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**INNOVATIONS, ADVANCED MEDICAL TECHNOLOGY PROJECTS,
AND TELEMEDICINE IN PERITONEAL DIALYSIS: GLUCOSE-FREE
SOLUTIONS AND A PROTOTYPE OF A CUTTING-EDGE CYCLER FOR
APD (AUTOMATED PERITONEAL DIALYSIS)**

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INTRODUCTION

Chronic Kidney Disease (CKD) is currently recognized as a preeminent and escalating public health concern, primarily due to its strong correlation with heightened morbidity and mortality rates. Data from the 2018 Global Burden of Disease (GBD) report are particularly salient, documenting a surge in CKD cases from approximately 11.3 million in 1990 to 21.3 million in 2016—a 90% increase in incidence over nearly three decades.¹ National data from Italy mirror this global trend; according to the Italian Dialysis and Transplant Registry (RIDT), there is a consistent upward trajectory in the number of patients requiring dialysis. This shift is driven by evolving socioeconomic determinants and increased life expectancy. Specifically, the rising prevalence of CKD can be attributed to an aging population coupled with the expanding burden of comorbidities, including hypertension, diabetes mellitus, and obesity.² While advancements in therapeutic interventions and the chronic nature of the pathology have contributed to reduced mortality, they have simultaneously necessitated a substantial increase in healthcare expenditure. Globally, the growing cohort of patients with End-Stage Renal Disease (ESRD) requiring Renal Replacement Therapy (RRT) poses a formidable economic challenge to healthcare infrastructures.³ In response to these challenges, the integration of digital health technologies has emerged as a pivotal strategy for cost containment and the enhancement of integrated care pathways. Telemedicine, in particular, facilitates a decentralized care model that allows vulnerable populations to receive treatment in a home-based setting, thereby eliminating the need for patient or provider travel. This modality serves as a systemic optimizer, improving patient quality of life while fostering a restructuring of healthcare delivery. Furthermore, digital health supports monitored hospital discharge, mitigates rehospitalization rates for chronic patients, reduces institutionalization among the elderly, and diminishes the necessity for healthcare-seeking migration. Within this framework, peritoneal dialysis (PD) represents a synergistic solution. Its future implementation may increasingly depend on its adoption as a first-line therapeutic approach, particularly for "late-presentation" patients who reach nephrological care in advanced uremic states.

1 CHRONIC KIDNEY DISEASE

1.1. Definition, Epidemiology, and Risk Factors

Chronic Kidney Disease (CKD) is defined as a prolonged clinical condition characterized by the progressive and irreversible impairment of renal function. According to established diagnostic criteria, CKD is identified by a Glomerular Filtration Rate (GFR) consistently below 60 ml/min/1.73 m² and/or an increase in the urinary albumin-to-creatinine ratio (ACR ≥ 30 mg/g) or when structural or functional abnormalities of the kidneys are present, regardless of GFR levels. Furthermore, the diagnosis encompasses structural or functional renal abnormalities, irrespective of the GFR. These manifestations may include objective indices of kidney damage, such as persistent proteinuria, albuminuria, or hematuria, as well as pathological findings derived from diagnostic imaging or histological examination via renal biopsy. For the condition to be formally classified as chronic, these clinical or structural alterations must be documented for a minimum duration of three to six months.⁴

Markers of kidney damage (1 or more)	Albuminuria (ACR ≥30 mg/g [≥ 3 mg/mmol]) Urine sediment abnormalities Persistent hematuria Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR <60 ml/min per 1.73 m ² (GFR categories G3a–G5)

ACR, albumin-to-creatinine ratio; GFR, glomerular filtration rate.

Criteria for chronic kidney disease (either of the following present for a minimum of 3 months).

Category	AER (mg/24 h)	ACR (approximately equivalent)		Terms
		(mg/mmol)	(mg/g)	
A1	<30	<3	<30	Normal to mild increased
A2	30–300	3–30	30–300	Moderately inc
A3	>300	>30	>300	Severely increa

ACR, albumin-to-creatinine ratio; AER, albumin excretion rate.

*Relative to the young adult level.

Albuminuria categories in chronic kidney disease.

Chronic Kidney Disease (CKD) is clinically staged according to the progressive decline in renal filtration capacity and the presence of biomarkers indicative of parenchymal damage. The current diagnostic framework utilizes the CGA classification system, which stratifies the disease based on Cause (C), Glomerular Filtration Rate (GFR) category (G1–G5), and Albuminuria category (A1–A3).

In accordance with GFR-based staging, CKD is categorized into the following six functional cohorts:

- Stage G1: Normal or high function (≥ 90 ml/min per 1.73 m²);
- Stage G2: Mildly decreased function (60–89 ml/min per 1.73 m²);
- Stage G3a: Mildly to moderately decreased function (45–59 ml/min per 1.73 m²);
- Stage G3b: Moderately to severely decreased function (30–44 ml/min per 1.73 m²);
- Stage G4: Severely decreased function (15–29 ml/min per 1.73 m²);
- Stage G5: Kidney failure (< 15 ml/min per 1.73 m²).⁵

KDIGO: Prognosis of CKD by GFR and albuminuria categories				Persistent albuminuria categories		
				Description and range		
				A1	A2	A3
				Normal to mildly increased <30 mg/g <3 mg/mmol	Moderately increased 30–300 mg/g 3–30 mg/mmol	Severely increased >300 mg/g >30 mg/mmol
GFR categories (mL/min/1.73 m ²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk. GFR, glomerular filtration rate.

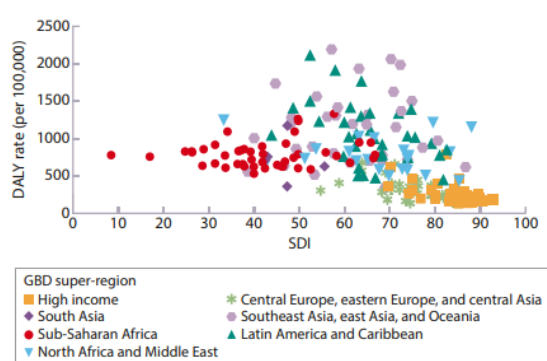
In recent decades, the global incidence and prevalence of Chronic Kidney Disease (CKD) have escalated markedly, primarily driven by the burgeoning impact of diabetes mellitus and cardiovascular disorders—now recognized as the principal determinants of renal failure. Defined by structural or functional renal abnormalities persisting for at least three months, CKD currently affects approximately 11% of the global adult population, exceeding 800 million individuals.^{6,7}

Data from the Global Burden of Disease (GBD) study estimate approximately 697.5 million cases worldwide, with China and India collectively accounting for one-third of the global burden. Other nations with significant disease prevalence (exceeding 10 million cases) include Brazil, the United States, and Indonesia, among others. In 2017 alone, CKD was directly responsible for 1.2 million deaths, while an additional 1.4 million cardiovascular-related deaths were attributed to underlying renal impairment. The total disease burden reached 61.3 million disability-adjusted life years (DALYs), with diabetic nephropathy identified as a primary contributor. The extensive cross-sectional analysis conducted by Mills et al., which integrated data from 33 studies across 32 countries and encompassed nearly half of the global population, reveals a significant burden of Chronic Kidney Disease (CKD) characterized by marked demographic disparities. On a global scale, the age-standardized prevalence is estimated at 10.4% for men and 11.8% for women, a gender differential that accounts for a total of approximately 497 million affected adults. This epidemiological distribution, however, is far from uniform, exhibiting extreme fluctuations across different sovereign territories. While South Korea maintains a relatively low prevalence of 4.5%, countries such as El Salvador report significantly higher rates, peaking at 25.7%. Such heterogeneity is equally evident within the European continent, where a systematic review of 13 nations documented a range extending from a minimum of 3.3% in Norway to a maximum of 17.3% in Northeastern Germany. Similar patterns of variation are observed across Asia, with prevalence rates fluctuating between 10.8% in China and 13.9% in Mongolia. Furthermore, the African continent presents the highest

overall regional prevalence at 15.8%, although this figure masks a profound internal divide: Northern Africa exhibits a comparatively lower rate of 6.1%, whereas Western Africa faces a substantially heavier burden, with prevalence reaching 19.8%. These statistics underscore the necessity of considering regional socioeconomic and environmental determinants when addressing the global expansion of renal pathologies. The substantial geographic disparities in disease prevalence suggest that conventional clinical drivers, such as diabetes mellitus and hypertension, are insufficient to fully account for the global epidemiological variance of Chronic Kidney Disease (CKD). Extensive studies have consistently pointed to diabetes and hypertension as the most influential factors in the development and progression of CKD, regardless of a country's income level.⁸ These conditions not only contribute to kidney damage but also complicate management, especially in aging populations where multiple health issues and medication use are common.⁹ Beyond these primary comorbidities, a complex constellation of demographic and socioeconomic determinants plays a pivotal role in modulating disease risk. These include individual lifestyle factors such as dietary habits and tobacco use, alongside broader environmental stressors like climate change, industrial pollution, and exposure to nephrotoxic environmental agents. Furthermore, the divide between urban and rural residency, coupled with varying exposure to infectious pathologies, introduces additional layers of complexity to the regional burden of renal impairment. The management of CKD is further complicated by the heterogeneity of public health frameworks, which dictate the efficacy of early detection programs and long-term clinical oversight. Disparities in healthcare economics and local clinical protocols lead to significant inequities in the availability of life-sustaining treatments. Consequently, access to renal replacement therapies, particularly dialysis, remains inconsistent on a global scale, leaving numerous regions with inadequate infrastructure to support the growing cohort of patients reaching end-stage renal disease.¹⁰ The lack of robust epidemiological surveillance in resource-limited settings represents a significant oversight, primarily due to the inherent difficulties in documenting longitudinal morbidity and mortality data.¹¹

Prevalence rates vary internationally, ranging from approximately 5% to 13%, with the highest figures reported in the United States and lower rates observed in Southern European countries. In Italy, current estimates suggest that around 7% of the population is affected.¹² In 2017, chronic kidney disease (CKD) affected an estimated 700 million individuals worldwide, making it more prevalent than several other major chronic conditions, including diabetes, osteoarthritis, and chronic obstructive pulmonary disease. That same year, CKD contributed to around 1.2 million deaths globally—exceeding the mortality rates of diseases such as tuberculosis and HIV, and nearing those associated with traffic-related injuries.¹³

At its core, Chronic Kidney Disease (CKD) represents a relentless clinical trajectory defined by the permanent degradation of the kidney's parenchymal integrity. This pathological transition is driven by a complex interplay of microvascular remodeling, metabolic dysregulation, and chronic oxidative stress, which collectively overwhelm the organ's limited homeostatic and regenerative capabilities. As functional nephrons are lost, the resulting persistent inflammatory milieu facilitates a cascade of fibrogenesis, leading to the progressive replacement of healthy tissue with non-functional scarring and a consequent depletion of residual renal capacity.¹⁴ The cellular mechanisms underpinning this decline often involve maladaptive compensatory hypertrophy of the remaining nephrons. While initially maintaining filtration, this process eventually precipitates intraglomerular hypertension and accelerated nephron attrition. The susceptibility to such decline is frequently established early in life through gestational complications or low birth weight, and is later exacerbated by systemic insults such as obesity, diabetes mellitus, and senescence. As the Glomerular Filtration Rate (GFR) diminishes and albuminuria becomes more pronounced, the clinical focus shifts toward the heightened risk of secondary cardiovascular events and premature mortality, which often occur well before the onset of end-stage renal failure.¹⁵ From a broader perspective, the epidemiological landscape of CKD has been profoundly reshaped by the global demographic shift toward an aging population and the surging prevalence of non-communicable diseases. To quantify this transition, longitudinal data from the Global Burden of Disease (GBD) framework (1990–2019) offer a comprehensive evaluation of incidence and mortality trends. These metrics, particularly disability-adjusted life-years (DALYs), highlight the necessity of an integrated research approach to address the escalating socioeconomic and clinical challenges posed by chronic renal impairment on a global scale.⁵

