	APOL1 mRNA silencing (reduces APOL1 expression)	Preclinical/early clinical	Aghajan et al., JCI Insight 2019
Baricitinib (JAK inhibitor)	Blocks cytokine-induced JAK-STAT signaling and APOL1 upregulation	Experimental/repurposing	Nystrom et al., JCI Insight 2022
STING pathway inhibitors	Attenuate interferon-stimulated APOL1 expression and inflammatory signaling	Preclinical	Wu et al., Immunity 2021
NLRP3 inflammasome blockers	Inhibit inflammasome activation/pyroptosis downstream of APOL1	Preclinical	Wu et al., J Clin Invest 2021

Table 1. Drugs under investigation for APOL1-mediated kidney disease.

Transplant implications

In the context of kidney transplantation, donor APOL1 genotype has emerged as a more consistent predictor of allograft outcomes than recipient genotype, particularly with respect to long-term graft survival. Several cohorts have shown that kidneys procured from deceased African American donors who carry two APOL1 renal-risk alleles display a significantly shorter allograft survival, even after adjusting for donor age, cold ischemia time, and HLA matching [19]. In contrast, the recipient's APOL1 risk status has not reliably correlated with five-year graft loss in most studies, suggesting that the intrinsic "health" of the graft – shaped by donor APOL1 expression – is the critical determinant. Case reports further support the donor-risk paradigm: Chang et al. described instances of de novo collapsing focal segmental glomerulosclerosis (FSGS) occurring in recipients of kidneys from donors later found to harbor two high-risk APOL1 alleles. In several of those cases, viral infections (e.g. CMV or BK viremia) served as plausible "second hits", triggering glomerular injury in a graft already genetically predisposed. These findings reinforce a "two-hit" model of APOL1 injury, wherein a high-risk donor background requires additional stressors to precipitate overt graft disease [20]. Because of this evidence, transplant programs increasingly consider APOL1 genotyping in donor evaluation, especially among donors of African ancestry. Some guidelines recommend counseling recipients about the increased graft risk when the donor carries a high-risk genotype [21]. However, the use of APOL1 genotyping in recipient decision-making remains controversial: the presence of the risk alleles in recipients has not consistently translated into worse short- or intermediate-term allograft survival across studies. Going forward, large-scale prospective studies (such as the APOLLO (APOL1 Long-term Kidney Transplantation Outcomes) study) are poised to clarify the magnitude of risk conferred by donor APOL1 status and to refine allocation strategies that balance graft utility with equity [22]. Meanwhile, the evidence supports that donor high-risk APOL1 genotype should be considered a relevant risk factor in transplant planning, while recipient genotyping must be interpreted with caution and in the context of broader immunologic, hemodynamic, and environmental influences.

Discussion

Testing for APOL1 genetic variants is recommended in selected clinical scenarios where the results may clarify diagnosis, prognosis, or influence management decisions. The strongest indications include unexplained non-diabetic proteinuric chronic kidney disease (CKD), particularly in patients of African ancestry with focal segmental glomerulosclerosis (FSGS) or glomerulosclerosis on biopsy without another clear etiology; HIV-associated nephropathy (HIVAN) or other forms of collapsing glomerulopathy, in which APOL1 high-risk genotypes markedly increase disease susceptibility and accelerate progression; early-onset CKD or a family history of ESRD in individuals of African or Afro-Caribbean descent, where APOL1 testing can assist in genetic counseling and risk stratification; and evaluation of living kidney donors of African ancestry, as donor – but not recipient – APOL1 genotype has been linked to long-term allograft survival. Routine population screening is not currently recommended, as the majority of individuals carrying two risk alleles do not develop kidney disease, highlighting the influence of "second-hit" factors such as viral infections, interferon exposure, or inflammatory stressors. Nonetheless, APOL1 testing is increasingly integrated into precision nephrology programs, helping clinicians tailor surveillance, manage secondary risk factors, and inform transplant counseling [23]. Interpretation of APOL1 genotyping requires a nuanced understanding of its probabilistic – not deterministic – nature. The presence of a high-risk genotype, defined by two risk alleles (G1/G1, G2/G2, or G1/G2), substantially increases the probability and rate of CKD progression, particularly in non-diabetic etiologies such as focal segmental glomerulosclerosis (FSGS), hypertensive nephrosclerosis, and HIV-associated nephropathy.

However, penetrance is incomplete: only a fraction (≈15-20%) of high-risk individuals develop clinically evident kidney disease, underscoring the importance of environmental and inflammatory "second hits" – for instance, viral infections, interferon exposure, or ischemic injury – that interact with the genetic background to precipitate renal damage. APOL1 results must always be interpreted in conjunction with histopathologic findings, clinical phenotype, and comorbid conditions. A biopsy can delineate specific glomerular lesions (e.g., collapsing FSGS, microvascular changes) that support APOL1-mediated pathology, while clinical context – such as hypertension, diabetes, or viral infection – helps differentiate genetic susceptibility from acquired injury. In transplant settings, donor high-risk status predicts reduced allograft survival, whereas recipient genotype alone does not consistently correlate with five-year graft outcomes. APOL1 genotyping refines risk stratification rather than providing a binary diagnosis. Its optimal use lies in integrated interpretation, combining genetic, histologic, and clinical dimensions to inform prognosis, surveillance intensity, and therapeutic decision-making – especially within precision nephrology and transplant counseling frameworks [24]. Genetic counseling for individuals tested for APOL1 risk variants should emphasize that the high-risk genotype confers susceptibility but not certainty of disease. Incomplete penetrance must be clearly explained to avoid undue anxiety or stigma. Counseling should also address ethical and psychosocial implications, including potential effects on insurability, employability, and family planning, which vary across jurisdictions and regulatory frameworks. Importantly, patients should be encouraged to focus on modifiable risk factors that can mitigate disease expression, such as optimal blood pressure control, renin-angiotensin-aldosterone system (RAAS) inhibition, and dietary sodium and protein moderation. Incorporating APOL1 education into broader CKD prevention programs can foster informed decision-making while minimizing genetic discrimination and promoting equitable access to testing and follow-up care [25].

In addition, we have reviewed the most recent literature on genetic testing in CKD and glomerular disease [26]. On this basis, we now propose a set of clear indications for practicing nephrologists facing isolated patients affected by CKD or specific nephropathies, which we have summarized in Box 1. This recommendation is based on the following factors, Prognosis / risk stratification**,** In Elliott et al. 2024 [26], both monogenic diagnoses (6.5% of patients) and high-risk APOL1 genotypes (5.5%) independently predicted faster eGFR decline and higher kidney failure risk [26]. Actionability, NKF 2024 consensus says nephrologists should actively integrate genetic testing into routine evaluation of suspected hereditary nephropathies, into donor assessment, and into longitudinal care planning, and provide algorithms for symptomatic and at-risk individuals [27]. Clinical utility in real-world CKD: A large prospective CKD panel study (>1,600 adults; RenaCARE) showed that ~21% had a positive genetic finding; in ~49% of those, the genetic result *replaced or reclassified* the working diagnosis, and physicians reported it changed management in >90% [28].

BOX 1. When should a clinical nephrologist order genetic testing?

1. CKD with unclear or atypical etiology (test broadly).

- Adults or children whose routine clinical, serologic and imaging work-up does not yield a clear cause ("CKD of unknown etiology").
- Includes patients with descriptive biopsy labels only (e.g. "FSGS", "interstitial nephritis", "nephrosclerosis") without an upstream driver.
- In the 5,727-patient cohort of Elliott et al. [26], a monogenic kidney disorder was found in 6.5% and a high-risk APOL1 genotype in 5.5%, and both were independently associated with higher kidney-failure risk (HR 1.72 and 1.67, respectively). Early genetic diagnosis therefore refines prognosis and therapy [29].

2. When a monogenic kidney phenotype is suspected.

2a. Stereotyped phenotypes with well-defined genes

- Persistent hematuria ± deafness/ocular signs → suspect COL4A3–COL4A5 (Alport spectrum).
- Steroid-resistant, collapsing or recurrent FSGS (child or young adult).
- Cystic kidney disease not fully compatible with "typical" late-onset ADPKD.
- CAKUT, especially bilateral or syndromic in pediatrics [27].

2b. Early-onset disease

- CKD/proteinuria/hematuria/HTA before 30-40 yrs without another explanation, higher monogenic yield across all 3 JCI 2024 cohorts and in 2025 frameworks [29].

2c. Kidney-plus presentations

- Kidney disease plus neurosensory, skeletal, endocrine, metabolic, neurologic, ocular or developmental features, think single-gene or ciliopathy [30].

3. Positive family history.

- ≥1 first or second degree relative with CKD, ESKD or transplant [29].

4. APOL1 testing in ancestry or phenotype appropriate patients.

- West African, Afro-Caribbean, African-American, Afro-Latin ancestry and collapsing FSGS or FSGS-like lesions, disproportionately aggressive "hypertensive" CKD or rapid eGFR loss.
- In living donor evaluation in these ancestries, as recommended by the NKF working group (2024) and reiterated in 2025 updates and the KDIGO APOL1 conference report [27].

5. Before accepting a related living kidney donor when hereditary disease is suspected.

- Donors biologically related to a recipient with proven or suspected COL4A, UMOD, PKD, or APOL1 mediated kidney disease should do targeted testing (familial variant or APOL1). This is now part of responsible donor evaluation in NKF 2024/2025 and in recent donor-genetics reviews [31].

6. When the molecular result changes management.

- To start a gene- or pathway-directed therapy (complement, CoQ10, RNAi, upcoming APOL1 drugs).
- To stop futile immunosuppression in monogenic podocytopathies
- To anticipate recurrence post-transplant and to organize cascade testing in the family [29].

7. Pediatric CKD

- In children 30-50% of CKD can be genetic (CAKUT, podocyte, ciliopathy, metabolic), so a broad exome is recommended [32].

Note: The most recent evidence (KDIGO 2024 on CKD evaluation, the NKF 2024/2025 report on genetics in nephrology, and 2025 studies combining exome sequencing with polygenic risk scores, PRS) shows that even in "unselected" CKD cohorts clinically actionable genetic findings are identified in ≈20% of patients. Together with the ongoing reduction in sequencing costs and the emergence of targeted mechanism based therapies (APOL1 inhibitors, complement directed drugs, CoQ10 pathway defects, etc), this strongly suggests that the threshold for ordering genetic studies will decrease in the near future.

Conclusion

The increased susceptibility to end-stage renal disease (ESRD) in individuals of African ancestry is influenced by variations in the APOL1 gene. While the precise molecular pathways leading to renal damage are still being investigated, current theories suggest that these variants may exert their effects through mechanisms such as altered cellular ion transport, mitochondrial dysfunction, and the requirement for additional stressors or “second hits”. The ongoing investigation into these complex mechanisms is crucial, as it directly informs the development of targeted therapies. Promising interventions, including agents that directly modulate APOL1 protein activity or inhibit downstream inflammatory cascades, offer the potential to mitigate disease progression and address the significant health disparities observed in APOL1-associated kidney disease. APOL1 genotyping represents a pivotal step toward precision nephrology, linking genetic risk with targeted prevention and emerging therapies. While a high-risk genotype increases susceptibility to kidney injury, its expression depends on environmental and clinical modifiers, underscoring the need for integrated interpretation and personalized management. Ongoing translational research and clinical trials promise to transform APOL1 from a genetic marker of risk into a therapeutic target, bridging discovery and clinical care for populations most affected by kidney disease.

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Metabolic Kidney Disease: A New Concept in the Interaction Between Obesity, Prediabetes, Diabetes and Liver Dysfunction

Articoli originali

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ABSTRACT

Metabolic abnormalities such as obesity, insulin resistance, prediabetes, type 2 diabetes and metabolic dysfunction-associated steatotic liver disease (MASLD) increasingly contribute to chronic kidney disease (CKD). Although often treated as separate entities, these conditions share common mechanisms – including glomerular hyperfiltration, adipokine imbalance, chronic low-grade inflammation, endothelial dysfunction and lipid accumulation – that initiate and sustain renal injury long before classical CKD becomes clinically evident.

The concept of Metabolic Kidney Disease (MKD) offers a unified framework that captures the continuum of renal involvement across the metabolic spectrum. Obesity- and prediabetes-related MKD frequently precede diabetic kidney disease, while MASLD – according to updated EASL-EASD-EASO guidelines – is a multisystem disorder with direct renal consequences. Mixed metabolic phenotypes further intensify metabolic stress, accelerating progression toward CKD.

Recognising MKD has important clinical implications. Expanded screening strategies may identify early renal alterations in individuals with metabolic vulnerability who are not targeted by traditional CKD criteria. Integrating metabolic evaluation into nephrology practice may facilitate earlier, more holistic interventions and ultimately improve cardio-renal outcomes.

KEYWORDS: Obesity, Type 2 diabetes, Prediabetes, Chronic Kidney Disease, Liver dysfunction, Cardiorenal metabolic syndrome, Albuminuria, Glomerular hyperfiltration

List of Abbreviations:

ACR – Albumin-to-creatinine ratio
AGEs – Advanced glycation end-products
AKI – Acute kidney injury
CKD – Chronic Kidney Disease
CKM – Cardiovascular-kidney-metabolic syndrome
CRMS – Cardio-renal-metabolic syndrome
DKD – Diabetic kidney disease
eGFR – Estimated glomerular filtration rate
GLP-1 RA – Glucagon-like peptide-1 receptor agonist
HbA1c – Glycated haemoglobin
IL-6 – Interleukin 6
MASLD – Metabolic dysfunction–associated steatotic liver disease
MKD – Metabolic kidney disease
NAFLD – Non-alcoholic fatty liver disease (former term for MASLD)
NF-κB – Nuclear factor kappa-light-chain-enhancer of activated B cells
ORG – Obesity-related glomerulopathy
PKC – Protein kinase C
RAAS – Renin–angiotensin–aldosterone system
ROS – Reactive oxygen species
SGLT2 – Sodium–glucose cotransporter 2
T2DM – Type 2 diabetes mellitus
TGF-β – Transforming growth factor beta
TNF-α – Tumor necrosis factor alpha

Introduction

Cardiovascular diseases and other non-communicable conditions remain the leading cause of death worldwide, accounting for nearly 70% of global mortality [1]. Diabetes mellitus, arterial hypertension, obesity, and chronic kidney disease (CKD) constitute the most prevalent chronic conditions contributing to this burden. CKD affects an estimated 9-13% of the population, with prevalence increasingly driven by the global epidemics of diabetes and obesity [2, 3].

In parallel, the prevalence of diabetes has doubled from 1990 to 2022, reaching over 828 million adults globally [4]. Similar trends are observed in Latin America and other regions, where obesity and metabolic dysfunction are now major determinants of cardiovascular and renal risk [5–10]. Importantly, mounting evidence indicates that kidney injury can arise before overt diabetes develops, occurring across the entire spectrum of metabolic disturbances, including obesity, prediabetes, insulin resistance, and metabolic dysfunction-associated steatotic liver disease (MASLD).

These interconnected processes form a continuum in which excess adiposity and adipose-tissue dysfunction induce systemic inflammation, endothelial injury, glomerular hyperfiltration, and neurohormonal activation. This “adipocentric” perspective has led to the recognition of the Cardio-Renal-Metabolic Syndrome (CRMS) as an integrated model encompassing cardiovascular, renal, and metabolic abnormalities [11–13].

Within this framework, the concept of Metabolic Kidney Disease (MKD) emerges as a unifying term describing kidney damage mediated primarily by metabolic dysfunction, even in the absence of

sustained hyperglycaemia. MKD encompasses kidney injury associated with obesity, prediabetes, type 2 diabetes, MASLD, and mixed phenotypes. Its early recognition may be essential to interrupt disease progression and reduce cardiovascular and renal complications.

Importantly, metabolic dysfunction precedes and amplifies kidney injury across the entire continuum of adiposopathy, insulin resistance, impaired glucose tolerance, type 2 diabetes and MASLD, highlighting that renal damage often develops before overt hyperglycaemia becomes clinically detectable.

Cardio-Renal-Metabolic Syndrome (CRMS)

The Cardio-Renal-Metabolic Syndrome (CRMS) provides the essential pathophysiological context from which Metabolic Kidney Disease emerges. Evidence accumulated over the last decade shows that excess adiposity – particularly visceral and ectopic fat accumulation – drives a systemic inflammatory state that disrupts cardiovascular, renal, and metabolic homeostasis [14]. Rather than isolated diseases, these conditions form an interconnected continuum in which dysfunction in one organ system accelerates injury in the others.

The American Heart Association defines CRMS as a systemic disorder characterized by pathophysiological interactions between metabolic risk factors, CKD, and cardiovascular disease (CVD), leading to multiorgan dysfunction and increased cardiovascular events [12]. This framework emphasizes the bidirectional nature of these interactions: CVD increases the likelihood of renal dysfunction; CKD amplifies cardiovascular risk; and metabolic abnormalities – including adipose-tissue dysfunction, insulin resistance, and subclinical inflammation – drive both processes simultaneously [15–18].

Three major biological pathways underpin CRMS:

1. Chronic low-grade inflammation, mediated by adipose-derived cytokines such as IL6 and TNFα, promoting endothelial dysfunction, oxidative stress, and vascular injury.
2. Insulin resistance, contributing to altered podocyte signaling, increased sodium reabsorption, impaired nitric oxide bioavailability, and early glomerular hyperfiltration.
3. Neurohormonal activation, including heightened activity of the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS), fostering vasoconstriction, hypertension, fibrosis, and progressive organ damage.

To support clinical stratification, the AHA proposes a staging system encompassing the entire spectrum of metabolic and cardiorenal dysfunction [12, 15]:

- Stage 0: No metabolic risk factors
- Stage 1: Excess or dysfunctional adiposity, including prediabetes
- Stage 2: Metabolic risk factors and/or moderate-to-high CKD risk
- Stage 3: Subclinical CVD with overlapping metabolic or renal risk
- Stage 4: Established CVD ± CKD (4a: without renal insufficiency; 4b: with renal insufficiency)

Within this continuum, the kidney is both target and mediator of metabolic injury. CRMS thus provides the conceptual foundation for MKD/ERM, clarifying how metabolic dysfunction – independent of glycaemic thresholds – initiates and amplifies renal injury.

Definition and Concept of Metabolic Kidney Disease (MKD/ERM)

Metabolic Kidney Disease (MKD), or *Enfermedad Renal Metabólica* (ERM), is an emerging and evolving concept that seeks to integrate the entire spectrum of renal injury associated with metabolic dysfunction. Rather than representing a single disease or a traditional histopathological entity, MKD reflects a continuum of pathophysiological alterations in which adipose-tissue dysfunction, insulin resistance, and chronic low-grade inflammation converge to drive early and progressive kidney damage. This view departs from classical models focused exclusively on hyperglycaemia or hypertension, and instead places the metabolic milieu – especially dysfunctional adiposity – at the centre of renal injury [13, 19] (Figure 1).

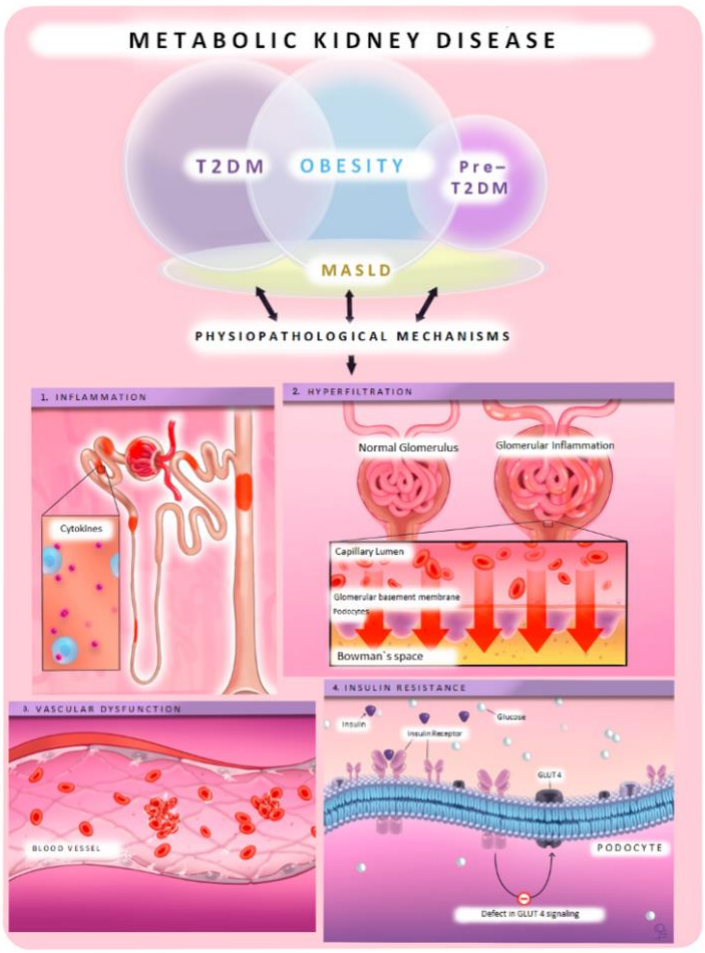

Figure 1. Common pathophysiological mechanisms in metabolic kidney disease (MKD). 1. Inflammation: increased cytokine and adipokine signalling leading to endothelial dysfunction, tissue remodelling, and fibrosis. 2. Hyperfiltration: intraglomerular hypertension and haemodynamic stress, contributing to podocyte injury and glomerulosclerosis. 3. Endothelial dysfunction: impaired nitric oxide bioavailability leading to altered autoregulation and vascular stiffness. 4. Insulin resistance: disrupted insulin signalling in target tissues (e.g., podocytes, hepatocytes) promoting metabolic stress, lipotoxicity, and apoptosis.

Adipose-tissue dysfunction plays a pivotal mechanistic role. Excess visceral fat promotes secretion of proinflammatory cytokines (TNF-α, IL-6), dysregulated adipokines (reduced adiponectina, elevated leptina), increased oxidative stress, and activation of the renin–angiotensin–aldosterone system (RAAS). These mechanisms favour afferent arteriolar vasodilation, intraglomerular

hypertension, podocyte stress, and alterations in glomerular permeability. Over time, these changes contribute to hypertrophy of glomerular structures, expansion of mesangial matrix, tubulointerstitial inflammation, and ultimately to a decline in glomerular filtration [20–24]. This continuum perspective aligns with current evidence, emphasizing that renal alterations frequently emerge during early metabolic imbalance, well before traditional diagnostic criteria for diabetes or CKD are met.

MKD as an Integrative Clinical Framework

The strength of the MKD concept lies in its ability to integrate metabolic phenotypes that traditionally have been described separately. Obesity, prediabetes, type 2 diabetes, MASLD, and their combinations share physiopathological pathways that converge on the kidney. Although the magnitude and temporal sequence of injury may differ, the kidney responds to metabolic stress in a largely stereotyped manner: early glomerular hyperfiltration, podocyte maladaptation, endothelial dysfunction, and progressive fibrosis.

This integrative framework does not negate existing terminology, such as Diabetic Kidney Disease (DKD) or CKD associated with metabolic syndrome, but rather seeks to connect them. DKD remains essential for describing renal injury in established diabetes. However, it does not encompass patients with obesity or prediabetes who show similar physiopathological patterns. Likewise, CKD associated with metabolic syndrome often remains an epidemiological description rather than a mechanistic one. MKD proposes a unifying perspective, highlighting the central role of metabolic dysfunction – whether hepatic, adipose, or pancreatic – in initiating and sustaining renal damage. Given its high prevalence and strong metabolic basis, MASLD should be formally recognised as a key determinant of renal vulnerability within the MKD spectrum, warranting systematic screening even in non-diabetic individuals.

Clinical Implications

Recognizing MKD as a distinct and broader clinical construct may help clinicians identify high-risk individuals who would not be screened under current CKD guidelines. It may also encourage early therapeutic interventions targeting adipose-tissue inflammation, insulin resistance, and metabolic stress before overt renal dysfunction becomes evident. Ultimately, MKD promotes a shift from reactive nephrology to a more preventive, metabolically informed approach, consistent with contemporary cardio-renal-metabolic frameworks.

Comparable patterns of early metabolic stress and altered body composition have been reported in kidney conditions characterised by organomegaly, where malnutrition and sarcopenia may develop despite preserved eGFR [25, 26], particularly in women due to the higher prevalence of hepatomegaly [27–29].

Furthermore, persistent inflammatory activation is a hallmark across CKD phenotypes. Evidence from anemia management [30], intravenous iron stewardship [31], and uremic toxin–driven vascular injury [32] highlights how metabolic and inflammatory disturbances can converge to amplify renal vulnerability, mirroring several mechanisms central to MKD.

Clinical Subtypes of Metabolic Kidney Disease

Metabolic Kidney Disease encompasses a spectrum of renal manifestations arising from distinct but interrelated metabolic disturbances. Although these conditions share common physiopathological

pathways – such as insulin resistance, adipose-tissue dysfunction, chronic inflammation, and endothelial injury – each metabolic phenotype imprints a characteristic pattern of renal involvement (Figure 2). In the following sections, we describe the major clinical subtypes of MKD, highlighting their specific mechanisms, histopathological features, and implications for early detection and progression.

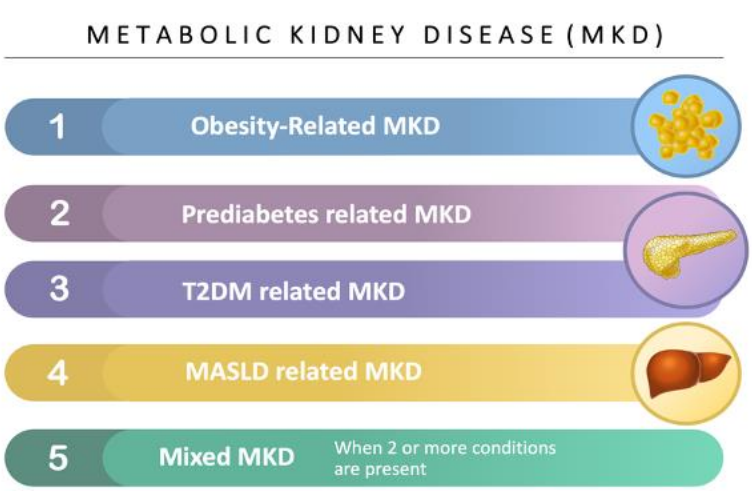

Figure 2. Proposed classification of metabolic kidney disease (MKD). Subtypes include obesity-related MKD, prediabetes-related MKD, T2DM-related MKD, MASLD-related MKD, and mixed MKD.

Obesity-Related- Metabolic Kidney Disease

Obesity represents one of the most consistent and well-established metabolic risk factors for the development and progression of kidney disease. Far from being a passive -energy storage compartment, adipose tissue – -particularly visceral fat accumulation – functions as an active endocrine and immunometabolic organ capable of modulating systemic inflammation, insulin sensitivity, oxidative stress, haemodynamics, and neurohormonal signalling [33–37]. These perturbations exert direct and indirect effects on renal structure and function, forming the basis of obesity-related- metabolic kidney disease.

From a haemodynamic standpoint, obesity is characterized by increased renal plasma flow, afferent arteriolar vasodilation, and elevated intraglomerular pressure. These early adaptations, largely mediated by hyperinsulinaemia, enhanced tubular sodium–glucose reabsorption, and heightened RAAS and sympathetic nervous system activity, culminate in glomerular hyperfiltration [36–38]. Persistent hyperfiltration contributes to enlargement of glomerular tuft volume and sets the stage for podocyte hypertrophy, detachment, and loss – events central to the initiation of proteinuria and progressive glomerulosclerosis.

Adipokines are central mediators of renal injury in obesity. Elevated leptin levels promote proliferation of mesangial cells, collagen deposition, and activation of profibrotic pathways, whereas reduced adiponectin impairs endothelial integrity and increases susceptibility to inflammation and oxidative stress [22, 37]. In parallel, secretion of cytokines such as IL6 and TNFα from dysfunctional adipose tissue fuels systemic lowgrade inflammation, promoting renal endothelial dysfunction, altered nitric oxide bioavailability, and microvascular injury.
Histopathological studies have described a recognizable phenotype in obesity-related kidney disease, known as obesity-elated glomerulopathy (ORG). Biopsies commonly reveal glomerulomegaly, mesangial expansion, podocyte -foot process widening, increased extracellular matrix deposition, thickening of the glomerular basement membrane, and variable degrees of

tubulointerstitial inflammation and fibrosis [38–42]. Although traditionally considered a benign or slowly progressive condition, recent data suggest that ORG may lead to significant proteinuria and decline in kidney function, especially when metabolic risk factors coexist or remain uncontrolled.
Importantly, obesity also amplifies the impact of other metabolic abnormalities – prediabetes, MASLD, dyslipidaemia, and hypertension – enhancing their deleterious effects on the kidney. This synergistic behaviour explains why obesity serves not only as a primary driver of MKD but also as a critical component in mixed metabolic phenotypes.
The recognition of obesity-related MKD underscores the need for early clinical identification of renal stress in individuals with overweight or obesity, even in the absence of diabetes or overt CKD. Given the potential reversibility of early haemodynamic changes and the benefits of weight reduction, pharmacological metabolic modulation, and lifestyle interventions, early detection represents a crucial opportunity for prevention and disease-modifying therapy.

Prediabetes-Related Metabolic Kidney Disease

Prediabetes represents an intermediate metabolic state between normoglycaemia and overt diabetes, characterised by impaired fasting glucose, impaired glucose tolerance, or elevated glycated haemoglobin according to current diagnostic criteria [43]. Although traditionally viewed as a precursor stage with modest clinical implications, accumulating evidence indicates that prediabetes is not a benign condition. Rather, it constitutes a metabolically active and pathophysiologically relevant state capable of inducing early renal injury through mechanisms that parallel, but do not require, sustained hyperglycaemia [44–46].
Several epidemiological studies have demonstrated a consistent association between prediabetes and an increased risk of incident CKD, reduced eGFR, and elevated albuminuria. In a prospective cohort exceeding 7,000 individuals with nearly nine years of follow-up, both impaired glucose tolerance and elevated HbA1c were independently associated with new-onset CKD, with hazard ratios ranging from 1.13 to 1.39 [44]. These findings have been confirmed by larger population-based analyses, including the REACTION study involving more than 250,000 Chinese adults, where prediabetes was identified as an independent predictor of CKD, particularly among men [47]. Meta-analyses reinforce this association, suggesting that even modest elevations in glucose metabolism confer a measurable increase in renal risk [46].
From a mechanistic perspective, renal injury in prediabetes is driven primarily by insulin resistance, hyperinsulinaemia, and intermittent postprandial hyperglycaemia. These alterations impair podocyte insulin signalling, reduce nephrin expression, and promote cytoskeletal instability, rendering podocytes more vulnerable to detachment and apoptosis [45, 48]. Concurrently, increased proximal tubular sodium-glucose reabsorption diminishes sodium delivery to the macula densa, blunting tubuloglomerular feedback and favouring afferent arteriolar vasodilation – enhancing glomerular hyperfiltration in a pattern similar to early diabetic kidney disease [45, 48].
Oxidative stress also plays a central role. Elevated production of reactive oxygen species, accumulation of advanced glycation end-products, and activation of protein kinase C pathways contribute to endothelial dysfunction, mesangial expansion, and increased glomerular permeability [48]. These changes manifest clinically as low-grade albuminuria and may precede overt abnormalities in eGFR.
Despite this growing evidence, prediabetes is not currently included among the recommended indications for CKD screening in most clinical guidelines [49]. Given the substantial prevalence of prediabetes worldwide and its clear association with early renal injury, incorporating individuals with prediabetes into CKD risk stratification strategies could facilitate earlier detection of kidney involvement and prompt implementation of preventive interventions.

Diabetes-Related Metabolic Kidney Disease

Type 2 diabetes mellitus (T2DM) remains the most common metabolic condition associated with chronic kidney disease worldwide, and diabetic kidney disease (DKD) continues to represent a major cause of end-stage kidney disease [50]. However, within the conceptual framework of Metabolic Kidney Disease, diabetes-related renal injury is understood not as an isolated entity, but as the intensification and culmination of metabolic disturbances that often originate much earlier – during obesity, insulin resistance, and prediabetes. This perspective highlights the continuity of metabolic stress across the glycaemic spectrum and underscores the shared mechanisms that unite DKD with other MKD subtypes.

Hyperglycaemia initiates and amplifies several interrelated pathways that contribute to renal damage. Among the earliest alterations is glomerular hyperfiltration, driven by increased proximal tubular sodium-glucose reabsorption mediated by SGLT2. This reduces solute delivery to the macula densa, blunts tubuloglomerular feedback, and promotes afferent arteriolar vasodilation, thereby increasing intraglomerular pressure [51]. Persistent hyperfiltration accelerates podocyte hypertrophy and detachment – lesions central to the development of albuminuria.

Glucotoxicity exerts direct cellular effects. Chronic exposure to elevated glucose levels induces oxidative stress, mitochondrial dysfunction, and accumulation of advanced glycation end-products (AGEs). These processes trigger mesangial expansion, altered extracellular matrix turnover, and thickening of the glomerular basement membrane [52, 53]. Importantly, lipotoxicity – driven by elevated circulating free fatty acids and ectopic lipid accumulation – amplifies these pathways by promoting endoplasmic reticulum stress, inflammation, and apoptosis in podocytes and tubular cells [54].

Inflammatory and fibrotic pathways further contribute to disease progression. Activation of protein kinase C (PKC), nuclear factor-κB (NF-κB), and transforming growth factor-β (TGF-β) promotes epithelial–mesenchymal transition, interstitial fibrosis, and glomerulosclerosis [55]. These processes often evolve silently for years before clinical manifestations appear, explaining why many patients show evidence of renal structural injury even at the time of diabetes diagnosis.

Although DKD has traditionally been described as a distinct clinical entity, MKD emphasizes that diabetes-related renal injury represents a continuum of metabolic renal stress, rather than a binary state emerging only after hyperglycaemia surpasses diagnostic thresholds. This broader view aligns with epidemiological observations showing that albuminuria, reduced eGFR, and microvascular injury can be detected in a significant proportion of individuals with newly diagnosed diabetes or even during the prediabetic phase.

Recognising diabetes-related MKD within this continuum has practical implications: it highlights the importance of early interventions targeting hyperglycaemia, insulin resistance, RAAS activation, and metabolic inflammation. Moreover, therapies such as SGLT2 inhibitors and GLP-1 receptor agonists – initially developed for glycaemic control – have demonstrated significant renal and cardiovascular protection precisely because they modulate many of these shared metabolic pathways.

MASLD-Related Metabolic Kidney Disease

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed non-alcoholic fatty liver disease (NAFLD), is now recognised as a multisystem metabolic disorder that extends well beyond the liver. The recent harmonized definitions and clinical practice guidelines issued jointly by EASL, EASD and EASO [56] underline the strong metabolic underpinnings of MASLD and its close association with insulin resistance, visceral fat accumulation, dyslipidaemia and systemic inflammation. This updated framework emphasizes that MASLD frequently coexists with other metabolic conditions and contributes to end-organ damage, including the kidney.

A growing body of evidence indicates that MASLD is independently associated with chronic kidney

disease (CKD). A comprehensive and authoritative review by Bilson, [57] summarized epidemiological and mechanistic data supporting a strong association between MASLD and increased CKD risk, even after adjusting for obesity, diabetes and hypertension. These observations confirm that MASLD is not simply a marker of metabolic syndrome but a condition with its own pathophysiological impact on renal structure and function.

Mechanistically, MASLD promotes renal injury through multiple interconnected pathways. Hepatic steatosis triggers the release of hepatokines (e.g., fetuin-A) and other inflammatory mediators, which aggravate insulin resistance, endothelial dysfunction, and oxidative stress. These systemic disturbances impair glomerular autoregulation and increase susceptibility to hyperfiltration and podocyte stress. Disturbances in lipid metabolism characteristic of MASLD facilitate the accumulation of toxic lipid intermediates, contributing to mitochondrial dysfunction and activation of pro-fibrotic cascades within the kidney.

A further layer of complexity arises from genetic predisposition. Variants such as PNPLA3, TM6SF2 and MBOAT7 – well-established determinants of liver disease severity in MASLD – have been associated with increased renal vulnerability, suggesting shared metabolic and inflammatory pathways between hepatic steatosis and CKD [58]. These data reinforce the concept that renal involvement in MASLD is not solely a consequence of coexisting metabolic abnormalities, but reflects intrinsic pathobiological processes linked to the disease itself.

Meta-analytic data continue to support the association between MASLD and kidney dysfunction. The landmark systematic review by Musso and colleagues [59] remains a frequently cited foundational analysis demonstrating increased CKD prevalence and incidence among individuals with NAFLD. While older, its conclusions align with contemporary findings and highlight persistent mechanistic plausibility across diverse populations.

Recognizing MASLD as a distinct subtype within the broader spectrum of Metabolic Kidney Disease has important clinical implications. Given its high global prevalence and frequent underdiagnosis, incorporating MASLD into CKD risk stratification frameworks may facilitate earlier identification of renal involvement. Furthermore, therapeutic strategies targeting hepatic steatosis – such as GLP-1 receptor agonists, weight reduction and lifestyle interventions – may confer renal benefits even in the absence of overt diabetes. As recent guidelines emphasize [60, 61], a comprehensive approach addressing metabolic dysfunction across organ systems represents a crucial step toward improving long-term outcomes.

Mixed Metabolic Kidney Disease

Mixed Metabolic Kidney Disease represents the convergence of multiple metabolic derangements acting simultaneously on renal structure and function. In clinical practice, this phenotype is increasingly common, reflecting the overlap between obesity, insulin resistance, prediabetes, type 2 diabetes, hypertension, dyslipidaemia and MASLD. Rather than functioning as isolated risk factors, these conditions interact through shared mechanisms that amplify metabolic stress on the kidney, accelerating the transition from early functional changes to established chronic kidney disease [38].

From a pathophysiological standpoint, mixed MKD embodies a state in which haemodynamic, inflammatory, hormonal and lipid-related disturbances reinforce one another. Excess visceral fat accumulation fuels chronic low-grade inflammation and adipokine dysregulation, worsening insulin resistance and promoting hyperinsulinaemia [22]. In parallel, progressive impairments in glucose tolerance intensify tubular sodium-glucose reabsorption, stimulating afferent arteriolar vasodilation and glomerular hyperfiltration [45]. When MASLD coexists, the release of hepatokines and proinflammatory mediators further exacerbates endothelial dysfunction, oxidative stress and microvascular injury [50].

These synergistic mechanisms produce a renal phenotype that is often more severe than the sum of its individual components. Patients with obesity and MASLD, for example, exhibit higher rates of

albuminuria and more pronounced declines in eGFR compared with individuals with either condition alone [62]. Similarly, the coexistence of prediabetes or early diabetes with hepatic steatosis and visceral fat accumulation results in more rapid structural changes – mesangial expansion, podocyte stress and tubulointerstitial fibrosis – even when glycaemic abnormalities remain modest [63].
Clinically, mixed MKD is frequently under-recognised. Traditional screening strategies tend to focus on single risk factors – most often diabetes – thereby missing individuals who harbour substantial renal risk due to the cumulative effect of multiple metabolic abnormalities. This oversight is particularly relevant in younger or non-diabetic individuals with obesity and MASLD, in whom early renal involvement may be subtle yet progressive.
Recognising mixed MKD as a distinct and increasingly prevalent phenotype underscores the importance of integrated metabolic assessment in the evaluation of CKD risk. A comprehensive approach – including assessment of adiposity, glycaemic status, hepatic steatosis, blood pressure and lipid profile – allows for earlier identification of individuals at high risk and supports targeted interventions aimed at modulating metabolic stress. Ultimately, the mixed MKD phenotype exemplifies the concept of Metabolic Kidney Disease: a continuum of renal injury shaped not by a single metabolic defect, but by the interplay of multiple overlapping disturbances acting across organ systems. Such multilayered interactions are increasingly documented across metabolic phenotypes, supporting the concept of mixed MKD as a clinically relevant and mechanistically distinct entity.

Screening and Clinical Implications

The recognition of Metabolic Kidney Disease (MKD) as a unified conceptual framework has important consequences for screening strategies, particularly in populations traditionally not considered at high risk for chronic kidney disease. Current screening algorithms [64] often prioritise individuals with established type 2 diabetes or long-standing hypertension, overlooking a substantial proportion of patients who exhibit renal involvement driven primarily by obesity, prediabetes, MASLD or combinations thereof. As a result, early stages of metabolic renal stress frequently remain undetected [12] until albuminuria or declines in eGFR become clinically evident.
Integrating MKD-oriented screening into routine nephrology workflows could meaningfully shift clinical practice toward earlier detection, streamlined risk stratification, and more timely initiation of preventive interventions, particularly in metabolically vulnerable individuals.

Who Should Be Screened?

Given the burden of metabolic dysfunction in modern populations, screening should extend beyond conventional high-risk groups. Individuals with the following characteristics merit evaluation for possible MKD (Figure 3):

- Obesity with increased visceral fat accumulation, even in the absence of diabetes or hypertension
- Prediabetes, particularly in those with impaired glucose tolerance or rising HbA1c
- MASLD, regardless of glycaemic status, as emphasised by recent international guidelines [56]
- Family history of type 2 diabetes, CKD or early cardiovascular disease [12]
- Coexistence of multiple metabolic abnormalities, including dyslipidaemia, hyperuricaemia or elevated liver enzymes

In these individuals, glomerular hyperfiltration and endothelial dysfunction – hallmarks of early MKD – may precede measurable reductions in kidney function, highlighting the importance of timely assessment.

It is important to acknowledge that current CKD guidelines still do not formally recommend routine kidney screening in individuals with prediabetes or MASLD. The evidence supporting such an approach is growing, yet prospective validation and consensus-driven recommendations are still needed to define optimal screening thresholds and intervals.

What Tests Should Be Performed?

A pragmatic and clinically accessible initial evaluation may include:

- Estimated glomerular filtration rate (eGFR) using creatinine or combined creatinine-cystatin C equations
- Urine albumin-to-creatinine ratio (ACR) to detect early glomerular injury
- Assessment of metabolic health, including fasting glucose, HbA1c, lipid profile, uric acid and markers of hepatic steatosis
- Imaging, where appropriate, to evaluate hepatic steatosis or adipose distribution

Importantly, mild elevations in ACR or upward drifts in eGFR (suggesting glomerular hyperfiltration) should not be dismissed as normal variants in individuals with metabolic abnormalities, but rather considered potential markers of MKD.

Clinical Integration

Incorporating MKD into routine practice involves adopting a more comprehensive view of metabolic health, recognising that renal involvement can occur long before diagnostic thresholds for diabetes or CKD are reached. Early identification enables timely implementation of therapeutic strategies – such as weight optimisation, dietary interventions, metabolic modulation and blood pressure control – that mitigate renal stress and may alter longterm trajectories.

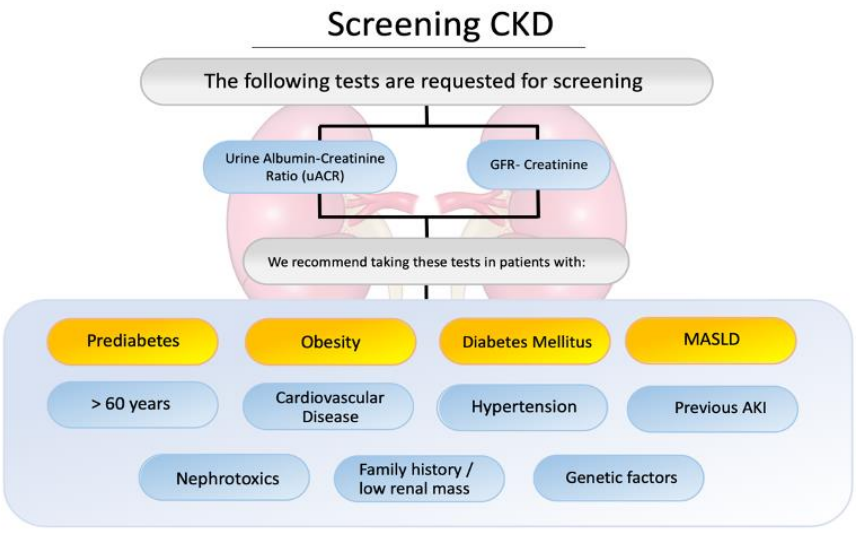

Figure 3. Recommended screening tests for chronic kidney disease (CKD). Screening includes estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (ACR). These tests are recommended for individuals with obesity, prediabetes, hypertension, T2DM, cardiovascular disease, prior AKI, or age >60 years.

Conclusions

Metabolic Kidney Disease represents an important conceptual and clinical evolution in our understanding of the interplay between metabolic dysfunction and renal health. This framework offers clinicians a more actionable understanding of metabolic renal risk, promoting earlier recognition of kidney involvement and more timely implementation of prevention strategies. By integrating obesity, prediabetes, type 2 diabetes, MASLD and mixed phenotypes within a single conceptual framework, MKD offers a more coherent representation of the pathophysiological processes driving early kidney injury in contemporary populations. This approach emphasises the central role of adipose tissue dysfunction, insulin resistance, chronic low-grade inflammation and lipid dysregulation as shared mechanisms across the metabolic spectrum.

Recognising MKD broadens opportunities for earlier diagnosis, particularly in individuals who would not be captured by traditional CKD screening criteria. It also underscores the need for multidimensional management strategies that address metabolic dysfunction across organ systems, rather than focusing solely on glycaemic control or blood pressure.

As the prevalence of metabolic disorders continues to rise globally, incorporating the MKD framework into clinical practice may offer a path toward more effective prevention and improved longterm renal and cardiovascular outcomes. This review highlights the importance of a unified, metabolically informed approach to kidney health – an approach that aligns with modern evidence and reflects the complex, interconnected nature of metabolic disease.

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The Fast-Track Program: A new Organizational Model to Enhance Living Donor and Pre-emptive Kidney Transplantation

Articoli originali

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ABSTRACT
Living donor kidney transplantation (LD KTx), especially when performed pre-emptively, remains the gold standard for treating end-stage renal disease (ESRD). In Italy, however, this resource remains underutilized due to significant organizational hurdles and protracted evaluation timelines. To overcome this limitation, a Fast-track program (FTp) was developed in our Center, aiming to perform the clinical work-up of donor and recipient candidates pairs (DR) in five consecutive days with dedicated schedules on outpatient basis.
The results so far obtained in twenty DR evaluated with the FTp indicate an important reduction in the time between the first consultation and LD KTx and a higher proportion of pre-emptive KTx compared to fifty-four DR studied with the traditional work-up protocol (Tp). By simplifying logistics for patients traveling from distant regions, this model could serve as a scalable template to improve transplant access and outcomes at both regional and inter-regional levels.

KEYWORDS: Living donor kidney transplantation, pre-transplant assessment, pre-emptive transplantation

Introduction

Kidney transplantation (KTx) is the gold standard treatment for end-stage renal disease (ESRD), as it provides superior quality of life, increased survival rates, and significant cost savings compared to dialysis [1–3]. However, major limitations of KTx remain the logistical barriers to perform recipient candidates suitability evaluation and the persistent imbalance between organ demand and the limited availability of donors.

In Italy in fact, approximately 6,000 patients, that is only 12% of all the patients on dialysis, are currently on the waiting list for a deceased donor (DD) KTx. Moreover, the average number of DD KTx in the last decade (2016-2025) was 1,697 per year, with a significant reduction to 1,487 in 2025 [4]. This imbalance translates into an average waiting time for DD KTx of 3.1 years, with increased likelihood of clinical events that may impair a patient's eligibility for transplantation.

In this challenging setting, living donor (LD) KTx represents a valuable source, offering better outcomes compared to DD KTx, both in terms of patient and graft survival [5–7]. These results were recently confirmed in our Country by the Italian National Transplant Center (CNT): according to the 2002-2022 report, the 5-year survival rate and graft survival for LD KTx were 96.8% and 94.2%, respectively, as compared to 91.5% and 88.7% for DD KTx [8]. These benefits are due to optimized donor selection, shorter ischemia times, and, in the case of related pairs, better immunological compatibility between the donor and the recipient.

Furthermore, living donation provides the ideal setting for pre-emptive transplantation, which is the most effective option for ESRD patients. Indeed, avoiding long-term dialysis is crucial: graft survival at 5 years drops to 58% for those on dialysis for over two years, compared to 78% for those treated for less than six months [9]. A recent meta-analysis showed that the relative risk of death and graft loss is significantly lower in patients who receive a LD pre-emptive KTx compared to those transplanted after starting dialysis [10].

While in some European countries LD KTx represents a high proportion of total annual KTx (45-50% in the Netherlands and 30-35% in the UK), in Italy this option is still underutilized (15-16%) [4, 11]. Besides cultural factors and regional disparities in transplant programs' availability, the main barrier to LD KTx diffusion lies in the logistical and organizational issues required to complete DR assessment. This evaluation is highly demanding, requiring numerous instrumental tests and specialist visits for both the donor and the recipient (Figure 1).

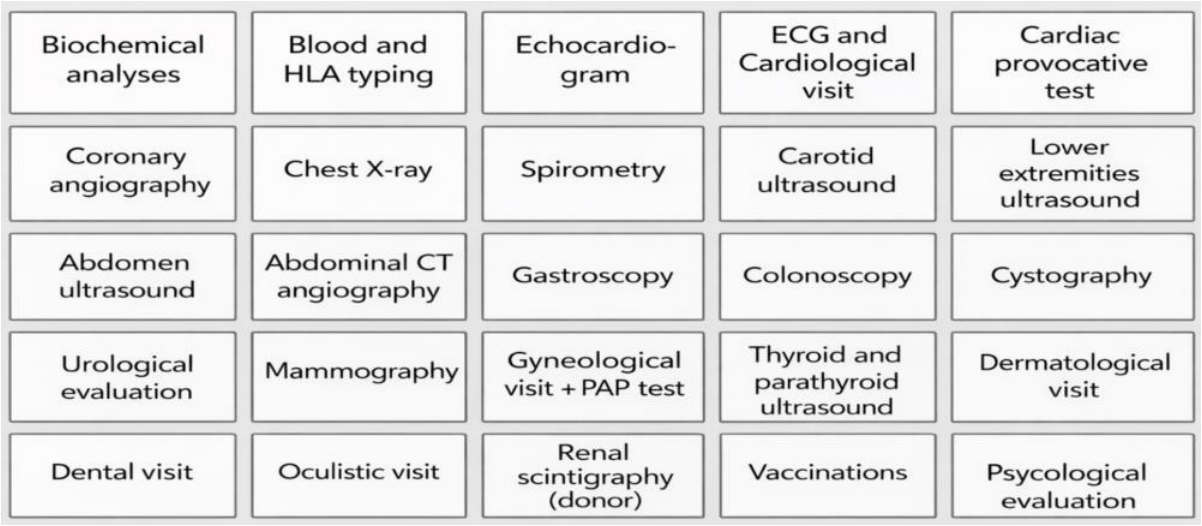

Figure 1. Instrumental tests and specialist visits required for donor and recipient and candidates assessment.

Moreover, this process is lengthened by the need to fulfill multiple steps and timelines dictated by bureaucratic and legal requirements.

A critical concern is that prolonged assessment times often force candidates to start dialysis before the transplant can occur. According to Habbous S. et al [12], among 478 LD KTx candidates, more than one third of patients had to start dialysis during the evaluation process, that took a mean time of 22 months to be completed, as compared to 10 months in patients who were transplanted pre-emptively.

Consequently, implementing organizational models that shorten the time required to complete the clinical work-up of DR represents an urgent need.

In this scenario, our Center developed a Fast-track program (FTp) in 2023, aiming to simplify and uniform the multidisciplinary LD KTx suitability assessment and promote pre-emptive LD KTx.

First, we will describe the entire evaluation process; subsequently, we will focus on the FTp structure and outcomes.

The organizational model for LD KTx suitability assessment

The multidisciplinary team dedicated to LD KTx program is led by a transplant nephrologist and surgeon supported by two transplant nurse managers and administrative staff.

The process starts after receiving via email the proposal for a DR from nephrologists working in the ESRD office or dialysis unit within our facility or external hospitals. After documentation review (medical history, biochemical profiles, donor abdomen ultrasound) within a week, an appointment is provided for a joint nephrological and surgical consultation.

These evaluations are conducted during dedicated clinic days (2-3 per month), which involve 2-3 DR per session, and which are always conducted by the same transplant nephrologist and surgeon. The day begins with a detailed informational session on KTx and LD KTx program, followed by individual visits of each DR for medical history collection, physical examination, and signing of informed consent forms. If no contraindications are found, a first-level immunological compatibility assessment (HLA typing, anti-HLA antibody testing), blood group confirmation, and baseline biochemical and urinary screening are scheduled within a week.

Once initial results are available (3-4 weeks), and if permissive, comprehensive instrumental exams, specialist consultations, and the psychological evaluation of DR are organized. Before the implementation of the FTp, the completion time for these steps at our Centre – without a dedicated schedule – was approximately 2-3 months (traditional protocol).
After obtaining medical, surgical, and psychological eligibilities to LD KTx, second-level immunological testing is repeated. Once results are available (2-3 weeks) and immunological compatibility is confirmed, the evaluation of DR by an independent third-party committee is organized to obtain medical clearance for the transplant. The evaluation sessions take place once a month, and the response is virtually immediate. Following committee approval, the donor candidate must appear before a judge to obtain the necessary legal authorization.

The final step before LD KTx is the anesthesiologic assessment of DR. Transplantation is typically performed in the following days. Figure 2 summarizes all the steps of LD KTx evaluation process.

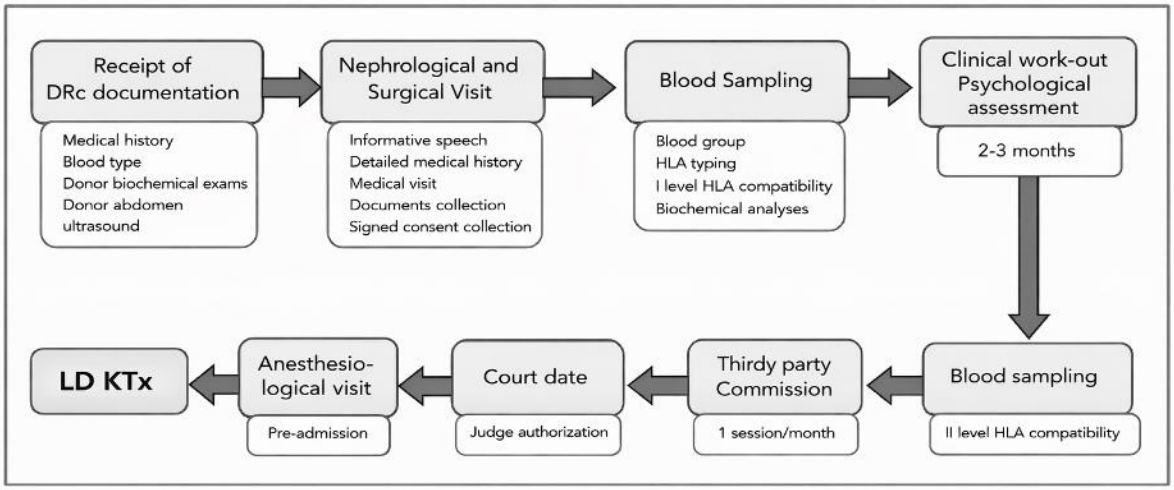

Figure 2. Organizational model for LD KTx suitability assessment.

The Fast-track program (FTp)

Launched in 2023, the FTp optimizes the DR evaluation by concentrating all instrumental tests and specialist visits into a single five-day outpatient window.

Based on the prescriptions provided by the nephrologist, the administrative office schedules all the examinations, Monday through Friday of the same week. For dialysis patients, peritoneal dialysis exchanges or hemodialysis sessions are planned directly in our dialysis unit when needed.

Of note, the couple's psychological evaluation begins during the *fast-track* week, where two meetings are scheduled for the donor and recipient (both as a couple and individually). The psychologist will then assess whether further meetings are necessary before determining the couple's psychological suitability to KTx.

Each DR receives a detailed list indicating the time, location, and contact information for each appointment. Table 1 shows an example of FTp.

Importantly, the nursing and administrative staff are always available to assist the DR during the *fast-track* days. At the end of the week, a "check-out" meeting allows the DR to directly book any additional tests, required in almost 50% of cases, that the various specialists may need, and that will be planned in the next 1-2 weeks. In particular, there are specific schedules dedicated to the transplant evaluation, that permit to obtain additional assessments. This organization gives the DR the opportunity to conclude the program in no more than 3 weeks.

During the *fast-track* week and in the following days, the nephrologist and the surgeon, coadiuvated by the nursing staff, can easily collect all the reports and evaluate together the clinical suitability for LD KTx.

At the moment, potentially all the DR might access to the FTp. Unfortunately, for logistic reasons only two DR per month can be evaluated through this pathway. The priorities are mostly related to the clinical status (pre-empitve first), and to the geographical provenance of the DR (origin outside Lombardy first).

Day of the Week	Time	Medical Service / Procedure	Facility / Location
MONDAY	09:00	Gynecological Visit + Transvaginal Ultrasound + PAP Test	Pad. Mangiagalli
	10:30	Dermatological Visit	Via Pace
	12:00	First Psychological Consultation	Pad. Alfieri (Psychiatry Clinic)
	14:00	First Ophthalmological Visit	Pad. Regina Elena
TUESDAY	10:30	Chest X-ray	Pad. Sacco
	11:40	Upper Abdomen CT Scan (with/without contrast)	Pad. Sacco
	12:30	Thyroid Color Doppler Ultrasound	Pad. Frigerio
	14:00	Simple Spirometry	Pad. De Palo
WEDNESDAY	08:40	Full Abdomen Ultrasound	Pad. Sacco
	11:40	Arterial/Venous Lower Limb & Carotid Color Doppler	Pad. Croff
	11:00	Esophagogastroduodenoscopy & Colonoscopy (with biopsy if needed)	Pad. Ponti
THURSDAY	09:30	Echocardiogram	Pad. Sacco
	10:00	First Cardiological Visit + ECG	Pad. Sacco
	12:00	Second Psychological Consultation	Pad. Alfieri (Psychiatry Clinic)
	14:00	Bilateral Mammography	Pad. Mangiagalli
	15:00	Check-out Meeting	Pad. Mangiagalli
FRIDAY	09:15	Sequential Renal Scintigraphy	Pad. Granelli

Table 1. Example of an FTp for a female kidney donor candidate. The brochure, provided to DR in advance, provides a detailed schedule for each day, including the facility of Policlinico Hospital where the exam is performed and the contact information for the referring physicians.

Fast-track program results

Since its implementation in March 2023, the FTp has significantly optimized the evaluation process for LD KTx at our Center. Between March 2023 and January 2026, twenty-three DR were evaluated using this streamlined protocol. Notably, five of these pairs (22%) came from outside the Lombardy region, highlighting the program's accessibility and regional impact.

The clinical outcomes for these 23 evaluated pairs are as follows:

- Twelve pairs (52%) successfully underwent LD KTx
- Two pairs were enrolled in the National Kidney Paired Donation ("crossover") program due to HLA incompatibility
- Two recipients received a DD KTx shortly after completing the Fast-track evaluation, while awaiting second-level immunological compatibility results
- Four pairs were deemed ineligible for LD KTx following the comprehensive assessment
- Three pairs are currently undergoing further clinical evaluation.

Table 2 shows the general basal characteristics of 54 DR who completed the pre-KTx assessment through the traditional protocol (Tp) and the 20 DR who were evaluated with the FTp in the period between March 2023 and December 2025.

Table 3 presents the results of the assessments performed with the two different pathways.

	Traditional protocol (Tp)	Fast-track program (FTp)
N. of DR	54	20
Recipient age at first visit, years	36±19	41±25
Donor age at first visit, years	51±10	53±10
ABO compatible (%)	44 (81)	20 (100)
Donor-recipient relationship (%)	Mother (26) Father (24) Wife (21) Husband (21) Other (8)	Mother (15) Father (25) Wife (40) Husband (20)
Pre-emptive at first visit, n (%)	29 (54)	11 (55)
Dialysis vintage at first visit, months	19±40	40±66
Recipient nephropathy (%)	Unknown (15) ADPKD (17) CAKUT (13) IgAN (13) Other (42)	Unknown (25) ADPKD (15) CAKUT (15) IgAN (10) Other (35)

Table 2. General features of 54 DR that were assessed with the traditional protocol and 20 DR that completed the FTp.

	Traditional protocol (Tp)	Fast-track program (FTp)
Studied DR, n.	54	20
LD KTx, n (%)	24 (45)	12 (60)
Months from 1st visit to KTx Median (25-75 cent)	9 (7-12)	6 (3-10)
Pre-emptive at KTx, n (%)	6 (25)	5 (42)
Months from 1st visit to LD KTx exclusion Median (25-75 cent)	6 (3-9)	3 (2-5)
DD KTx, n (%)	4 (7)	2 (10)

Table 3. Results of DR assessment with the Tp and the FTp.

At the time of initial consultation, approximately half of all LD KTx candidates in both groups were not on dialysis.

The FTp demonstrated significant logistical and clinical advantages over the Tp:

- **Reduced Time to Transplantation**: The median time from the initial nephrological and surgical consultation to KTx decreased from 9 months (Tp) to 6 months (FTp). Remarkably, 25% of the transplants performed under the FTp (3 out of 12) were completed within just 3 months of the first visit.
- **Increased Pre-emptive Rates**: The percentage of pre-emptive transplants was higher in the FTp group (42%) compared to the Tp group (25%), despite the similar proportion of pre-emptive patients at the first visit.
- **Faster Ineligibility Determination**: For pairs ultimately deemed ineligible for LD KTx, the time to reach an exclusion decision was halved – dropping from 6 months (Tp) to 3 months (FTp). This efficiency allowed eligible recipients to be placed on the deceased donor (DD) waiting list much earlier.
- **Ineligibility Rates**: 40% of DRc studied with FTp were ultimately deemed ineligible, compared to 55% in the Tp group.

Conclusions

The implementation of the Fast-track Program represents a significant paradigm shift in the management of LD KTx.

By addressing the logistical bottlenecks inherent in traditional assessment pathways, this model could achieve dramatic reduction in evaluation timeframes and costs and optimization of pre-emptive KTx.

By simplifying logistic for patients, especially for those coming from distant regions, the FTp could represent a template to improve and uniform LD KTx access. We are evaluating the possibility to offer to the extra region patients low-cost accommodations during the FTp.

Notably, the condensed work-up structure allows the transplant team to easily and rapidly collect reports and elaborate the clinical and surgical suitability judgement.

The limitation of the results presented in this paper certainly is the limited number of DR assessed with the FTp so far. It is important to underscore that the program is actually in a preliminary phase, but the aim for the next future is to increase the number of monthly fast-track assessment, extending the program to patients eligible for pre-emptive DD transplantation and implementing the FTp at a regional and inter-regional level, in order to increase the number of LD and pre-emptive KTx.

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The Role of Tocilizumab in Kidney Transplantation: A Narrative Review on Desensitization and Antibody-Mediated Rejection Treatment

In depth review

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ABSTRACT
Kidney transplantation is generally considered as the best therapeutic approach for patients with end-stage kidney disease. A considerable proportion of patients on the transplant waiting list, nearly one-third, present anti-Human Leukocyte Antigen donor-specific antibodies, a condition that tends to reduce the chances of receiving a transplant and increases the risk of immunological complications after transplantation. Among the different factors influencing graft survival, the immune response remains central in determining long-term outcomes. Antibody-mediated rejection remains a significant clinical challenge, as it contributes to both acute damage and progressive graft deterioration, ultimately affecting its survival. Interleukin-6 has been implicated in several inflammatory and immune regulatory pathways. In kidney transplantation, it is thought to participate in the mechanisms that favor the persistence of plasma cells and the interaction between T and B lymphocytes, thereby sustaining antibody production. By modulating Interleukin-6 signaling, it may be possible to interfere with these processes and limit the extent of alloimmune injury. Tocilizumab, an Interleukin-6 receptor antagonist originally developed for autoimmune conditions, has recently been investigated in the kidney transplant field. Preliminary reports suggest that it could play a role both in desensitization strategies for highly sensitized patients and in the management of antibody-mediated rejection, supporting its potential as an additional option in kidney transplantation.

KEYWORDS: interleukin-6, desensitization, chronic antibody-mediated rejection, kidney transplantation, tocilizumab

Introduction

Kidney transplantation (KT) remains the gold standard treatment for end-stage kidney disease (ESKD), providing superior survival, quality of life, and cost-effectiveness compared to dialysis [1, 2]. Approximately 30% of patients on the kidney transplant waiting list are sensitized, as indicated by panel reactive antibody (PRA) levels greater than 0%, and nearly 15% are classified as highly sensitized (HS), with PRA levels exceeding 80%. Pre-formed anti-donor specific antibodies (DSAs) constitute a major immunological barrier, often preventing transplantation and prolonging dialysis dependence in HS patients [3, 4]. The presence of DSAs cannot only limit access to KT but also increase the risk of antibody-mediated rejection (AMR) after transplantation, adversely affecting both short- and long-term graft survival rates [3, 5]. Morever, post-transplant development of de novo DSAs can occur, exerting a detrimental effect on graft survival comparable to that of preformed DSAs [6]. These antibodies can lead to AMR, a significant complication that occurs in approximately 1-10% of kidney transplant recipients overall and in nearly 30% of KT recipients with pre-formed DSAs desensitized before transplantation. AMR represents a major cause of progressive and irreversible graft dysfunction, and it poses a significant therapeutic challenge [7].

Attempts to inhibit the DSA production, to remove or reduce the serum levels, to decrease their strength, or, at last, to modify their activity are therefore important. New desensitization (DES) protocols have been developed in the latest years, usually applied before KT (or rarely in the early post-transplant period) in HS patients, intending to make possible the access to transplantation [8–11], and different scheme therapies have been used to treat AMR episodes in the post-transplant period [12–15].

The most common strategies of desensitization and AMR treatment protocols include the use of low or high doses of intravenous Immunoglobulins (IVIg), and anti-CD20 monoclonal antibody-Rituximab (RTX) alone or combined with plasmapheresis (PLEX), which are considered the current standard of care (SC) [16, 17]. These approaches aim to down-regulate B cell activity, reduce antibody production, and promote antibody removal with the aim of facilitating transplantation in HS patients and managing AMR in post-transplant period. However, despite their widespread use, these strategies remain largely empirical and not supported by standardized protocols or high-level evidence. In approximately 25-30% of patients, the antibody cannot be effectively eliminated prior to KT [18, 19], and clinical outcomes following AMR treatment remain suboptimal.

Recent studies have failed to demonstrate a clear beneficial effect of SC in AMR management [20–22], and a multicenter randomized trial comparing PLEX/IVIg with or without RTX showed no significant improvement in chronic AMR outcomes [23]. Similarly, other therapy options, such as Bortezomib or Eculizumab, did not achieve nephroprotective endpoint in KT [24, 25]. These limitations highlight a major unmet need for more effective and targeted therapies to improve graft outcomes in this high-risk population.

Alternative therapies targeting cytokine immune pathways have gained attention in KT treatment protocols. Of relevant interest was Interlukin 6 (IL-6), which is known to have a deleterious impact on inflammatory and immune response [26]. In KT, IL-6 can promote antibody production, acute and/or chronic rejection in solid organ transplantation [27]. Recently, IL-6 has become a therapeutic target in KT.

Tocilizumab (TCZ), the first-in-class humanized monoclonal antibody targeting the IL-6 receptor, can bind to both soluble and membrane-bound forms of the IL-6 receptor, thereby blocking IL-6 activity [28]. The efficacy of TCZ was confirmed in a clinical trial involving patients with Castelman disease; it is now approved for the treatment of several autoimmune-mediated diseases [29]. Starting from these data, many authors have analyzed the role, the impact, and the space that TCZ can have in KT.

Another IL-6 targeting agent has also been evaluated in small clinical studies, Clazakizumab – a monoclonal antibody that directly binds IL-6 rather than the IL-6 receptor – has shown encouraging preliminary results in desensitization and AMR treatment in HS patients [30–32].

This narrative review article gives an overview of the molecular mechanisms of IL-6 blockade that provide the rationale for the use of TCZ in KT. In addition, we aimed to summarize the limited clinical evidence on this topic, particularly regarding the use of TCZ for desensitization of anti-HLA-immunized kidney transplant candidates on the WL, and for patients who have developed AMR after transplantation. These emerging therapies further support the pivotal role of IL-6 signaling in modulating alloimmune responses and provide a broader therapeutic context in which TCZ should be considered.