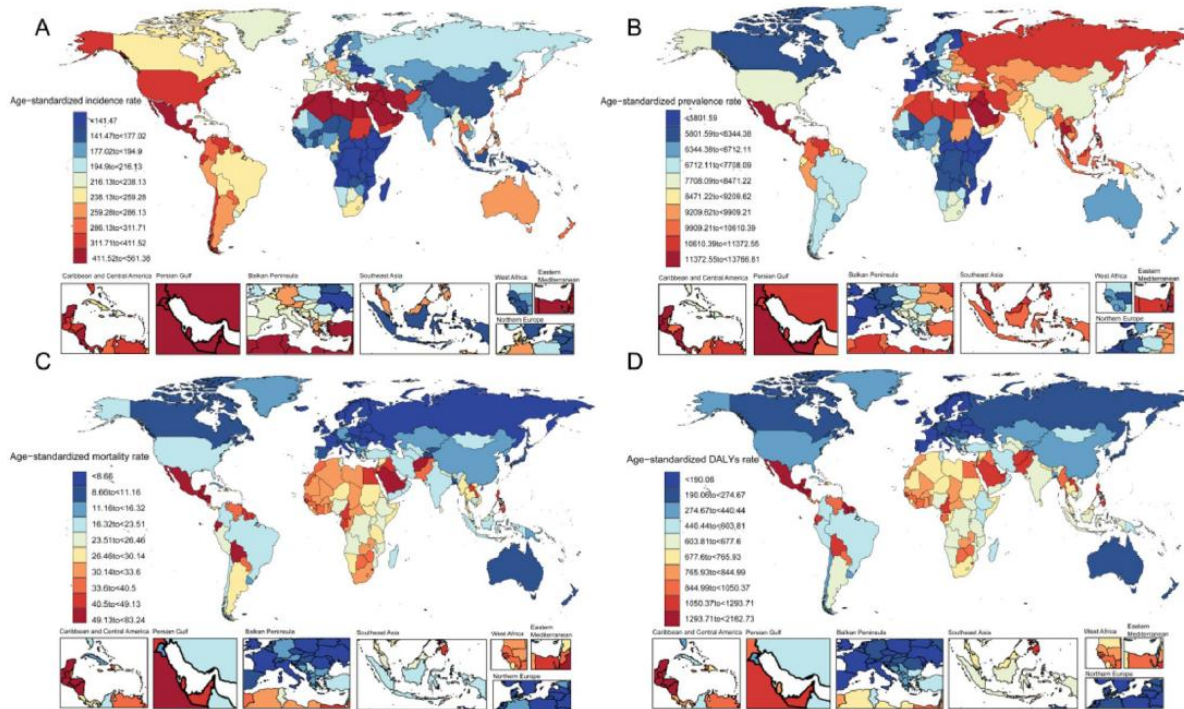


Age-standardized chronic kidney disease disability-adjusted life-year (DALY) rates for each location by sociodemographic index (SDI), both sexes combined, 2019. GBD, global burden of disease. Reproduced from Global Burden of Disease 2019: GBD cause and risk summaries chronic kidney disease.

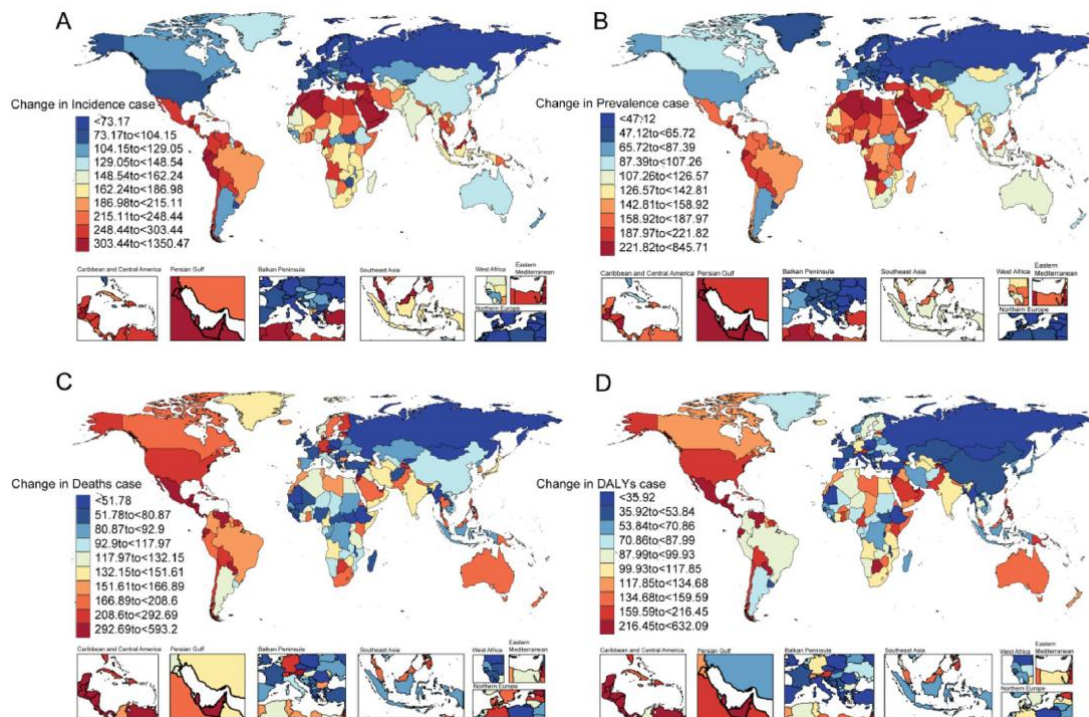
To further elucidate the global burden of renal impairment, recent investigations—most notably by Qin et al.—have examined how demographic and epidemiological transitions correlate with systemic development markers. Central to this analysis is the Socio-demographic Index (SDI), a composite

metric ranging from 0 to 1 that synthesizes fertility patterns, educational attainment, and income distribution.¹⁶ By stratifying regions according to their SDI, researchers can bridge the gap between a nation's developmental status and its clinical outcomes. This is complemented by the Healthcare Access and Quality (HAQ) Index, which provides a risk-adjusted mortality scale (0–100) across 32 conditions, offering a standardized benchmark for evaluating healthcare performance and accessibility across diverse geopolitical territories.¹⁷ Utilizing the comprehensive GBD 2019 dataset, which spans over 200 countries and 369 pathologies, these studies allow for a nuanced understanding of how risk factor exposure evolves in parallel with societal development. Beyond the fundamental metabolic drivers of hypertension and fasting hyperglycemia, the analysis integrates the impact of excessive body mass, sedentary lifestyles, and nutritional imbalances. Furthermore, the inclusion of nephrotoxic environmental stressors as a significant risk category aligns with the previously discussed necessity of a multifactorial etiological approach.¹⁸ A critical component of this epidemiological surveillance is the application of the Population Attributable Fraction (PAF). This metric estimates the proportion of the disease burden that could theoretically be averted by the elimination of specific risk factors. By synthesizing data from meta-analyses and national health registries, the PAF provides a quantitative foundation for preventive strategies, identifying high-impact areas for clinical and public health interventions. Consequently, the intersection of SDI and HAQ indices with robust risk-factor modeling facilitates a more sophisticated reorganization of healthcare delivery, transitioning from reactive treatment to proactive, evidence-based prevention and management of Chronic Kidney Disease.^{19,20}

The clinical management of Chronic Kidney Disease (CKD) is hindered by its prolonged asymptomatic progression, as uremic symptoms typically emerge only during advanced functional decline. This clinical latency underscores the necessity of early diagnostic intervention to mitigate the elevated risk of cardiovascular events and progression toward terminal renal failure. Effective early detection relies on the dual assessment of estimated glomerular filtration rate (eGFR) and albuminuria, which serve as primary biomarkers for identifying renal attrition in its initial stages. Systematic screening is particularly imperative for high-risk cohorts, including the elderly and individuals with a family history of nephropathy. Furthermore, clinical vigilance must be prioritized for patients presenting with hypertension, diabetes, or metabolic syndrome, as well as those with histories of cardiovascular disease, nephrolithiasis, or chronic exposure to nephrotoxic agents.¹⁴



Geographic distribution of age-standardized incidence rate (A), age-standardized prevalence rate (B), age-standardized mortality rate (C), and age-standardized disability-adjusted life years rate (D) of CKD in 204 countries and territories.¹⁶



Geographic distribution of change in incidence cases (A), change in prevalence cases (B), change in deaths cases (C), and change in disability adjusted life years cases (D) of CKD in 204 countries and territories.¹⁶

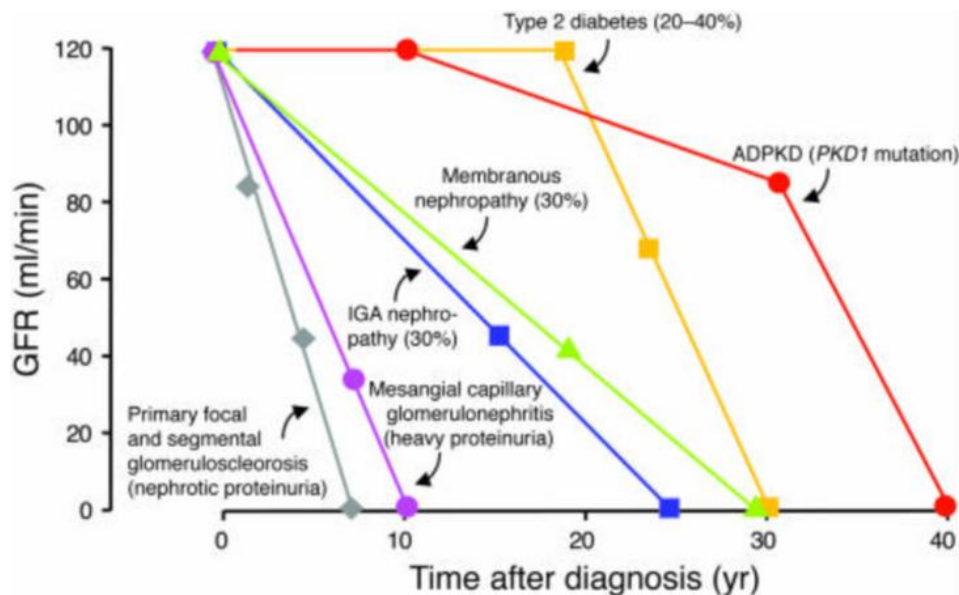
1.2. Overview of Pathogenesis and Pathophysiology

The origins of Chronic Kidney Disease (CKD) are inherently multifactorial, involving a complex interaction of metabolic and systemic triggers. Globally, the primary drivers are fasting hyperglycemia (associated with diabetes mellitus) and elevated systolic blood pressure, which

collectively contribute to nearly two-thirds of the total disease burden.²¹ Beyond these predominant comorbidities, renal impairment is frequently secondary to specific clinical pathologies, including glomerulonephritis, autosomal dominant polycystic kidney disease (ADPKD), and systemic autoimmune conditions such as lupus nephritis. Furthermore, lifestyle-related determinants—specifically an elevated Body Mass Index (BMI), nutritional imbalances, and sedentary behavior—act as significant catalysts for disease progression. These factors, when combined with exposure to nephrotoxic environmental hazards, create a synergistic risk profile that accelerates the global expansion of chronic renal pathologies.

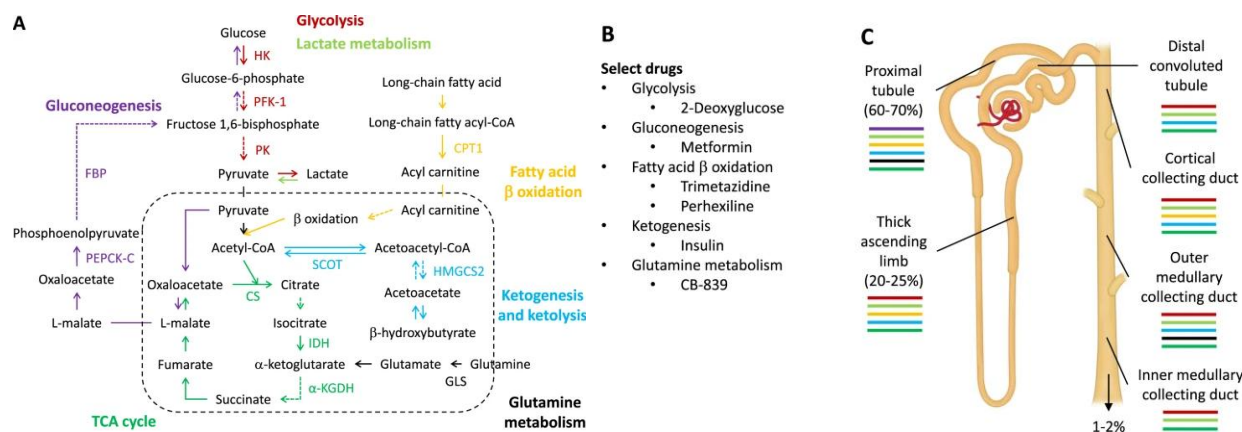
Cause	Frequency
Diabetic nephropathy (type 2 diabetes mellitus)	30%-50%
Diabetic nephropathy (type 1 diabetes mellitus)	3.9%
Vascular and hypertensive nephropathies	27%
Nephropathies of unknown origin	20%
Primary glomerulonephritis	8-10%
Chronic tubulointerstitial nephritis	3.6%
Secondary glomerulonephritis or vasculitis	2.1%
Hereditary nephropathies or cystic diseases (especially autosomal dominant polycystic kidney disease)	3-8%
Chronic interstitial nephropathies	< 5%
Plasma cell dyscrasias or neoplasm	2.1%
Sickle cell nephropathy	<1%

Main Causes of Chronic Kidney Disease



The progressive nature of chronic kidney disease. The progression to ESRD, as underlined by the progressive decline of GFR, is highly variable. Here is reported the natural history of autosomal-dominant polycystic kidney disease (ADPKD) in patients with PKD1 mutation in the PKD1 gene as an example of genetic renal disease. Progressive renal disease occurs in 20–40% of patients with type 2 diabetes. Progression to renal failure occurs in 30% of patients with IgA nephropathy after a follow-up of 25 years. Similarly, 30% of patients with membranous nephropathy reach ESRD within the 30-year follow-up period. A more rapid course is observed for patients with mesangial capillary glomerulonephritis or primary focal and segmental glomerulosclerosis, who possess persistently high urinary protein excretion rates.²²

Despite the diverse etiological origins of renal pathologies, they invariably gravitate toward common deleterious pathways characterized by persistent oxidative stress, systemic inflammation, and chronic fibrogenesis, ultimately culminating in irreversible nephron attrition. Central to this progression is the complex interplay between systemic hypertension and renal structural integrity, a relationship mediated by the Renin-Angiotensin-Aldosterone System (RAAS), dietary sodium dynamics, and autonomic dysregulation.²³ The RAAS serves as a primary driver of renal decline through its dual role in blood pressure regulation and fluid homeostasis. Specifically, Angiotensin II facilitates vasoconstriction and sodium retention while simultaneously promoting distal nephron reabsorption via aldosterone stimulation. Scientific evidence highlights that intrarenal RAAS activation often precedes clinical symptoms. For instance, animal models of metabolic dysfunction (Nagai et al.) have demonstrated elevated Angiotensin II levels prior to the onset of overt nephropathy, with ACE inhibitors and ARBs providing nephroprotection independent of systemic blood pressure. Similarly, clinical observations in IgA nephropathy (Nishiyama et al.) confirm that urinary angiotensinogen levels serve as a biomarker for localized RAAS hyperactivity, which is effectively mitigated by pharmacological blockade.^{24,25} Dietary sodium intake remains a critical, yet often unaddressed, factor in hypertensive renal damage. While global guidelines recommend a threshold of <2 g/day, actual consumption levels frequently double this limit. Meta-analytical data (He et al.; McMahon et al.) indicate a clear dose-response relationship between salt reduction and blood pressure mitigation, with low-sodium interventions resulting in a nearly 36% reduction in albuminuria among early-stage CKD patients. However, the clinical impact of sodium is modulated by salt sensitivity—a phenotype prevalent in approximately half of the hypertensive population. This condition, influenced by genetic predispositions, aging, and sympathetic activity, is not only associated with accelerated glomerular filtration rate (hyperfiltration) but also with extra-renal target organ damage, including hypertensive retinopathy and left ventricular hypertrophy.^{26,27} The kidney's bidirectional communication with the central nervous system via the reno-renal reflex underscores the role of sympathetic overactivity in renal progression. Efferent sympathetic signaling modulates renin release and vascular resistance, while afferent signals sustain a state of autonomic arousal that promotes end-stage renal failure. The therapeutic potential of modulating this pathway was explored through renal denervation. Initial findings from the SYMPPLICITY HTN-2 trial suggested significant efficacy in resistant hypertension; however, the subsequent sham-controlled SYMPPLICITY HTN-3 trial failed to replicate these results, showing no statistically significant difference in systolic blood pressure reduction. This discrepancy has led to a more cautious, albeit continuing, investigation into the role of autonomic modulation in chronic renal management.^{27,28}

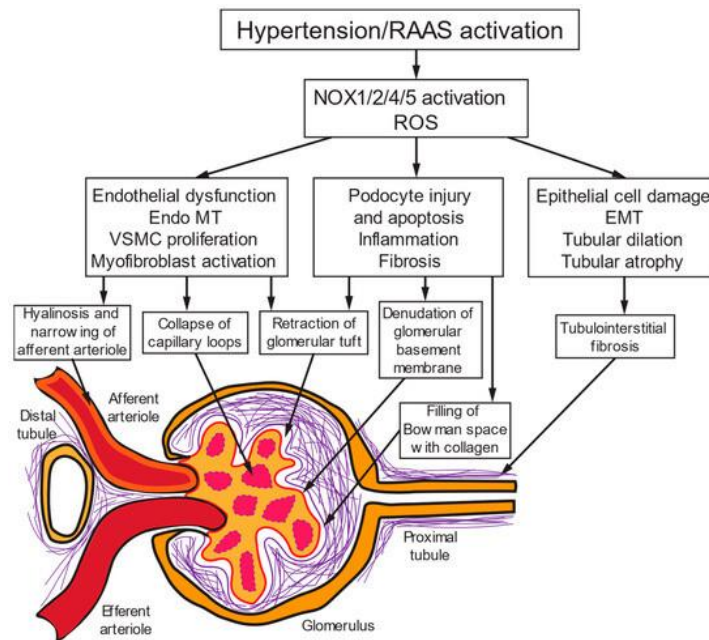


A Major metabolic pathways in the kidney. To make the figure comprehensible, only rate-limiting or key enzymes are shown, and arrows that contain multiple enzymatic steps are shown as dashed arrows. The box surrounded by the dashed line indicates mitochondria. FBP fructose 1,6-bisphosphatase, PEPCK-C cytosolic phosphoenolpyruvate carboxykinase, HK hexokinase, PFK-1 phosphofructokinase-1, PK pyruvate kinase, CPT1 carnitine palmitoyltransferase I, HMGCS2 mitochondrial HMG-CoA synthetase, SCOT succinyl-CoA:3-ketoacid-CoA transferase, GLS glutaminase, CS citrate synthase, IDH isocitrate dehydrogenase, α -KGDH α -Ketoglutarate dehydrogenase. **B** Examples of approved or investigational drugs targeting the metabolic pathways. **C** Major metabolic pathways in nephron segments. Colors of bars correspond to the colors of pathway names in panel A. The percentages indicate the percent of the filtered sodium reabsorbed or excreted.²⁹

Persistent systemic hypertension acts as a primary catalyst for the structural and functional deterioration of the kidney, manifesting as hypertensive nephrosclerosis. This condition stands as the second leading cause of mortality among the CKD population, underscored by a relentless remodeling of the renal parenchyma. The hemodynamic stress of chronic pressure elevation triggers a cascade of vascular, glomerular, and tubular injuries, which collectively shift the renal environment toward a profibrotic state. The hallmark of this progression is the pathological accumulation of extracellular matrix (ECM) components, predominantly collagen, within the interstitial space. This process is orchestrated by the aberrant activation of renal myofibroblasts, the principal cellular effectors of renal scarring. These myofibroblasts exhibit a diverse ontogeny, emerging from a multifactorial pool of progenitor sources:

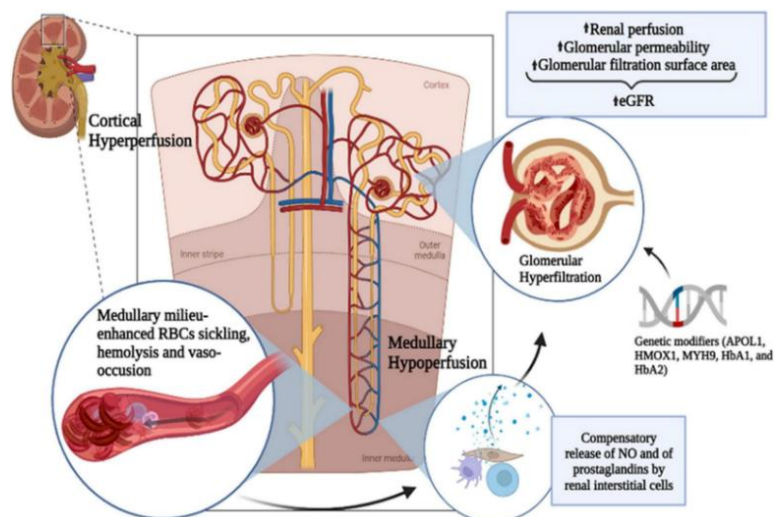
- Local Populations: Activation of resident interstitial fibroblasts and pericytes.
- Cellular Plasticity: Phenotypic conversion via Epithelial-to-Mesenchymal Transition (EMT) and Endothelial-to-Mesenchymal Transition (EndoMT).
- Systemic Recruitment: Infiltration of circulating fibrocytes and progenitor cells derived from the bone marrow.

The convergence of these cellular pathways leads to a progressive replacement of functional nephrons with non-contractile fibrous tissue, irreversibly compromising renal filtration and homeostatic capacity.²³



An intricate network of pathways leads to renal nephrosclerosis in hypertension. Hypertension and RAAS (renin–angiotensin–aldosterone system) activation initiate a cascade of events, including NOX activation and ROS generation, which induce endothelial dysfunction, inflammation, and epithelial-to-mesenchymal transition (EMT). The resulting podocyte injury and apoptosis contribute to the denudation of the glomerular basement membrane. Concurrently, endothelial-to-mesenchymal transition (EndoMT), vascular smooth muscle cell (VSMC) proliferation, and myofibroblast activation occur, leading to hyalinosis and narrowing of the afferent arteriole, the collapse of capillary loops, and retraction of the glomerular tuft. Epithelial cell damage and EMT lead to tubular dilation, atrophy, inflammation, and fibrosis, ultimately resulting in tubulointerstitial fibrosis and the filling of Bowman’s space with collagen.³⁰

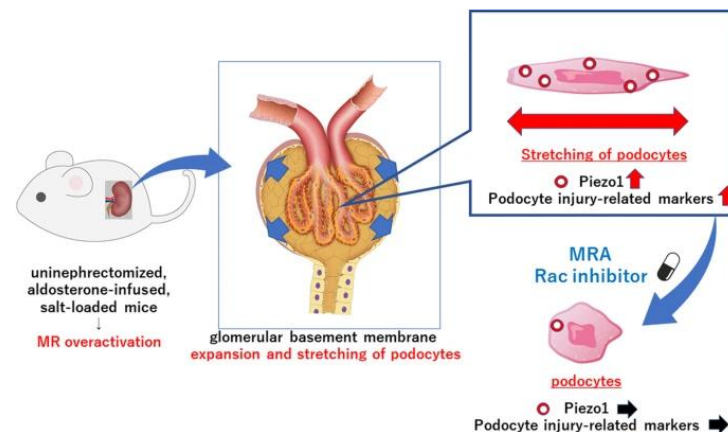
Renal damage may also occur in healthy individuals following the consumption of high-protein meals or during pregnancy, as well as in patients with obesity, diabetes mellitus, or autosomal dominant polycystic kidney disease. Sick cell disease (SCD), characterized by chronic hemolysis, vaso-occlusion, and organ damage, is often a cause of CKD due to glomerular hyperfiltration.³¹



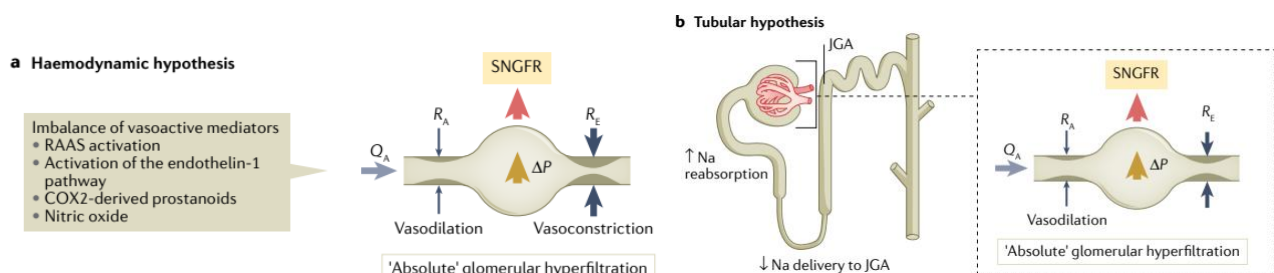
Mechanism of SCD-induced glomerular hyperfiltration. The hypoxic, acidic, and hyperosmolar environment of the renal medulla promotes the polymerization of HbS and the sickling of RBCs. Slow blood rheology in the vasa recta aggravates the vaso-occlusion and leads to ischemia that can advance to infarction. As a compensatory mechanism, medullary prostaglandins and nitric oxide (NO) are secreted leading to an increased renal cortical flow. It was suggested that prostaglandins are released by renal interstitial cells. Genetic modifiers such as APOL1, HMOX1, MYH9, HbA1, and HbA2 and increased renal perfusion coupled with increased glomerular permeability and glomerular filtration surface area may enhance glomerular hyperfiltration in SCD.³¹

The following mechanistic framework delineates the primary pathophysiological drivers of chronic renal deterioration, characterized by a transition from initial compensatory responses to irreversible structural damage:

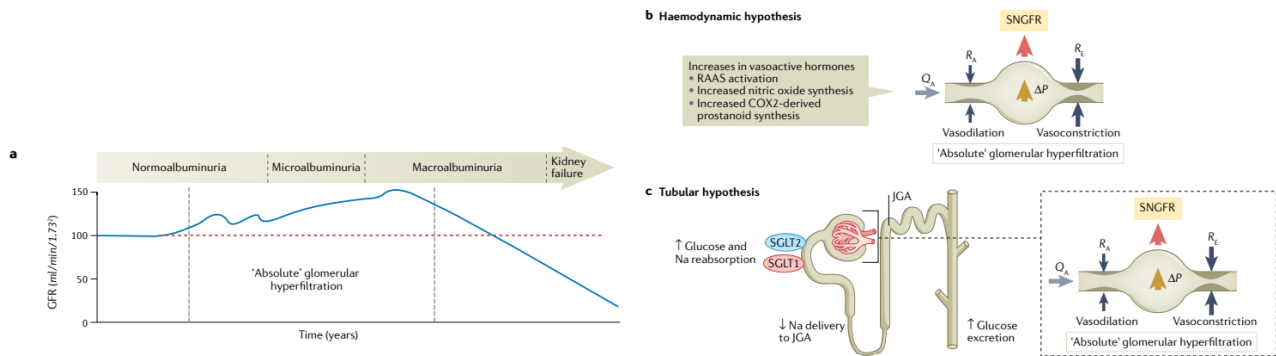
- **Renal Hyperfiltration and Glomerular Hypertension:** Renal hyperfiltration functions as an early, maladaptive compensatory mechanism following nephron loss, characterized by an elevation in single-nephron glomerular filtration rate (SNGFR). This supraphysiological increase in capillary pressure and flow induces mechanical stress on podocytes and endothelial cells, precipitating proteinuria and glomerulosclerosis. While "absolute" hyperfiltration occurs in kidneys with a preserved nephron count (often seen in early diabetes or obesity), "relative" hyperfiltration arises when the remaining functional units attempt to maintain total GFR despite a reduced nephron population. Persistent SNGFR elevation invariably accelerates the transition from functional compensation to progressive renal decline.^{32,33}



Relations between podocytes, Piezo1, and MR. In hypertensive models of MR overactivation, renal glomeruli are distended, podocytes are stretched, Piezo1 is upregulated, and podocyte injury-related marker levels are elevated. Administration of MRA or Rac inhibitors inhibited these changes. MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; Rac, RAS-related C3 botulinum toxin substrate.³⁴



Potential origins of obesity-related glomerular hyperfiltration. a According to the haemodynamic hypothesis, activation of vasoactive hormones in obesity results in a reduction in glomerular afferent arteriolar resistance (R_A), which leads to an increase in glomerular transcapillary hydraulic pressure difference (ΔP) and eventually an increase in single-nephron glomerular filtration rate (SNGFR), and 'absolute' glomerular hyperfiltration. b According to the tubular hypothesis, increased proximal tubular sodium reabsorption in obesity results in a reduction in sodium chloride delivery to the juxtaglomerular apparatus (JGA) and the deactivation of tubuloglomerular feedback, eventually leading to a rise in SNGFR, and thus increasing SNGFR. Q_a , glomerular capillary plasma flow; RAAS, renin-angiotensin-aldosterone system.³³

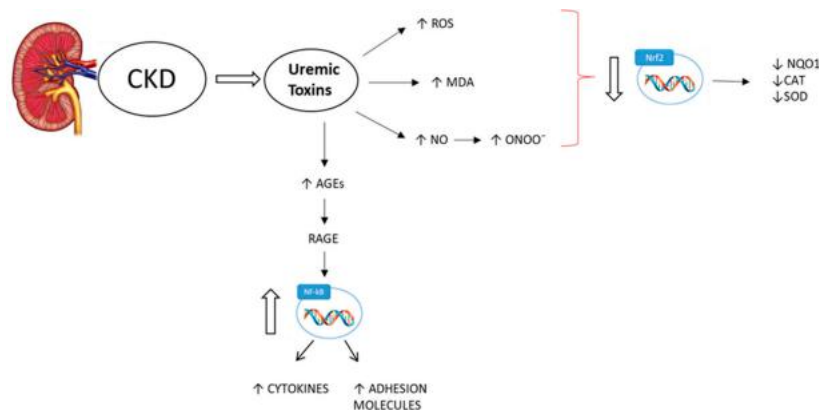


'Absolute' glomerular hyperfiltration in diabetes mellitus. a | During the course of diabetes, an early increase in the glomerular filtration rate (GFR) is often followed by a progressive increase in urinary albumin excretion, and subsequent progressive loss of kidney function, which is greatly accelerated by the onset of macroalbuminuria or overt proteinuria.

b | According to the haemodynamic hypothesis, the activation of vasoactive hormones leads to a reduction in afferent arteriolar resistance (R_a) and a parallel increase in efferent arteriolar resistance (R_e), resulting in increases in glomerular capillary plasma volume flow rate (Q_a), glomerular transcapillary hydraulic pressure difference (ΔP) and eventually single-nephron GFR (SNGFR).

c | According to the tubular hypothesis, increased glucose in the glomerular ultrafiltrate leads to augmented glucose delivery to the proximal tubule and increased sodium-coupled glucose reabsorption through sodium-glucose co-transporter-2 (SGLT2) and sodium-glucose co-transporter-1 (SGLT1), resulting in a reduction in sodium delivery to the juxtaglomerular apparatus (JGA). These effects reduce the tubuloglomerular feedback signal by promoting the local release of renin and angiotensin, which results in a reduction in adenosine production and consequently a reduction in R_a and an increase in R_e . The resulting intraglomerular haemodynamic changes lead to an increase in intraglomerular hydraulic pressure and SNGFR.³³

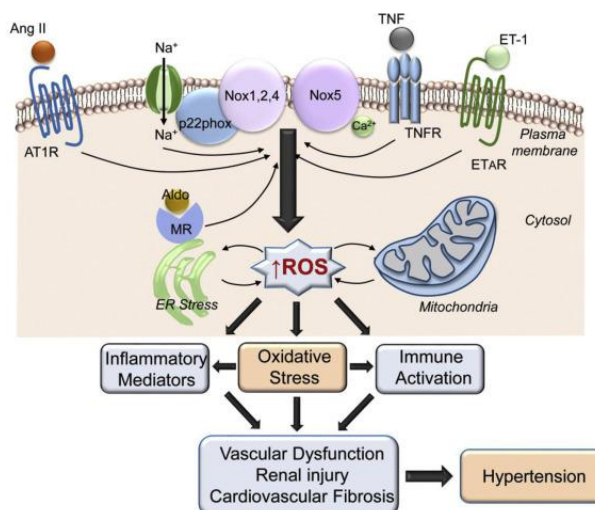
- **Oxidative Stress and Redox Imbalance:** In the context of Chronic Kidney Disease (CKD), the pathophysiology is deeply influenced by a systemic disruption of redox homeostasis. This state arises when the cumulative generation of reactive oxygen species (ROS)—driven predominantly by mitochondrial respiratory chain dysfunction and the aberrant activation of NADPH oxidase (NOX) isoforms—outpaces the buffering capacity of endogenous antioxidant systems.^{35,36}



During chronic kidney disease (CKD), there is a considerable increase in oxidative stress due to uremic toxins. There are increases in reactive oxygen species (ROS), nitric oxide (NO) and markers of oxidative stress—such as malondialdehyde (MDA), peroxynitrite (ONOO⁻) and advanced glycation end products (AGEs), which interact with AGE receptors and determine the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), with a consequent increase in cytokines and adhesion molecules. The oxidative stress condition is reflected in a reduction in the activity of the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) and, consequently, of the expression of antioxidant and cytoprotective enzymes such as NAD(P)H dehydrogenase [quinone] 1 (NQO1), catalase (CAT) and superoxide dismutase (SOD).³⁷

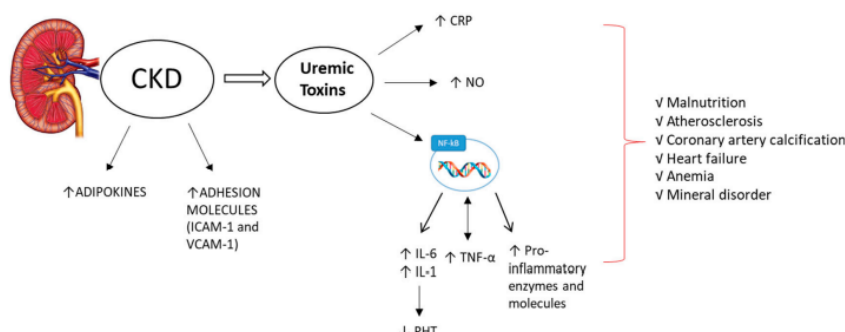
As renal function declines, this oxidative burden intensifies, reaching its clinical peak during dialysis. At the molecular level, this imbalance facilitates extensive macromolecular damage, including lipid peroxidation, protein carbonylation, and significant genomic instability evidenced by the formation of 8-hydroxy-2'-deoxyguanosine (8-OH-dG).³⁸ The interplay between oxidative stress and chronic inflammation is further cemented by the activation of pro-inflammatory transcription factors, such as NF- κ B, and the systemic accumulation of advanced glycation end-

products (AGEs). These factors collectively suppress the Nrf2-mediated antioxidant response, establishing a self-perpetuating cycle of ischemia, programmed cell death (apoptosis), and interstitial fibrogenesis. Ultimately, this feed-forward loop transforms localized metabolic insults into irreversible structural damage, characterizing the progressive nature of the disease.^{37,39,40}



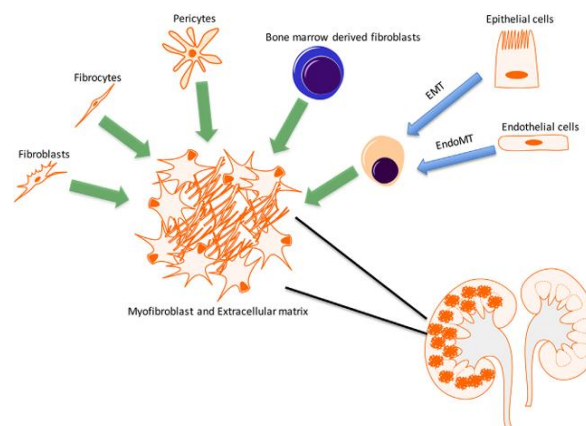
Oxidative stress as a unifying factor in hypertension. Prohypertensive factors, eg, angiotensin II (Ang II), endothelin-1 (ET-1), aldosterone (Aldo), and salt (Na), induce activation of NADPH oxidases (Noxs) that generate reactive oxygen species (ROS), which influence multiple systems involved in the pathophysiology of hypertension. AT1R, angiotensin II type 1 receptor; ER, endoplasmic reticulum; ETAR, endothelin-1 type A receptor; MR, mineralocorticoid receptor; TNF, tumour necrosis factor; TNFR, tumour necrosis factor receptor.⁴¹

- **Chronic Low-Grade Inflammation:** A hallmark of CKD, this state is sustained by the release of pro-inflammatory cytokines (IL-1, IL-6, TNF- α) and chemokines from injured tubular epithelial cells and dysfunctional adipose tissue. This inflammatory milieu recruits innate immune cells, promotes insulin resistance, and exacerbates systemic complications such as atherosclerosis and erythropoietin resistance. Furthermore, gut-derived uremic toxins, including indoxyl sulfate and p-cresyl sulfate, intensify this response by upregulating NF- κ B and COX-2 signaling, thereby linking intestinal dysbiosis to systemic and neuro-inflammatory outcomes.^{42–45}



During chronic kidney disease (CKD), increases ($\uparrow$) in adipokines and in adhesion proteins (such as ICAM-1 and VCAM-1) are observed. Uremic toxins play a very important role in the onset and progression of the inflammatory state, by increasing C-reactive protein (CRP), nitric oxide (NO) and a marked activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), which lead to increased levels of pro-inflammatory cytokines, such as interleukin-6 and -1 (IL-6, IL-1). These also suppress ($\downarrow$) parathyroid hormone (PTH) secretion, as well as enhancing the levels of tumor necrosis factor- α (TNF- α) and pro-inflammatory enzymes and molecules. This process leads to an exacerbation of the inflammatory state and is responsible for the onset or aggravation of various complications, such as malnutrition, atherosclerosis, coronary artery calcification, heart failure, anemia and mineral disorders.⁴²

Renal Fibrogenesis and Myofibroblast Activation: The final common pathway of renal failure is characterized by the excessive deposition of extracellular matrix (ECM) proteins, such as collagens I, III, and IV. Myofibroblasts, the primary effectors of this process, exhibit high α -SMA expression and originate from a heterogeneous pool including resident fibroblasts, pericytes, and bone marrow-derived progenitors. The TGF- β /Smad signaling axis remains the master regulator of this fibrotic remodeling, though the specific contribution of pericytes and other niche-specific cells continues to be a subject of intense investigation due to challenges in lineage-tracing specificity.⁴⁶⁻⁵²