Methodology

For this narrative review, a literature search was performed using PubMed, Web of Science, and the Cochrane Library. The search employed the keywords: “kidney transplantation”, “interleukin-6”, “desensitization”, “antibody-mediated rejection”, “chronic active antibody-mediated rejection”, and “tocilizumab”, and covered the period between January 2015 and January 2024. We considered all relevant articles published in English up to the time of writing, focusing on the clinical use, recent advances, and safety profile of TCZ in desensitization DES protocols and treatment of antibody-mediated rejection in KT. The population studied consisted of HS patients on the transplant waiting list and KT patients who manifest biopsy-proven AMR.

In all the studies the intervention involved the use of TCZ at a dosage of 8 mg/kg, up to a maximum of 800 mg monthly in monotherapy or combined with standard of care (SC) therapy for at least 6 months of treatment. The expected outcomes for studies where TCZ was used in DES protocol were made by reduction rate of DSAs serum levels, the degree of B and T cells maturation, and access to transplantation after 6 months of treatment. Whereas the expected outcomes for studies where TCZ was used to treat AMR were to be compared to baseline data, with outcomes assessed by comparing the initial and final kidney graft function (eGFR and proteinuria), DSAs levels expressed as mean fluorescence intensity (MFI) and histological changes. Assessment of patient and graft survival rates was included in the outcomes of AMR treatment studies.

Exclusion criteria comprised follow-up periods of less than six months, studies that included pediatric patients and animals, single case reports, SC different from RTX + PLEX + IVIg, TCZ used in KT with graft dysfunction with other indication rather than AMR, and research published in languages other than English.

We identified 22 studies where TCZ was used in the setting of KT. We excluded studies that did not meet our inclusion criteria, as shown in the flow Diagram 1.

We would like to point out that this study did not adhere to PRISMA guidelines and was not registered in PROSPERO, as a full systematic review was beyond the scope and objectives of the article.

Donor-specific antibody

Sensitization is defined by the presence of anti-Human Leukocyte Antigen (HLA) antibodies and is quantified using panel reactive antibody (PRA), a measure that reflects the risk of a positive crossmatch [33]. Preformed DSAs arise from prior exposure to HLA antigens via transplantation, pregnancy, or transfusion, and can impact transplant eligibility [34]. De novo DSAs develop in 13-30% of previously non-sensitized recipients, typically within the first year. Risk factors include high HLA mismatches (especially DQ), insufficient immunosuppression, nonadherence, and graft inflammation due to infection, ischemia, and rejection [35, 36].

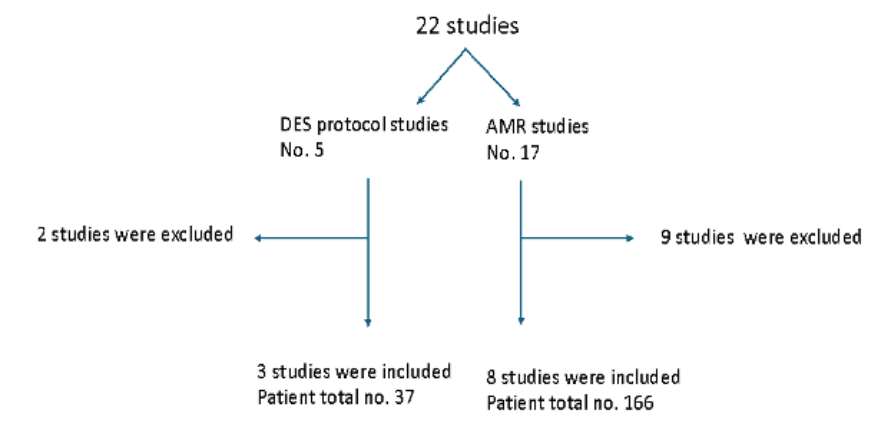

Diagram 1. Flow diagram of study selection.

Detection relies on Luminex single antigen bead assays. Clinically significant DSAs are usually defined by mean fluorescence intensity (MFI) thresholds of ≥3000 for class I and ≥5000 for class II of HLA [3, 37].

Antibody-mediated rejection

AMR results from antibody-driven injury to the microvascular endothelium, primarily driven by DSAs. The diagnosis of AMR in KT relies on a multimodal approach that integrates clinical, serological, and histopathological data, as well as molecular data when available. Clinically, AMR typically presents with graft dysfunction, such as rising serum creatinine, new-onset or worsening proteinuria, or hypertension. These signs are nonspecific and may overlap with other causes of allograft injury, including T cell-mediated rejection, calcineurin inhibitor nephrotoxicity, or recurrent primary disease. Therefore, kidney allograft biopsy remains the gold standard for the definitive diagnosis of AMR.

Histopathological assessment is guided by the Banff 2022 [38] classification, which provides standardized criteria for the diagnosis and reporting of AMR.

Diagnosis is based on the integration of three main categories of evidence:

- *Histologic evidence of acute or chronic tissue injury:* Microvascular inflammation (MVI), with glomerulitis (g > 0) and/or peritubular capillaritis (ptc > 0), in the absence of recurrent or de novo glomerulonephritis.
  Intimal or transmural arteritis (v > 0). Thrombotic microangiopathy (TMA) not attributable to other causes and/or acute tubular injury without alternative explanation.
- *Evidence of antibody–endothelial interaction*, demonstrated by at least one of the following: linear C4d deposition in peritubular capillaries, detected by immunohistochemistry or immunofluorescence; moderate or severe microvascular inflammation, defined as a combined score of glomerulitis and peritubular capillaritis (MVI = g + ptc) ≥ 2; increased expression of validated gene transcripts in the biopsy, strongly associated with AMR, as assessed by molecular diagnostics.
- *Serologic evidence of circulating DSAs*: detection of circulating DSA remains a central criterion. In the absence of detectable DSA, positive C4d staining in peritubular capillaries and/or detection of validated gene expression consistent with antibody-mediated injury may provide supportive evidence.

The Banff 2022 introduced two additional diagnostic categories to better capture the spectrum of antibody-mediated injury:

Probable AMR:

Defined as cases with incomplete fulfillment of classic AMR criteria – typically positive DSA with sub-threshold histologic findings, or ambiguous molecular signals – where antibody-mediated injury is suspected but not fully confirmed.

MVI, DSA-negative and C4d-negative:

Refers to cases with significant MVI in the absence of DSA or C4d. These are not classified as classical AMR but are recognized as clinically relevant and require careful clinicopathologic correlation.

Furthermore, acute tubular injury is no longer considered sufficient for AMR diagnosis in isolation. Likewise, arterial intimal fibrosis is no longer accepted as evidence of active antibody-mediated injury without additional supportive findings.

Chronic active AMR is characterized by persistent or recurrent microvascular injury, most notably glomerulitis (g) and peritubular capillaritis (ptc), reflecting inflammation of glomerular and peritubular capillary compartments. These lesions are semiquantitatively scored, and a combined MVI score (g + ptc) ≥ 2 strengthens the suspicion for AMR.

Additional histological features may include intimal or transmural arteritis, TMA, or acute tubular injury, not attributable to other causes. Chronic injury markers – such as transplant glomerulopathy and interstitial fibrosis/tubular atrophy – often coexist and influence prognosis [39].

Role of IL-6 in Kidney Transplantation

In 1986, Kishimoto et al. identified IL-6 as B-cell stimulating factor 2 (BSF-2) and its role in the promotion of immunoglobulin synthesis by activated B cells [40]. Aberrant IL-6 production and signaling contribute to chronic immune, cardiovascular, neuroendocrine, and metabolic disorders, as well as tumorigenesis [41]. It is a pleiotropic cytokine and is implicated in innate and adaptive immunity response, cellular and humoral response, determining itself the main factor of graft damage in KT [27] (Figure 1).

An increase of IL-6 in serum, urine, and biopsy tissue is observed during kidney allograft rejection, and levels correlate with the degree of inflammatory cell infiltration in human KT recipients [41]. Moreover, in the setting of a brain death donor, the pro-inflammatory process mediated by IL-6 starts before organ procurement [42]. Additionally, the kidney cold static preservation promotes the upregulation of intra-graft IL-6 production after the organ transplantation. This process promotes the pro-inflammatory cells' recall, cytokine production, and up-regulation of adhesion molecules, which lead to graft damage/injury. IL-6 promotes the CD8+ T cell memory expansion and CD4+ T cell differentiation to Th17, which are implicated in acute and chronic graft rejection [43]. In a murine model of KT, following the graft rejection, intra-graft expression of IL-6 was upregulated and Foxp3+ Tregs were decreased [44]. Foxp3+ Tregs are critical for maintaining immune homeostasis and immune tolerance in transplantation [45]. IL-6 is a main growth factor involved in the differentiation of B cells to IgG-secreting plasmablasts and plasma cells, so the upregulation of antibody production in KT can lead to AMR [27, 46]. Morever, IL-6 is implicated in innate immunity by binding Natural Killer (NK) cells, subsequently, it induces cytotoxicity to endothelial cells and promotes collagen synthesis by fibroblast and endothelial cell activation, which results in chronic graft injury [27]. This theory was also confirmed in the experimental model of chronic allograft nephropathy, in which interstitial fibrosis/tubular atrophy (IFTA) was shown to be mediated by the presence of chemokines and cytokines, including IL-6 produced by B cells [47]. Due to its pleiotropic activity, IL-6 has become a therapeutic target; it was supposed that inhibiting IL-6 signaling effectively reduces B cell

activation, plasmablast differentiation, and antibody production (both primary and recall). B-cell depletion resulted in decreased intra-graft B cells, chemokines, and IL-6 levels, limiting in this way the allograft interstitial fibrosis and tubular atrophy, leading to better tolerance and graft survival rates [48]. IL-6 inhibition can also promote regulatory T cells (T-reg) generation, which counterbalances the effects of alloreactive Th17 lymphocytes [49]. Indeed, Chandran et al. showed that KT recipients with biopsy-proven intra-graft inflammation treated with IL-6 inhibitor developed significantly higher proportions of Treg as well as substantially lower proportions of T effector cells as compared to control patients, indicating that IL-6 inhibition shifts T cell maturation towards Tregs in the absence of IL-6 signaling [50].

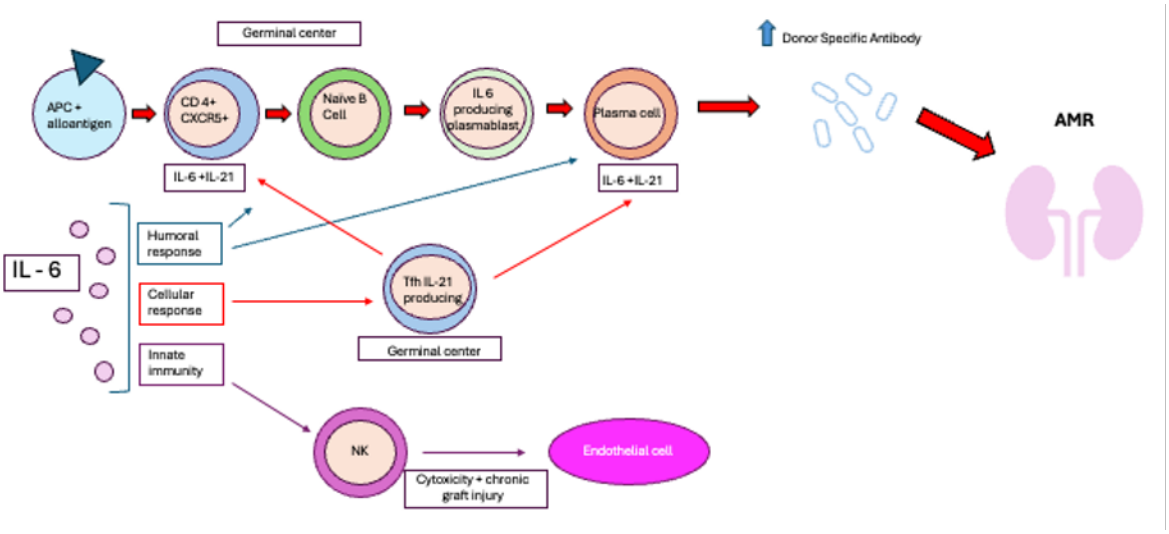

Figure 1. Role of IL-6 in immunity. IL-6 involvement in humoral, cellular and innate immune responses. IL-6 production by APCs is an important stimulus for IL-21 production by naive T cells which mature toward the Tfh phenotype expressing CXCR5 and IL-21. Naive B cells migrate to the germinal centers in response to CXCR5+ Th cells. This activates B cell maturation to memory B cells and IL-6 producing plasmablasts that further promote germinal center formation and progression to antibody-producing plasma cells driving pathogenic antibody production and tissue injury. Impact of anti–IL-6/IL-6R therapy on reducing Tfh activation and subsequent plasmablast and plasma cell development with reductions in pathogenic antibody production and tissue injury. IL-6 by binding NK cells can induce cytotoxicity toward endothelial cells and promotes collagen synthesis by fibroblast and endothelial cell activation, which results in chronic graft injury. AMR: antibody-mediated rejection; APC: antigen-presenting cell; DSA: donor-specific HLA antibody; IL: interleukin; Tfh: T-follicular helper cells; NK: natural killer.

Role of Tocilizumab in Kidney Transplantation

TCZ is a humanized monoclonal antibody (IgG1 subclass) that binds IL-6 Receptor (IL-6R). It has been approved for the treatment of moderate to severe rheumatoid arthritis and idiopathic juvenile arthritis [51]. Many studies have shown that using TCZ as an add-on therapy induced an intense relative reduction of DSAs in terms of MFI; although the reduction was not clinically significant, it was a tendency to induce lower post-transplantation antibody rebound [52]. Moreover, TCZ appears to be a safe and feasible strategy for managing AMR in sensitized kidney transplant recipients [53].

The mechanism of action of TCZ is illustrated in Figure 2.

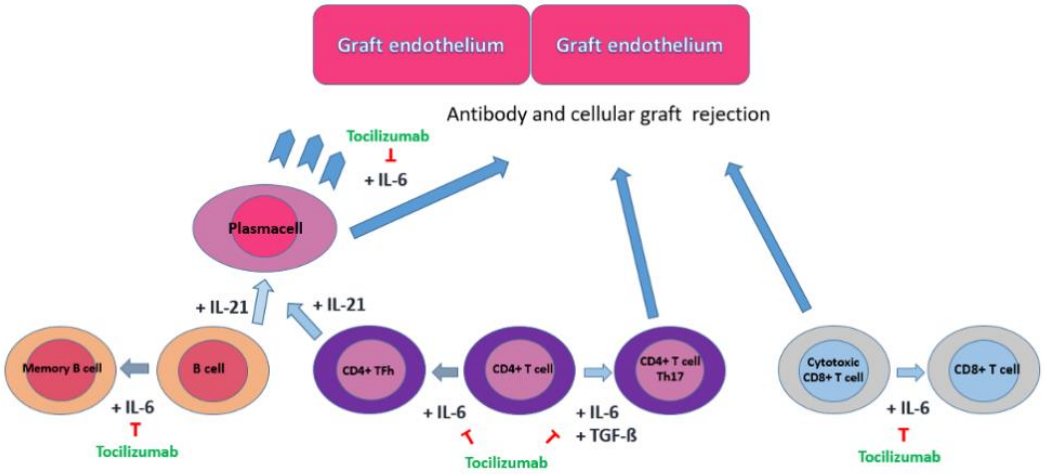

Figure 2. IL-6 receptor targets of Tocilizumab in the development of AMR. Impact of Tocilizumab inhibiting IL-6 pathway can reduce Tfh activation and subsequent plasmablast and plasma cell development with reductions in pathogenic antibody production and tissue injury. In addition, anti–IL-6 therapy inhibits T effector cell function and enhances Treg cell/Breg cell differentiation which likely inhibits DSA formation and allograft injury. AMR: antibody-mediated rejection; IL-6: interleukin-6; IL-21: interleukin-21; Tfh: T-follicular helper cell.

Efficacy of Tocilizumab in Desensitization Protocols for Highly Sensitized Kidney Transplant Candidates

The use of TCZ in desensitization protocols for HS kidney transplant candidates remains an area of emerging investigation. Preclinical data derived from an HLA-incompatible skin graft mouse model suggest that TCZ not only reduces circulating anti-HLA antibody levels but also significantly decreases the frequency of antibody-secreting plasma cells in both the bone marrow and spleen, supporting its potential role in modulating humoral alloimmune responses [54].

In clinical settings, TCZ has been evaluated both as monotherapy and as part of combination regimens. The following is a synthesis of three principal studies investigating the efficacy of TCZ in HS patients, with specific focus on changes in DSA levels, lymphocyte subset dynamics, access to transplantation, and posttransplant outcomes.

A summary of the findings is presented in Table 1.

Vo et al. evaluated the efficacy of TCZ in a cohort of 10 HS kidney transplant candidates who had previously failed standard desensitization (SC) protocols involving IVIG and RTX. Patients received IVIG (2 g/kg on days 0 and 30) and TCZ (8 mg/kg on day 15), followed by monthly TCZ infusions for six months. TCZ enabled transplantation in 50% of participants. A statistically significant reduction in DSA MFI was observed ($p = 0.03$), and no episodes of AMR were detected in posttransplant surveillance biopsies. The treatment was well tolerated, suggesting that TCZ may represent a valuable adjunct in desensitization protocols for HS patients unresponsive to conventional therapy [55].

Daligault et al. investigated TCZ monotherapy in 14 HS patients on the transplant waitlist, all with anti-HLA DSAs exhibiting MFI ≥10,000. Patients received monthly TCZ infusions (8 mg/kg). The therapeutic goal was to reduce DSA MFI values below the 10,000 thresholds. While a modest reduction in both the number and intensity of DSAs was achieved, the response was insufficient to enable clinically meaningful desensitization. Only one patient proceeded to transplantation after TCZ monotherapy, whereas 11 required subsequent SC therapy, which allowed successful transplantation in eight cases. The authors concluded that TCZ monotherapy provides limited benefit in treatment-naïve HS patients, due to its modest and narrow impact on DSA reduction [56].

In a third prospective single-center study conducted by Jouve et al., TCZ monotherapy was assessed in 13 naïve HS patients with DSAs >10,000 MFI. Patients received 8 mg/kg every four weeks for six months. Immunologic endpoints included quantitative and qualitative changes in anti-HLA DSAs (MFI, panel reactive antibody [PRA] levels), as well as phenotyping of T and B cell subsets, including follicular helper T cells (Tfh), regulatory T cells (Tregs), and circulating cytokine/chemokine profiles (IL-6, IL-6R, IL-21, CXCL10, CXCL13). After six months, DSA MFI values showed only marginal changes without statistical significance, and no variation in PRA levels was detected. TCZ had negligible effects on CD3+ T cell and B cell compartments, except for a significant increase in naïve B cells ($p = 0.020$) and a decrease in post-germinal center B cells. No significant changes were observed in Th cells, Tregs, or circulating cytokine/chemokine levels. None of the patients achieved transplant eligibility following TCZ monotherapy. However, seven eventually underwent successful KT after receiving adjunctive SC therapy. The authors concluded that TCZ monotherapy had limited efficacy as a standalone desensitization strategy, though its effect on B-cell maturation may support its use in preventing post-transplant humoral rebound [57].

As summarized in Table 1, two of the three reviewed studies demonstrated that TCZ monotherapy exerts only modest effects on DSA reduction and access to transplantation in HS patients. In contrast, when combined with SC protocols, TCZ appears to enhance transplant eligibility and may contribute to reducing the risk of post-transplant AMR. These findings suggest that the primary role of TCZ may lie not in its desensitizing capacity per se, but rather in its ability to modulate long-term humoral alloimmune responses and prevent post-transplant DSA rebound, thereby potentially improving graft survival rates.

Encouraging and similar data have also been recorded in studies conducted in other types of solid organ transplantation. Sommer et al. examined the effect of TCZ in cardiac transplant patients who had pre-transplant pre-formed DSA and received TCZ in the context of desensitization protocols. Post-transplant rejection rates were significantly lower than those of controls, and no graft failures were reported. This suggests TCZ's potential in reducing DSA rebound and preventing graft rejection, though the benefits likely stemmed from its use in a multi-drug combo therapy regimen [58].

Efficacy of Tocilizumab in Antibody-Mediated Rejection in Kidney Transplant Patients

This section summarizes evidence from eight clinical studies assessing the efficacy of TCZ in the treatment of AMR with particular focus on its effects on renal allograft histopathology, graft function over time, DSA trends, graft and patient survival, and safety profile.

All key findings of those studies are presented in Table 2.

Efficacy of Tocilizumab in Acute Antibody-Mediated Rejection in Kidney Transplant Patients

In a single-center retrospective observational study, Potteboun et al. [59] studied the efficacy of TCZ as an adjunct to SC therapy in seven KT recipients with biopsy-proven acute antibody-mediated rejection (a-AMR). DSAs levels were measured at the time of diagnosis and monitored longitudinally over a 24-month follow-up period. This study provides novel insights into the therapeutic potential of IL-6 blockade in the setting of a-AMR, a condition associated with a high risk of progression to chronic AMR and subsequent graft dysfunction or loss. Given the central pathogenic role of DSAs in AMR, therapeutic strategies aimed at depleting circulating antibodies or suppressing their production are of critical importance. While SC therapy-PLEX, IVIg, and RTX-typically result in a modest reduction of DSA levels (approximately 15-35%, depending on the specificity of anti-HLA antibodies and the intensity of PLEX), the authors identified a 50% reduction in DSA MFI as a clinically relevant threshold, reflective of a meaningful immunologic response with potential impact on graft survival. In this case series, the addition of TCZ to SC therapy was associated with stabilization or improvement of renal function in all patients, along with a notable reduction in DSA levels in most

cases. These findings suggest that TCZ may enhance the efficacy of conventional immunomodulatory strategies in patients with a-AMR and could play a role in delaying or preventing the progression of alloimmune-mediated graft injury. However, the limited sample size and retrospective design underscore the need for prospective controlled trials to validate these preliminary observations.

Study	Design / Setting	Population	Intervention	Outcomes	Main results			
					Outcomes on DSAs	Transplantation Rate	Immunological Findings	Key Conclusions
Vo et al. Transplantation 2015 [55]	Phase I/II uncontrolled, single-center	10 HS patients refractory to IVIG + RTX +/- PLEX	IVIG (2 g/kg on days 0 & 30) + TCZ (8 mg/kg on day 15) monthly × 6 months + IVIG at D0 and D30	Efficacy – % of patients receiving Kidney transplant – rejection at 6 months biopsy – DSAs at 6 months	Significant DSA MFI reduction (p = 0.03) No DSAs at M6	5/10 (50%) transplanted	No AMR in post-transplant biopsies M6 1 AMR at M12, no graft loss	TCZ effective as adjunct in SC-refractory patients
Daligault et al. Transplantation Direct 2021 [56]	Phase II uncontrolled, single center	14 naïve HS patients with DSA ≥10,000 MFI First DES attempt	TCZ monotherapy (8 mg/kg every 4 weeks x 6 months) No other prior or DES therapies	Efficacy – MFI of anti-HLA immunodominant Ab – Number of anti-HLA Ab with MFI>10000 – % of patients received transplant	Modest DSA decline, insufficient for clinical DES	1/14 transplanted with TCZ; 8/11 transplanted after rescue SC	No AMR data	TCZ monotherapy has limited efficacy in naïve HS patients
Jouve et al. AJT 2021 [57]	Controlled non-randomized, single-center	13 naïve HS patients with DSA >10,000 MFI Control group: HS patients remaining in dialysis without DES attempt; healthy subjects	TCZ monotherapy (8 mg/kg every 4 weeks × 6 months) No other prior or DES therapies	Rates evolution of: Tfh 1, 2, and 17 Treg; plasmablasts, plasma-cells, B memory cells; evolution of anti HLA Ab MFI	Marginal MFI reduction; no significant PRA change T population: no significant changes in Tfh 1, 2, 17 Treg B population: blocking post germinal B cells, plasmablasts, plasma-cells	0/13 transplanted with TCZ; 7 transplanted after SC	No AMR data	TCZ monotherapy has limited efficacy in naïve HS patients

Table 1. Tocilizumab for Desensitization in Highly Sensitized Kidney Transplant Candidates. Abbreviations: Ab, antibody; AMR, antibody-mediated rejection; DES, desensitization; IVIG, intravenous immunoglobulin; HS, highly sensitized; MFI, mean fluorescence intensity; SC, standard of care; DSA, donor-specific antibodies; KT, kidney transplant; TCZ, tocilizumab; RTX, rituximab; T fh, T follicular helper cells; T reg, T regulatory cells.

Study (Year)	Design / Sample	Type of AMR	Baseline data	TCZ Use	Histological Outcomes	Renal Function (eGFR and/or proteinuria)	DSA Response	Key Notes
Choi et al. Am J Transplant 2017 [60]	Open-label case study, n=36	Chronic active	Mean eGFR 48.4 ml/min/1.73m2 DSAs + 91,7% Mean DSAs 1.91	Rescue therapy 6–36 months	↓ g + ptc (p=0.0175), ↓ C4d (p=0.0318)	Stable eGFR at 36 months (38.8 ± 10.4 ml/min/1.73 m2 in adults) over 3.26 years	↓ DSA (p=0.043 at 24 months)	First report; abrupt TCZ withdrawal led to graft loss
Lavacca et al. Clin Transplant 2020 [62]	open-label case study n=15	Chronic active	Mean eGFR 45.1 ml/min/1.73m2 Mean of proteinuria 1.1 g/day DSA + 100%	First-line monotherapy	↓ g+ ptc at 6 months (p=0.014). no changes in C4d deposition or chronic lesions (cg and IFTA) (p= 0.206, p= 0.180, p= 0.608 respectively)	Stable eGFR and proteinuria eGFR decline 4.4 mL/ min/1.73 m2 after 12 months of treatment vs 10.5 ml/min/ min/1.73m2/year baseline 1.1 before treatment and 1 g/day after treatment	↓ DSA 22600, pre-TCZ and 18200 post-TCZ	First-line TCZ effective in active inflammation
Potteboun et al. Transplant Direct 2020 [59]	Retrospective, single-center n=7	Acute	DSAs + 100%%	Adjunct to SC	Not reported	Improved/stabilized in all patients	↓ DSA in 4/6 patients (reduction of 50%)	Acute AMR setting; TCZ enhanced DSA reduction
Kummar et al. Kidney360 2020 [63]	Observational single-center cohort study n=10	Chronic active	DSA+ 80%	Adjunct, to SC Belatacept in 7 patients	↓ g+ptc and C4d at 12 months (4.8 ± 1.4 to 4.2 ± 2.0; p = 0.39)	eGFR: 42 ± 18 to 37±24 ml/min/1.73 m2; P = .27), and the slope of eGFR decline remained unchanged (−0.14 ± 0.9 to −0.33 ± 1.1; p = 0.25).	↓ DSA (NS) (p=0.629)	Combined with Belatacept; 47.3% discontinued TCZ
Massat et.al. Am J Transplant 2021 [64]	Retrospective, single-center n=46 9/46 Control group 37/46	Chronic active and mixed	DSAs were present in 66,7% of patients Mean eGFR 40ml/min/1.73m2 Mean g + ptc 3.0+/-0.82	9/46 Rescue 12 months	↓ g + ptc ↓ t (0.07)	No differences between groups (↓ eGFR by – 4 ml/min/1.73m2/year)	↓ DSA In MFI at 12 months (−48 ± 44%)	TCZ rescue therapy provide significant DSAs reduction
Noble et al. Front Med 2021 [65]	Retrospective, single-center n=40	Chronic active	Mean e-GFR 43 ± 17 ml/min/1.73m2 Mean proteinuria 1± 0.9 g/L DSAs + 55%	7/40 TCZ in monotherapy; 33 /40 TCZ + SC	No change in g+ptc	Stable (e-GFR p=0.12 and proteinuria p=0.95 at 6 month and p=0.28 at 12 months)	Not assessed	Baseline severity predicted graft loss
Khairallah et al. Clin Transplant 2023 [66]	Retrospective, single-center n=38	Chronic active	Mean e-GFR 41±17 ml/min/1.73m2, mean proteinuria 0.6 ± 0.5g DSAs + 82%	35/38 rescue 3/38 first line	↓ interstitial inflammation (p=0.03), no change in others	↓ slope of eGFR decline (p=0.002) 34 ± 15 ml/min/1.73 m2 at 3 months 36 ± 15 ml/min/1.73 m2 by 6 months no significant change in terms of proteinuria (p=0.07	No change MFI of DSA Baseline 3450 At 6months 4000	DSA unchanged despite functional stabilization
Boonpheng et al. Clin Transplant 2023 [67]	Retrospective, single-center n=11	Chronic active	64% DD-Cf-DNA mean proteinuria 1.19 g/g	Mixed (6 rescue, 5 first-line)	Limited data (2 biopsies) ↓ g+ptc	Stable eGFR, ↓ proteinuria (NS, p=0.7) eGFR of 57 ± 18 ml/min/1.73 m2 pretreatment eGFR of 56 ± 17 ml/min/1.73 m2 at 6 months and 60 ± 24 ml/min/1.73 m2 at 12 months proteinuria baseline 1.19g/g and 0.97g/g at 12 months	↓ dd-cfDNA (p=0.01 ant 6 moths), ↓ DSA (p=0.047 at 12 months)	First to monitor dd-cfDNA; potential biomarker use

Table 2. Tocilizumab for the treatment of AMR in kidney transplantation. Abbreviations: NA, not assessed; SC, standard of care; TCZ, tocilizumab; e-GFR, estimated glomerular filtration rate; AMR, chronic antibody-mediated rejection; DSAs, donor-specific antibodies; ptc, peritubular capillaritis; g, glomerulitis; cg, chronic glomerulopathy; IFTA, interstitial fibrosis and tubular atrophy; DD-Cf-DNA, Donor Derived Cell free DNA; NS, not significant.

Efficacy of Tocilizumab in Chronic Active Antibody-Mediated Rejection in Kidney Transplant Patients

The first clinical investigation into the use of TCZ in chronic active AMR (ca-AMR) was conducted by Choi et al. [60], who evaluated 36 kidney transplant recipients with biopsy-proven, SC-resistant ca-AMR. Patients received monthly intravenous infusions of TCZ at 8 mg/kg (maximum dose: 800 mg) for a treatment duration ranging from 6 to 36 months. Baseline histological assessments revealed high Banff scores [61] for microvascular inflammation, including glomerulitis and peritubular capillaritis, along with C4d deposition hallmarks of active AMR. After 12 months of TCZ treatment, follow-up biopsies performed in nine patients demonstrated a significant reduction in glomerulitis ($p = 0.0175$), peritubular capillaritis, and C4d staining ($p = 0.0318$). These changes reflect an attenuation of the immunologic injury. Glomerulitis and peritubular capillaritis are typically associated with poor long-term graft prognosis. DSA levels were monitored quarterly, while renal function was assessed via estimated eGFR, and was evaluated monthly throughout the study period. A sustained decline in DSA levels was observed, particularly for immunodominant specificities, with a statistically significant reduction noted at 24 months of therapy ($p = 0.043$). At six years post-ca-AMR diagnosis, graft and patient survival rates were 80% and 91%, respectively. Treatment discontinuation in four patients due to financial constraints ($n = 3$) or clinical indications ($n = 1$) was associated with subsequent graft loss. The authors hypothesized that abrupt cessation of TCZ may have triggered an IL-6 rebound effect, exacerbated by IL-6 accumulation during prolonged receptor blockade. Notably, all four patients experiencing graft failure harbored class II DSAs (HLA-DQ or HLA-DR). Among patients who remained on therapy, renal function was stable, with no significant decline in eGFR at 36 months. Lavacca et al. evaluated the efficacy and safety of TCZ as a first-line therapeutic approach in KT recipients with biopsy-proven ca-AMR. In this open-label, prospective study conducted between 2016 and 2018, 15 patients meeting Banff criteria for ca-AMR [38, 61] were enrolled. None of the participants had received prior targeted anti-rejection therapy. TCZ was administered intravenously at a dose of 8 mg/kg (maximum 800 mg) every four weeks. One patient with advanced graft dysfunction was converted to Belatacept-based maintenance immunosuppression prior TCZ initiation. Patients were followed for a median duration of 20.7 months. Outcome measures included graft function (assessed by eGFR rate and proteinuria), patient survival, serum levels of DSAs and anti-angiotensin II type 1 receptor antibodies (AT1R-Abs), histopathological changes, and adverse events. Protocol biopsies were performed at 6 months post-treatment initiation to assess early histological response. TCZ treatment was associated with stabilization of eGFR and proteinuria, along with a significant reduction in circulating DSA levels ($p = 0.002$). Histological analysis demonstrated a reduction in microvascular inflammation, particularly in glomerulitis and peritubular capillaritis scores. However, no significant improvements were observed in chronic injury markers, including interstitial fibrosis/tubular atrophy and C4d deposition. These findings suggest that TCZ, when used as first-line therapy in ca-AMR, may contribute to the attenuation of active alloimmune injury and stabilization of graft function, although its impact on chronic injury progression remains limited. eGFR and 24-hour proteinuria showed stabilization at the 12-month follow-up. eGFR declined by 10.5 mL/min/1.73 m^2 (median) in the 12 months before ca-AMR diagnosis compared with 4.4 mL/ min/1.73 m^2 the first year after diagnosis. Median proteinuria at diagnosis and at the 12-month follow-up were 1.1 and 1 g/day, respectively. Mean MFI values significantly declined after TCZ treatment (22600 pre-TCZ and 18200 post-TCZ with complete negativization in one patient). This trend was also confirmed for AT1R-Ab [62].

A retrospective study conducted by Kumar et al. evaluated the efficacy of TCZ in 10 kidney transplant recipients with biopsy-proven ca-AMR refractory to SC therapy. Notably, seven of these patients were maintained on Belatacept-based immunosuppression. Serial graft biopsies were performed at baseline and one year following initiation of TCZ therapy. At 6 months post-treatment initiation, there was an improvement in the mean of eGFR, but not statistically significant, while proteinuria levels remained unchanged throughout follow-up. A reduction in DSA MFI was also observed at 6 months, although this did not reach statistical significance ($p = 0.5$). Histological analysis demonstrated a reduction in microvascular inflammation following 12 months of TCZ therapy, mirroring the findings reported by Choi et al. [60]. Specifically, reductions in glomerulitis, peritubular capillaritis, and C4d deposition were noted, as detailed in Table 2. TCZ was discontinued in 47.3% of patients (18/38 in the overall cohort), after a median treatment duration of 10.4 months. In three cases, the decision to withdraw TCZ was made upon stabilization of graft function, highlighting the ongoing uncertainty regarding optimal treatment duration. Discontinuation was also necessitated by the development of HPV-positive tonsillar carcinoma in one patient, and by infectious complications in four others. Collectively, the studies by Choi et al. and Kumar et al. demonstrate consistent histological improvements in patients with refractory ca-AMR treated with TCZ, particularly in the reduction of MVI ($p = 0.0175$) and C4d deposition ($p = 0.0318$), suggesting a potential disease-modifying role for IL-6 blockade in this setting [63].