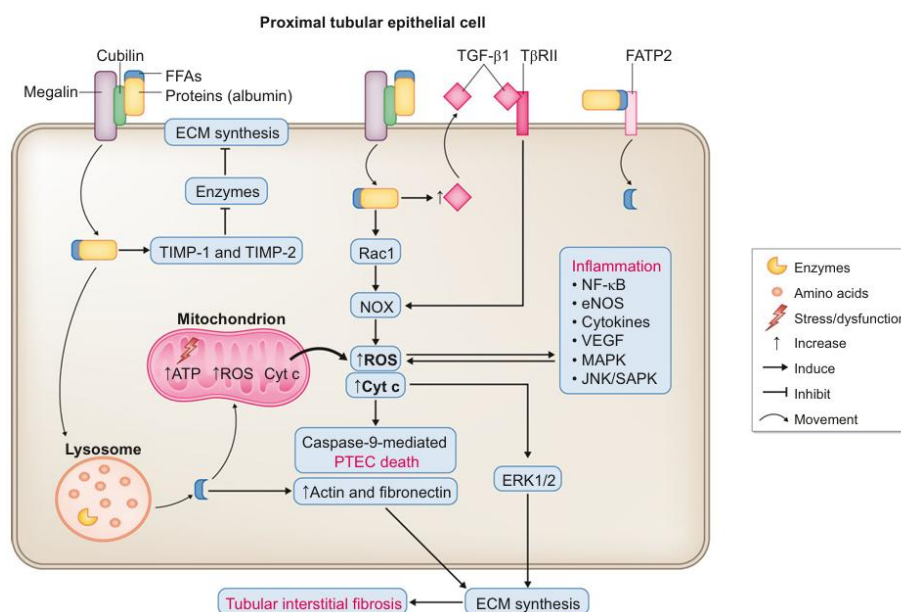


Schematic illustration of the possible origins of myofibroblasts in renal fibrosis. Interstitial myofibroblasts are commonly regarded as the extracellular matrix producing cells. There are many different types of cells contributing to the pool of myofibroblast progenitor cells. Fibroblasts and pericytes in the interstitium are commonly considered as the most predominant contributors to myofibroblast population. Fibrocytes and bone marrow-derived fibroblasts circulating in the peripheral blood have been shown to incorporate and contribute to the pool of myofibroblasts. Epithelial and endothelial cells have been suggested as the potential source of myofibroblasts through the process of EMT and EndoMT respectively; however many studies have shown contradicting evidence and whether EMT and EndoMT exist require further investigation.⁴⁶

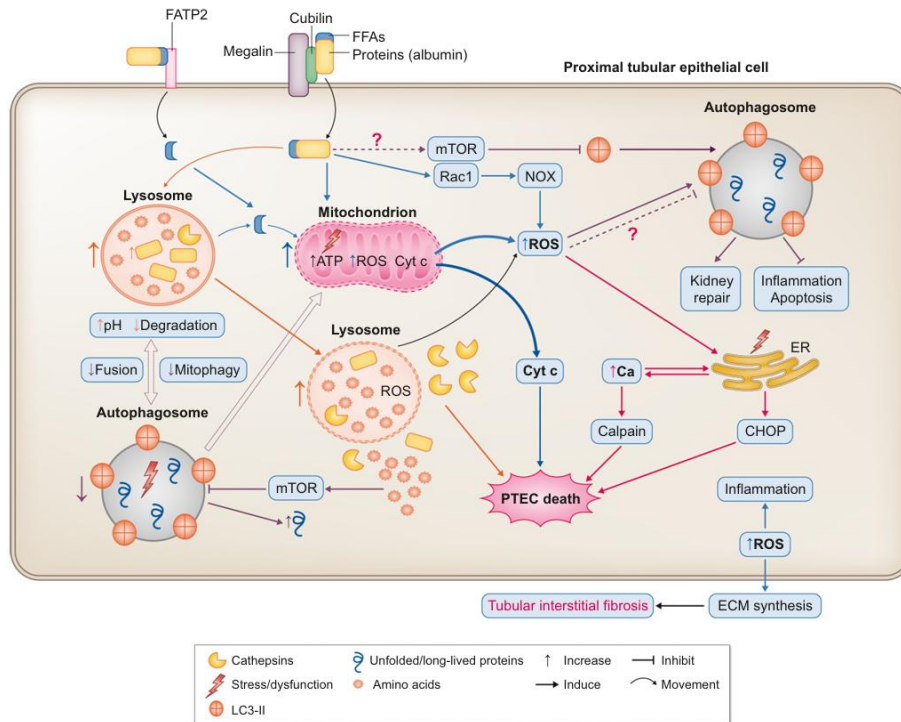
- Phenotypic Plasticity (EMT and EndoMT): Tubular epithelial-to-mesenchymal transition (EMT) and endothelial-to-mesenchymal transition (EndoMT) involve the loss of original cellular identity and the acquisition of mesenchymal traits. While the complete transdifferentiation of epithelial cells into myofibroblasts in vivo is debated, "partial EMT" is recognized as a significant contributor to interstitial injury through the secretion of profibrotic secretomes. Similarly, EndoMT, driven by TGF- β signaling, reflects a specialized form of plasticity that enhances the fibrogenic cell population, although definitive quantification is complicated by the overlapping markers of different cell lineages.⁵³⁻⁶¹
- Bone Marrow-Derived Progenitors (BMDCs): Mesenchymal progenitors originating from the bone marrow home to the injured kidney. While these cells contribute to the α -SMA-positive population, their direct role in collagen synthesis appears secondary. Current evidence suggests that BMDCs primarily function through paracrine mechanisms, releasing mediators that amplify

the localized inflammatory and fibrogenic environment rather than serving as the primary structural architects of the fibrotic matrix.⁵⁰

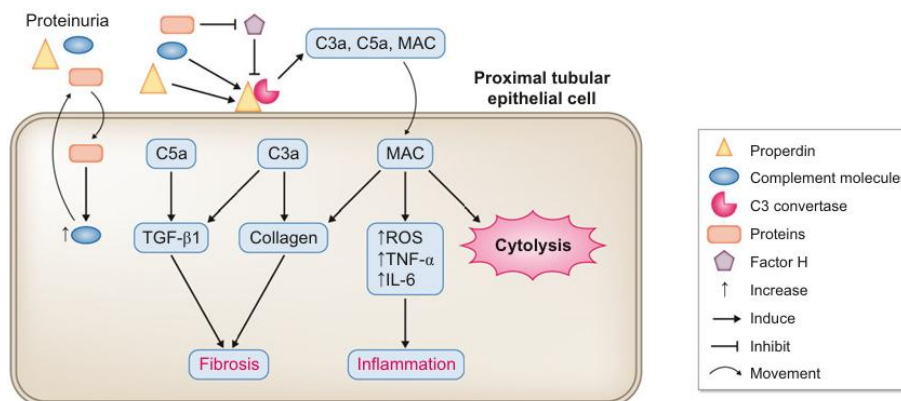
- **Microvascular Rarefaction and Hypoxia:** Progressive CKD is inextricably linked to the erosion of peritubular capillary density, a phenomenon known as capillary rarefaction. This loss of microvascular integrity, detectable even in systemic tissues (omental fat, skeletal muscle, and myocardial tissue), induces chronic tubular hypoxia and activates hypoxia-inducible factors (HIFs), which further drive fibrotic and inflammatory signaling. Maintaining microvascular homeostasis is thus a critical therapeutic objective to interrupt the bidirectional link between renal deterioration and systemic cardiovascular risk.⁶²
- **Pathogenic Proteinuria:** Beyond its role as a diagnostic marker, proteinuria acts as a potent tubular toxin. The filtration of excessive proteins, particularly albumin, triggers oxidative stress and pro-inflammatory signaling within tubular epithelial cells. This sustained proteotoxicity amplifies tubulointerstitial damage and accelerates the progression toward end-stage renal disease, establishing a self-perpetuating cycle of glomerular and tubular injury.^{63–66}



Intracellular ROS activation and its effect on PTECs in proteinuria/albuminuria. ROS production is one of the major players in the pathogenesis of tubulointerstitial injury. Reuptake of massive urinary filtered proteins, particularly albumin, leads to Rac1-mediated NOX activation and ROS synthesis. Reabsorbed albumin also increases ROS accumulation in the cytoplasm by causing mitochondrial dysfunction. Reabsorbed albumin is transported to lysosomes, and albumin-bound FFAs are transported further to tubular mitochondria after either albumin degradation into amino acids in lysosomes or receptor-mediated endocytosis. FFA molecules are also reabsorbed from the ultrafiltrate by FATP2 and transported to mitochondria. In the mitochondria, FFAs accelerate mitochondrial ROS synthesis leading to the loss of mitochondrial membrane potential and the release of ROS and Cyt c into the cytoplasm. Cyt c activates caspase-9-pathway-mediated PTEC apoptosis. Accumulated ROS induces the activation of NF- κ B, eNOS, proinflammatory cytokines, VEGF, MAPK and JNK/SAPK. Most of these are potent proinflammatory factors as well as induce ROS generation enabling a vicious cycle of tubulointerstitial injury. Furthermore, ROS is involved in TGF- β -mediated ECM synthesis and expansion that results in interstitial fibrosis, which can also occur independently of TGF- β 1 induction. Notably, the accumulating ECM components need to be degraded and normalized. However, this regulatory mechanism is broken by albumin-induced TIMP-1 and TIMP-2 which block a family of zinc metal-dependent enzymes that degrade one or more ECM proteins. In addition, FFAs can promote ECM development by enhancing the expression of α -smooth muscle cell actin and inducing the secretion of fibronectin which is present in tubulointerstitial fibrosis. ATP, adenosine triphosphate; Cyt c, cytochrome complex; eNOS, endothelial nitric oxide synthase; FATP2, fatty acid transport protein-2; JNK/SAPK, Jun N-terminal kinases/stress-activated protein kinases; MAPK, p38 mitogen-activated protein kinase; NOX, nicotinamide adenine dinucleotide phosphate oxidase; Rac1, Rho-related C3 botulinum toxin substrate 1; TIMP-1, tissue inhibitor of metalloproteinase 1; TIMP-2, tissue inhibitor of metalloproteinase 2; VEGF, vascular endothelial growth factor.⁶⁷



Proteinuria-induced dysfunctional autophagy, lysosomal membrane permeabilization and endoplasmic reticulum stress. Proteinuria initially activates autophagy in PTECs by increasing ROS generation to protect cells from injury. However, prolonged exposure of filtered proteins to PTECs starts to render toxic tubular effects by suppressing autophagic activities (e.g. mitophagy, basal autophagy and lysophagy), allowing the accumulation of defective organelles such as mitochondria and toxic intracellular molecules such as long-lived proteins, which promote progressive tubular injury. Accumulated defective mitochondria increase intracellular ROS and induce PTEC death, leading to tubulointerstitial inflammation, fibrosis and nephron loss. Reabsorbed albumin can inhibit basal autophagy by activating mTOR after lysosomal degradation into amino acids, thereby allowing the accumulation of long-lived proteins in the cytoplasm. Furthermore, massive proteinuria leads to an increase in the number and mass of lysosomes, but it results in decreased lysosomal enzymatic and degradation activities. Massive proteinuria also overwhelms lysosomal pathways and leads to LMP allowing the release of lysosomal ROS and cathepsins into the cytoplasm. In the cytoplasm, cathepsins cause PTEC death. In addition, LMP may cause a decline in autophagosome clearance of defective lysosomes. Moreover, proteinuria leads to ER stress via at least two molecular processes, including increased ROS and intracellular calcium levels in PTECs. Subsequently, ER stress causes calpain and/or CHOP pathways-mediated PTEC death. ATP, adenosine triphosphate; CHOP, CCAAT/enhancer-binding protein homologous protein; Cyt c, cytochrome complex; ER, endoplasmic reticulum; FATP2, fatty acid transport protein-2; LC3-II, microtubule-associated protein light chain 3-II; LMP, lysosomal membrane permeabilization; mTOR, mammalian target of rapamycin; NOX, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase; Rac1, Rho-related C3 botulinum toxin substrate 1.⁶⁷



The roles of proteinuria-mediated activated complement products in PTECs. Complement molecules are not filtered from the glomerulus but during proteinuria, these molecules appear in the tubular lumen and can activate the alternative pathway of the complement system. Properdin along with filtered other complement molecules leads to complement activation through binding to PTECs and functioning as a docking station for the assembly of alternative pathway C3 convertase. Properdin stabilizes C3 convertase and enhances AP amplification leading to the generation of C3a and C5a anaphylatoxins and MAC. C3a promotes tubulointerstitial fibrosis by inducing the synthesis of collagen and TGF-β1 in PTECs. C5a promotes tubulointerstitial fibrosis by inducing collagen synthesis. MAC can contribute to the development of tubulointerstitial fibrosis by inducing collagen synthesis. In addition, MAC induces ROS, TNF-α and IL-6, as well as promoting tubulointerstitial injury and cytolysis of PTECs. Furthermore, filtered plasma proteins can facilitate tubular complement activation except for filtered complement components. For example, urinary transferrin induces C3 expression and biosynthesis in PTECs, which is secreted into the tubular lumen. Besides, urinary albumin assists with properdin-mediated assembly and docking of C3 convertase at the surface of PTECs by inhibiting tubular cell binding with factor H. IL-6, interleukin 6; MAC, membrane attack complex; TNF-α, tumor necrosis factor-α.⁶⁷