A retrospective study investigated the efficacy of TCZ as adjunctive SC in nine kidney transplant recipients with biopsy-proven graft rejection. Of these, six patients were diagnosed with ca-AMR, while the remaining three exhibited mixed rejection characterized by features of both AMR and T cell-mediated rejection. All patients had detectable circulating DSAs at the time of diagnosis and had demonstrated resistance to prior SC therapies. TCZ was administered intravenously at a dose of 8 mg/kg (maximum 800 mg) monthly. Outcomes were compared to those of a control group comprising 37 patients with AMR who had received SC therapy alone. At 12-month follow-up, the TCZ-treated group exhibited a significant reduction in the MFI of DSAs across both HLA class I and class II antigens ($p = 0.01$). Despite this immunological response, there were no statistically significant differences between the TCZ and control groups in terms of graft survival or decline in renal function over the same period. Histopathological evaluation revealed a modest improvement in inflammatory indices, including a reduction in tubulitis scores, following TCZ treatment. However, the progression of AMR-related lesions and chronic glomerulopathy remained largely comparable between the two cohorts. The incidence of infections did not differ significantly between TCZ-treated patients and those receiving SC alone [64].

Noble et al. [65] recently published a single-center retrospective study evaluating the efficacy of TCZ in 40 KT recipients with biopsy-proven ca-AMR. TCZ was administered intravenously at a dose of 8 mg/kg (maximum 800 mg) every four weeks. Seven patients received TCZ as first-line monotherapy, whereas the remaining patients were treated with TCZ in combination with other immunosuppressive agents, including corticosteroids (52.5%), RTX (40%), PLEX (20%), and anti-thymocyte globulin (5%). One patient had received Belatacept prior TCZ initiation, and 18 additional patients were converted to Belatacept-based maintenance immunosuppression following the diagnosis of AMR and the initiation of TCZ. The primary endpoints were changes in graft function, assessed by eGFR rate and proteinuria, and histological progression at one year. Compared with baseline values, no statistically significant differences were observed in eGFR decline ($p = 0.102$) or proteinuria ($p = 0.28$) after 12 months of TCZ therapy. Likewise, histopathological assessment revealed no significant changes in Banff lesion scores after one year of treatment. During follow-up, six patients (15%) experienced graft loss. These patients had more severe baseline clinical and histological parameters compared with the rest of the cohort, including lower baseline eGFR (24.5 ± 16 mL/min/1.73 m^2), higher levels of proteinuria (1.8 ± 1.0 g/L), and more advanced chronic injury

on biopsy, with significantly higher scores of tubular atrophy (ct; p = 0.007), interstitial fibrosis (ci; p = 0.002), and intimal arteritis (v; p = 0.001). The study did not include longitudinal monitoring of donor-specific antibodies (DSAs) or systematically report adverse events related to TCZ, thus limiting the interpretation of immunological efficacy and safety outcomes.

Khairallah et al. [66] conducted a retrospective study to evaluate the impact of TCZ on allograft function and histopathological features in 38 kidney transplant recipients with biopsy-proven ca-AMR. Among the included patients, 35 had previously failed SC therapies, while TCZ was administered as first-line therapy in the remaining three. At the time of TCZ initiation, 15 patients had detectable DSAs. TCZ was administered intravenously at a dose of 8 mg/kg monthly. Follow-up biopsies were performed in approximately half of the cohort after a median of 5.1 months from treatment initiation. Histological analysis revealed a significant reduction in interstitial inflammation scores (p = 0.03), while other Banff parameters such as glomerulitis, tubulitis, peritubular capillaritis, arteritis, glomerulosclerosis, and C4d deposition-remained unchanged. No significant variation in DSA levels was observed following TCZ treatment (p = 0.5). Graft function remained stable during the six months following TCZ initiation. A significant deceleration in the rate of eGFR decline was observed, with a difference in slope of 2.6 mL/min/1.73 m^2 per month before and after treatment initiation (p = 0.002). Proteinuria did not change significantly over the observation period (p = 0.07).

Boonpheng et al. conducted a study involving 11 kidney transplant recipients with biopsy-proven ca-AMR treated with TCZ. DSAs and donor-derived cell-free DNA (dd-cfDNA) were serially monitored to assess immunologic activity and allograft injury during follow-up. In six patients, TCZ was initiated following failure of SC therapy, while in the remaining five patients was used as a first-line treatment. At six months, a significant reduction in dd-cfDNA levels was observed (p = 0.01), suggesting a potential attenuation of alloimmune-mediated graft injury. Among the six patients who completed 12 months of treatment, ddcfDNA levels remained significantly reduced compared to baseline at both six and twelve months (p = 0.05 and p = 0.04, respectively). The authors also reported a decline in the MFI of immunodominant DSAs over time. While the reduction did not reach statistical significance at six months (p = 0.13), it became significant at twelve months (p = 0.047), indicating a potential immunomodulatory effect of IL-6 inhibition on humoral alloimmunity. Graft function remained stable during TCZ treatment. The eGFR rate at six months did not differ significantly from baseline (p = 0.25), and in the subgroup of patients treated for at least 12 months, eGFR remained unchanged at six and twelve months (p = 0.29 and p = 0.48, respectively). Proteinuria showed a decreasing trend, but the differences were not statistically significant; mean proteinuria declined from 1.19 g/g at baseline to 0.97 g/g at twelve months (p = 0.70). Only two patients underwent follow-up biopsies after 16 months of treatment, which revealed modest improvements in microvascular inflammation [67].

Tocilizumab safety profile

Adverse events are summarized in Table 3. Across published studies, the safety profile of TCZ in KT recipients has been overall acceptable and comparable to that observed in other clinical settings. The most frequently reported adverse events were infectious complications, particularly bacterial and viral infections, consistent with the immunomodulatory effects of IL-6 blockade.

In the largest available series, Choi et al. [60] reported infectious events in approximately 25–30% of patients treated for ca-AMR, while Lavacca et al. [62] documented infections in one-third of their cohort, mainly urinary and respiratory tract infections and cytomegalovirus (CMV) viremia. Similarly, Kumar et al. [63] observed infections in 50% of patients, including opportunistic infections, and in several cases, this led to treatment discontinuation. In other retrospective cohorts [64–66], the incidence of infections ranged from 20% to 30%, without a statistically significant difference

compared to SC therapy. Boonpheng et al. [67] reported three non-severe events (uncomplicated diverticulitis, localized herpes zoster, and mild COVID-19), and Potteboun et al. [59] observed no serious adverse events in acute AMR patients. In the desensitization setting, TCZ was very well tolerated across three studies [55–57], with no severe infections reported.

The most common infectious events included urinary tract infections, respiratory infections, CMV reactivation, herpes zoster, and, less frequently, gastrointestinal infections. No invasive fungal infections were documented.

Non-infectious adverse events were uncommon. One case of HPV-positive tonsillar carcinoma was reported during prolonged TCZ treatment; the event was not directly TCZ-related [63], and a single episode of diverticulitis [67]. Mild, transient laboratory abnormalities (e.g., elevated transaminases) were occasionally described but were not clinically significant. Only one study reported a cardiovascular event in two patients: non-ST-segment elevated myocardial infarctions and one stroke. However, the causal relationship with TCZ therapy is not clear. There were no reports of TCZ-related nephrotoxicity. Importantly, several studies reported no significant increase in infection rates compared with SC alone [64], suggesting that TCZ does not substantially increase the infectious burden when used in experienced transplant centers with appropriate prophylaxis and monitoring. TCZ infusion was overall well tolerated across the included studies.

Overall, TCZ demonstrates a favorable and manageable safety profile in kidney transplant recipients. Infectious events remain the main clinical concern but are generally controllable. The drug is well tolerated both as adjunctive therapy for AMR and as part of desensitization strategies, supporting its use in selected high-risk populations under close clinical surveillance.

Critical Comparison and Limitations of Studies Evaluating Tocilizumab in AMR

Across the current body of literature, TCZ has emerged as a potentially effective therapeutic agent for the management of AMR, particularly in patients who are refractory to SC therapies. Although most available studies are single-center, retrospective, and non-randomized, with limited sample sizes (ranging from 7 to 40 patients per study) and often lacking adequately matched control groups, they consistently demonstrate a significant attenuation of microvascular inflammation, including reductions in glomerulitis and peritubular capillaritis scores, accompanied by stabilization of renal allograft function.

In the pivotal study by Choi et al. [60], TCZ administered as rescue therapy was associated histological improvements and sustained reductions in DSA levels over a long-term follow-up, supporting its disease-modifying potential in ca-AMR. Similarly, Kumar et al. [63] and Lavacca et al. [62] reported concordant findings, with significant reductions in microvascular inflammation and stabilization of e-GFR, although DSA declines were more variable and not consistently statistically significant across all patients. By contrast, the study by Noble et al. [65], which included a larger and more heterogeneous cohort of patients treated with TCZ in combination with other immunomodulatory agents, did not show significant changes in either histological lesions or functional parameters after one year of therapy. This discrepancy may be attributable to more advanced chronic injury at baseline, differences in treatment timing and duration, and the absence of standardized immunological monitoring protocols. Importantly, heterogeneity in treatment duration – ranging from a few months to three years –, timing of TCZ administration (first-line vs rescue therapy), and baseline histopathological severity likely influenced clinical and immunological outcomes. Furthermore, the use of TCZ as monotherapy versus combination therapy represents an additional source of variability. While some studies suggested promising effects of TCZ monotherapy in mitigating microvascular inflammation, most cohorts received combination regimens, making it challenging to isolate the specific contribution of IL-6 blockade.

Study	Infection	Others
Vo et al. Transplantation 2015 [55]	1 episode of colonic diverticulitis with perforation (possible correlation with TCZ)	Anemia and hypertension during time of treatment. 1 episode of acute pulmonary edema unrelated to TCZ and
Daligault et al. Transplantation Direct 2021 [56]	1 episode of Spondylodiscitis	Hypogammaglobulinemia
Jouve et al. AJT 2021 [57]	1 episode of spondilodiscitis	hypogammaglobulinemia
Choi et al. Am J Transplant. 2017 [60]	13/36 5 CMV viremia 3 BKV viremia 7 bacterial infections	3/36 1 stroke 2 NSTEMI 1/36 transient visual disturbance 8/36 hypogammaglobulinemia
Lavacca et al. Clin Transplant. 2020 [62]	5/15 bacterial Infection 4/5 UTI 1/5 low respiratory tract infection 1/15 encephalitis of undefined origin 2/15 interstitial lung disease infection	4/15 hypogammaglobulinemia 3/15 asymptomatic mild alterations in liver enzymes
Pottebaum et al. Transplant Direct. 2020 [59]	1/7 CMV esophagitis	1 potential hypersensitivity reaction
Kummar et al. Kidney360. 2020 [63]	3/ 19 bacterial infections 1/10 viral with HSV	5/10 leukopenia 1/19 severe diarrhea
Massat et al Am J Transplant. 2021. [64]	6/9 (SC+TCZ) * 2 bacterial infections 2 viral infections 2 fungal infections	NA
Noble et al. Front Med. 2021 [65]	NA	NA
Khairallah et al. Clin Transplant. 2023 [66]	3/38 CMV viremia 3/3 BKV viremia 1/3 EBV viremia 1/38 pneumonia 1/38 cellulitis 3/38 pyelonephritis	15/3 leucopenia 16/38 thrombocytopenia 7/38 asymptomatic mild alterations in liver enzymes
Boonpheng at al. Clin Transplant. 2023 [67]	1/11 VZV 1/11 uncomplicated diverticulitis 1/11 mild covid 19 infection 1/11 clostridium difficile colitis	NA

Table 3. Tocilizumab Adverse effects. NA, not assessed. CMV: cytomegalovirus; BKV: poliomavirus BK; EBV: Epstein-Barr virus; VZV: varicella zoster virus; HSV: herpes simplex virus; NSTEMI: non–ST-segment elevation myocardial infarction; UTI: urinary tract infection; TCZ: tocilizumab. *There were no significant differences between the SC group and the SC+TCZ group.

The timing of intervention and extent of baseline histological injury also appear to modulate therapeutic response. In acute AMR, early initiation of TCZ (Potteboun et al.) was associated with stabilization of graft function and significant reductions in DSA levels, suggesting a beneficial effect on ongoing alloimmune injury. In contrast, in ca-AMR, TCZ consistently reduced microvascular inflammation and C4d deposition but exhibited limited effects on chronic injury parameters such as IFTA, transplant glomerulopathy, and intimal arteritis, particularly in patients with advanced structural damage at baseline (e.g., Noble et al.). These findings support the hypothesis that IL-6 blockade may exert its maximal therapeutic effect when introduced in earlier phases of the disease, before the establishment of irreversible chronic allograft injury.

Additional mechanistic insights were provided by Khairallah et al. [66] and Boonpheng et al. [67], who explored eGFR slope dynamics and donor-derived cell-free DNA (dd-cfDNA), respectively, as surrogate markers of graft injury and immunological activity. Khairallah et al. observed a significant deceleration in the rate of eGFR decline following TCZ initiation, even in the absence of significant DSA changes, suggesting an anti-inflammatory effect independent of antibody clearance. Boonpheng et al. demonstrated both dd-cfDNA and DSA reductions over 12 months, indicating a dual anti-inflammatory and immunomodulatory mechanism of IL-6 blockade. Importantly, the

therapeutic benefit of TCZ appeared more pronounced in early or moderate ca-AMR, whereas its impact in advanced stages with extensive fibrosis and glomerulopathy remained limited.

By targeting IL-6 signaling, TCZ can reduce DSA levels, suppress their production, and mitigate histological damage in both the short and long term.

Given the lack of standardized treatment algorithms for AMR, accumulating evidence supports a potential role for TCZ as an adjunctive therapy, particularly in patients with inadequate responses to SC. By targeting the IL-6 signaling pathway, TCZ has the capacity to modulate both humoral and inflammatory components of the alloimmune response, reduce DSA production, and attenuate histological injury in both the short and long term.

Within this therapeutic landscape, Belatacept, a fusion protein that selectively inhibits CD28-mediated T-cell co-stimulation, may represent a synergistic partner for TCZ. Its calcineurin inhibitor-sparing properties and capacity to suppress T-cell activation make it an attractive strategy for high-immunological-risk recipients. Data from randomized phase 3 trials (BENEFIT and BENEFIT-EXT) have shown reduced DSA production with Belatacept, supporting the rationale for dual targeting of both T- and B-cell compartments to achieve more effective immunological control, reduce microvascular inflammation, and prevent DSA rebound [68, 69]. Consequently, the combination of TCZ and Belatacept represents a promising and biologically rational therapeutic approach that warrants further evaluation in prospective clinical trials, particularly in patients with high immunological risk or resistance to conventional therapies.

Alternatives in IL-6 pathway inhibition – Clazakizumab

Clazakizumab is a humanized monoclonal IgG1 antibody that bind with high affinity and neutralizes human IL-6. In 2016 it was used to treat 10 patients with chronic AMR. Findings from this study demonstrating a stabilization of eGFR after initiation of clazakizumab therapy (eGFR −24 months [52], 0 month [38], +12 months [41], and +24 months [38]), reductions in DSA levels and Banff scores for C4d and g + ptc scores. The authors noted a trend to reductions in total IgG levels and an increase in Treg cells at 24 months post treatment [30]. In a randomized, double-blind, placebo-controlled, parallel-group phase II pilot trial conducted and published in 2021, that included 20 KT patients with DSA-positive AMR after a median of 10.6 years post-transplantation. KT patients were randomly assigned to receive Clazakizumab or a placebo to assess safety, tolerability, and efficacy of the molecule. Within 12 weeks of therapy DSA MFI decreased by 77%, without significant differences in AMR and T-cell–mediated rejection between the two groups. The key results of the secondary endpoint analysis were a slowed decline in eGFR and, after extended treatment, modulation of rejection-associated gene expression patterns, reduction of C4d scores, and, in some patients, resolution of AMR activity. These results were promising [31].

In addition to TCZ, Clazakizumab has been investigated in early-phase studies involving 20 HS kidney transplant candidates. Clazakizumab desensitization protocols, after PLEX + IVIg, appear safe with significant reductions in HLA class I and II antibodies. The treatment allowed 18 of 20 patients to receive transplantation with no de novo DSA generation [32].

The data suggest that Clazakizumab can reduce circulating DSA levels and modulate humoral alloimmune responses, potentially facilitating access to transplantation in difficult-to-match patients. Compared with TCZ, Clazakizumab may provide a more complete and sustained blockade of IL-6 signaling, although evidence remains limited and mostly derived from small, non-randomized cohorts. Ongoing randomized trials, including the IMAGINE trial (NCT03744910), will be crucial to clarify the role of IL-6 inhibition in kidney transplantation.

Comparative Therapeutic Landscape of AMR: IL-6 Blockade, CD38 Targeting, and Complement Inhibition

Over the past decade, increasing understanding of the complex immunopathology of antibody- AMR has prompted the development of several novel therapeutic strategies beyond conventional ones. So, IL-6 blockade with tocilizumab and Clazakizumab, CD38-targeting monoclonal antibodies, proteasome inhibition, and complement inhibition represent the most promising emerging approaches. Each of these strategies acts on distinct – but potentially complementary – pathogenic pathways of AMR, and their comparison provides important insights into future treatment algorithms.

CD38-targeting monoclonal antibodies, including Daratumumab and Felzartamab, have recently emerged as a promising class of agents with a distinct and potentially more rapid mechanism of action. CD38 is highly expressed on plasma cells and NK cells, two key effector populations in AMR pathogenesis. By targeting CD38, these agents deplete both DSA-producing plasma cells and Fc receptor–expressing NK cells, thus intervening at multiple levels of the alloimmune cascade. Felzartamab, evaluated in a randomized, placebo-controlled phase 2 trial in late AMR, demonstrated histologic resolution of AMR activity in over 80% of patients after six months of therapy, with a marked reduction in MVI scores and AMR transcriptomic activity, along with significant depletion of circulating NK cells. These effects occurred despite minimal changes in immunodominant DSA levels, supporting the hypothesis that targeting effector mechanisms downstream of DSA may be sufficient to attenuate graft injury. Importantly, dd-cfDNA levels – a biomarker of active allograft injury – declined rapidly during treatment, although recurrence of molecular and histologic activity was observed after therapy cessation, indicating that prolonged or combination regimens may be required [70].

Daratumumab, an anti-CD38 antibody with a well-established safety profile in hematology, has been used off-label in several case reports and small series involving both early and late AMR. These studies consistently showed reduction in DSA mean fluorescence intensity, NK cell depletion, attenuation of MVI, and stabilization or improvement of graft function. In some cases, significant dd-cfDNA reduction paralleled these effects, further supporting its immunomodulatory potential [71–74]. Notably, sequential or combination strategies, such as Daratumumab followed by TCZ, have been associated with enhanced and more sustained immunologic responses, suggesting a synergistic effect between plasma cell depletion and IL-6 blockade [75].

Similarly, complement inhibition, particularly with anti-C5 (eculizumab), has shown promise in acute AMR by attenuating complement-mediated endothelial injury and reducing C4d deposition, but its effect on long-term graft survival remains uncertain, and its use is currently limited to selected high-risk cases or rescue therapy [25].

Taken together, these findings underscore the heterogeneity and complementarity of available immunomodulatory strategies. While IL-6 blockade primarily targets upstream inflammatory and B cell–mediated pathways, CD38-targeting antibodies intervene at both the level of antibody production and effector mechanisms, resulting in rapid attenuation of rejection activity even in late stages. Proteasome and complement inhibition offer additional therapeutic angles, targeting upstream plasma cell survival and downstream complement-mediated injury, respectively. In this context, rational combinatorial or sequential approaches may offer the most effective strategy for patients with refractory or advanced AMR. Ongoing phase 3 trials with Felzartamab (TRANSCEND) and Daratumumab (DARTABMR)-based regimens are expected to define their position in the therapeutic armamentarium, and their potential integration with IL-6 blockade or other targeted therapies may further improve allograft outcomes in high immunological risk populations.

Conclusions

The current evidence on the use of TCZ for the treatment of AMR and for desensitization in HS kidney transplant candidates is promising but remains limited. Most available studies are retrospective, include small patient cohorts, and lack randomized controlled trials (RCTs), which hinders the ability to draw definitive conclusions regarding the efficacy of TCZ either as monotherapy or in combination with standard therapies. Larger, prospective, randomized studies are needed to better define the role of TCZ in these contexts and to optimize treatment protocols. TCZ has shown encouraging results in attenuating microvascular inflammation, stabilizing graft function, and reducing DSA levels, particularly when used as rescue therapy in patients with AMR refractory to SC. Its continuation after transplantation in patients undergoing desensitization may be justified, as it could help prevent DSA rebound and reduce the risk of post-transplant humoral rejection, especially in highly sensitized recipients. These findings suggest that TCZ could be strategically positioned as both an adjunctive therapy and a maintenance option in selected high-risk patients.

In summary, IL-6 pathway inhibition represents a promising and biologically targeted strategy in the management of AMR and desensitization in kidney transplantation. However, further high-quality studies are required to determine the optimal timing, duration, and combination strategies for IL-6 blockade.

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Bidirectional Interaction Between the Gastrointestinal System and the Kidney: Pathophysiological and Clinical Perspective

In depth review

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ABSTRACT

The gastrointestinal (GI) system and the kidneys, though anatomically separate, are functionally interconnected through shared responsibilities in maintaining fluid-electrolyte balance, acid-base homeostasis, immune regulation, and hormonal signaling. Disruptions in one system often lead to secondary complications in the other, highlighting the need for a comprehensive understanding of their bidirectional interactions. Kidney involvement in GI diseases commonly results from mechanisms such as fluid loss, malabsorption, systemic inflammation, and exposure to toxins, as seen in conditions like inflammatory bowel disease (IBD), celiac disease, liver failure, and enteric infections. Conversely, GI complications frequently arise in the context of chronic kidney disease (CKD), dialysis, and immunosuppressive therapies post-transplantation, manifesting as symptoms including uremic gastropathy, anorexia, and enteropathy. This review explores these interactions under two main categories: renal complications of GI diseases and GI manifestations of kidney disorders. It also discusses the underlying pathophysiological mechanisms and clinical implications, emphasizing the importance of an integrated, multidisciplinary approach. By highlighting current knowledge gaps, the review aims to foster future research in this complex and clinically significant area. Understanding these bidirectional interactions can inform individualized patient care and improve outcomes in both GI and renal disease contexts.

KEYWORDS: Gastrointestinal system, Kidney diseases, Gut-kidney axis

Overview of Gastrointestinal System and Kidney Interactions

The gastrointestinal (GI) system and kidneys are two distinct systems that play critical roles in maintaining intracorporeal homeostasis. Although there is no direct anatomical connection between these systems, there is a close cooperation through many physiological processes such as fluid-electrolyte balance, acid-base regulation, immune responses and hormonal signaling. Therefore, pathological conditions affecting one system can also influence the other [1]. This interaction is seen clinically in the form of kidney dysfunction that develops during GI diseases and GI complications that occur in kidney diseases [2].

Kidney involvement in GI diseases is often mediated by fluid and electrolyte loss, malabsorption, toxin exposure, or systemic inflammation. In particular, kidney function may be directly or indirectly affected in inflammatory bowel diseases (IBD), celiac disease, liver failure and enteric infections [3–6]. Similarly, the GI system can be significantly affected by kidney diseases. Complications such as uremic gastropathy, enteropathy and anorexia are common in patients with chronic kidney disease (CKD), and treatments such as hemodialysis and peritoneal dialysis may further exacerbate GI symptoms [7, 8]. In addition, post-transplant infections due to immunosuppression and drug side effects may also lead to GI complications [9, 10]. The main interactions between the GI system and the kidneys are shown in Figure 1.

In this review, kidney involvement in GI system diseases and GI complications arising in kidney diseases will be examined under two separate headings; the pathophysiological basis and clinical reflections of this interrelationship will be discussed (Table 1). The aim is to better understand these complex interactions in pediatric and adult patients and to draw attention to the importance of a multidisciplinary approach. It is also aimed to lay the groundwork for future research by revealing the knowledge gaps in these areas.

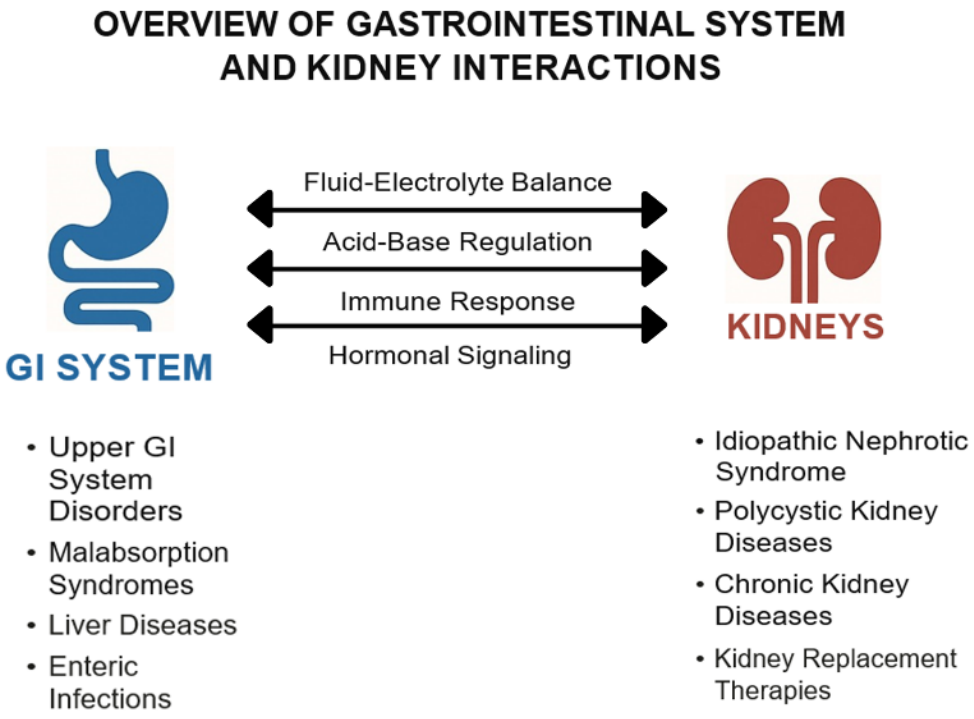

Figure 1. Bidirectional interactions between gastrointestinal system and the kidney.

Mechanisms of Kidney Involvement in GI Diseases	
Upper GI System Disorders	
GERD	Use of PPI and associated ATIN
	Use of PPI and PPI-related nephropathy
***H. pylori* Infection**	Systemic inflammation induced by persistent infection
	Immune complex-mediated kidney injury due to mucosal IgA secretion
	Metabolic disturbances such as insulin resistance and dyslipidemia due to *H. pylori*
Malabsorption Syndromes	
Inflammatory Bowel Diseases	Nephrolithiasis and nephrocalcinosis due to enteric hyperoxaluria
	Glomerulonephritis due to antigen-specific immune responses
	AKI and CKD due to systemic inflammation, medication toxicity, and malnutrition
Celiac Disease	IgAN due to galactose-deficient IgA1
	CKD due to increased intestinal permeability and immune activation
	Diabetic nephropathy due to high prevalence of T1DM
	Nephrolithiasis due to intestinal malabsorption or altered renal handling
	UTI due to impaired urinary tract motility, dysfunction of the bladder, changes in gut microbiota
Liver Diseases	
Primary Hyperoxaluria	Nephrolithiasis/nephrocalcinosis and associated CKD due to hepatic enzyme deficiencies in glyoxylate metabolism
Wilson's Disease	Tubular dysfunctions due to copper deposition
	Glomerular involvement due to immune complex-mediated mechanisms
	Drug-induced nephrotoxicity caused by chelation therapy
Chronic Liver Disease	Decreased kidney perfusion and reduced GFR due to splanchnic vasodilation, activation of RAAS system and sympathetic nervous system
	Systemic inflammation due to impaired hepatic detoxification
	Hepatorenal syndrome due to advanced liver disease
Enteric Infections	
STEC-HUS	Endothelial damage and subsequent thrombotic microangiopathy due to systemic dissemination of Shiga toxins
	GI System Involvement in Kidney Diseases
Idiopathic Nephrotic Syndrome	Edema of the bowel wall due to hypoalbuminemia
	Mesenteric arterial thrombosis due to hypercoagulable state
	Spontaneous bacterial peritonitis due to immunosuppression
	Peptic ulcer disease and drug-related mucosal injury due to steroid therapy
Polycystic Kidney Disease	Polycystic liver disease due to ADPKD
	Congenital hepatic fibrosis due to ARPKD
Chronic Kidney Disease	Uremic gastropathy or delayed gastric emptying due to uremia
	GI bleeding due to mucosal fragility and platelet dysfunction
	Abdominal discomfort or paralytic ileus due to bowel wall edema
	Systemic inflammation due to translocation of endotoxins
	Alterations in the gut microbiome (dysbiosis) due to uremia
	Constipation due to restricted fluid intake, dietary limitations, and phosphate binders
	Protein-energy wasting and deficiencies in essential nutrients due to decreased appetite
Kidney Replacement Therapies	Hypotension-related gut hypoperfusion, mesenteric ischemia and colonic angiodysplasia-related bleeding due to hemodialysis
	Increased intra-abdominal pressure, leading to early satiety, gastroesophageal reflux, abdominal fullness, or hernias due to peritoneal dialysis
	Bacterial or sclerosing encapsulating peritonitis
	Nausea, diarrhea, oral ulcers, and anorexia due to immunosuppressive therapy
	Opportunistic infections due to immunosuppressive therapy

Table 1. Mechanisms of kidney involvement in GI system diseases and GI involvement arising in kidney diseases. GI: Gastrointestinal, GERD: Gastroesophageal reflux disease, PPI: Proton-pump inhibitor, ATIN: Acute tubulointerstitial nephritis, IgA: Immunoglobulin A, AKI: Acute kidney injury, CKD: Chronic kidney disease, IgAN: Immunoglobulin A nephropathy, T1DM: Type 1 diabetes mellitus, UTI: Urinary tract infection, GFR: Glomerular filtration rate, RAAS: Renin-angiotensin-aldosterone system, STEC-HUS: Shiga toxin-producing *Escherichia coli*-hemolytic uremic syndrome, ADPKD: Autosomal dominant polycystic kidney disease, ARPKD: Autosomal recessive polycystic kidney disease.

Material and Methods

This article is a narrative review that examines the bidirectional interactions between the GI system and the kidneys, focusing on the underlying pathophysiological mechanisms and associated clinical outcomes, comprehensively reviewing of the current literature. Methodological rigor and principles of reproducibility were applied during both the literature selection and manuscript preparation processes. The literature search was conducted using the PubMed, Scopus, and Web of Science databases, covering publications from January 2000 to December 2024. Results were limited to studies published in English. The keywords and their combinations used were: “gastrointestinal system”, “kidney diseases”, “gut-kidney axis”, “renal replacement therapies”, and “microbiota”. The study included case reports and original research examining GI system findings or mechanisms in different stages of kidney disease, as well as review articles directly related to the topic. Publications and abstracts with limited relevance to the topic or that did not directly examine the kidney-GI relationship were excluded from the study.

In this narrative review, experimental studies such as animal models were used to understand potential biological pathways. While observational studies were evaluated to determine the relationships between the GI system and the kidneys in human populations, interventional studies provided the strongest evidence for potential effects. Unless supported by evidence from multiple study types, definitive causal statements were avoided, and neutral terms such as associated or linked were used.

Kidney Involvement in Gastrointestinal Diseases

Upper Gastrointestinal System Disorders

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is a common chronic condition characterized by the retrograde flow of gastric contents into the esophagus, resulting in symptoms such as heartburn, regurgitation, and, in some cases, esophagitis. The pathophysiology of GERD involves a combination of factors including lower esophageal sphincter dysfunction, impaired gastric emptying, and increased intra-abdominal pressure. GERD affects a significant proportion of the global population and often requires long-term pharmacological management, particularly with proton pump inhibitors (PPIs), which are the mainstay of treatment. Although PPIs are effective in controlling acid-related symptoms and healing mucosal damage, their long-term use has raised concerns regarding potential adverse effects, including those on kidney functions [11].

One of the most recognized renal complications associated with PPIs is acute tubulointerstitial nephritis (ATIN). In a pediatric study, 11.1% of patients with ATIN had a history of PPI use [12]. This is an immune-mediated hypersensitivity reaction characterized by interstitial inflammation and tubular injury. Clinically, PPI-induced ATIN may present with non-specific symptoms such as fatigue, nausea, or subtle kidney dysfunction, often leading to underdiagnosis. Histological confirmation through kidney biopsy typically reveals interstitial edema, lymphocytic infiltration, and eosinophils [12].

Recent studies have identified an association between chronic PPI use and an increased risk of CKD and kidney failure in adults. Although a direct causal relationship is still under investigation, repeated or subclinical episodes of ATIN, as well as PPI-induced alterations in magnesium homeostasis and gut microbiota, have been proposed as contributing mechanisms [13]. The risk of PPI-related nephropathy appears to be more pronounced in elderly patients, individuals with pre-existing kidney impairment, and those using PPIs for prolonged periods without appropriate clinical

indication. Importantly, PPI-related kidney injury may be partially reversible if recognized early and the offending agent is discontinued [14].

These findings underscore the need for cautious and evidence-based prescribing of PPIs, emphasizing regular reassessment of their indication and duration. In patients requiring long-term acid suppression, kidney function should be periodically monitored, and alternative therapies may be considered when appropriate.

Helicobacter pylori Infection

Helicobacter pylori (*H. pylori*) is a gram-negative, spiral-shaped bacterium that colonizes the gastric mucosa and is a well-established cause of chronic gastritis, peptic ulcer disease, and gastric malignancies. Beyond its GI manifestations, H. pylori infection has been increasingly studied for its potential systemic effects, including those on kidney function [15].

Several epidemiological and experimental studies have suggested a link between chronic *H. pylori* infection and kidney impairment, although the exact mechanisms remain incompletely understood, and pediatric data are limited. One proposed pathway involves systemic inflammation induced by persistent infection. *H. pylori* stimulates the release of pro-inflammatory cytokines such as interleukin-6, tumor necrosis factor-alpha, and C-reactive protein, which may contribute to endothelial dysfunction and glomerular injury, particularly in individuals with pre-existing susceptibility [16]. A second pathway is the activation of the immune complex-mediated mechanism due to mucosal immunoglobulin A (IgA) secreted against *H. pylori.* Chronic *H. pylori* infection has been associated with the development of immune-mediated renal diseases, including IgA nephropathy (IgAN). Molecular mimicry and immune cross-reactivity between bacterial antigens and kidney tissues may play a role in this association [17]. In addition, *H. pylori* may contribute to metabolic disturbances such as insulin resistance and dyslipidemia, which are recognized risk factors for CKD [18]. Although a direct causal relationship has not been definitively established, the cumulative evidence indicates that chronic infection could act as a modifiable risk factor in the progression of kidney dysfunction [18]. Moreover, in kidney transplant recipients, *H. pylori* infection is of particular clinical relevance due to the immunosuppressed state, which may alter the typical presentation and increase the risk of GI complications such as peptic ulcer disease and bleeding. Additionally, chronic *H. pylori* infection may contribute to systemic inflammation, potentially affecting graft function and long-term outcomes. Some studies in adults have suggested that pre-transplant screening and eradication of *H. pylori* may reduce the incidence of post-transplant GI morbidity and support better kidney graft survival [19]. In a study evaluating adult patients with membranous nephropathy and *H. pylori* infection, the mean proteinuria value before eradication therapy was 2.42 ± 3.24 g/day, while three months after eradication therapy, the proteinuria level decreased to 1.26 ± 1.73 g/day ($p = 0.031$) [20].

In another study, a high urine albumin-to-creatinine ratio was detected in adult patients with *H. pylori*-positive peptic ulcers, and a significant 51.5% decrease in the albumin-to-creatinine ratio was observed in these patients after eradication therapy [21]. These results suggest that eradication therapy is beneficial in alleviating kidney damage and reducing the risk of CKD.

Overall, while further research is needed to clarify the causal pathways, current data highlight a possible connection between *H. pylori* infection and renal involvement through systemic inflammation, immune dysregulation, and metabolic derangement. These findings raise important considerations regarding the evaluation and management of *H. pylori* in patients with or at risk of kidney disease.

Malabsorption Syndromes

Inflammatory Bowel Diseases

Inflammatory bowel diseases (IBD), which include Crohn's disease and ulcerative colitis, are chronic immune-mediated conditions of the GI tract. While ulcerative colitis is typically limited to the colon with continuous mucosal inflammation, Crohn's disease may affect any segment of the GI tract and is characterized by transmural, patchy inflammation. IBD frequently begins in adolescence or early adulthood and follows a relapsing-remitting clinical course. Although primarily affecting the GI system, IBD is associated with numerous extraintestinal manifestations involving the skin, joints, eyes, liver, and kidneys. Several mechanisms contribute to kidney involvement in IBD, including metabolic disturbances related to malabsorption, drug-induced nephrotoxicity, immune-mediated glomerular disease, and structural complications such as nephrolithiasis and nephrocalcinosis [22].

Kidney involvement is increasingly recognized in children with IBD, yet remains underdiagnosed. One of the most clinically significant kidney complications is enteric hyperoxaluria, particularly in patients with Crohn's disease involving the terminal ileum or those who have undergone ileal resection. Under normal physiological conditions, dietary calcium binds to oxalate in the intestinal lumen, forming insoluble complexes that are excreted in the feces. However, in IBD with fat malabsorption, unabsorbed fatty acids bind calcium, leaving oxalate unbound and more readily absorbed in the colon. This process is exacerbated by increased intestinal permeability and alterations in gut microbiota, particularly the depletion of *Oxalobacter formigenes*, a commensal bacterium that degrades oxalate. The result is enteric hyperoxaluria, which increases the risk of calcium oxalate nephrolithiasis and nephrocalcinosis. In chronic cases, nephrocalcinosis can lead to tubulointerstitial nephritis, interstitial fibrosis, and eventually CKD. Therefore, regular monitoring of kidney functions and urinary parameters is essential, especially in patients with extensive small bowel disease or surgical resections [23].

Emerging evidence suggests that glomerulonephritis (GN) in IBD may result either from antigen-specific immune responses originating in the inflamed gut or from shared genetic and environmental risk factors. GN appears both as an extraintestinal manifestation and as a potentially unrelated co-existing condition, with IgAN being the most frequently reported subtype. Although pediatric data are limited, the observed reduction in proteinuria with enteric budesonide therapy in adult patients with IgAN supports a pathogenic link between intestinal and kidney inflammation [24]. A study utilized bioinformatic and machine learning approaches to identify shared immune-infiltrating features, cross-talk genes, and pathways between IgAN and IBD using datasets from the Gene Expression Omnibus. Immune infiltration analyses revealed no major differences in immune cell profiles between the two diseases. Ten diagnostic cross-talk genes were identified, among which *FDX1* and *NFKB1* were notably elevated in the kidneys of IBD mouse models. Pathway analysis revealed 15 shared signaling pathways, highlighting lipid metabolism as a key contributor. These findings shed light on common immune mechanisms underlying IBD and IgAN, offering potential targets for further research [25].

The risk of acute kidney injury (AKI) and CKD is increased in IBD. The mechanisms underlying this association are not fully understood, but factors such as systemic inflammation, medication toxicity, and malnutrition may contribute. In an adult study assessing the prevalence of AKI and CKD in IBD, the results showed that individuals with IBD had a higher risk for both AKI (HR = 1.96) and CKD (HR = 1.57) compared to those without IBD, even after adjusting for demographic, lifestyle and health factors. Similar risks were found for Crohn's disease and ulcerative colitis. Younger participants had stronger associations between IBD and kidney outcomes [26]. However, in another study, analyses based on genome-wide association data from individuals of European descent revealed that genetic

predisposition to Crohn's disease was significantly associated with an increased risk of CKD, while no such causal association was observed for ulcerative colitis. Furthermore, inverse Mendelian randomization analysis showed that genetic predisposition to CKD did not increase the risk of developing IBD, Crohn's disease or ulcerative colitis. These findings suggest that Crohn's disease has a unidirectional causal effect on CKD and underscore the need for routine renal function monitoring in patients with Crohn's disease [27]. In a cross-sectional study of pediatric patients, one-quarter of 56 IBD patients had evidence of kidney disease, either previously diagnosed or detected by ultrasonography. Kidney length was significantly reduced compared to healthy peers. Use of infliximab was associated with smaller kidneys, while enteral nutrition correlated with preserved kidney size. These findings suggest that children with IBD are at risk for CKD, especially in severe cases, highlighting the need for early renal monitoring in this population [28].

Celiac Disease

Celiac disease is a chronic, immune-mediated enteropathy triggered by the ingestion of gluten – a protein found in wheat, barley, and rye – in genetically susceptible individuals. The pathophysiology involves an inappropriate immune response primarily in individuals carrying HLA-DQ2 or HLA-DQ8 alleles. Upon gluten exposure, tissue transglutaminase (tTG) modifies gluten peptides, increasing their affinity for HLA-DQ2/DQ8 molecules on antigen-presenting cells. This leads to the activation of gluten-specific CD4+ T cells in the lamina propria, resulting in the production of pro-inflammatory cytokines and tissue-damaging immune responses. Concurrently, anti-tTG autoantibodies are produced, which serve as both diagnostic markers and contributors to mucosal injury. The intestinal mucosa displays characteristic histological changes, including villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes, ultimately leading to malabsorption [29]. Celiac disease can present with both GI symptoms and a wide range of extraintestinal manifestations, including anemia, growth failure, osteoporosis, and even neurologic or renal involvement.

To investigate the association between celiac disease and kidney disease, genome-wide association from non-overlapping European cohorts was used and a Mendelian randomization study examining ten kidney traits was conducted. The analysis showed that genetic liability to celiac disease was causally associated with an increased risk of IgAN, chronic GN and a modest decrease in estimated glomerular filtration rate [30]. Although pediatric data are limited, findings from a meta-analysis have also shown that adult population with celiac disease have a significantly increased risk of developing kidney diseases, including IgAN and CKD. These findings highlight the need for greater clinical awareness and routine renal monitoring in patients with celiac disease to support early detection and prevention of kidney-related complications [4].

The IgAN is the most common primary GN worldwide, characterized by the deposition of IgA – particularly galactose-deficient IgA1 (Gd-IgA1) – in the glomerular mesangium. This triggers mesangial proliferation, inflammation, and eventually leads to varying degrees of proteinuria, hematuria, and progressive kidney dysfunction. Although the precise pathogenesis remains incompletely understood, IgAN is believed to result from a multi-hit process involving abnormal IgA1 glycosylation, the formation of autoantibodies against Gd-IgA1, and immune complex deposition in the kidney [31]. A potential link between IgAN and celiac disease has been increasingly recognized, given their shared immunological features and genetic predispositions – particularly involving HLA-DQ2/DQ8 alleles. In celiac disease, chronic mucosal inflammation and increased intestinal permeability may facilitate enhanced systemic exposure to dietary antigens and microbial components, leading to overproduction of aberrantly glycosylated IgA1. Moreover, mucosal immune activation in the gut-associated lymphoid tissue may promote the generation of nephritogenic IgA immune complexes that subsequently deposit in the glomeruli. Some studies have also suggested that a gluten-free diet may reduce proteinuria in patients with both IgAN and celiac

disease, supporting the idea of gut-kidney axis involvement [4]. In a case series, kidney biopsies from nine IgAN patients, four of whom had celiac disease, were analyzed for the presence of IgA-tTG co-deposits. Circulating tTG antibodies were measured and frozen tissue sections were examined for colocalization of IgA and tTG. Among the celiac patients, three showed IgA-tTG deposits in the kidney, including two people who had not yet been diagnosed with celiac disease at the time of biopsy. Interestingly, no such deposits were observed in the patient on a gluten-free diet with known celiac disease [32].

In celiac disease, CKD may not only arise as a consequence of IgAN, but also through gut-kidney axis dysregulation, where increased intestinal permeability and immune activation contribute to systemic inflammation and kidney injury. Compromise of the intestinal barrier integrity may allow bacterial lipopolysaccharides to translocate into the systemic circulation. This translocation promotes systemic inflammation and uremic toxicity, both of which are recognized drivers in the onset and progression of CKD [7].

Diabetic kidney disease is increasingly observed in children as the prevalence of type 1 diabetes mellitus (T1DM) rises. Celiac disease, which shares genetic susceptibility with T1DM – especially via HLA-DR3-DQ2 and DR4-DQ8 – coexists in 3-12% of pediatric cases [7]. Celiac disease may also be an independent risk factor for both microvascular and macrovascular complications, potentially through mechanisms like intestinal malabsorption, micronutrient deficiencies such as folate, B vitamins, and hyperhomocysteinemia [33]. These findings support routine screening for celiac disease in T1DM patients and highlight the need for further research into the gut-kidney and gut-vascular axes in this context.

The association between celiac disease and urolithiasis was first reported in the 1970s, with studies identifying hyperoxaluria in over half of affected children [34]. More recent data confirm an elevated risk of recurrent kidney stones – particularly oxalate stones – in individuals with celiac disease. Stone formation requires urinary supersaturation with certain solutes, but in celiac disease, this may be exacerbated by intestinal malabsorption or altered renal handling of compounds like oxalate, calcium, and citrate. These imbalances promote crystallization and stone development [35]. Additionally, gut microbiota dysbiosis plays a role; reduced levels of butyrate-producing bacteria like *Roseburia* lead to increased intestinal oxalate absorption and inflammation, further promoting lithogenesis [36]. This complex interplay between gut permeability, immune activity, and microbial metabolism may explain the higher prevalence of kidney stones in celiac disease.

Individuals with celiac disease have a higher frequency of urinary tract infections (UTIs). This is due to a variety of factors, including impaired urinary tract motility, dysfunction of the bladder, changes in gut microbiota that can promote urinary contamination, reduced immune defense mechanisms, and dysregulated immune responses. In a study evaluating the association between celiac disease and UTIs in the absence of anatomical abnormalities, 22.7% of 97 patients with celiac disease reported at least one episode of UTI, with a female predominance. In the majority of cases, the UTI occurred before the diagnosis of celiac disease. Notably, the cumulative probability of being UTI-free by the age of 18 years was significantly lower in women with celiac disease compared to the general population [37]. These findings point to a possible increased risk of UTIs in female celiac disease patients and potentially warrant closer clinical attention.

Liver Diseases

Primary Hyperoxaluria

Primary hyperoxaluria (PH) is a group of rare, autosomal recessive metabolic disorders characterized by hepatic enzyme deficiencies involved in glyoxylate metabolism. These defects lead to the overproduction of oxalate in the liver, which subsequently binds with calcium to form calcium

oxalate crystals. While oxalate is normally a minor end-product excreted by the kidneys, in PH, its excessive hepatic production surpasses kidney excretion capacity, resulting in crystal deposition in any organ. PH is classified into three types based on the specific hepatic enzyme affected. PH type 1 (PH1), the most severe and common form, results from mutations in the *AGXT* gene encoding the liver-specific enzyme alanine: glyoxylate aminotransferase. PH type 2 (PH2) is due to defects in *GRHPR*, and PH type 3 (PH3) involves mutations in *HOGA1*; both are also expressed in the liver but tend to present with milder clinical manifestations [38].

In PH, calcium oxalate crystals deposit primarily in the kidney tubules and interstitium, resulting in nephrocalcinosis and nephrolithiasis. The mechanical damage caused by the crystals, combined with inflammation and fibrosis, contributes to the development of tubulointerstitial nephritis. Progressive accumulation and stone formation ultimately lead to a decline in glomerular filtration rate and CKD. In many patients with PH1, this progression leads to kidney failure at an early age [38]. To date, distinct clinical forms of PH1 have been identified. Infantile oxalosis typically manifests within the first six months of life, presenting with nephrocalcinosis and early-onset kidney failure. In contrast, childhood-onset cases more commonly begin with symptoms related to kidney stone formation, such as renal colic, hematuria, or urinary tract infections. Additional presentations include disease recurrence following kidney transplantation and, in rare instances, recurrent kidney stones appearing later in adulthood [39]. A nationwide study evaluating the overall clinical characteristics of patients with PH1 found that 92.4% of patients had nephrolithiasis/nephrocalcinosis even at the time of diagnosis. Although individuals with infantile oxalosis were diagnosed at a younger age compared to individuals with childhood-onset PH1, they exhibited more advanced CKD or kidney failure requiring dialysis at the time of diagnosis [40]. Therefore, given the risk of early and progressive kidney involvement in PH, even in asymptomatic stages, timely evaluation of kidney function is essential; close collaboration between nephrology and gastroenterology is crucial to ensure comprehensive and coordinated patient care.

Wilson's Disease

Wilson's disease is a rare autosomal recessive disorder caused by mutations in the *ATP7B* gene, which encodes a copper-transporting ATPase responsible for incorporating copper into ceruloplasmin and excreting excess copper into the bile. Defective *ATP7B* leads to the accumulation of free copper in various tissues, most notably the liver, central nervous system, and cornea. Clinical manifestations are highly variable and age-dependent, ranging from hepatic dysfunction in children and adolescents to neurological and psychiatric symptoms in older individuals [41].

Although kidney involvement is less commonly recognized, it is a relevant extrahepatic manifestation of Wilson's disease, particularly in untreated or advanced cases. Copper deposition in the kidneys may lead to tubular dysfunction, which can be present as aminoaciduria, low-molecular-weight proteinuria, hypercalciuria, or renal tubular acidosis, particularly the distal type. In some patients, nephrolithiasis and hypophosphatemia have also been reported [42]. Moreover, glomerular involvement, although rare, may manifest as proteinuria or even nephrotic syndrome, and IgAN potentially due to immune complex-mediated mechanisms [43]. Chelation therapy with agents such as D-penicillamine may also influence kidney function, either by improving copper overload or, conversely, causing drug-induced nephrotoxicity in some cases [44]. Thus, regular monitoring of kidney parameters should be performed in the management of Wilson's disease, especially in patients receiving long-term chelation therapy.

Chronic Liver Diseases

Chronic liver disease encompasses a wide range of progressive liver disorders that lead to sustained liver inflammation, fibrosis, and ultimately cirrhosis. It can result from various etiologies including

viral hepatitis (especially hepatitis B and C), autoimmune hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), metabolic and genetic disorders (such as Wilson's disease or alpha-1 antitrypsin deficiency), and biliary tract diseases like primary sclerosing cholangitis. Over time, continuous liver damage impairs hepatic synthetic, metabolic, and detoxifying functions, potentially leading to complications such as portal hypertension, hepatic encephalopathy, ascites, coagulopathy, and increased susceptibility to infections [7].

Chronic liver disease and kidney involvement are closely interconnected through complex systemic and local mechanisms. As chronic liver disease progresses, portal hypertension develops, leading to splanchnic vasodilation. This vasodilation reduces the effective circulating blood volume, resulting in decreased kidney perfusion. In response, the body activates compensatory systems such as the renin-angiotensin-aldosterone system, the sympathetic nervous system, and antidiuretic hormone, which together cause renal vasoconstriction and subsequently a significant drop in glomerular filtration rate [5]. Furthermore, impaired hepatic detoxification allows bacterial endotoxins and inflammatory cytokines to enter the circulation, enhancing systemic inflammation and exacerbating kidney dysfunction. Additional contributing factors include acidosis, hyponatremia, hypoalbuminemia, and sepsis, all of which can further impair kidney function [45].

Hepatorenal syndrome (HRS) is a form of functional kidney failure that occurs in individuals with advanced liver disease, most commonly cirrhosis, in the absence of other identifiable structural kidney abnormalities. Based on the duration and progression of kidney dysfunction, HRS is currently classified into two main types: HRS-AKI and HRS-CKD [46].

HRS-AKI is characterized by:

- A rapid decline in kidney function, typically identified by an acute rise in serum creatinine (≥0.3 mg/dL within 48 hours or ≥50% from baseline within seven days) in patients with cirrhosis and ascites.
- It usually occurs following precipitating events such as infections, GI bleeding, or excessive diuretic use.

HRS-CKD refers to:

- A gradual and sustained impairment in kidney function lasting three months or longer,
- Long-standing portal hypertension and diuretic-resistant ascites.

Management of HRS includes prompt identification and treatment of precipitating factors such as infections, GI bleeding, or excessive diuretic use, administration of albumin together with vasoconstrictors such as terlipressin, and early evaluation for liver transplantation when indicated [46]. Given the intricate interplay between the liver and kidneys, early recognition and collaborative management of renal dysfunction in patients with chronic liver disease is essential to improve outcomes and guide appropriate therapeutic strategies.

Enteric Infections

Shiga toxin-producing *Escherichia coli*

Shiga toxin-producing *Escherichia coli* (STEC) infection is primarily a GI illness characterized by abdominal cramping, watery diarrhea that often progresses to bloody diarrhea (hemorrhagic colitis), and, in some cases, fever and vomiting. The GI manifestations are largely attributed to the direct mucosal damage caused by Shiga toxins, which are released by the bacteria in the colon. These toxins disrupt the intestinal epithelial barrier, leading to inflammation, epithelial cell apoptosis, and capillary hemorrhage. Colonoscopy or histological examination in severe cases may reveal mucosal

edema, ulcerations, and hemorrhagic lesions predominantly in the distal colon. Importantly, while the GI symptoms are self-limiting in most patients, a subset – particularly young children and the elderly – are at risk for extraintestinal complications such as STEC-hemolytic uremic syndrome (HUS) (STEC-HUS) [47].

The pathogenic mechanism of kidney involvement in STEC-HUS is primarily driven by the systemic dissemination of Shiga toxins, particularly Stx2, following disruption of the intestinal epithelial barrier. Once in circulation, Shiga toxins exhibit high affinity for globotriaosylceramide (Gb3) receptors, which are abundantly expressed on endothelial cells within the kidney glomeruli. Upon binding to Gb3, the toxins are internalized and inhibit protein synthesis by inactivating the 60S ribosomal subunit, leading to endothelial cell apoptosis and dysfunction. This endothelial injury initiates a prothrombotic state characterized by platelet activation, increased release of von Willebrand factor, and reduced production of antithrombotic mediators such as prostacyclin and nitric oxide. The result is widespread microvascular thrombosis, particularly in glomerular capillaries, which manifests clinically as thrombotic microangiopathy. The ensuing microthrombi cause mechanical damage to erythrocytes, leading to microangiopathic hemolytic anemia, while the consumption of platelets contributes to thrombocytopenia. Concurrently, the glomerular filtration barrier becomes compromised, resulting in AKI, typically presenting with oliguria or anuria, elevated serum creatinine, and signs of fluid and electrolyte imbalance. Proteinuria and hematuria are frequently observed in urinalysis [47]. There is no specific therapy for STEC-HUS, and treatment is primarily supportive, focusing on fluid and electrolyte management, blood pressure control, and, in severe cases, renal replacement therapy. While most pediatric patients recover fully with appropriate supportive care, a subset may develop long-term complications such as CKD, hypertension, or proteinuria [48].

As can be seen, the kidney pathology in STEC-HUS illustrates the critical role of the gut-kidney axis, wherein enteric infections can precipitate severe extraintestinal consequences. STEC-HUS remains one of the leading causes of AKI in children and poses significant clinical challenges due to its rapid onset and potential for long-term renal sequelae.

Gastrointestinal System Involvement in Kidney Diseases

Idiopathic Nephrotic Syndrome

Idiopathic nephrotic syndrome (INS) is the most common glomerular disease in children and also affects adults, though with differing histopathological profiles. It is defined by the classic triad of massive proteinuria (>3.5 g/day), hypoalbuminemia, and generalized edema. In pediatric populations, minimal change disease is the most frequent histological subtype, while in adults, focal segmental glomerulosclerosis and membranous nephropathy are more common. Although the precise pathogenesis of INS remains incompletely understood, immune dysregulation – particularly involving T and B-cell dysfunction and circulating permeability factors – has been implicated in podocyte injury and proteinuria [49]. While the kidney manifestations are central to the diagnosis, INS is increasingly recognized as a multisystem disorder, including those affecting the GI system. GI involvement is often secondary to the systemic consequences of hypoalbuminemia, edema, thrombotic tendency, and immunosuppressive therapy [50].

One of the most common GI manifestations in INS is edema of the bowel wall, which may lead to abdominal discomfort, nausea, vomiting, and even paralytic ileus. In severe cases, bowel wall thickening can mimic conditions such as IBD or ischemia on imaging studies [51]. Additionally, the hypercoagulable state associated with INS increases the risk of mesenteric arterial thrombosis, a rare but life-threatening complication that can present with acute abdominal pain [52]. Moreover,

patients with INS are at increased risk for infections, including spontaneous bacterial peritonitis, especially in those with ascites. The use of corticosteroids and other immunosuppressants further compromises GI immunity and mucosal defense, predisposing to opportunistic infections, peptic ulcer disease, and drug-related mucosal injury [53]. Malabsorption of fat-soluble vitamins (particularly vitamin D) may also occur due to protein loss and intestinal edema, contributing to metabolic bone disease in the long term [54]. Therefore, GI assessment and monitoring are essential components of comprehensive care in patients with INS, particularly in those with persistent hypoalbuminemia or GI symptoms.

Polycystic Kidney Diseases

Polycystic kidney disease (PKD) comprises a group of inherited disorders characterized by the progressive development of fluid-filled cysts in the kidneys, ultimately leading to kidney failure. The two main genetic forms are autosomal dominant PKD (ADPKD) and autosomal recessive PKD (ARPKD), each with distinct clinical and genetic profiles. ADPKD is the most common hereditary kidney disorder, typically caused by mutations in the *PKD1* or *PKD2* genes. It usually manifests in adulthood with bilateral kidney enlargement, hypertension, and gradual loss of kidney function. ARPKD, in contrast, is a rarer and more severe form, caused by mutations in the *PKHD1* gene and often present in infancy or early childhood with enlarged echogenic kidneys. While kidney manifestations are the hallmark of both forms, GI involvement is an important aspect of the disease, particularly in relation to hepatic and biliary complications [55].

In ADPKD, one of the most frequent extrarenal manifestations is polycystic liver disease (PLD), which occurs in up to 80% of patients over the age of 30 [56]. Although often asymptomatic, extensive liver cysts may cause abdominal distension, early satiety, gastroesophageal reflux, and even mechanical bowel compression. Cyst infection or hemorrhage can also cause acute abdominal pain and mimic intra-abdominal sepsis [57]. In ARPKD, the most prominent GI-related manifestation is due to congenital hepatic fibrosis, which can lead to portal hypertension. This may result in splenomegaly, esophageal varices, hematemesis, and ascites, posing serious risks, especially in pediatric patients. The combination of hepatobiliary and kidney dysfunction in ARPKD is sometimes referred to as a hepatorenal fibrocystic disease [58]. In both forms of PKD, GI symptoms may also arise from complications of CKD, such as uremic gastropathy, anorexia, and nausea, or from treatment-related factors, including immunosuppressive therapy following transplantation [57]. Thus, careful GI assessment is essential in the multidisciplinary management of PKD patients, particularly those with advanced disease or hepatic involvement.

Chronic Kidney Diseases

Chronic kidney disease is a progressive condition characterized by a sustained reduction in glomerular filtration rate and the accumulation of uremic toxins. While the kidney and cardiovascular consequences of CKD are well known, GI involvement is also frequent and significantly affects morbidity, nutritional status, and quality of life. Many of the GI manifestations in CKD stem from uremia-related metabolic disturbances, chronic inflammation, altered intestinal permeability, and the effects of therapeutic interventions [59].

Common uremic symptoms such as anorexia, nausea, vomiting, metallic taste, and weight loss are frequently reported and may reflect uremic gastropathy or delayed gastric emptying. In advanced stages, mucosal fragility and platelet dysfunction can predispose patients to GI bleeding, while bowel wall edema may cause abdominal discomfort or paralytic ileus [2]. Uremia also contributes to impaired gut barrier function, leading to increased intestinal permeability – often referred to as "leaky gut" – which facilitates the translocation of endotoxins and contributes to systemic inflammation through the gut-kidney axis [7].

Oral and esophageal manifestations, including dry mouth, oral ulcers, gingivitis, and uremic fetor, are commonly observed [60]. In parallel, CKD is associated with significant alterations in the gut microbiome (dysbiosis), including the proliferation of urease-producing and proteolytic bacteria. This dysbiosis increases the generation of gut-derived uremic toxins such as indoxyl sulfate and p-cresyl sulfate, which have been implicated in endothelial dysfunction, cardiovascular disease, and further progression of kidney injury [61].

Gastrointestinal motility disturbances are also common; constipation often results from fluid restriction, a low-fiber diet, oral iron supplementation, or use of phosphate binders. Conversely, diarrhea may occur due to certain medications such as magnesium-based antacids, antibiotics or infectious etiologies, especially in immunosuppressed patients [62]. Nutritional impairment is another major consequence of GI involvement in CKD. Reduced oral intake due to GI symptoms, combined with malabsorption and inflammation, can lead to protein-energy wasting and deficiencies in essential nutrients, including fat-soluble vitamins, vitamin B12, and folate. This contributes to muscle wasting, frailty, and increased vulnerability in elderly CKD patients [63].

In summary, the GI system plays a central and multifaceted role in the clinical course of CKD. A comprehensive understanding and management of GI involvement is essential to improve outcomes, reduce complications, and enhance the overall well-being of CKD patients.

Kidney Replacement Therapies

Kidney replacement therapies (KRT), including hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation, are life-sustaining treatments for patients with kidney failure. Each modality has distinct physiological impacts and potential GI complications, which should be considered in patient management and nutritional planning. GI symptoms may arise due to the dialysis process itself, associated fluid shifts, metabolic changes, or immunosuppressive therapy [8].

Hemodialysis is the most commonly used modality for KRT. GI complications during or after dialysis sessions are frequent and may include nausea, vomiting, abdominal cramps, and hypotension-related gut hypoperfusion. HD is also associated with increased gut permeability, which can facilitate endotoxemia and systemic inflammation [64]. Constipation is common due to restricted fluid intake, dietary limitations, and phosphate binders [65]. Rare but serious GI complications include mesenteric ischemia and colonic angiodysplasia-related bleeding, particularly in long-term HD patients [66].

Peritoneal dialysis involves the instillation of dialysate into the peritoneal cavity, and its GI manifestations are often related to increased intra-abdominal pressure, leading to early satiety, gastroesophageal reflux, abdominal fullness, or hernias [67]. Peritonitis is a significant complication and may present with abdominal pain, fever, and diarrhea or paralytic ileus [68]. Chronic exposure of the peritoneum to dialysate can lead to sclerosing encapsulating peritonitis, a rare but severe condition causing intestinal obstruction [69]. Additionally, glucose absorption from dialysate may exacerbate dyslipidemia, insulin resistance, and obesity, contributing indirectly to metabolic complications that affect gut function [70].

While kidney transplantation restores kidney function and offers superior quality of life, it introduces unique GI risks, primarily due to immunosuppressive therapy. Common GI side effects of calcineurin inhibitors and mTOR inhibitors include nausea, diarrhea, oral ulcers, and anorexia [71]. Mycophenolate mofetil is particularly associated with diarrhea, colitis, and GI bleeding, sometimes mimicking IBD [72]. Strategies to mitigate drug-related GI adverse effects include dose splitting, using enteric-coated formulations, or switching to an alternative immunosuppressive class when feasible [72–74]. Opportunistic infections, such as cytomegalovirus colitis or *Clostridioides difficile* infections, are more frequent in the post-transplant setting. They should be considered in

patients with new or worsening GI symptoms; cytomegalovirus infection can be initially screened with polymerase chain reaction (PCR) or antigen testing, while *Clostridioides difficile* should be evaluated with stool toxin assays or PCR [75, 76]. Moreover, long-term immunosuppression also increases the risk of GI malignancies, including colorectal and gastric cancers [77].

Conclusion

The complex and dynamic interplay between the GI system and the kidneys reflects a bidirectional relationship in which dysfunction in one organ system can significantly impact the other. GI symptoms are common across all stages of kidney disease and may arise from uremia, dialysis modalities, immunosuppressive therapies, or alterations in gut microbiota. Conversely, GI disorders such as infections, inflammatory conditions, and medication-induced mucosal injury can contribute to kidney injury through immune activation, systemic inflammation, or volume and electrolyte disturbances. Recognizing these interactions is crucial for early diagnosis, targeted management, and prevention of complications. A multidisciplinary approach that incorporates nephrologic and gastroenterologic expertise will be essential to optimize outcomes in patients affected by these intertwined organ systems.

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Membranous Nephropathy Preceding Systemic Sclerosis: An Unusual Presentation of Systemic Sclerosis sine Scleroderma

Case Reports

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ABSTRACT

Background. Membranous nephropathy (MN) is generally primary, but it can also occur as a secondary form in association with infections, neoplasms or autoimmune diseases. Systemic Sclerosis (SSc), especially in its sine scleroderma forms or in its early stages, rarely manifests itself as MN.

Case report. A 60-year-old woman with onset of nephrotic syndrome and histological picture of MN, in the absence of systemic manifestations. The patient subsequently developed episodes of acute renal failure, recurrent proteinuria and clinical-serological signs suggestive of autoimmune connective tissue disease, including increasing ANA titre with anticentromere pattern and onset of Raynaud's phenomenon. The second renal biopsy showed an evolving picture with extensive interstitial fibrosis and severe arteriosclerosis, consistent with a secondary form of MN. The patient was treated with the Ponticelli regimen and subsequently with rituximab, achieving significant clinical remission. In light of the capillaroscopy and autoantibody profile, a diagnosis of very early systemic SSc (sine scleroderma) was made.

Discussion. This case highlights how MN can represent an early and atypical manifestation of SSc sine scleroderma, preceding systemic manifestations by years. The negative anti-PLA2R test, the presence of antinuclear autoantibodies and rapid histological progression pointed towards a secondary autoimmune aetiology. Repeated renal biopsy and immunological monitoring proved to be key tools for diagnosis and therapeutic management.

Conclusion. MN secondary to SSc sine scleroderma is a rare but important condition that requires attention and a multidisciplinary approach. Early classification as a secondary form allows for targeted therapy and potentially prevents progression to end-stage renal failure.

KEYWORDS: membranous nephropathy, systemic sclerosis, scleroderma

Introduction

Membranous nephropathy (MN) is considered an autoimmune glomerulonephritis. It is classified as idiopathic or primary in most cases, but it can also occur as a secondary form associated with infections, neoplasms, drugs or autoimmune diseases [1]. Systemic Sclerosis (SSc), particularly in its sine scleroderma variant or in its very early stages, is rarely associated with MN. Typical renal manifestations of scleroderma include scleroderma renal crisis (SRC), characterised by malignant hypertension, rapid reduction in glomerular filtration rate and typical vasculitic lesions such as fibrinoid necrosis of interlobular arterioles and arcuate arteries. Proliferative glomerulonephritis can occur in patients with SSc, especially in overlap forms with systemic lupus erythematosus (SLE), with histological features ranging from mesangial glomerulonephritis to diffuse proliferative forms, sometimes with immune complex deposition. In such contexts, renal biopsy plays a central role in distinguishing atypical CRS from immune-mediated glomerulonephritis potentially susceptible to immunosuppressive therapy [2]. More rarely, cases of rapidly progressive glomerulonephritis (RPGN) with crescents have been reported, in some cases associated with autoantibodies (ANCA), and forms of focal segmental glomerulosclerosis (FSGS) that may present with nephrotic syndrome [3]. An exceptional but documented entity is MN secondary to scleroderma, which typically manifests with nephrotic syndrome and an atypical course compared to primary MN. Several reviews have highlighted that, beyond scleroderma renal crisis, a spectrum of glomerular diseases may occur in systemic sclerosis, including proliferative glomerulonephritis and, rarely, membranous nephropathy [2]. In some cases described, MN was the first renal manifestation of SSc sine scleroderma or very early scleroderma, preceding the appearance of the cutaneous and systemic features of the rheumatic disease by years. The negativity of anti-PLA2R antibodies, the presence of anti-nuclear autoantibodies (ANA, in particular anti-centromere) and signs of chronic vasculopathy support a secondary aetiology in these patients [4]. Only sporadic clinical cases have been reported in the literature in which MN represents the first or only renal manifestation in patients with scleroderma or overlap connective tissue syndromes. In some cases, the diagnosis of MN preceded that of the rheumatic disease, similar to what was observed in our patient. This atypical presentation can delay clinical classification and the correct therapeutic approach [5]. The presence of antinuclear antibody tests with anti-centromere antibodies (ANA) with extractable nuclear antigen tests (ENA) and Raynaud's phenomenon may be early signs of an underlying autoimmune disease. The negativity of anti-PLA2R antibodies in these patients supports the secondary origin of nephropathy, as does the association with signs of chronic vasculopathy and severe proteinuria [6]. Systemic scleroderma (SSc) is characterised by a wide spectrum of renal complications, including scleroderma renal crisis (SRC), proliferative glomerulonephritis, overlap nephropathy with systemic lupus erythematosus (SLE) and, more rarely, nephrotic syndromes. In a Thai cohort of 26 patients with SSc who underwent renal biopsy, 19% had nephrotic syndrome, with a histological diagnosis of class V lupus nephritis. In contrast, isolated membranous nephropathy was not formally reported, while the most common presentation was rapidly progressive glomerulonephritis (RPGN) (53.9%) [7]. Proteinuria in the nephrotic range is a rare indication in SSc not associated with SLE and often requires biopsy to rule out secondary glomerular forms. The definitive diagnosis is based on the correlation between clinical, serological and histopathological data, given that the clinical presentation may not be typical: in some patients with SRC, for example, nephrotic range proteinuria and normal blood pressure have been found, which are atypical manifestations compared to the classic picture [8]. Renal biopsy is essential in cases of SSc with significant proteinuria or active urinary sediment, even in the absence of obvious signs of CRS, to identify treatable forms of glomerulonephritis, such as MN or lupus nephritis [9]. Secondary membranous nephropathy can, albeit rarely, be a renal manifestation of SSc. This association seems to emerge mainly in very early forms or in sine scleroderma variants, in which renal disease precedes the onset of the systemic and

cutaneous manifestations typical of the rheumatic disease [10]. This case adds to the scarce reports of membranous nephropathy as an early manifestation of systemic sclerosis, providing long-term follow-up with sequential biopsies and evolving serological and capillaroscopic evidence.