A significant global challenge in nephrology is the emergence of Chronic Kidney Disease of unknown etiology (CKDu), a condition that defies conventional risk profiles. Unlike traditional CKD, which is primarily driven by diabetes and hypertension, CKDu predominantly affects young male laborers in agricultural regions of Central America and South Asia. The disease follows a subclinical and silent trajectory, often remaining undetected until advanced stages, thereby complicating clinical management and public health interventions.⁶⁸ The pathogenesis of CKDu is fundamentally multifactorial, arising from a synergy of environmental, occupational, and lifestyle determinants. Key drivers include:

- Occupational and Thermal Stress: Intensive labor in high-temperature environments—particularly in sugarcane and banana plantations—leads to chronic dehydration and heat stress. This triggers renal damage via the vasopressin axis and the activation of the polyol pathway (aldose reductase/fructokinase), which induces tubular injury.
- Agrochemical and Environmental Toxicity: Persistent exposure to herbicides and pesticides, such as glyphosate, paraquat, and organochlorines, represents a major nephrotoxic risk. This is often compounded by the consumption of unsafe drinking water contaminated with heavy metals (arsenic, cadmium, lead) or fluoride, which are difficult to remediate at the domestic level.⁶⁹
- Dietary and Biological Insults: Vulnerability is further exacerbated by the ingestion of nephrotoxins like ochratoxin A through locally harvested crops, or acute kidney injury resulting from snake envenomation.
- Genetic Predisposition: Susceptibility is modulated by a family history of renal disease and specific genetic polymorphisms in genes such as CYP1A1, GSTM1, and KIM1, which may govern the individual metabolic response to environmental toxins.

Addressing the CKDu crisis requires a dual strategy focused on rigorous prevention and accessible management. Proactive public health measures, such as community education on hydration and the regulation of hazardous agrochemicals, are essential to mitigate the incidence of new cases. For patients already experiencing functional decline, innovative surgical interventions like 3D-guided nephron-sparing surgery or minimally invasive ablation offer potential benefits for localized lesions. Furthermore, in resource-limited endemic regions, renal replacement therapy (RRT) must be adapted to local infrastructure. Initiatives such as the "PD First" model in Sri Lanka highlight the efficacy of peritoneal dialysis in expanding care accessibility. Similarly, state-sponsored programs like the Aarogyasri initiative in India demonstrate the necessity of providing universal access to hemodialysis and transplantation to bridge the socioeconomic gap in renal care.⁷⁰

Molecular Mechanisms in CKD Pathogenesis:

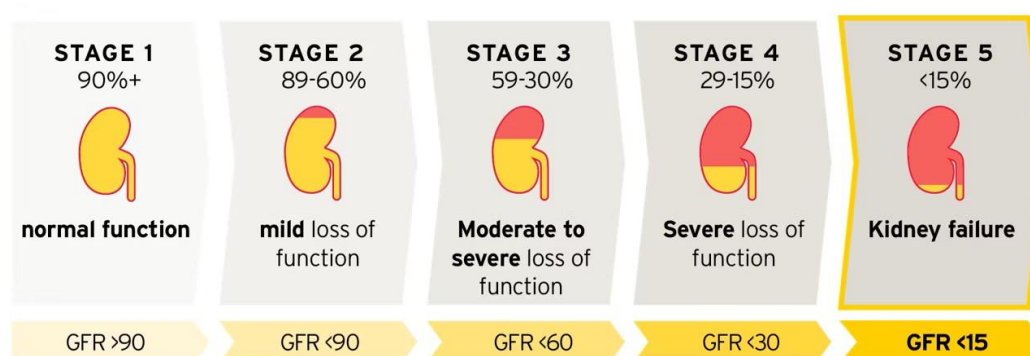
- Transforming Growth Factor-Beta (TGF- β): A central mediator of fibrosis, TGF- β stimulates ECM production and inhibits its degradation through Smad-dependent and Smad-independent signaling pathways.
- Nuclear Factor-Kappa B (NF- κ B): A transcription factor regulating inflammatory cytokines and chemokines, activated by oxidative stress and angiotensin II.
- Renin-Angiotensin-Aldosterone System (RAAS): RAAS overactivation contributes to glomerular hypertension, proteinuria, and fibrosis.
- Hypoxia-Inducible Factors (HIFs): These factors mediate cellular responses to hypoxia and promote fibrosis via pro-fibrotic and angiogenic signaling.
- Mitochondrial Dysfunction: Impaired mitochondrial function leads to energy depletion, increased ROS production, and cell death.

1.3. Clinical Picture

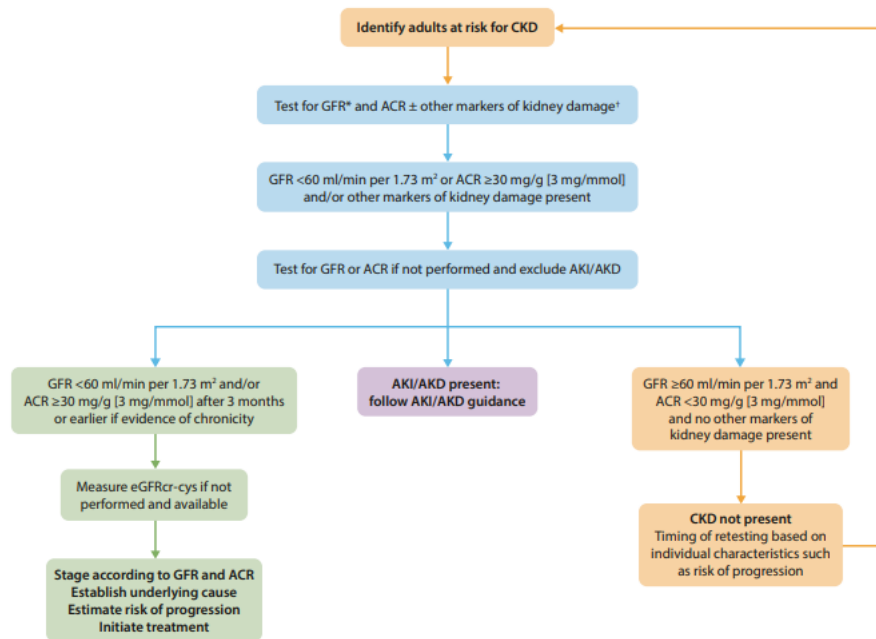
The progressive decline in kidney function, particularly the reduction in glomerular filtration rate (GFR), underlies most of the clinical and metabolic alterations seen in renal insufficiency. In addition, endocrine dysfunction contributes to further complications.

CKD progression is accompanied by distinct physiological changes across its stages:

- Early Stages (G1–G3a): Hyperfiltration and compensatory hypertrophy maintain glomerular filtration rate (GFR) but initiate glomerular and tubular injury.
- Intermediate Stages (G3b–G4): Continued nephron loss results in declining GFR, increased proteinuria, and intensified inflammation and fibrosis.
- End Stage (G5): Severe nephron depletion leads to uremia, necessitating renal replacement therapy.



The KDIGO guidelines propose a screening algorithm for the diagnosis and staging of chronic kidney disease (CKD) in adults.



Screening algorithm for diagnosis and staging of chronic kidney disease (CKD) in adults. Risk factor conditions are listed in Table 5. *For recommended methods to estimate glomerular filtration rate (eGFR), see Section 1.2. † Markers of kidney damage other than albuminuria may also be used to diagnose CKD, but albumin-to-creatinine ratio (ACR) and GFR are still required to determine stage and estimate risk of progression. Acute kidney disease (AKD) is defined by the abnormalities of kidney function and/or structure with implications for health and with a duration of ≥ 3 months.²⁸ The orange boxes indicate actions in people at risk for CKD and in whom testing should be performed. The blue boxes indicate testing steps. The green boxes indicate the identification of CKD and its stages and the initiation of treatment. The purple box indicates the identification of AKD/acute kidney injury (AKI). Please also see the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury.

The clinical landscape of Chronic Kidney Disease (CKD) is defined by a multisystemic deterioration that follows the progressive erosion of the glomerular filtration rate (GFR). As renal functional reserve is exhausted, the loss of homeostatic control manifests through a complex array of metabolic, endocrine, and electrolyte disturbances.

- ❖ **Nitrogenous Waste Elimination:** During the initial phases of renal decline, the kidneys maintain homeostatic levels of metabolic byproducts through compensatory nephron hyperfiltration. Urea, synthesized via hepatic protein catabolism, serves as an inconsistent marker due to its sensitivity to dietary protein intake and significant tubular reabsorption. In contrast, creatinine provides a more stable assessment of filtration; however, its serum concentration typically remains within reference ranges until the Glomerular Filtration Rate (GFR) undergoes a substantial reduction, often falling below 60% of normal capacity.
- ❖ **Fluid Regulation:** Early to moderate renal impairment is characterized by a diminished urinary concentrating ability. The resulting osmotic diuresis in surviving nephrons manifests clinically as polyuria and nocturia. While systemic fluid balance is often preserved through the mid-stages of the disease, advanced stages are marked by an inability to manage water intake, leading to pathological fluid sequestration and peripheral edema.

- ❖ **Electrolyte Balance:** Sodium homeostasis is remarkably resilient, as surviving nephrons increase their fractional excretion to compensate for the diminishing filtration surface. Conversely, potassium regulation remains stable only until the terminal stages of CKD. The subsequent onset of hyperkalemia represents a critical clinical milestone, necessitating urgent intervention to prevent fatal cardiac arrhythmias.
- ❖ **Acid-Base Homeostasis:** The kidney regulates systemic pH through the excretion of titratable acids (phosphates and ammonium) and the reclamation of bicarbonate. Once the GFR descends below the 30–40 mL/min threshold, these mechanisms fail, resulting in metabolic acidosis. Initially mitigated by respiratory compensation, chronic acidosis eventually triggers the mobilization of alkaline bone salts, contributing to skeletal demineralization.
- ❖ **Mineral and Bone Metabolism (CKD-MBD):** This systemic syndrome involves a complex disruption of the calcium-phosphate axis. The early decline of the Klotho protein induces resistance to FGF23, a phosphaturic hormone. The compensatory rise in FGF23, while initially preventing hyperphosphatemia, ultimately suppresses Vitamin D activation and precipitates secondary hyperparathyroidism. This hormonal imbalance drives bone remodeling and extensive vascular calcification, significantly elevating cardiovascular risk.
- ❖ **Erythropoietin Production and Anemia:** Advanced CKD is almost invariably associated with normochromic normocytic anemia. While the primary driver is the deficient renal synthesis of erythropoietin, the etiology is multifactorial. Contributing factors include uremic marrow suppression, iron sequestration driven by chronic inflammation (hepcidin-mediated), reduced erythrocyte longevity, and nutritional deficiencies (Vitamin B12/Folate), all of which are exacerbated by the oxidative stress and blood loss inherent to dialysis therapy.

1.4. Treatment

1.4.1. Conservative therapy

In alignment with the most recent KDIGO Clinical Practice Guidelines, the management of Chronic Kidney Disease (CKD) has transitioned toward an integrated, multidisciplinary strategy. This approach combines stringent pharmacological interventions with structured lifestyle modifications to slow disease progression and mitigate the heightened risk of cardiovascular mortality. **Lifestyle and Dietary Interventions:** Clinical evidence underscores the necessity of non-pharmacological management as the foundation of renal care. Key pillars include:

- **Physical Activity and Weight Management:** Adults with CKD are advised to achieve at least 150 minutes of moderate-intensity exercise weekly, tailored to individual cardiovascular tolerance and frailty. In pediatric populations, the threshold increases to 60 minutes daily. Furthermore, the

avoidance of sedentary behavior and the maintenance of an optimal Body Mass Index (BMI) are essential to reduce metabolic complications.

- **Nutritional Paradigms:** Current guidelines advocate for a shift toward plant-based dietary patterns and the minimization of ultra-processed foods.
- **Smoking cessation.**
- **Protein Titration:** For non-dialysis CKD G3–G5, a daily protein intake of 0.8 g/kg is recommended. While high intake (>1.3 g/kg) should be avoided, very low-protein diets (0.3–0.4 g/kg) supplemented with keto-analogues may be considered under strict supervision. Conversely, protein restriction is contraindicated in children due to growth risks and in elderly patients with sarcopenia.
- **Sodium Restriction:** A daily sodium intake of <2 g (approx. <5 g of salt) is suggested to manage blood pressure and volume status, except in specific sodium-wasting nephropathies.