Case report

A 60-year-old woman with proteinuria (4 g/day) at baseline, normal renal function and arterial hypertension. The immunological profile showed positive ANA with a titre of 1:320 and an anticentromere pattern. The first renal biopsy was performed (Figure 1), showing a histological picture compatible with membranous nephropathy (stage I-II), with no glomeruli evaluable by immunofluorescence. Screening for a neoplastic aetiology was performed, with negative results. Given the low risk of progression, ACE inhibitor therapy (enalapril 20 mg every 12 hours) was initiated.

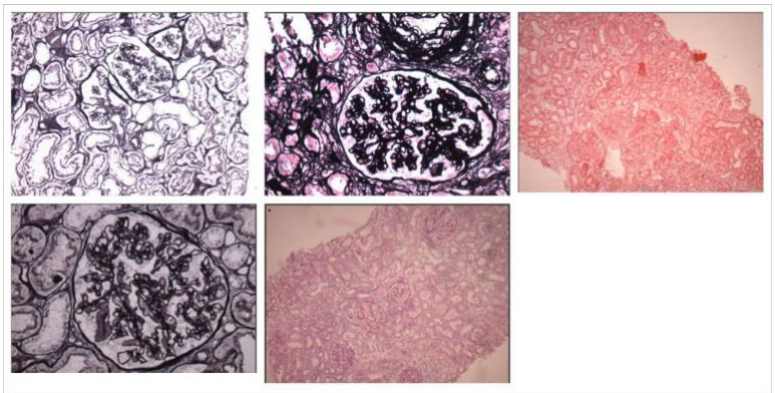

Figure 1. Diffuse thickening of the glomerular basement membrane is observed in the absence of mesangial proliferation. Overall renal architecture is preserved, with no evidence of interstitial fibrosis or tubular atrophy.

Twenty-four months later, episode of hypertensive crisis with PRES (Posterior Reversible Encephalopathy Syndrome), in particular bilateral visual acuity reduction, improved after intravenous nitroglycerin infusion. Kidney injury was found with creatinine rising to 2.3 mg/dl, proteinuria of 6 g/day, ANA positive with a titre of 1:640 with anticentromere pattern. A second renal biopsy was performed (Figure 2 and 3), confirming the picture of MN, with associated interstitial fibrosis in approximately 65% of the parenchyma, tubular atrophy (IFTA) and severe hyaline arteriosclerosis; immunofluorescence showed capillary deposits of IgG (+++), C3 (++) and IgM (+).

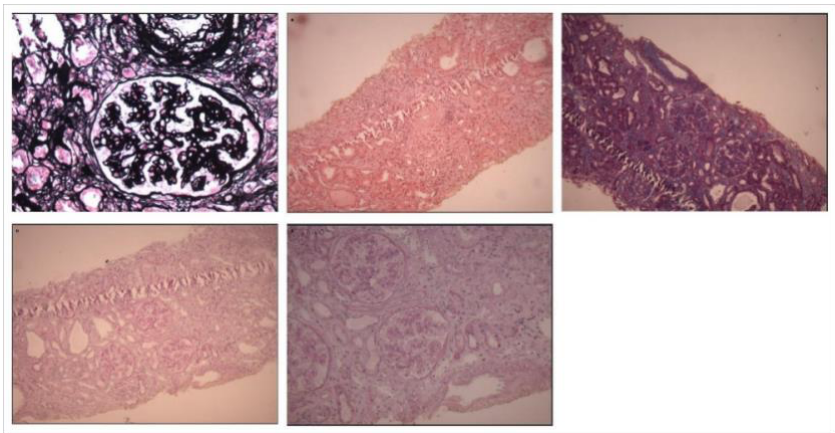

Figure 2. MN with marked progression of chronic damage, characterized by extensive interstitial fibrosis and tubular atrophy, associated with severe arteriolosclerosis.

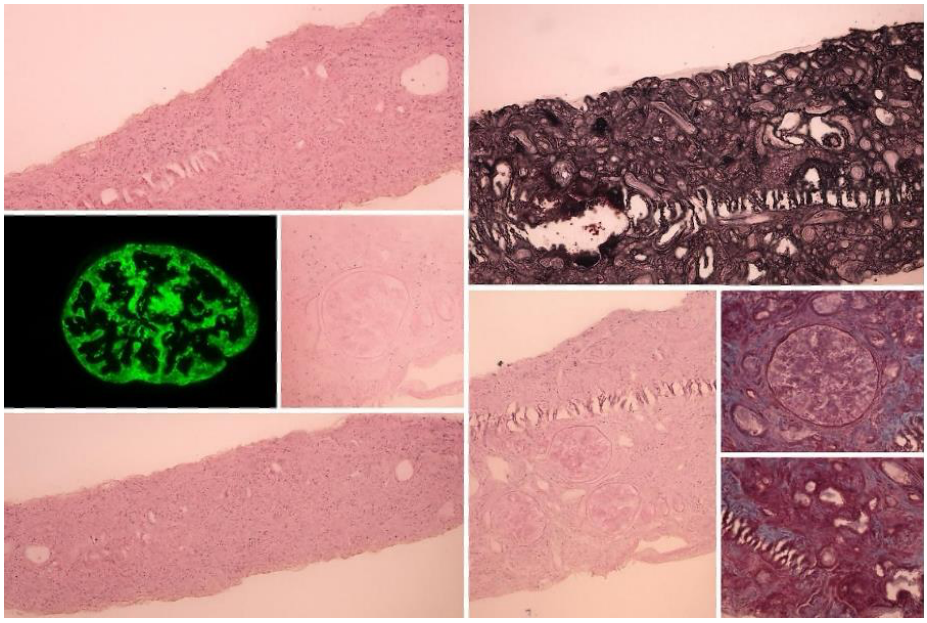

Figure 3. Evidence of advanced chronic damage with extensive interstitial fibrosis, tubular atrophy, and severe arteriolosclerosis. Immunofluorescence shows granular deposits along the glomerular capillary walls

The anti-PLA2R antibody test is negative. Immunosuppressive treatment is started for six months according to the Ponticelli regimen (cyclophosphamide and corticosteroids), achieving complete remission and improvement in renal function with creatinine 1.4 mg/dl, negativisation of proteinuria (0.5 g/day) and good control of blood pressure with enalapril 20 mg every 12 hours. After 48 months, Raynaud's phenomenon appeared in the hands with associated recurrence characterised by proteinuria 5 g/day, creatinine 1.78 mg/dL, albumin 3.7 g/dL. ANA positive with titre 1:5180 with anticentromere pattern and ENA positive with evidence of Scl-70. Rituximab 1 g was started and repeated after 14 days, with complete remission until month 72. At 80 months, the condition was in remission (proteinuria <0.1 g/day, creatinine 1.5 mg/dL). At 96 months, further relapse with the appearance of peripheral oedema, proteinuria 3 g/day, creatinine 1.9 mg/dL and albumin 2.6 g/dL. A rheumatological evaluation is performed, including periungual capillaroscopy, which reveals a typical picture compatible with early-stage scleroderma: presence of megacapillaries and vascular arborisation, without areas of avascularisation, indicative of early microvascular damage. Instrumental screening tests for organ involvement (high-resolution chest CT, spirometry, echocardiogram) are within normal limits. In light of the capillaroscopy findings and the clinical-serological profile, a diagnosis of very early SSc (sine scleroderma) is made. For insurance reasons, the use of rituximab is not authorised, and therapy with cyclophosphamide at a dosage of 2 mg/kg/day for six months is reintroduced. At 108 months of follow-up, the patient presented reduced edema and normotension, stable creatinine (1.9 mg/dl), proteinuria 7 g/day and normal albumin 3.4 g/dl. On the way to achieve partial remission (Table 1, Figure 4).

Time	Creatinine (mg/dL)	eGFR (ml/min)	Proteinuria (g/die)	Albumin (g/dL)	Therapy
zero	0.77	92	4.0	2.7	None
Month 24	2.15	26	6.0	3.8	Treatment plan Ponticelli
Month 48	1.5	40	5.0	3.6	None
Month 72	1.8	32	3.4	4.5	Rituximab
Month 80	1.5	40	0.3	4.6	Remission
Month 96	1.9	28	3.0	2.6	Cyclophosphamide
Month 108	1.95	27	7.0	3.4	Follow-up

Table 1. Clinical and biochemical follow-up over time and corresponding therapies

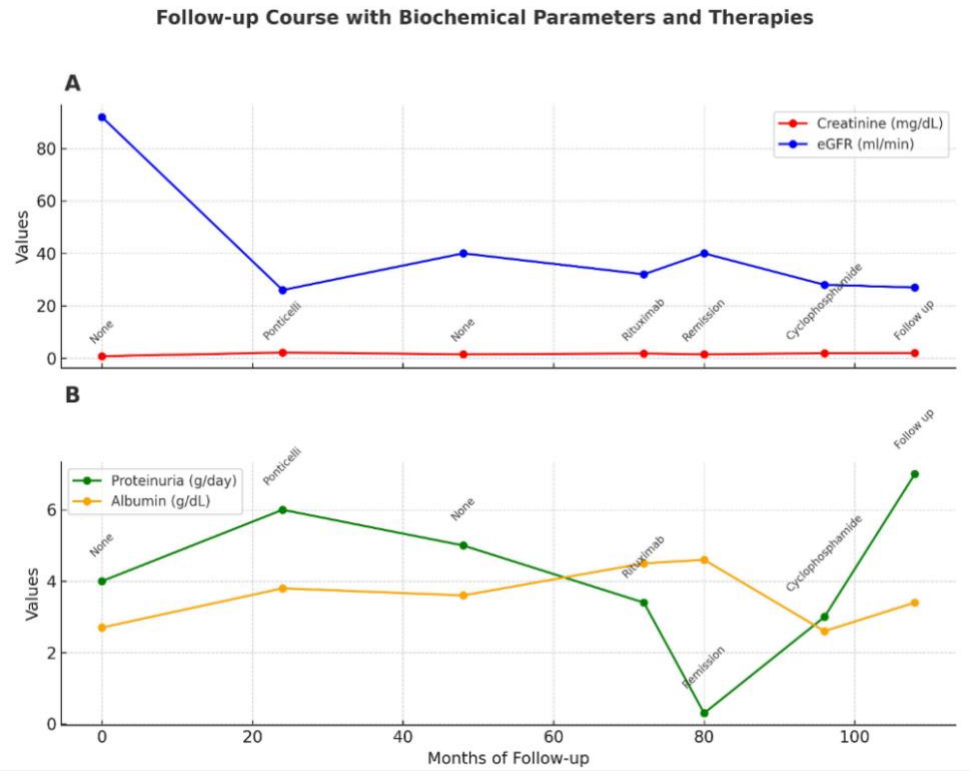

Figure 4. Follow-up course over 108 months. (A) Trends of serum creatinine and estimated glomerular filtration rate (eGFR). (B) Trends of proteinuria and serum albumin. Major therapeutic interventions (Ponticelli regimen, rituximab, cyclophosphamide) and clinical outcomes (remission, relapse, partial remission) are indicated along the curves.

Discussion

Anti-phospholipase A2 receptor antibodies of type M (anti-PLA2R) are the most specific serological biomarker for MN and, in typical clinical contexts, allow diagnosis without the need for renal biopsy. Their presence correlates strongly with disease activity and can be used to monitor therapeutic response [11]. In patients with MN, repeat renal biopsy may be crucial in cases of atypical clinical presentations, lack of response to treatment, or recurrence of nephrotic syndrome. The primary MN tends to follow a relatively indolent course, with progressive proteinuria but stable renal function; conversely, rapid deterioration of renal function, the onset of severe hypertension, or the presence of marked vascular and interstitial damage suggest a possible secondary form or overlapping glomerular disease [11].

Repeating the biopsy can provide information for reformulating the diagnosis, stratifying risk and adapting the therapeutic strategy, as illustrated in the case presented, in which the repeat examination revealed fibrotic progression with severe arteriosclerosis and immune deposits compatible with secondary MN and suspected overlapping disease. A limitation of this case is that the first renal biopsy lacked immunofluorescence analysis, which prevented the demonstration of immune complex deposition at disease onset. Nevertheless, this shortcoming was compensated by the subsequent biopsy, which provided immunopathological confirmation and, together with serological evolution, supported the diagnosis of secondary membranous nephropathy. This type of reassessment is particularly indicated when serology (e.g., anti-PLA2R negative) or the clinical picture does not align with a primary form [12].

Several studies support the importance of repeated biopsy even in cases of clinical recurrence after a phase of remission, especially when the response to immunosuppressive treatments is no longer

predictable or there is suspicion of transition to a new nosological entity (e.g., in patients with evolving systemic autoimmune diseases). Sequential histopathological monitoring therefore allows for personalised, evidence-based management of kidney disease [13]. For MN, progression to interstitial fibrosis and IFTA is generally slow and gradual, correlating proportionally with the duration and severity of proteinuria and the presence of episodes of acute renal failure. Marked interstitial and vascular involvement at onset, or accelerated progression of IFTA within a few years, are atypical features of primary MN and should raise suspicion of a secondary form or associated glomerular disease. In the case described, the second biopsy documented 65% interstitial fibrosis with severe arteriolosclerosis in a patient who had an almost normal biopsy two years earlier. This histological picture suggests an underlying chronic autoimmune vasculopathy, consistent with a subsequent diagnosis of SSc sine scleroderma. However, the interpretation of rapid histological progression as definitive evidence of secondary MN should be made with caution. Similar changes may also represent the natural course of MN under conditions of persistent nephrotic-range proteinuria and rising serum creatinine, irrespective of whether the disease is ultimately classified as primary or secondary. The negativity for anti-PLA2R and the presence of severe early hypertension reinforce the suspicion of a secondary mechanism, not immunologically mediated by classic anti-podocyte autoantibodies [14]. In primary MN, IFTA develops more slowly and generally in untreated patients or those with massive proteinuria persisting for more than 5 years. When a rapid course is observed, it is crucial to reassess the overall clinical picture and consider a re-biopsy to look for histological changes or secondary vascular complications [15]. The identification of new glomerular antigens has revolutionised the diagnostic approach to NM, especially in so-called “seronegative” cases, i.e. those with negative anti-PLA2R and anti-THSD7A antibodies. In the past, such cases were often classified as idiopathic or secondary MN based on clinical criteria, but today the existence of a variety of associated antigens is recognised, each potentially linked to a distinct clinical phenotype. Among the main antigens recently described are: NELL-1 (Neural epidermal growth factor-like 1) associated with elderly patients or those with occult solid neoplasms, but also found in non-paraneoplastic forms [16]; Exostosin 1/2 (EXT1/EXT2), detected mainly in young patients, often with systemic autoimmune diseases, particularly systemic lupus erythematosus [17]; Semaforin 3B (SEMA3B), observed in paediatric forms, but also described in adults with non-classical phenotypes [16]; Protocadherin 7 (PCDH7) and HTRA1: emerging antigens currently under study, associated with clinical-pathological patterns that are not yet well defined [18].

The discovery of new glomerular antigens has called into question the classic distinction between primary and secondary MN. In many cases, the identification of the target antigen allows for a more precise definition of the aetiology and correlates the histopathological picture with specific clinical phenotypes. This conceptual evolution suggests that the traditional classification may become obsolete and that, in the future, direct antigen typing on glomerular tissue using immunohistochemistry or mass spectrometry may guide diagnosis and therapeutic choices in a more targeted manner [19]. In the clinical case described, the double negativity for anti-PLA2R and the absence of obvious signs of secondary MN at onset initially pointed towards an idiopathic form. However, the clinical evolution and subsequent histological data (severe vasculopathy, recurrent proteinuria, onset of Raynaud’s phenomenon and ANA autoantibodies) raised the suspicion of a developing systemic autoimmune form. It is likely that, if a more advanced glomerular antigen analysis had been available, it could have identified an alternative antigen, suggesting a secondary origin from the outset.

Conclusion

The case presented is a particularly rare example of MN secondary to SSc sine scleroderma, characterised by an atypical clinical course, in which renal manifestations preceded the overt onset of systemic rheumatic disease by several years. This unusual time sequence highlights how important it is to adopt a multidisciplinary approach and maintain close follow-up in patients with apparently idiopathic MN but who have unconventional clinical or laboratory signs. Several factors pointed towards a diagnosis of secondary MN of a systemic autoimmune nature during follow-up: the persistent negativity of anti-PLA2R antibodies, a highly specific serological marker of primary MN; the early presence of severe arterial hypertension, unusual in the idiopathic form; the histological finding of marked arteriolosclerosis and extensive interstitial fibrosis in a short period of time; the progressive increase in ANA titre with anticentromere pattern, suggestive of systemic connective tissue disease; the appearance of Raynaud's phenomenon as an indicator of systemic microangiopathy; and finally, the favourable response to immunosuppressive therapy, both with the Ponticelli regimen and with rituximab, capable of inducing significant clinical remissions. This case highlights the importance of maintaining a high index of diagnostic suspicion in patients with seronegative MN, especially when atypical clinical or laboratory indicators coexist. Early classification as MN secondary to systemic autoimmune disease in its early stages or sine scleroderma allows for the timely initiation of targeted therapy and potentially prevents progression to chronic renal failure. Ultimately, repeat renal biopsy and dynamic immunological monitoring remain key tools for refining the differential diagnosis and optimising therapeutic management in complex clinical scenarios.

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Unexpected Reduction in Glucose Ultrafiltration Associated to a Continuously "Full Abdomen" Prescription After Introducing a Long Icodextrin Dwell: A Case Series

Case reports

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ABSTRACT
The decline in residual renal function (RRF) and the increasing peritoneal membrane permeability often require a progressive increase in glucose concentrations and the use of icodextrin (ICO) for the long dwell to maintain adequate ultrafiltration (UF). When these strategies are no longer effective and ultrafiltration failure (UFF) develops, patients typically need to be transferred to hemodialysis (HD).
We describe four cases in which the introduction of a daytime dwell with ICO was associated with an unexpected and rapid decline in glucose UF with a full abdomen (overnight in Automated Peritoneal Dialysis (APD) and daytime in Continuous Ambulatory Peritoneal Dialysis (CAPD)), which was "resolved" by reintroducing an empty abdomen for part of the day, even while maintaining ICO. The observed phenomenon seems to be less related to the specific solution used during the daytime dwell and more to the continuous 24-hour full abdomen prescription.

KEYWORDS: peritoneal dialysis, icodextrin, ultrafiltration, ultrafiltration failure

Introduction

The peritoneal dialysis (PD) prescription is influenced by residual renal function (RRF) and peritoneal membrane permeability. Over time, RRF tends to decline while peritoneal permeability generally increases. To maintain adequate solute clearance under these conditions, it becomes necessary to increase fill volumes and the number of exchanges. At the same time, to ensure sufficient ultrafiltration (UF), higher glucose concentrations and icodextrin (ICO) solutions for the long dwell are commonly used [1].

We report a case series in which the introduction of ICO for the long dwell was associated with a marked reduction in nocturnal UF, which was reversed by "reducing" the dialysis prescription through the reintroduction of an empty abdomen for part of the day. Although rare, the characteristics and magnitude of the observed phenomenon have relevant practical and theoretical implications, particularly considering that ultrafiltration failure (UFF) remains a leading cause of dropout from PD, accounting for 13.5% of transfers to hemodialysis (HD) in Italy in 2024 [2].

Materials and Methods

We report a series of four cases observed in the peritoneal dialysis units of two Italian centers between 2016 and 2024.

These cases, along with additional ones from two other centers, were discussed during conferences, scientific meetings, and through personal communications. Of the seven cases discussed, three were excluded because, at the time the phenomenon was observed, the dialysis prescription was significantly modified in terms of volumes, dwell times, and glucose concentrations. These changes made it impossible to accurately compare UF achieved with glucose before and after the introduction of ICO for the long dwell.

The UF values reported represent mean values calculated over variable time periods, as indicated in more detail in the text and figures.

All patients except one are on APD, likely due to the availability – starting in 2016 – of new Remote Patient Management (RPM) platforms.

All APD patients performed their final drainage manually in a seated position, while the patient on CAPD carried out all exchanges via Video-dialysis under the supervision of a center-based dialysis nurse [3].

The cases are presented in chronological order.
The clinical decisions taken were guided by individual patient-specific factors, detailed in each case report. As all interventions were part of routine clinical care, the relevant Ethics Committee deemed that no formal review was required beyond ensuring patient anonymity and obtaining informed consent for treatment and publication of anonymized data.

Since these observations derive from routine clinical practice, some otherwise relevant information – such as residual diuresis and its variations, peritoneal permeability assessment, and changes in diuretic therapy – was not recorded. This limitation does not affect the validity of the observations, as they were made prior to any therapeutic changes and under an unchanged dialysis prescription. This condition allowed for a reliable comparison of UF achieved with glucose before and after switching to daytime dwell with ICO. Statistical comparison was limited to Case 3, in which mean UF values recorded over eight consecutive weeks were compared across the five dialysis treatment days (Monday to Friday). Given the small number of data points, the nonparametric Kruskal-Wallis test

for paired data was applied.

Cases Description

Table 1 summarizes the clinical characteristics and dialysis prescriptions of the patients.

All patients started with PD as their first renal replacement therapy, although the observed phenomenon occurred at treatment initiation (incident patient) only in Case 2.

CLINICAL CASE	1	2	3	4
AGE (at start PD -yrs-)	53.9	47.1	72.3	60.5
GENDER	M	M	M	M
ESRD	DM	IgAN	NS	NS
BSA (m^2)	2.25	1.81	1.72	1.68
RESIDUAL GFR (ml/min)	0	6	<3	<3
INITIAL PD PRESCRIPTION WITH FULL ABDOMEN (24 hrs a day)				
PD modality	APD	APD	CAPD	APD **
NIGHT	15 L – 2.27% *	10 L – 1.36%	ICO (1.5 L)	10 L-1.36 / 5L-2.27%
DAY	ICO (1.5 L)	ICO (1.0 L)	(2 L- 2.27%) × 2	ICO (1.0 L)
SUBSEQUENT PD PRESCRIPTION				
TIME OF INTERVENTION (months) ***	53.7	0.72	8.2	11.2 **
NIGHT	15 L – 2.27%	10 L – 1.36%	**EMPTY**	10 L -1.36 / 5 L-2.27%
DAY	**EMPTY**	**EMPTY**	(2 L – 2.27%) × 3	**ICO – 6 hrs**
FOLLOW-UP				
STOP PD (months)	68.1	4.6	60.4	NO
REASON	HD (social)	Transplant	Death	IN PD

Table 1. Patient's characteristics, dialysis prescription with ICO and, after the occurrence of UFF, without ICO for the entire day (Cases 1–3) or for part of the day (Case 4). *Occasional use of 5 L of 3.86% glucose solution. **The PD prescription illustrated refers to the reintroduction of ICO with manual drainage at midday. DM: diabetes mellitus; IgAN: IgA Nephropathy, NS: Nephroangiosclerosis. * It is the time between the start of the PD and the observed phenomenon.**

Clinical Case 1 – Unexpected Increase in Nocturnal UF Following Discontinuation of Daytime Icodextrin Dwell in an APD Patient

The patient initially started peritoneal dialysis on CAPD in another country. After 33 months, he switched to APD (15 L of 2.27% glucose solution) with an ICO daytime dwell (Continuous Tidal Peritoneal Dialysis, CTPD), drained at the start of the evening cycler session. Despite initially satisfactory UF, both nocturnal and daytime UF progressively declined during APD. After an additional 5 months, due to poor adherence to fluid and salt intake restrictions (despite excellent compliance with dialysis therapy), an arteriovenous fistula (AVF) was created. However, due to severe peripheral vasculopathy, fistula maturation was difficult. In the following months, a combined treatment was initiated, consisting of daily APD and once-weekly HD. Because of persistent non-compliance with dietary restrictions, presence of anuria, reduced cardiovascular tolerance to HD, and poor AVF maturation, HD frequency had to be increased to twice weekly, and APD continued daily. Additionally, 5 liters of 3.86% glucose solution were intermittently used (at least once per week). Over time, AVF function improved, along with more effective HD clearance. Consequently, 54 months after starting PD, the dialysis prescription was modified by discontinuing the daytime ICO dwell (Nightly Tidal Peritoneal Dialysis, NTPD).
Within a few days, a significant increase in nocturnal UF was observed, rising from 642 ± 158 mL/session to 1.130 ± 222 mL/session (+76.4%), eliminating the need for the 3.86% glucose solution.

Moreover, the improved UF achieved with the NTPD regimen allowed for a reduction in UF during HD, improving HD tolerance, although body weight remained essentially unchanged due to

persistently high fluid intake. The data relating to haemodialysis parameters are shown in Figure 1. The UF increase was sustained until the patient was definitively transferred to HD, due to social reasons, 14 months after reintroducing a daytime empty abdomen. The average UF during the month preceding drop-out from PD was still 1.1342 ± 138 mL/die.

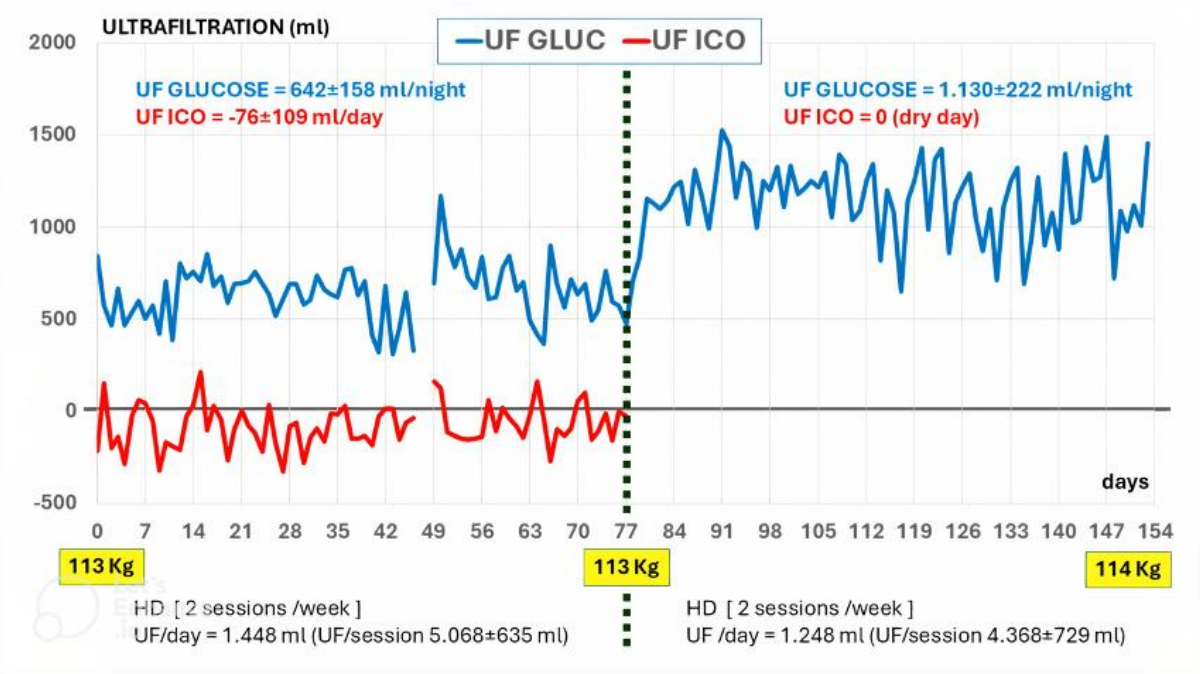

Figure 1. Clinical Case 1. Daily nocturnal (glucose) and daytime (ICO) UF derived from Sharesource data, comparing mean UF during the 10 weeks prior (nocturnal UF 642 ± 158 ml; daytime UF −76 ± 109 ml) and the 10 weeks following icodextrin discontinuation (nocturnal UF increased to 1.130 ± 222 ml). In both periods, two HD sessions per week (mainly UF) were performed. The greater glucose UF after switching to an empty abdomen translated into a reduced UF during HD sessions, but did not result in a reduction of body weight, which remained essentially unchanged.

Clinical Case 2 – Unexpected Reduction of Nocturnal UF at the Start of Dialysis Treatment (Training Phase) Associated with the Use of Icodextrin for Daytime Dwell and Resolved by Restoring an Empty Abdomen During the Day

The patient initiated renal replacement therapy with an incremental Continuous Cycling Peritoneal Dialysis (CCPD) prescription (5 L of 1.36% and 5 L of 2.27% glucose solution, and 2.5 L of ICO for the daytime dwell). In the days immediately following the start of PD, during home training, a gradual reduction of UF was observed not only during the icodextrin daytime dwell but also during the nocturnal glucose exchanges (Figure 2). UF became negative, requiring – without benefit – an increase in glucose concentrations. UF returned to baseline values after the usual 1-2 day interruptions of training (training was suspended during the weekend), but decreased again upon resumption in the following days. Definitive discontinuation of ICO daytime dwell, after 16 days, allowed restoration of adequate nocturnal UF with a reduced glucose concentration (10 L of 1.36%) until kidney transplantation, which was performed 5 months after initiation of dialysis (Figure 2).

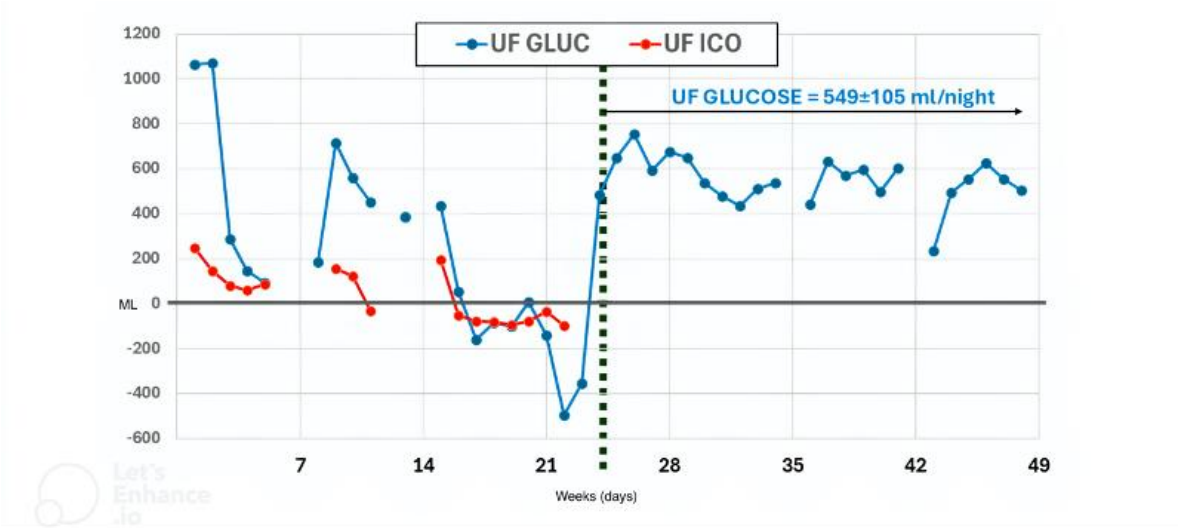

Figure 2. Clinical Case 2. Incident patient at the start of APD training. During the first two days, PD prescription was 5 L of 1.36% and 5 L of 2.27% of glucose, then reduced to 10 L of 1.36% from day 3 onwards, until transplantation. The interruptions shown in the graphic correspond to treatments skipped during training and subsequently due to the incremental PD prescription (6 days per week). A continuously full abdomen resulted in a progressive worsening of nocturnal UF (in this case also affecting icodextrin), which was resolved by switching to an empty abdomen. However, as shown, the first day after skipping a session was associated with lower UF, likely due to "reconstitution" of the residual volume.

Clinical Case 3 – Is the Issue the Icodextrin Solution or a Continuously Full Abdomen?

The patient, with severe ischemic dilated cardiomyopathy and limited autonomy, initiated renal replacement therapy with CAPD via telemedicine (two daytime 4-hour exchanges with 2 L of 2.27% glucose solution each, and 1.5 L of icodextrin for a 16-hour nocturnal dwell). Exchange duration was defined according to a pre-established telecare schedule. To preserve residual renal function and due to the unavailability of the telecare caregiver on weekend, the Saturday dialysis scheme was limited to two exchanges (2 L of 1.36% from 8:00 to 12:00 and 1.5 L of ICO from 12:00 to 20:00), while from Saturday evening to Monday morning the patient remained with an empty abdomen. After several weeks, a pattern of insufficient ultrafiltration (UF) emerged, showing a weekly trend. Specifically, UF gradually declined from Monday to Friday, particularly during daytime glucose dwells (Table 2, Figure 3A).

Based on previous experience, the icodextrin exchange was therefore discontinued, maintaining an empty abdomen overnight and increasing the number of daytime exchanges from two to three 4-hour exchanges using 2.27% glucose solution. Over the following two weeks, mean daily total UF improved significantly, increasing from −42 ± 299 ml/die to +425 ± 347 ml/die after 1 week and +567 ± 149 ml/die after 2 weeks following the restoration of an empty abdomen. Importantly, the progressive reduction of UF from Monday to Friday disappeared (Figure 3-B). To optimize depuration by minimizing telemedicine contacts, an attempt was made to reintroduce a nocturnal dwell with 2.27% glucose. Although reduced UF was expected during the nocturnal glucose dwell, the phenomenon observed with icodextrin – progressive reduction of daytime glucose UF from Monday to Friday – recurred (Figure 3-C). The patient therefore returned to the Daytime Ambulatory Peritoneal Dialysis (DAPD) scheme with three daytime exchanges of 1.36%, 2.27%, and 2.27%, maintaining an empty abdomen overnight. Mean UF values over the following 8 weeks are reported in Table 2 and Figure 3-D.

	PRE (NIGHT FULL) – 8 weeks			POST (NIGHT EMPTY) – 8 weeks		
SOLUTION (type)	**1,36%**	**2,27%**	**ICO**	**1,36%**	**2,27%**	**2,27%**
DWELL TIME (hrs)	**4**	**4**	**16**	**4**	**4**	**4**
Monday	-294 ±126	325 ±75	481 ±79	-121 ±59	269 ±134	381 ±66
Tuesday	38 ±127	150 ±168	356 ±138	-181 ±97	225 ±175	350 ±139
Wednesday	-156 ±95	-38 ±48	397 ±77	–	125 ±122	363 ±86
Thursday	-363 ±54	-356 ±77	275 ±158	-163 ±82	325 ±103	344 ±88
Friday	-425 ±130	-294 ±95	250 ±125	-144 ±95	356 ±126	344 ±81
	p<0,001	p<0,001	p<0,01	N.S.	p<0,05	N.S.
DWELL TIME (hrs)	**4**	**NO**	**6**	**NO**	**4**	**4**
Saturday	-263 ±162	–	406 ±88	–	181 ±75	319 ±86

Table 2. Mean of UF values over 8 consecutive weeks for each exchange, before and after icodextrin discontinuation. Differences between weekdays were all significant in the PRE period, whereas in the POST period, only the difference in UF recorded during the second exchange remained significant (Kruskal-Wallis test).

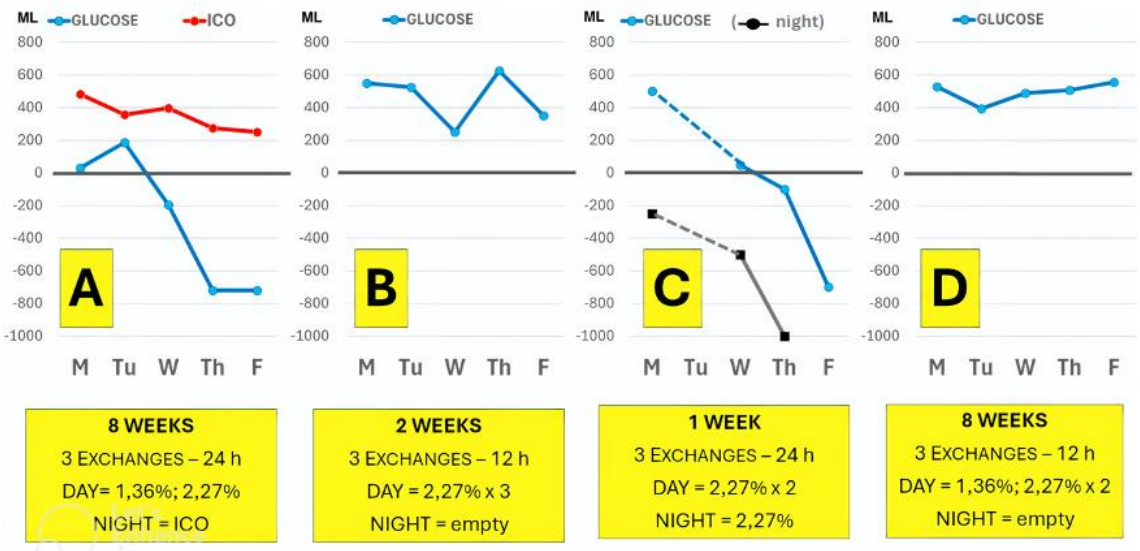

Figure 3. Clinical Case 3. Patient on CAPD. A) Initial PD scheme of 3 exchanges: two 4-hour glucose exchanges (2 L of 1.36%, 2 L of 2.27%) and 2 L of icodextrin for the night. From Monday to Friday the total UF from the two glucose exchanges (thick blue line with dot) progressively declined. It is likely that Monday values were affected by residual volume reconstitution. Values represent the means of the corresponding exchanges recorded over 8 consecutive weeks. B) The patient switched to a nighttime empty abdomen with an additional 4-hour daytime glucose exchange (2 L of 2.27% × 3). Total UF was higher and, importantly, remained stable from Monday to Friday. C) Return to scheme A but with nocturnal glucose (black dotted line with square) instead of icodextrin. As expected for a 16-hour nocturnal dwell, UF became negative; but unexpectedly, UF recorded during the short daytime dwells (each lasting 4 hours, thick dotted blue line with dot), progressively decreased from Monday to Friday, as in scheme A with icodextrin. This trial scheme was limited to 1 week. D) Final scheme of three daytime exchanges with an empty abdomen for 12 hours. UF remained stable from Monday to Friday (as in A, mean values recorded over 8 consecutive weeks).

Clinical Case 4 – Nocturnal UF With Glucose and Daytime UF With Icodextrin in APD Are Preserved by Restoring an Empty Abdomen for Part of the Day ("Midday Icodextrin Drainage")

The patient, on NTPD for 7 months, introduced a daytime icodextrin dwell for depurative needs (CCPD). Nocturnal UF decreased rapidly (from 682 ± 85 ml/night in the two preceding weeks to progressively −12 ml after 4 days of the daytime dwell), without compensation from daytime UF achieved with icodextrin (ranging from 146 to 361 ml), resulting in a reduction of total UF (Figure 4-A). After 4 days, the patient returned to the NTPD regimen, with restoration of previous UF values (667 ± 105 ml/night in the following two weeks). Three months later, icodextrin was reintroduced but drained manually after 5-6 hours of dwell time (duration determined by the patient's work

needs). Nocturnal UF decreased slightly, but total UF increased significantly due to the considerable UF obtained with ICO (from 146 to 361 ml/die with a full abdomen daily to 279 ± 103 ml/die with a midday icodextrin drainage) (Figure 4-B).

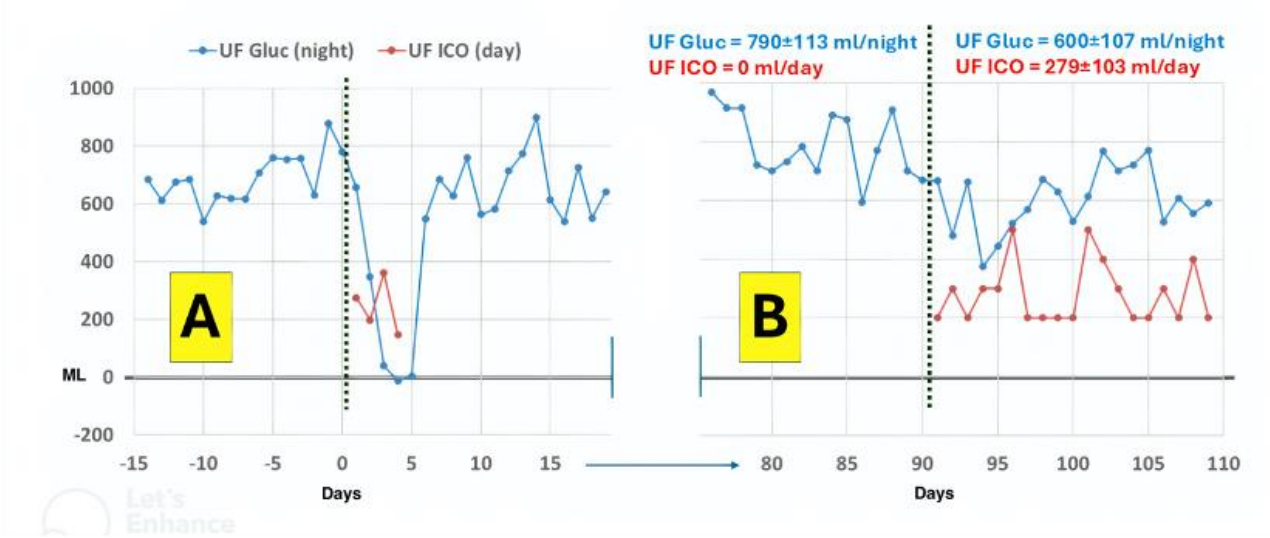

Figure 4. Clinical Case 4. Patient on APD. Box A: initial introduction of icodextrin, then discontinued after only 4 days due to marked reduction of nocturnal UF. The pattern is consistent with that described in the other cases. Box B: Ninety days after the first attempt, a final icodextrin fill was again prescribed which the patient manually drained at midday (according to professional activity), generally after a 5-6 hour of dwell. Manual drainage was recorded by the patient on a dedicated chart after collection in a graduated container. Values are therefore approximated to 100 ml, but there is no overestimation due to overfill as the filled volume is recorded by the Cycler.

Discussion

Ultrafiltration failure represents an important cause of dropout from peritoneal dialysis, with its incidence increasing over time due both to the progressive decline in RRF and to structural and functional alterations of the peritoneal membrane [4]. In general, UFF is managed by increasing glucose concentrations and fill volumes, as well as by using ICO for the long dwell [1, 5].

In all reported cases, a continuously full abdomen achieved through a daytime (in APD) or nighttime (in CAPD) icodextrin dwell was associated with a significant and unexpected reduction in UF obtained during the remaining part of the day with glucose (nocturnal cycles in APD and daytime dwells in CAPD). Another feature is the gradual yet rapid onset and disappearance (within 2-3 days) of this phenomenon (Figure 5). This finding is unexpected both because the condition of a constantly full abdomen should prevent the repeated formation of residual volume (RV) – which is inevitably reabsorbed during daytime hours with an empty abdomen – and because, in all these cases, a final manual drainage (performed in the sitting position) was prescribed to avoid icodextrin drainage occurring while the patient was still supine. In all cases, the glucose concentrations used after discontinuation of ICO dwell remained unchanged (in Case 1 and Case 2, they were even reduced).
At last, regarding the magnitude of the observed phenomenon: the variation in UF generated by glucose after introducing the continuously full abdomen with icodextrin ranged from −43% to over −100% (in three of the four cases, glucose UF became negative), corresponding to an absolute daily value reduction of 488 ml to 1200 ml.
The four cases reported here illustrate how adequate UF could be restored simply by maintaining an empty abdomen for part of the day, and how this effect occurred within a relatively short timeframe. The key question is why the introduction of a long dwell with icodextrin (and, in Case 3,

even with glucose) was occasionally associated with reduced glucose ultrafiltration during the remaining dwells/cycles. Although the underlying pathophysiology could not be thoroughly investigated in routine clinical practice, the available data suggest the following considerations.

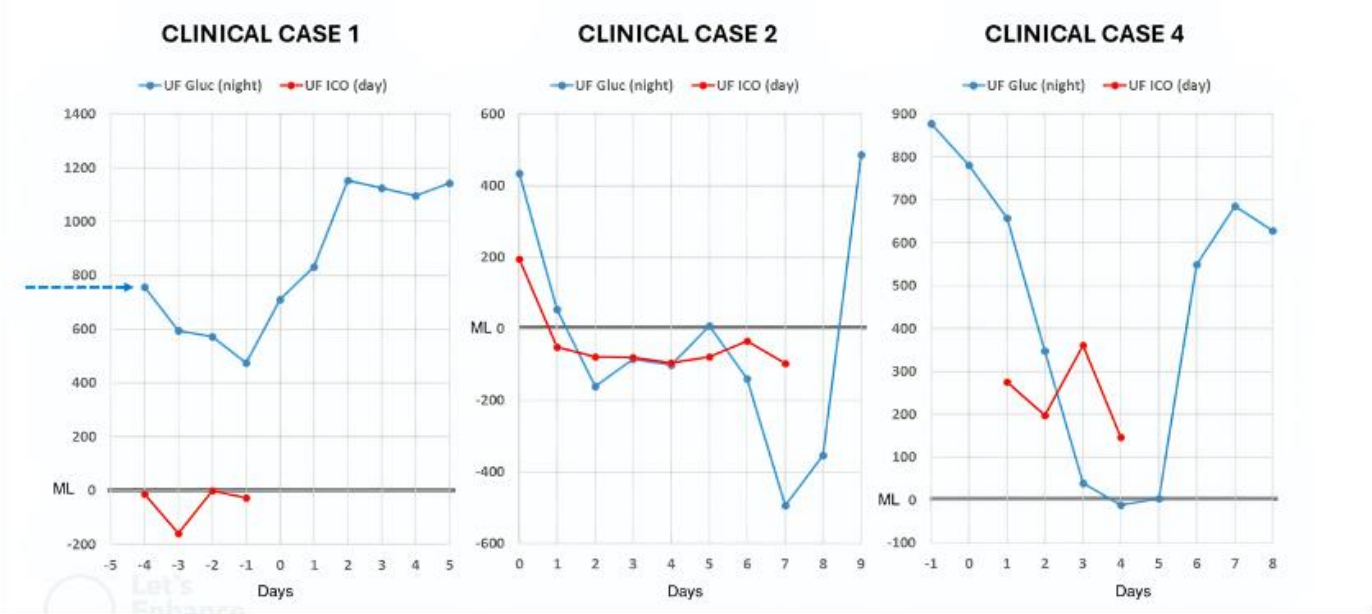

Figure 5. Daily UF generated by glucose and icodextrin at the times of their introduction and discontinuation. As shown, changes occur within 2-3 days and are considerable. For each day, UF values are derived from the initial drainage and the subsequent nocturnal session.

Type of solution and role of icodextrin

The use of icodextrin is recommended for long dwells, particularly in patients with high peritoneal transport status [6]. Several reports have demonstrated greater efficacy when icodextrin is employed in more than one exchange per day. The first two cases appear to suggest a causal role of icodextrin in triggering, through unknown mechanisms, the observed phenomenon. However, in the third case, the progressive reduction of glucose UF recurred even when glucose – not icodextrin – was used for the long nighttime dwell. Most notably, in clinical Case 4, the negative effect disappeared when icodextrin was manually drained after 5-6 hours of dwell, suggesting that the underlying determinant of the phenomenon was the continuously full abdomen, regardless of the type of solution employed. Finally, although it is well established that UF with icodextrin can vary considerably between individuals [7] and is influenced by peritoneal transport status [6], intraperitoneal pressure, dwell duration, and PD modality [8–10], effects such as those described here on glucose UF, have not previously been reported.

Residual Volume

Intermittent treatments entail the continuous reformation of RV, which may reduce UF, while an excessively elevated RV can impair UF during continuous treatments [11]. In the reported cases, the opposite was observed. After a short period with an empty abdomen – even if only occasional, such as during holidays (Clinical Case 3) or during training (Clinical Case 2) – nocturnal UF returned to "high" levels, only to decrease again in the following days. This does not imply that RV reformation did not occur, but rather that the increase in UF was sufficient to outweigh its effect.
Furthermore, catheter displacement, even if only temporary, has always been ruled out as the most frequent cause of increased VR. Finally, it should be emphasized that all APD patients described had been trained to perform both the initial drainage and, most importantly, the final drainage in the sitting position.

Alterations in peritoneal permeability

Peritoneal permeability alterations are generally considered an important cause of UFF, typically associated with “irreversible” structural changes of the membrane. In contrast, the rapid recovery of UF and the “normalization” of permeability indices in our cases would suggest the predominance of functional rather than structural mechanisms.

Peritoneal membrane rest

It has long been known that temporary discontinuation of PD (for 4 weeks or longer) with transfer to HD allows recovery of UF and improvement of peritoneal permeability [12]. In our cases, PD was never discontinued.

Increased lymphatic absorption or leakage

An important cause of UFF – although difficult to assess and usually diagnosed by exclusion – is increased lymphatic absorption, for which APD with a daytime empty abdomen is often recommended, a strategy that also proved effective in our experience. However, in the cases reported here, the main issue was not the UF of the daytime dwell, but rather that of nocturnal APD, or, in clinical Case 3 (CAPD), of the daytime glucose dwells. This observation suggests a “time-dependent” leakage or increased lymphatic absorption. In all patients, conventional leakages (pleuroperitoneal communication, subcutaneous leakage, hydrocele/hernia) were excluded, whereas lymphatic absorption was not evaluated. Only one outdated study [13] compared UF in seven unselected patients transferred from CAPD to DAPD (nighttime empty abdomen), hypothesizing lymphatic absorption as a possible cause of reduced UF. However, UF did not vary significantly (728 ± 377 ml with 4 exchanges vs 761 ± 288 ml with 3 exchanges and an empty nighttime abdomen), although there was a significant but modest reduction in daily glucose load (from 146 ± 37 to 131 ± 37 g, $p < 0.01$). By contrast, our cases were all selected based on the marked UF variation occurring when a continuously full abdomen with icodextrin was adopted.

Estimation of the phenomenon and open issues

Overall, considering the number of patients initiated on PD in the two Centers, the incidence of this phenomenon can be estimated at <5% of PD patients, although it is possible that the same mechanism may act, to a lesser degree, in a larger number of individuals. In the past, when icodextrin was not available, a common solution to UFF was the midday drainage of the last fill. At that time, it was, in a sense, natural to attribute reduced UF to glucose reabsorption. However, the observations made with icodextrin suggest that, in rare cases, other time-dependent factors may also play a role in influencing dialysate reabsorption.

Conclusions

In conclusion, in rare cases of UFF, restoring an empty abdomen for several hours may rapidly restore adequate UF. The aim of our work is not to propose a solution to the problem of UFF but, given its practical relevance, to suggest reconsidering – when UF represents the most critical issue – the use of an empty abdomen for part of the day, according to dialysis prescriptions used in the past. It is possible that different factors, with variable impact from patient to patient, may have contributed to the genesis of such cases. In our opinion, this phenomenon warrants further investigation through larger observational studies or, ideally, randomized controlled trials.

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Critical review of the manuscript for important intellectual content: Giulia Boni Brivio, Irene Santinello, Agnese Cappelletti, Marco Heidempergher, Althea Cossettini, Romina Graziani, Giusto Viglino, Loris Neri

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Applicazione sequenziale di tecniche di depurazione extracorporea in un paziente critico con trauma maggiore e insufficienza multiorgano

Nefrologo in corsia

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ABSTRACT
Il trauma maggiore rappresenta una delle principali sfide in terapia intensiva, spesso complicato da insufficienza multiorgano. Questo caso clinico descrive la gestione di un paziente di 47 anni con trauma pelvico da schiacciamento, complicato da rabdomiolisi, insufficienza renale acuta, shock settico e danno epatico. L'approccio terapeutico ha incluso l'uso sequenziale di tecniche di depurazione extracorporea – filtri ad alto cut-off (EMIC2®), emoadsorbimento (CytoSorb®), e membrane multifunzione (Oxiris®) – per il supporto renale, la rimozione di mioglobina, citochine, endotossine e bilirubina. L'integrazione tempestiva e personalizzata di queste tecnologie ha contribuito al recupero completo della funzione renale ed epatica, sottolineando l'importanza di un approccio intensivo, multidisciplinare e tecnologicamente avanzato nella gestione del paziente critico.

PAROLE CHIAVE: danno renale acuto, CVVHD, sindrome da schiacciamento, emoadsorbimento, sepsi

Introduzione

Il trauma maggiore rappresenta una delle principali cause di mortalità e morbilità nei pazienti giovani e adulti, configurandosi come una delle emergenze sanitarie più complesse e impegnative a livello globale. L'impatto sistemico di un evento traumatico può determinare un'alterazione profonda dell'equilibrio fisiologico, con conseguenze che vanno ben oltre il danno anatomico iniziale.

La gestione dei pazienti politraumatizzati richiede un approccio rapido, integrato e multidisciplinare, che non si limita alla stabilizzazione delle funzioni vitali e al controllo delle lesioni emorragiche, ma si estende al monitoraggio continuo e al supporto dinamico della funzione d'organo. Nei pazienti critici, infatti, il trauma può innescare una cascata di risposte infiammatorie e metaboliche che aumentano il rischio di complicanze gravi come lo shock settico, l'insufficienza multiorgano (MOF, multi organ failure), la coagulopatia e il danno d'organo acuto.

Tra le complicanze più frequenti, il danno renale acuto (AKI) assume un ruolo centrale, spesso correlata a fattori come l'ipoperfusione, la rabdomiolisi, l'uso di farmaci nefrotossici o la sepsi. In particolare, la rabdomiolisi – comune nei traumi da schiacciamento – rappresenta una condizione potenzialmente letale per il rilascio massivo di mioglobina e altri metaboliti tossici nel circolo sistemico, con conseguente rischio di danno tubulare acuto.

In questo contesto, le strategie di depurazione extracorporea stanno assumendo un ruolo sempre più rilevante, non solo per la sostituzione della funzione renale, ma anche come strumenti terapeutici avanzati per la modulazione della risposta infiammatoria, la rimozione di tossine specifiche e il supporto degli organi compromessi. L'evoluzione delle tecnologie dialitiche ha infatti reso disponibili dispositivi in grado di affrontare condizioni cliniche complesse in modo più mirato ed efficace [1].

Caso clinico

Nel dicembre 2023, un paziente di 47 anni è stato ricoverato in Terapia Intensiva a seguito di un grave trauma da schiacciamento nella regione pelvica. Il trauma ha provocato sublussazione e dislocazione delle articolazioni sacroiliache e pubiche, nonché fratture multiple a carico delle creste iliache e della sinfisi pubica. È stato quindi sottoposto a intervento chirurgico, comprensivo di fissazione esterna anteriore del bacino, cateterismo vescicale sovrapubico e colostomia.

Il paziente ha sviluppato un danno renale acuto (AKI), con creatinina sierica pari a 3,3 mg/dL e oligoanuria, secondaria a rabdomiolisi (CPK >14.000 UI/L e mioglobina 16,5 mcg/L). È stata quindi avviata una terapia sostitutiva renale continua (CKRT) con emodialisi veno-venosa continua (CVVHD), utilizzando il set Multifiltrate® con filtro ad alta cut-off EMIC2® (Fresenius Medical Care, Bad Homburg, Germania), per trattare l'insufficienza renale e favorire la rimozione della mioglobina. L'anticoagulazione regionale è stata gestita con citrato di calcio (CiCa).

I dettagli del trattamento sono riportati nella Tabella 1 e nella Figura 1.

Due giorni dopo, a causa della persistenza della rabdomiolisi, è stata aggiunta in serie con il filtro EMIC2® una cartuccia adsorbente (Cytosorb®, CytoSorbents Corporation, Monmouth Junction, NJ, USA). Sono stati effettuati due cicli di 24 ore di emoadsorbimento-emodialisi, con progressiva riduzione dei livelli di CPK (8.000 UI/L dopo il secondo ciclo).

Giorni	0	2	5	6	7	12	17	21	22	24	30	35	38	41	55
NO CKRT	x										x			x	x
Tipologia CKRT															
-CVVHD		x	x	x	x	x									
-CVVHDF							x	x	x	x		x	x		
Membrana CKRT															
-EMIC2®		x	x	x	x	x									
-CYTOSORB®			x 24 h	x 24 h				x 24 h	x 24 h						
-AN69-ST								x	x	x		x	x		
-OXIRIS®							x 72h								
Parametri CKRT															
Qb (ml/min)		100	100	100	100	100	160	100	120	100		100	100		
Qd (ml/h)		2000	2000	2000	2000	2000	1500	1000	1200	1000		1000	1000		
Qpre (ml/h)							1500	1000	1200	1000		1000	1000		
Qpost (ml/h)							300	300	300	300		300	300		
CiCa		x	x	x	x	x	x					x	x		
EPBM								x	x	x					
Esami di laboratorio															
PCR (mg/l)	<3	308	660	550	407	426	447	284	113	84	83	46	30	103	68
CPK (x10^3 U/L)	2	9	>14	>14	8	6	2	0.9	0.5	0.9	0.4	0.2	0.1	0.05	0.06
SCr (mg/dl)	1.4	3.3	3.1	4.1	3.8	3.6	4.0	2.6	2.6	2.6	2.4	2.7	2.5	1.8	1.1
Bilirubina totale (mg/dl)	0.4	1.1	1.1	1.3	14.3	19.2	22.6	45.2	14.2	6.7	3.2	2.7	2.0	1.4	1.1

Tabella 1. Parametri e metodi della terapia sostitutiva renale eseguita durante il ricovero. CKRT: Continuous Kidney Replacement Therapy; CVVHD: Continuous veno-venous hemodialysis; CVVHDF: Continuous veno-venous hemodiafiltration; Qb: flusso sangue; Qd: flusso dialisato; Qpre: reinfusione pre-filtro; Qpost: reinfusione post-filtro; CiCa: Anticoagulazione regionale calcio-citrato; EPBM: Eparina a basso peso molecolare; CRP: Proteina C reattiva; CPK: Creatinfosfochinasi; SCr: Creatinina sierica.

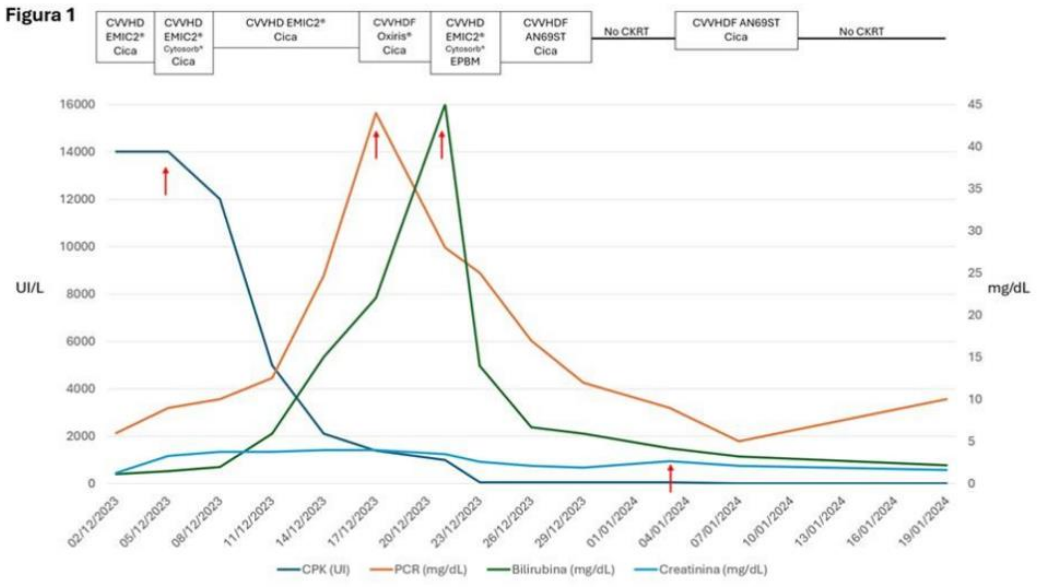

Figura 1. Andamento dei principali esami ematochimici in relazione alle differenti strategie di trattamento extracorporeo.

Pochi giorni dopo, le condizioni cliniche del paziente sono peggiorate con l'insorgenza di shock settico. Le emocolture hanno identificato la positività per Corynebacterium tuberculostearicum, un tampone del muscolo gluteo sinistro ha rivelato la presenza di Phocaeicola dorei e un tampone cutaneo ha isolato Candida auris. Oltre al trattamento medico, comprensivo di supporto vasopressorio (noradrenalina fino a 0,15 mcg/kg/min) e terapia antibiotica e antifungina (Ceftazidime-Avibactam, Linezolid, Fosfomicina, Metronidazolo e Anidulafungina), veniva avviato un ciclo di emodiafiltrazione veno-venosa continua (CVVHDF) con utilizzo del filtro AN69 modificato (Oxiris®, Baxter, IL, USA) con anticoagulazione CiCa. Il trattamento è stato proseguito per 72 ore fino alla stabilizzazione emodinamica, che ha consentito la sospensione del supporto vasopressorio.

Nel frattempo, il paziente ha sviluppato un danno epatico iatrogeno acuto con grave iperbilirubinemia (GOT 164 U/L, GPT 120 U/L, GGT 902 U/L, ALP 349 U/L, bilirubina fino a 45 mg/dL), con conseguente accumulo di citrato e aumento del rapporto calcio totale/calcio ionizzato fino a 2,6. Di conseguenza, l'anticoagulazione regionale con citrato è stata sostituita con eparina a basso peso molecolare a livello sistemico, e sono stati avviati due cicli aggiuntivi di emoadsorbimento-emodialisi per favorire la rimozione della bilirubina (peso molecolare 47 kDa), utilizzando il filtro AN69 standard in serie con Cytosorb®.

La funzionalità epatica è gradualmente migliorata e la diuresi è stata ristabilita grazie a stimolazione diuretica (output urinario di 80 mL/h). La CVVHDF con filtro AN69 standard è proseguita per altre due settimane fino al completo recupero della funzione renale (creatinina 1,1 mg/dL al 24 gennaio 2024).

Dopo tre mesi dal ricovero in Terapia Intensiva, il paziente è stato trasferito in Medicina Interna.

Discussione

Questo caso illustra l'importanza di una gestione intensiva, flessibile e tecnologicamente avanzata nei pazienti critici con trauma maggiore e complicanze multisistemiche. Le decisioni terapeutiche sono state guidate dalla patofisiologia del paziente, con un'attenta valutazione della tempistica e dell'intensità del supporto extracorporeo. Secondo le linee guida KDIGO (Kidney Disease Improving Global Outcomes), la terapia sostitutiva renale (RRT, renal replacement therapy) va avviata precocemente nei casi di oligoanuria, iperkaliemia refrattaria, sovraccarico idrico e acidosi severa [2]. Tuttavia, nel contesto della rabdomiolisi, la semplice dialisi convenzionale può non essere sufficiente a garantire una rimozione efficace delle molecole di medio peso molecolare, come la mioglobina (17 kDa) [3]. Da qui è nato l'interesse per l'utilizzo di membrane dialitiche ad alto o medio cut-off e dispositivi di emo-adsorbimento. Le membrane come EMIC2® (con cut-off di 40 kDa) consentono la rimozione di molecole tossiche senza eccessiva perdita di albumina [4]. Parallelamente, le cartucce adsorbenti come CytoSorb®, composte da microsfere polimeriche con vasta superficie, offrono un'ulteriore possibilità di riduzione delle citochine infiammatorie e tossine. Questi strumenti trovano indicazione non solo nelle rabdomiolisi gravi, ma anche nelle sepsi, nelle sindromi da iperinfiammazione e nei casi di insufficienza epatica, per la rimozione della bilirubina non coniugata [5, 6].

Un altro aspetto di rilievo nella gestione dei pazienti critici è rappresentato dalle infezioni nosocomiali e dallo sviluppo di sepsi o shock settico. Circa il 20% dei pazienti ricoverati in Terapia Intensiva sviluppa uno stato settico, che richiede un trattamento combinato tra antibiotici ad ampio spettro e terapie extracorporee per ridurre l'impatto delle risposte infiammatorie sistemiche. Dispositivi come Oxiris®, che combinano funzioni filtranti, convettive e adsorbenti, sono progettati per affrontare simultaneamente le esigenze di depurazione ematica e rimozione di endotossine e mediatori infiammatori [7].

Inoltre, anche il danno epatico acuto, iatrogeno o infettivo, rappresenta una complicanza frequente nei pazienti sottoposti a terapia intensiva prolungata. L'accumulo di bilirubina (peso molecolare ~47 kDa) in circolo, oltre a indicare un danno epatocellulare, può interferire con numerosi processi fisiologici e compromettere la funzione di altri organi. In questi casi, l'emoadsorbimento con Cytosorb® si è dimostrato efficace nella rimozione selettiva della bilirubina e di altre tossine lipofile [8].

Tutte queste tecnologie richiedono una gestione precisa, soprattutto per quanto riguarda l'anticoagulazione. Sebbene l'anticoagulazione regionale con citrato sia attualmente la più raccomandata nelle CKRT (Continuous Kidney Replacement Therapy), la sua applicazione può essere controindicata in caso di grave insufficienza epatica, poiché il metabolismo del citrato avviene principalmente a livello epatico. In questi casi, è necessario passare ad anticoagulazione sistemica con eparine a basso peso molecolare.

È evidente l'importanza delle diverse strategie di depurazione extracorporea (BP, blood purification) nella gestione di pazienti in Terapia Intensiva estremamente complessi, non solo come supporto renale, ma anche come ponte per preservare la funzione d'organo attraverso il ripristino dell'omeostasi idro-elettrolitica e l'ottimizzazione delle interazioni multi-organo.
Inoltre, è da notare come i ricoveri prolungati in Terapia Intensiva possano comportare numerose complicanze, richiedendo un approccio terapeutico sequenziale. L'efficacia di tale approccio è stata recentemente esemplificata anche nella gestione della pandemia da COVID-19 [9].

Conclusione

Questo caso clinico evidenzia come l'integrazione sequenziale di diverse tecniche di depurazione extracorporea possa essere determinante nella gestione di pazienti critici con complicanze multi-organo. Le tecniche di depurazione extracorporea sono risultate fondamentali non solo per il supporto renale, ma anche per:

- la rimozione della mioglobina nella rabdomiolisi,
- la riduzione di citochine ed endotossine nella sepsi,
- la depurazione della bilirubina nel danno epatico.

L'esperienza mostra inoltre che la scelta e la tempistica di applicazione di queste tecniche influenzano significativamente la prognosi del paziente. Tuttavia, persistono limiti importanti:

- Mancanza di linee guida specifiche per la scelta delle modalità di depurazione extracorporea,
- Accesso limitato a tecnologie avanzate in molti centri,
- Alto costo dei dispositivi,
- Necessità di formazione specifica del personale.