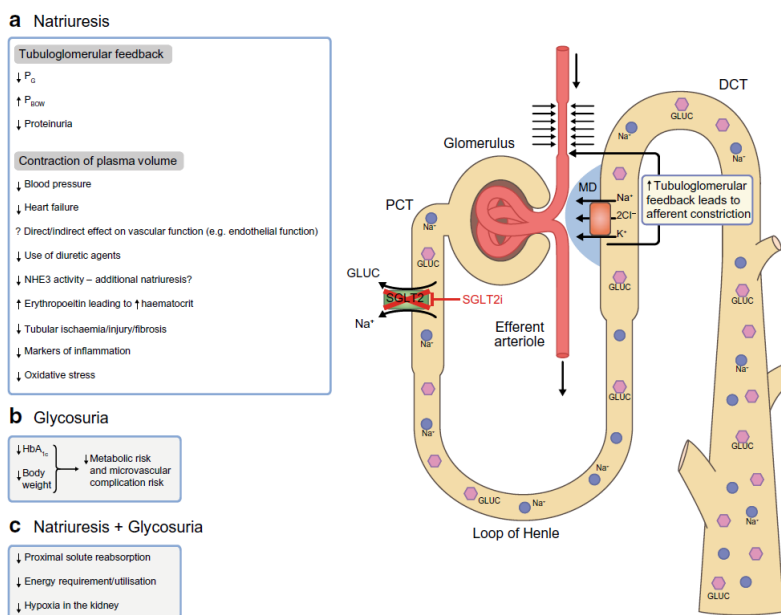
Hemodynamic and Glycemic Control: Rigorous control of systemic pressure and glucose metabolism remains paramount in preserving residual nephron function:

- **Blood Pressure Targets:** A target systolic blood pressure (SBP) of <120 mmHg is recommended for adults using standardized measurements, provided it is tolerated. In pediatric cases, the target is a mean arterial pressure (MAP) $\leq$ 50th percentile for age and height.
- **Pharmacological Nephroprotection:** The use of Renin-Angiotensin System inhibitors (RASi) - either Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) - is the gold standard for patients with albuminuria (A2 and A3), with or without diabetes. Doses should be titrated to the highest tolerated level, and therapy should ideally be maintained even if eGFR falls below 30 mL/min. Reduce proteinuria and slow CKD progression.

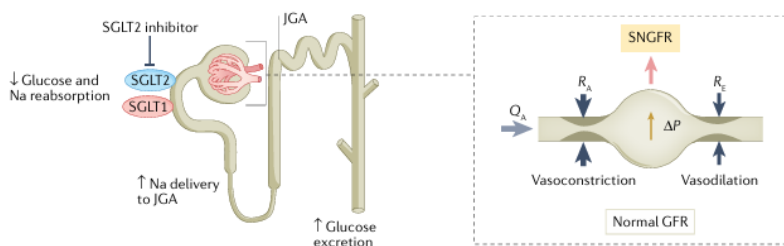
Emerging Therapeutic Frontiers: The pharmacological landscape has been revolutionized by the introduction of classes providing significant cardiorenal benefits:

- **SGLT2 Inhibitors:** These agents are now strongly recommended (Grade 1A) for adults with T2D and CKD, or those with heart failure/significant albuminuria (> 200 mg/g), provided eGFR is $\geq$ 20 mL/min. They may be continued even if eGFR subsequently declines. The Sodium-glucose cotransporter-2 inhibitors have demonstrated efficacy in reducing hyperfiltration, proteinuria, and cardiovascular risk.
- **Mineralocorticoid Receptor Antagonists (MRAs):** Nonsteroidal MRAs (e.g., finerenone) are indicated for patients with T2D and persistent albuminuria despite optimized RASi therapy, specifically to reduce the risk of progression and cardiovascular events.

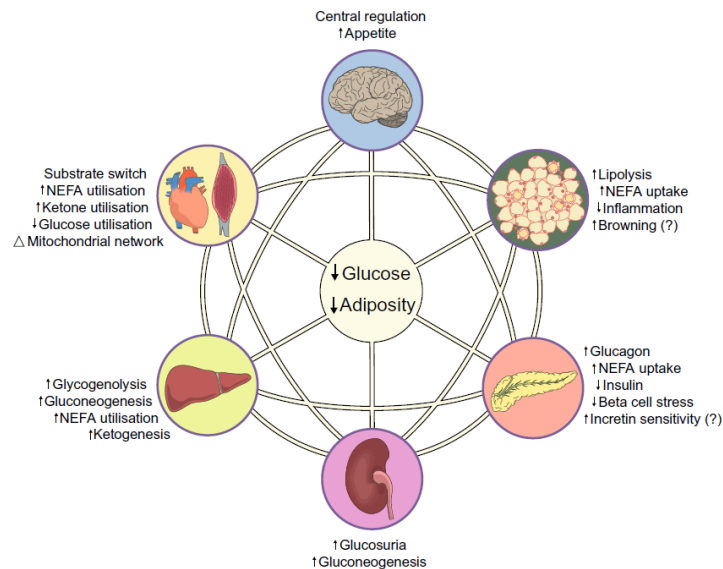
- GLP-1 Receptor Agonists: Long-acting GLP-1 RAs are recommended for patients with T2D who do not meet glycemic targets with metformin and SGLT2i, prioritizing those with proven cardiovascular benefits.



Physiological mechanisms implicated in changes in renal function following inhibition of SGLT2. (a) Natriuresis activates tubuloglomerular feedback, which decreases P_G and increases P_{Bow} , thereby reducing the transcapillary pressure gradient, GFR and albuminuria. The natriuretic effects of SGLT2 inhibitors are also associated with a sustained contraction in plasma volume and enhanced distal delivery of solutes to medullary nephron segments. Increased energy requirements for solute reabsorption are offset by a compensatory increase in erythropoietin production, which raises the haemoglobin concentration. Finally, SGLT2 inhibition is also associated with suppression of tubular injury pathways, and reduced circulating and tissue markers of inflammation and oxidative stress in experimental models. (b) Glucosuria is associated with improved glycaemic control and weight loss. (c) Sodium and glucose loss in urine may reduce proximal tubular ischaemia. This may also affect energy utilisation pathways in the medulla, thereby increasing erythropoietin production to enhance renal oxygen delivery. DCT, distal convoluted tubule; GLUC, glucose; MD, macula densa; PCT, proximal convoluted tubule; SGLT2i, SGLT2 inhibition.⁷¹



The effects of SGLT2 inhibition on 'absolute' glomerular hyperfiltration in diabetes mellitus. In patients with diabetes and poor glycaemic control, sodium-glucose linked co-transporter-2 (SGLT2) inhibition reduces reabsorption of glucose and sodium in the proximal tubule. The resulting increase in sodium delivery to the juxtaglomerular apparatus (JGA) leads to vasoconstriction of the afferent arteriole, whereas the vascular tone of the efferent arteriole is unaffected or decreases. The glomerular plasma flow rate (Q_A) and intraglomerular capillary pressure decreases and single-nephron glomerular filtration rate (SNGFR) returns to normal levels. ΔP , glomerular transcapillary hydraulic pressure difference; R_A , afferent arteriolar resistance; R_E , efferent arteriolar resistance.³³



The nexus of metabolic changes contributing to reduced plasma glucose and adiposity following inhibition of SGLT2. SGLT2 inhibitor treatment triggers a reduction in insulin:glucagon ratio that increases hepatic glycogenolysis and gluconeogenesis. Renal gluconeogenesis is also modulated by SGLT2 inhibition. The unnecessary utilisation of glucose is constrained by increased peripheral oxidation of fat facilitated by increased lipolysis in adipose tissue and augmented NEFA uptake from the circulation. Ketones are also generated by the liver and act as an alternative and efficient energy substrate for metabolism. Other efficacies in peripheral energy metabolism are also triggered, including changes in mitochondrial network homeostasis. SGLT2 inhibition increases hunger and modulates central regulation of glucose control and adiposity. In adipose tissue, altered fat utilisation may also reduce inflammation and augment fat browning. In the long term, there are additional effects in the pancreas to reduce beta cells stress and improve incretin sensitivity.⁷¹

Metabolic and Cardiovascular Risk Mitigation: Comprehensive CKD care involves the stabilization of internal milieu and the prevention of atherosclerotic events:

- **Metabolic Acidosis and Electrolytes:** Pharmacological or dietary interventions should be considered when serum bicarbonate falls below 18 mmol/L. Potassium management requires an individualized approach, prioritizing the reduction of bioavailable potassium (processed foods) and utilizing potassium exchange resins before considering RASi discontinuation.
- **Lipid and Antiplatelet Therapy:** Statin-based regimens are recommended for adults ≥ 50 years with CKD, regardless of eGFR. For secondary prevention of cardiovascular events, low-dose aspirin remains the standard of care.
- **Uric Acid Management:** Intervention is recommended for symptomatic hyperuricemia (e.g., gout), preferably using xanthine oxidase inhibitors. However, uric acid-lowering therapy is not currently suggested solely to delay CKD progression in asymptomatic patients.

Current nephrology research is pivoting from advancing therapeutic frontiers in renal management via systemic control toward precision-targeted interventions aimed at the molecular drivers of chronic renal attrition.

- **Immunomodulatory and Anti-Inflammatory Agents:** To disrupt the "cytokine storm" of advanced CKD, therapies targeting the IL-6/TNF- α axes and small-molecule NF- κ B inhibitors are being evaluated for their ability to arrest inflammatory nephron attrition.

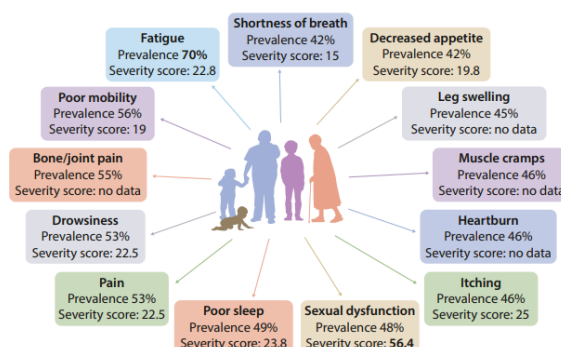
- **Redox Modulation:** Strategies focusing on mitochondrial preservation and Nrf2 pathway activation (e.g., Bardoxolone methyl or N-acetylcysteine) aim to break the feed-forward loop of oxidative stress, protecting the renal parenchyma from ROS-induced apoptosis.
- **Antifibrotic Strategies:** By targeting the "final common pathway" of organ failure, agents such as TGF- β inhibitors and pirfenidone are under investigation to inhibit myofibroblast activation and prevent the replacement of functional nephrons with non-contractile extracellular matrix.

The management of pharmacological therapy in chronic kidney disease (CKD) demands a rigorous stewardship model to navigate the profound pharmacokinetic alterations and mitigate the high risk of iatrogenic injury.

Effective clinical safety begins with precision dosing, where standard eGFR equations are often replaced by more accurate Cystatin C-based or measured GFR assessments, particularly in patients with non-steady-state volume distributions or extreme body mass. This is supported by proactive pharmacovigilance, involving the systematic screening for nephrotoxins and the continuous monitoring of serum drug levels for medications with narrow therapeutic windows. To address the risks of polypharmacy, the implementation of "sick day" protocols is essential. This involves a strategic 48–72-hour suspension of agents like metformin, RAS inhibitors, and SGLT2 inhibitors during acute illness or prior to surgery to prevent acute kidney injury (AKI) and metabolic acidosis. Furthermore, specialized safety paradigms must govern radiocontrast use, prioritizing Group II/III Gadolinium agents to avoid nephrogenic systemic fibrosis, and reproductive stewardship, which requires the continuous evaluation of teratogenic risks to align therapeutic regimens with the reproductive goals of the patient.

1.4.2. Renal replacement therapy

The transition from conservative management to Renal Replacement Therapy (RRT) is a critical clinical milestone, determined by a synthesis of objective metabolic markers and subjective patient symptomatology.



Common symptoms, prevalence, and severity in people with chronic kidney disease. To aid comparison of symptom severity scores across different outcome measures, all mean severity scores were converted to a 0–100 scale, where a higher score indicates greater severity. Adapted from Fletcher BR, Damery S, Aiyegbusi OL, et al. Symptom burden and health-related quality of life in chronic kidney disease: a global systematic review and meta-analysis.

Current guidelines advocate for a transition based on clinical urgency rather than a strict numerical threshold of glomerular filtration, although planning for access typically commences when the GFR falls within the 15–20 mL/min/1.73 m² range. The decision to initiate dialysis is primarily driven by the emergence of uremic complications that are no longer manageable through pharmacological or dietary means. These include:

- **Refractory Metabolic Derangements:** Medically resistant acid-base imbalances (metabolic acidosis) and life-threatening electrolyte abnormalities, such as persistent hyperkalemia, necessitate immediate dialytic intervention.
- **Systemic Uremic Syndrome:** The presence of neurological manifestations (uremic encephalopathy or neuropathy), serositis (notably uremic pericarditis), and intractable pruritus signals a critical accumulation of nitrogenous waste products.
- **Gastrointestinal and Nutritional Decline:** Progressive anorexia and a deteriorating nutritional status that remains refractory to specialized dietary intervention are key indicators of advancing uremia.
- **Volume and Hemodynamic Instability:** An inability to control volume overload (resulting in congestive heart failure or pulmonary edema) or malignant hypertension through diuretic therapy and sodium restriction is a primary indication for starting RRT.