In conclusione, un approccio terapeutico basato su tecnologie extracorporee combinate e adattate al quadro clinico può migliorare significativamente gli esiti nei pazienti critici, a condizione che venga implementato precocemente e in ambienti dotati delle competenze e delle risorse necessarie.

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Sindrome nefrosica e insufficienza renale rapidamente progressiva in paziente con componente monoclonale: un caso clinico

Nefro-quiz: tu cosa faresti?

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ABSTRACT
Presentiamo il caso di una donna di 53 anni con sindrome nefrosica, progressivo peggioramento della funzione renale, anemia e riscontro di componente monoclonale IgG lambda. Il quadro clinico era caratterizzato da proteinuria in range nefrosico, sedimento urinario attivo, ipocomplementemia selettiva (C3 ridotto), splenomegalia e linfoadenopatie multiple. Gli esami immunologici e infettivologici risultavano negativi. L'elettroforesi sierica e urinaria documentava una componente monoclonale IgG λ con marcato incremento delle catene leggere libere λ. È stata eseguita biopsia renale per definire il quadro istopatologico e orientare la gestione terapeutica. Il caso evidenzia l'importanza di un tempestivo inquadramento multidisciplinare nelle nefropatie associate a gammopatia monoclonale di significato renale (MGRS).

PAROLE CHIAVE: Sindrome Nefrosica, Proteinuria, Complemento, Gammopatie Monoclonali, Biopsia Renale

Presentazione del caso

Una donna caucasica di 53 anni veniva inviata all'osservazione nefrologica presso il Policlinico di Bari per sindrome nefrosica in quadro di progressivo deterioramento della funzione renale e anemia.

Anamnesi

L'anamnesi familiare era negativa per nefropatie. In anamnesi patologica remota si segnalava un episodio di tubercolosi in età giovanile. La paziente riferiva buono stato di salute fino al novembre 2022, quando veniva ricoverata presso l'Unità Operativa di Cardiologia del P.O. "Di Venere" per miocardite. In tale occasione si documentava:

- Creatinina sierica (sCr): 1,41 mg/dL
- Proteinuria: 200 mg/mmol
- Leucocituria: 500 cellule/µL
- Elettroforesi proteica: "probabile componente monoclonale"

La TC del torace evidenziava linfoadenopatie multiple (diametro massimo 2,4 cm) in sede epi-aortica, finestra aorto-polmonare, subcarenale e ascellare bilateralmente.

A partire da giugno 2024 la paziente riferiva un calo ponderale di 12 kg, comparsa di edemi declivi ed episodi di macroematuria.
Nel novembre 2024 accedeva al Pronto Soccorso per anemia (Hb 8,3 g/dL) e peggioramento della funzione renale (sCr 3,39 mg/dL). Un mese dopo si ripresentava per ulteriore riduzione dell'emoglobina (7,8 g/dL) e incremento della sCr (3,6 mg/dL), venendo ricoverata in Nefrologia.

Esami strumentali e laboratoristici

L'ecografia renale mostrava reni in sede, di dimensioni ai limiti superiori della norma (rene destro 125 mm, sinistro 137 mm), con spessore cortico-midollare conservato; si evidenziava splenomegalia. All'ingresso presso la Nefrologia del Policlinico di Bari (dicembre 2024) si documentava:

- sCr 3,84 mg/dL (eGFR 13 ml/min/1,73 m^2)
- Proteinuria 8,3 g/24h (precedentemente 11 g/24h)
- Albuminuria 5 g/24h
- Albumina sierica 2,7 g/dL
- Hb 9,5 g/dL
- Piastrine 84×10^3/µL
- C3 ridotto (0,66 g/L), C4 nei limiti
- Quantiferon positivo

Esame urine: sedimento attivo con >40 emazie/HPF e 10–20 leucociti/HPF; urinocoltura negativa.

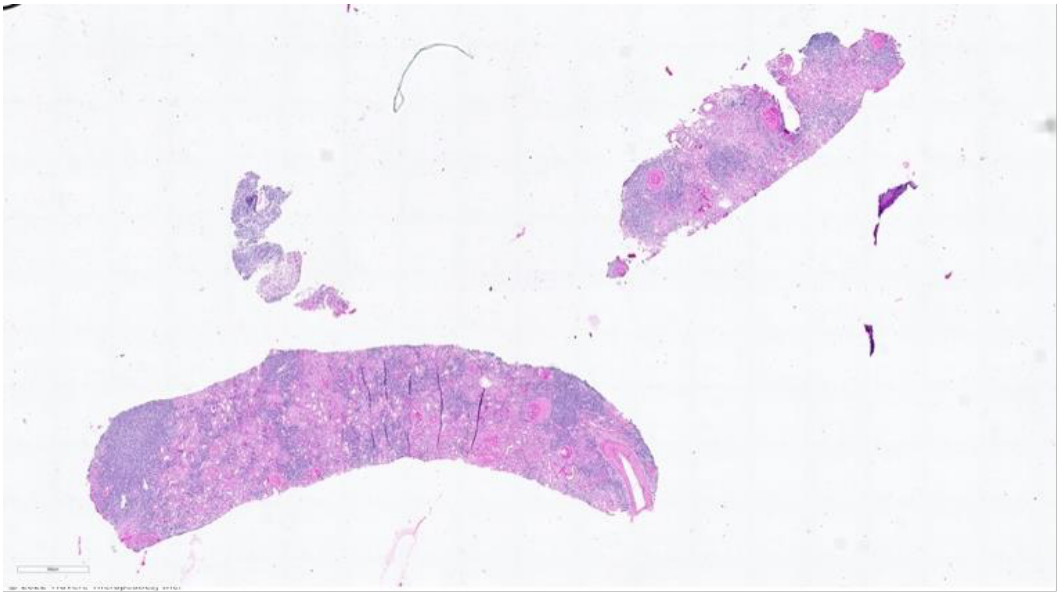
Le indagini autoimmuni (ANA, ANCA, anti-GBM, anti-PLA2R) risultavano negative. Sierologie per HIV, HBV e HCV negative. L'elettroforesi sierica evidenziava una componente monoclonale IgG λ (0,19 g/dL). Le catene leggere libere sieriche mostravano λ 589 mg/L, κ 17,42 mg/L con rapporto κ/λ alterato. Nelle urine si documentava proteinuria di Bence Jones λ (51,8 mg/24h) e IgG λ completa (50,54 mg/24h).

Iter diagnostico

In data 30 dicembre 2024 veniva eseguita biopsia renale percutanea eco-guidata al fine di definire il pattern istopatologico e orientare la gestione terapeutica, tenendo in considerazione alcuni aspetti principali tra cui:

- Sindrome nefrosica con sedimento attivo
- Progressivo declino della funzione renale
- Ipocomplementemia selettiva (C3 ridotto)
- Presenza di componente monoclonale IgG λ
- Evidenza di catene leggere monoclonali sieriche e urinarie
- Segni sistemici (calo ponderale, splenomegalia, linfoadenopatie, citopenie)

Veniva eseguita analisi del frustolo bioptico in microscopia ottica, microscopia elettronica e immunofluorescenza.



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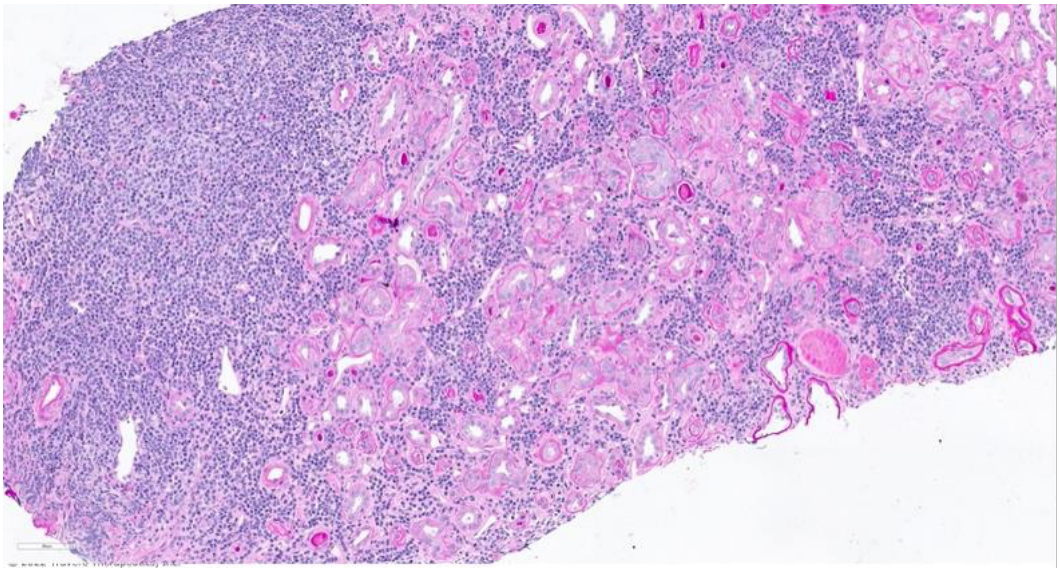

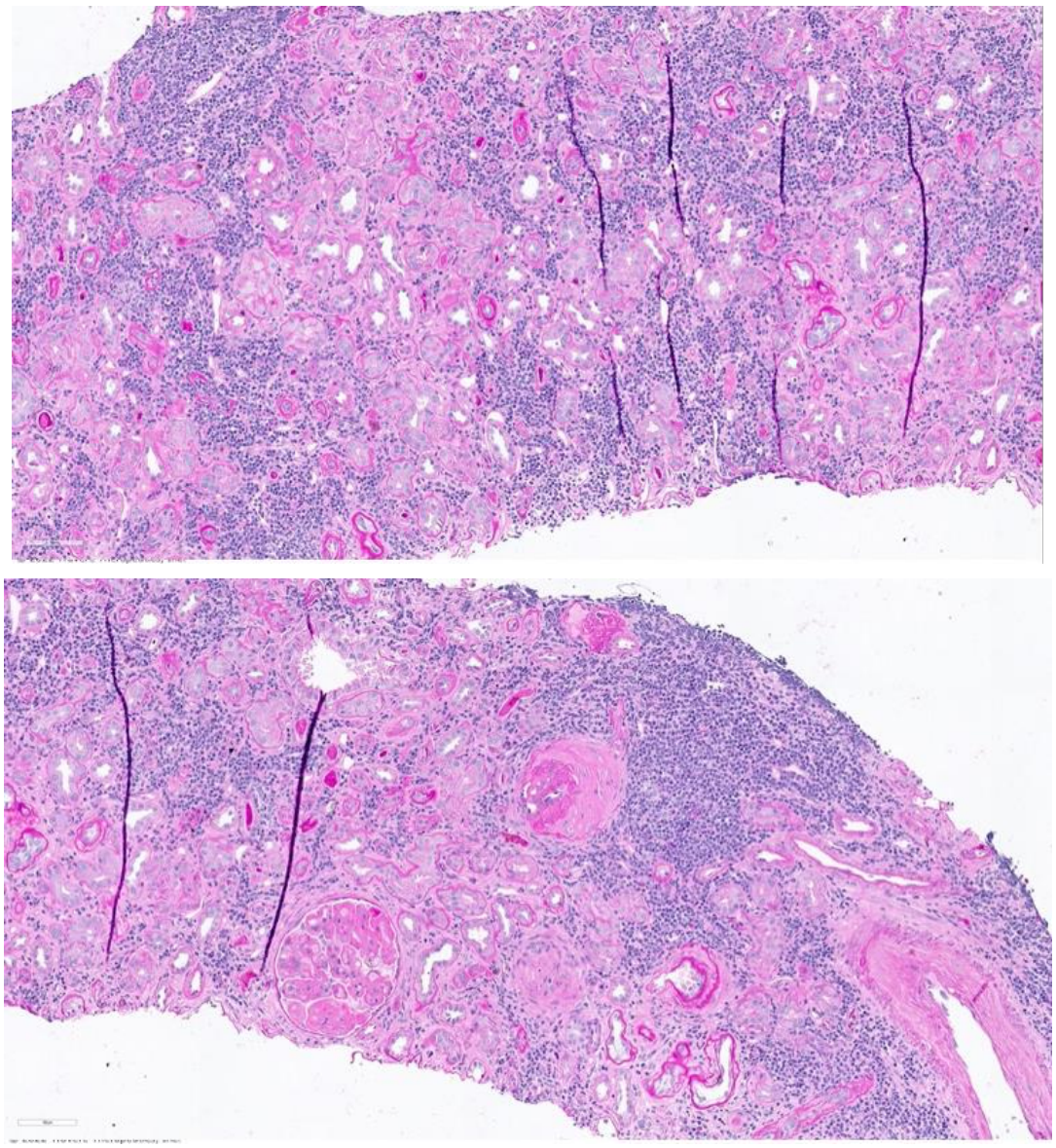

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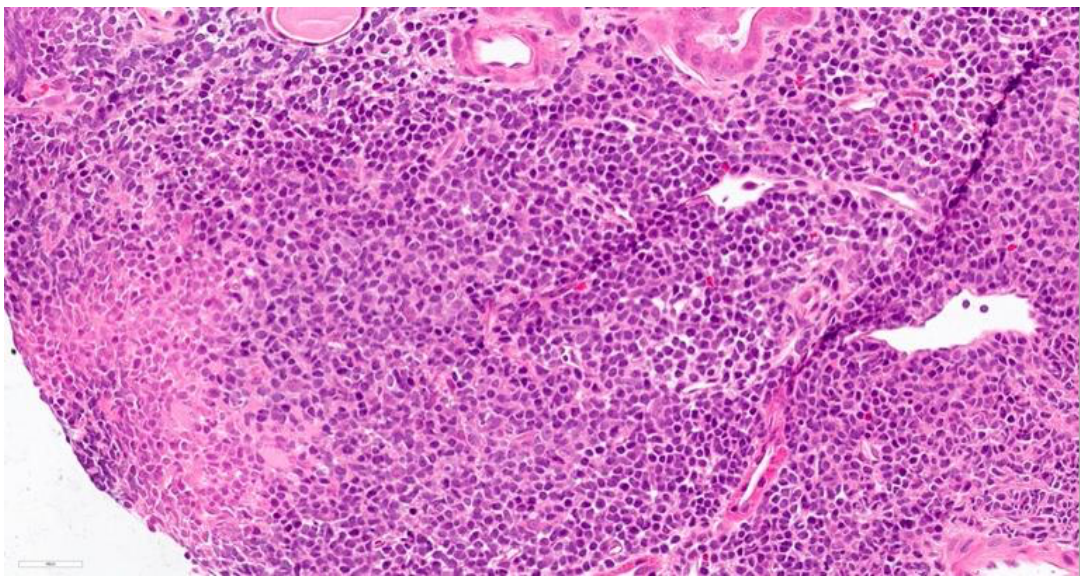

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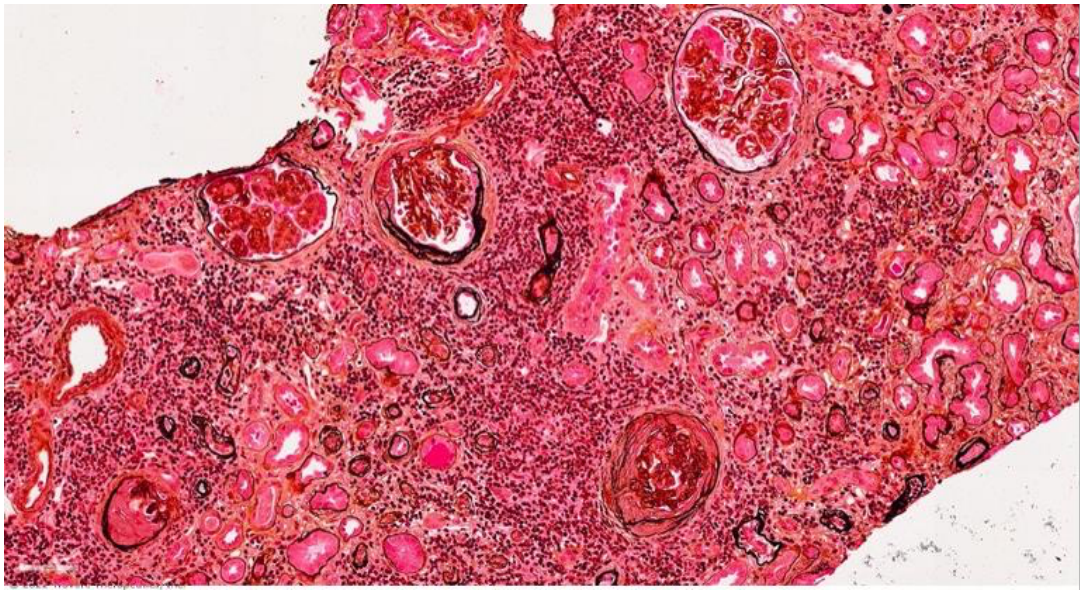

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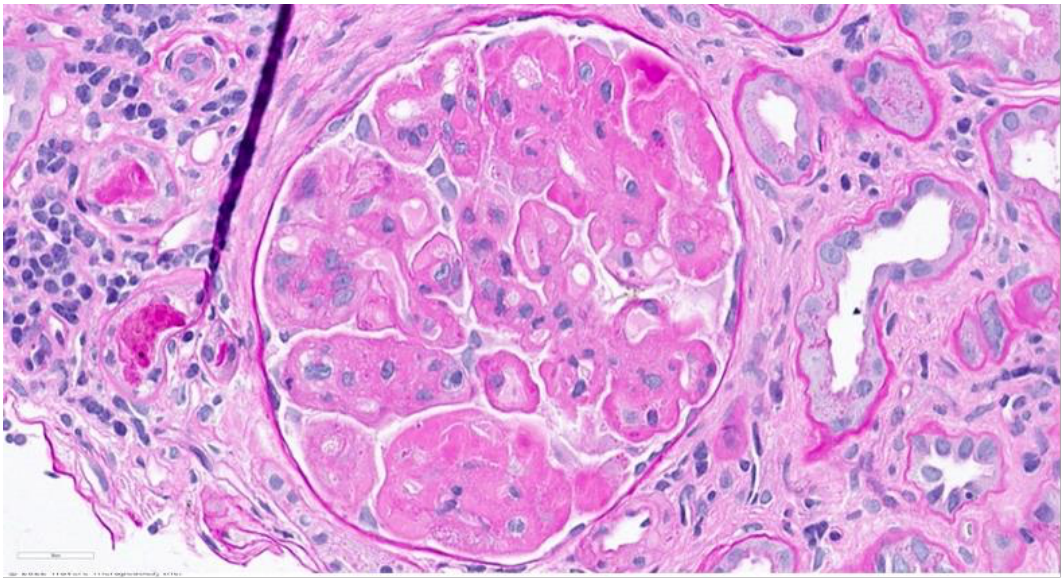

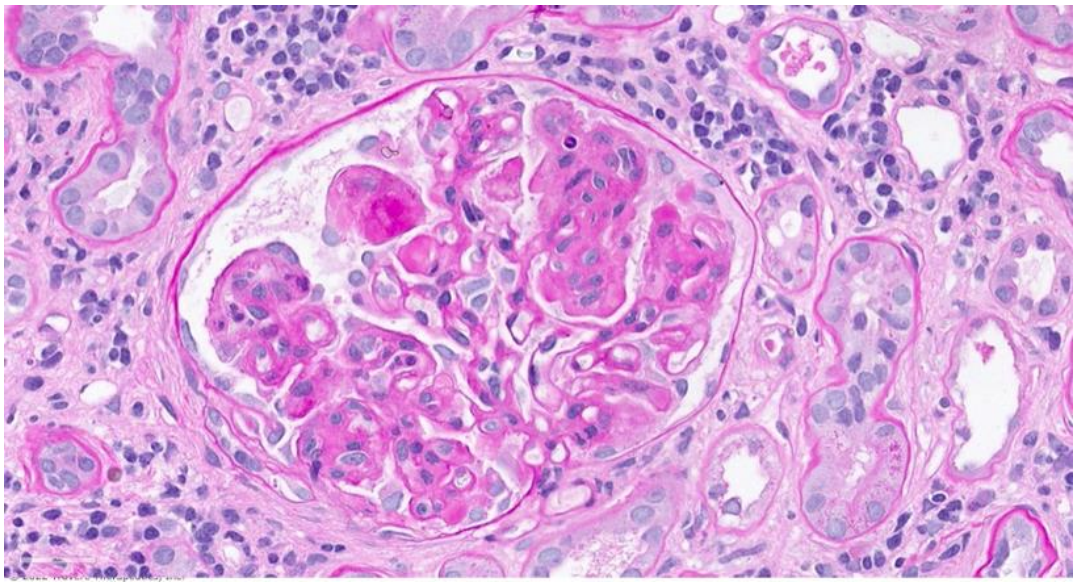

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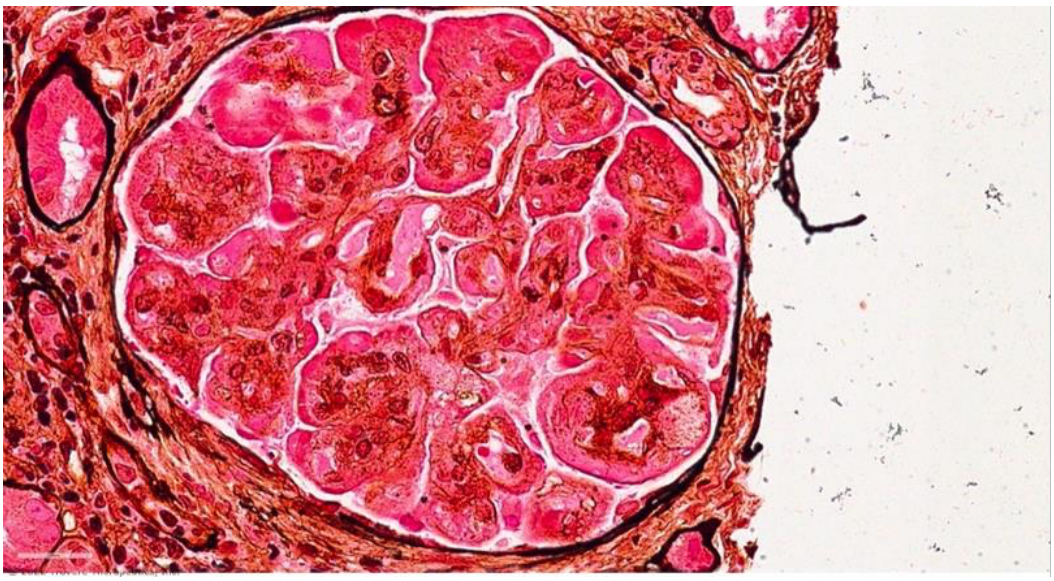

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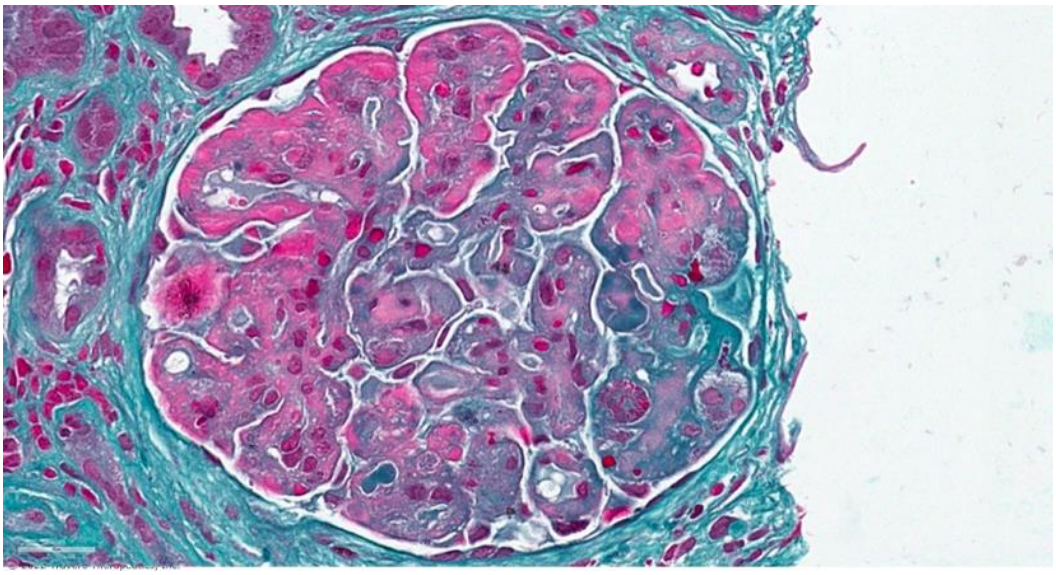

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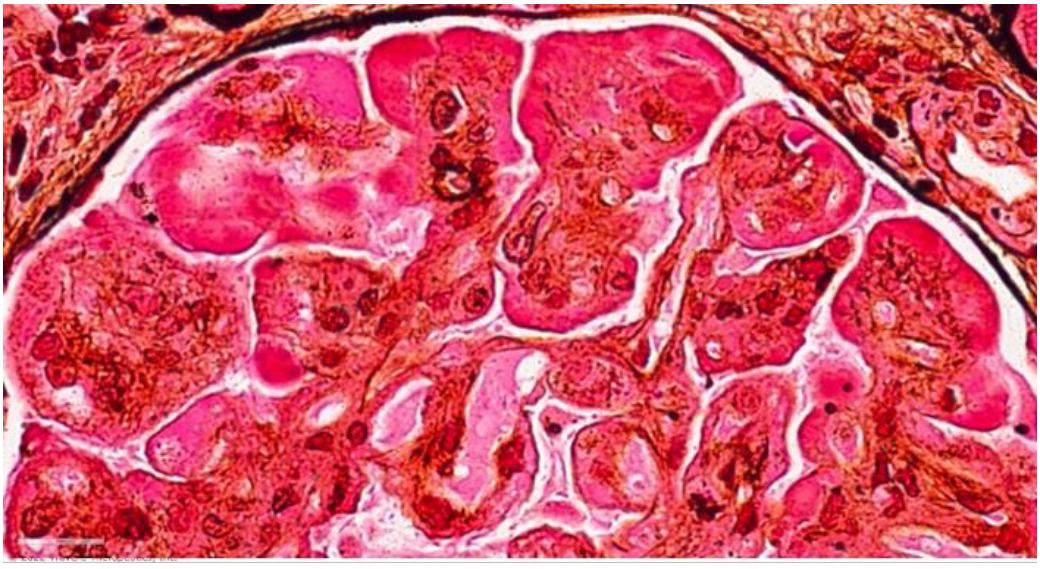

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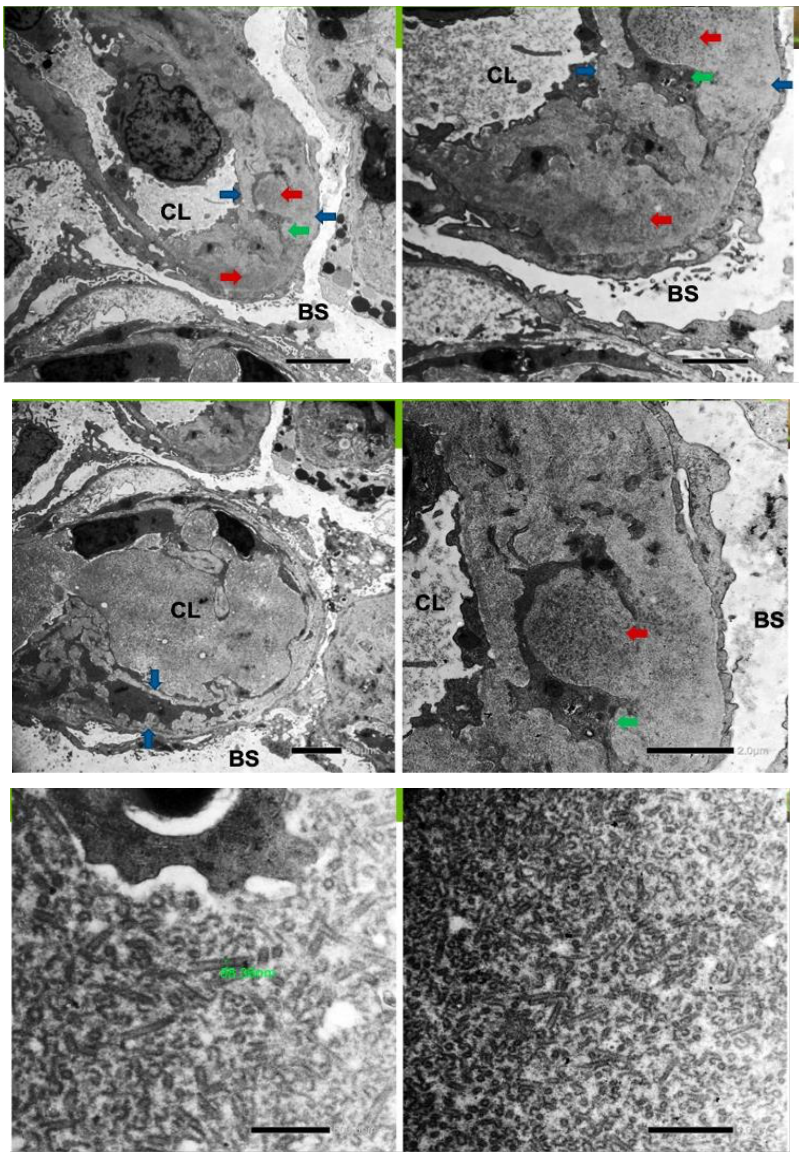

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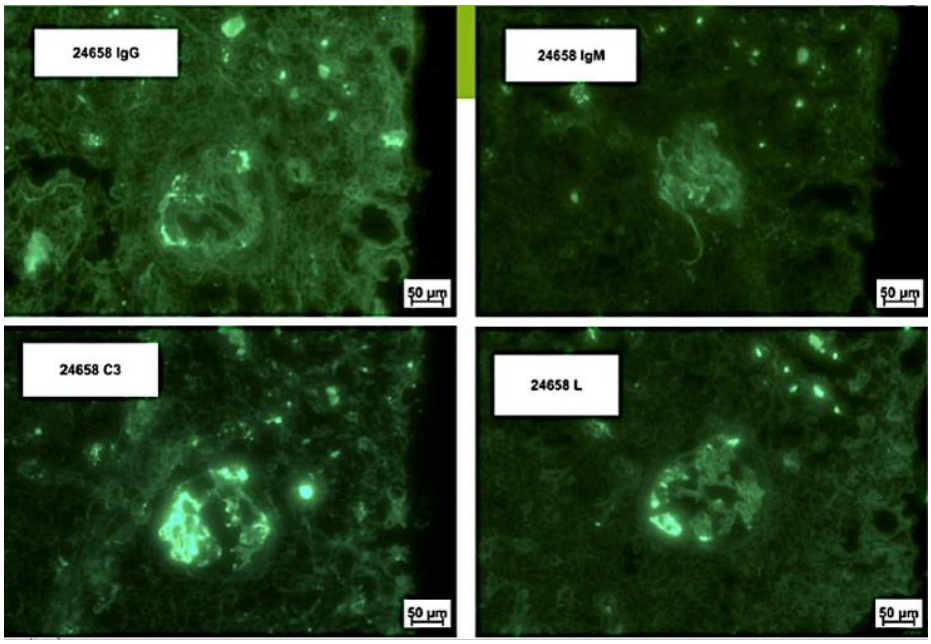

Immunofluorescenza.

E adesso mettiamoci alla prova!

Alla luce del quadro clinico e laboratoristico descritto, quale diagnosi ipotizzereste? E quale trattamento riterreste più appropriato?

La soluzione nel nostro prossimo numero!

In memoria del Prof. Claudio Ponticelli

In ricordo di

Prof.ssa Gabriella Moroni

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Claudio Ponticelli

Il 1° gennaio scorso si è spento a Milano, all'età di 89 anni, il Professor Claudio Ponticelli, nefrologo di chiara fama internazionale ed imprescindibile punto di riferimento per generazioni di Nefrologi Italiani. Fino agli ultimi giorni della sua vita, nonostante il declino fisico, ma non intellettuale, ha dedicato le proprie energie al progresso della nostra disciplina, partecipando attivamente a congressi scientifici, offrendo il proprio esempio e la propria esperienza alle nuove generazioni di Nefrologi e continuando la propria produzione scientifica, con alcuni suoi contributi che vedranno la luce postumi.

La produzione scientifica del Prof. Ponticelli costituisce una pietra miliare nella storia della nefrologia italiana. Dotato di una straordinaria prontezza analitica e di una visione lungimirante, ha saputo anticipare l'evoluzione della nostra disciplina con tenacia e dedizione, divenendo un punto di riferimento non solo nazionale, ma anche sovranazionale.

Oltre all'indiscusso valore accademico, Ponticelli si distingueva per la sua integrità e libertà intellettuale, caratteristiche entrambe mantenute con dignità anche di fronte alle inevitabili avversità che possono occorrere lungo il cammino personale e professionale di ciascuno di noi. Il suo agire è stato costantemente guidato dall'etica della cura e dalla convinzione che l'assistenza sanitaria d'eccellenza debba essere un diritto garantito ad ogni paziente.

Sostenitore convinto della cooperazione tra specialisti, ha promosso studi randomizzati spontanei che hanno elevato gli standard di cura e la condivisione del sapere. Negli ultimi anni, pur non potendo più esercitare l'attività clinica diretta, ha rivolto il suo interesse verso ambiti di ricerca maggiormente speculativi, continuando parallelamente a fornire contributi seminali sugli argomenti a lui più cari, in particolare le glomerulonefriti e la gestione della terapia immunosoppressiva nei pazienti sottoposti a trapianto di rene.

Sebbene i riconoscimenti pubblici non siano sempre stati proporzionati al suo effettivo valore, l'influenza del Prof. Ponticelli resta viva attraverso le sue numerose pubblicazioni scientifiche, che hanno formato generazioni di medici. La sua vasta produzione scientifica (oltre 650 pubblicazioni su riviste internazionali) ha abbracciato l'intera patologia glomerulare; si ricorda, in particolare, il suo contributo fondamentale nello studio della nefropatia membranosa – il cui protocollo terapeutico di riferimento porta ancora oggi il suo nome – oltre alle ricerche sulle nefropatie a lesioni minime, a sclerosi focale, a depositi di IgA e nefrite lupica.

Custodire la sua eredità è quindi oggi un dovere imprescindibile per preservare quel connubio di rigore scientifico e profonda umanità che egli ha saputo incarnare magistralmente durante tutta la sua carriera.

"*Che la terra gli sia lieve*"