To ensure a seamless transition and reduce the morbidity associated with emergency dialysis initiation, proactive planning is essential. Clinical consensus suggests preparing for preemptive kidney transplantation or permanent dialysis access (such as an arteriovenous fistula or peritoneal catheter) when the GFR reaches the <15–20 mL/min threshold, or when validated risk-prediction models indicate a >40% probability of requiring KRT within a two-year horizon. This "planned" approach is associated with significantly better outcomes, including lower rates of catheter-related infections and reduced cardiovascular stress, compared to "crash" starts. Furthermore, it allows for cognitive and nutritional assessments to ensure the patient is physically and psychologically prepared for the chosen modality.

Often, the management of end-stage renal disease (ESRD) necessitates the implementation of Renal Replacement Therapy (RRT), a clinical spectrum encompassing hemodialysis, peritoneal dialysis, and kidney transplantation. Each modality is designed to substitute for the lost excretory and homeostatic functions of the native kidneys, though they differ significantly in their physiological approach, technological requirements, and impact on patient quality of life.

Dialytic therapies function as a bridge or a long-term maintenance strategy by utilizing semipermeable membranes to facilitate the removal of uremic toxins and excess fluid.

- ❖ Hemodialysis (HD): This modality relies on an extracorporeal circuit where blood is pumped through a synthetic dialyzer. Solute clearance is primarily driven by diffusion across a concentration gradient, while fluid removal is achieved through ultrafiltration via hydrostatic pressure. Although HD provides rapid clearance of small molecules, it is often associated with hemodynamic instability and requires permanent vascular access, such as an arteriovenous fistula or a CVC. From a pharmacoeconomic perspective, the maintenance of a patient on chronic hemodialysis imposes a substantial burden on healthcare systems, with contemporary literature estimating annual expenditures to be approximately €35,000 per individual.⁷²
- ❖ Peritoneal Dialysis (PD): As a more physiological, home-based alternative, PD utilizes the patient's own peritoneum as a biological dialysis membrane. Through the instillation of a hypertonic glucose solution via an indwelling catheter, waste products are removed via diffusion and convection. PD is noted for its superior preservation of residual renal function and greater lifestyle flexibility, though it carries a long-term risk of peritoneal membrane fibrosis and glucose-mediated metabolic stress. A standard peritoneal dialysis (PD) solution typically utilizes a fill volume of two liters and is composed of essential electrolytes—specifically sodium, magnesium, calcium, and chloride—alongside a buffering agent such as lactate, bicarbonate, or a combination of both. To facilitate the daily removal of surplus fluid (defined as peritoneal ultrafiltration, UF) and to enhance convective transport (peritoneal clearance), an osmotic agent is included in the formulation. Following a dwell period of 4 to 8 hours, the effluent is drained from the peritoneal cavity and replaced with fresh dialysate. This procedure can be managed through two primary modalities:
 - Continuous Ambulatory Peritoneal Dialysis (CAPD): A manual method involving 4 to 5 exchanges performed throughout the day.
 - Automated Peritoneal Dialysis (APD): An automated process utilizing a mechanical cycler, typically conducted overnight for a duration of 8 to 10 hours.
- ❖ Kidney Transplantation: Is the Gold Standard and remains the definitive therapeutic goal for eligible ESRD patients, offering the only true restoration of both the kidney's filtration capacity and its essential endocrine functions, such as erythropoietin production and vitamin D activation. In terms of Clinical Outcomes, compared to chronic dialysis, transplantation is associated with a dramatic reduction in cardiovascular mortality and a significant improvement in neurocognitive and physical function. Despite its clinical superiority, the global application of kidney transplantation is severely constrained by a critical scarcity of donor organs and the complications associated with long-term immunosuppressive therapy. While these regimens are indispensable for preventing allograft rejection, they paradoxically introduce significant secondary morbidities,

including opportunistic infections, increased oncological risk, and drug-induced nephrotoxicity - most notably from the chronic use of calcineurin inhibitors. To address these limitations, the field is advancing toward revolutionary biological and technological frontiers:

- Xenotransplantation (Exotransplantation): This approach has emerged as a groundbreaking strategy to alleviate the organ shortage. Recent experimental milestones involving the transplantation of genetically engineered porcine kidneys into human recipients demonstrate the potential of using animals as a scalable organ source. By utilizing advanced gene-editing tools to mitigate hyperacute rejection and zoonotic risks, xenotransplantation could virtually eliminate transplant waiting lists.
- The Bionic Kidney: Beyond biological substitutes, the development of the biohybrid artificial kidney represents a fusion of nanotechnology and regenerative medicine. These implantable devices are designed to combine high-efficiency synthetic filtration membranes with a bioreactor containing living renal tubule cells. This dual-system aims to replicate not only the kidney's filtration capacity but also its essential metabolic and endocrine functions, potentially offering a permanent solution that bypasses the need for both dialysis and chronic immunosuppression.

1.4.3. New therapeutic frontiers

Anti-Inflammatory and Antioxidant Strategies

New frontiers are being explored in anti-inflammatory and antioxidant strategies for chronic kidney disease (CKD), aiming to reduce oxidative stress and inflammation—key drivers of disease progression and cardiovascular complications. Although following a healthy diet and engaging in physical activity can offer benefits, poor adherence often necessitates pharmacological therapies and supplements. Vitamins, minerals, and plant-derived compounds represent promising therapeutic approaches due to their antioxidant and anti-inflammatory properties.

Vitamins and Minerals

Magnesium: Regulates blood pressure and reduces inflammation; deficiency is linked to vascular calcification and mortality.⁷³

Selenium: A cofactor of glutathione peroxidase, often deficient in dialysis patients; enhances antioxidant defense.⁷⁴

Phosphorus: Hyperphosphatemia is common in CKD and associated with calcification and mortality; manageable with binders and plant-based diets.⁷⁵

Vitamin C: A powerful antioxidant, often deficient due to dietary restrictions and dialysis loss; beneficial but must be dosed cautiously.^{76,77}

Vitamin E: Reduces lipid peroxidation; clinical studies show mixed results, but promising effects in hemodialysis.^{78–80}

Vitamin D: Regulates RAAS, NF-κB, and TGF-β; improves kidney function and reduces fibrosis and inflammation.^{77,81–84}

Vitamin A (ATRA): Attenuates glomerular and tubular inflammation through inhibition of the TLR4/NF-κB pathway.⁸⁵

Vitamin B1 (Thiamine): Essential for glucose metabolism; benfotiamine improves endothelial function and antioxidant capacity.^{86–88}

Anti-inflammatory and antioxidant activities of the minerals (selenium and phosphate) and vitamins detailed in this study, with evaluation of the pathways involved. Decreased (↓) or increased (↑).³⁷

Anti-Inflammatory Activity		Antioxidant Activity	Experimental Model and References
↑Magnesium	↓CRP		Human study; [84]
↑Selenium		↑GSH-Px ↓ROS	Human study; [87]
↓Phosphate	↓FGF23 ↓PTH		Human study; [90,92,123,124]
↑Vitamin C	↑hydroxylase/monooxygenase co-factor	↓MDA ↓tissue lipid oxidation ↑tissue GSH ↑Co-antioxidant vit.E ↓ROS	Human study; [98] Animal model; [99]
↑Vitamin E	↓8-OHdG	↓lipid peroxidation ↓NADPH activity ↓inflammatory mediators	Cellular and animal model; [101] Animal model; [102] Human study; [108]
↑Vitamin D	↓NF-κB signaling pathway ↓RAAS ↓TGF-β/Smad ↓Wnt/β-catenin		Animal model; [114] Cellular and animal model; [115] Animal model; [116] Cellular and animal model; [117]
↑Vitamin A	↓TLR4/NF-κB signaling pathway		Animal model; [118]
↑Vitamin B1		↓plasma lactate levels	Human study; [119]

8-OHdG, 8-hydroxy-2-deoxyguanosine; FGF 23, Fibroblast growth factor 23; GSH-Px, Glutathione peroxidase; MDA, Malondialdehyde; NADPH, Nicotinamide adenine dinucleotide phosphate hydrogen; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PTH, Parathyroid Hormone; RAAS, renin–angiotensin–aldosterone system; ROS, Reactive oxygen species; TGF-β/Smad, Transforming growth factor-β/Smad; TLR4, Toll-like receptor 4; Vit. E, Vitamin E.

Plant-Derived Metabolites

- Quercetin: A flavonoid with antioxidant, antidiabetic, and anti-inflammatory activity; improves renal biochemical and histological parameters.
- Curcumin: A pigment from *Curcuma longa*; reduces oxidative stress, fibrosis, inflammation, and improves mitochondrial and intestinal function.
- Resveratrol: A stilbenoid found in grapes and berries; modulates NF-κB and Nrf2, protects against fibrosis, oxidative stress, and muscle atrophy.
- Cordycepin: An adenosine derivative from *Cordyceps militaris*; reduces inflammation and oxidative stress via TLR4/NF-κB.
- HEA: A *Cordyceps* compound active against tubulointerstitial fibrosis; modulates TGF-β/Smad and NF-κB pathways.

- *Coreopsis tinctoria*: Rich in flavonoids, reduces renal damage, inflammation, and fibrosis in diabetic models; acts on AMPK, TGF- β /Smad, and NF- κ B pathways. Also lowers lipid levels via ADRP and improves intestinal permeability.
- *Phyllanthus niruri*: A tropical plant with high flavonoid and polyphenol content; enhances SOD, CAT, and GPx activity, protecting the kidney from oxidative stress.
- *Allicin*: A sulfur compound from garlic; improves renal function and reduces CKD-related hypertension via AT1, Nrf2/Keap1, and eNOS pathways. Its efficacy is comparable or superior to losartan.
- *Ursolic Acid*: A triterpenoid found in fruits and spices; reduces inflammation, fibrosis, and muscle loss via NF- κ B, STAT3, and myostatin. It may also lower bilirubin, which is linked to mortality in dialysis patients.
- *EGCG (Epigallocatechin-3-gallate)*: A green tea polyphenol with potent antioxidant activity; neutralizes ROS, chelates metals, activates Nrf2, and inhibits the NLRP3 inflammasome. Improves proteinuria, creatinine, and reduces uremic toxins like methylguanidine. Protects against diabetic nephropathy, glomerulonephritis, and ischemia-reperfusion injury.

The anti-inflammatory and antioxidant activities of the described plant-derived metabolites, With evaluation of the involved pathways which can result Decreased ($\downarrow$) or increased ($\uparrow$).³⁷

	Anti-Inflammatory Activity	Antioxidant Activity	Experimental Model and References
<i>Quercetin</i>	$\downarrow$ FGF23 $\downarrow$ PTH	$\downarrow$ LDH $\downarrow$ SOD	Animal model; [130]
<i>Curcumin</i>	$\downarrow$ VEGF $\downarrow$ TGF- β $\downarrow$ CTGF $\downarrow$ fibronectin and collagen IV $\downarrow$ iNOS and $\downarrow$ COX-2 $\downarrow$ TNF- α $\downarrow$ MCP-1 $\downarrow$ JNK/NF- κ B $\downarrow$ NLRP3	$\downarrow$ NO and $\downarrow$ ONOO ⁻ $\downarrow$ O ₂ ⁻ and $\downarrow$ H ₂ O ₂ $\uparrow$ SOD $\uparrow$ CAT $\uparrow$ GSR $\uparrow$ HO-1 $\uparrow$ GST $\uparrow$ NQO1 $\uparrow$ GCL	Animal model; [131,132] Cellular model; [133–137] Animal model; [138–141]
<i>Resveratrol</i>	$\downarrow$ NF- κ B $\downarrow$ pro-inflammatory cytokines and enzymes	$\uparrow$ Nrf2 $\uparrow$ antioxidant enzymes	Human study; [143,145] Animal model; [146–148]
<i>Cordycepin</i>	$\downarrow$ NF- κ B $\downarrow$ TNF- α $\downarrow$ IL-6 $\downarrow$ IL-1 β $\downarrow$ TGF- β 1/Smad		Animal model; [153] Cellular model; [154] Human study and cellular model; [155]
<i>Flavonoids of C. tinctoria</i>	$\downarrow$ NF- κ B signaling pathway $\downarrow$ COX-2 $\downarrow$ MCP-1 and $\downarrow$ collagen IV $\downarrow$ AMPK $\downarrow$ TGF- β /Smad		Animal model; [158,160] Cellular model; [161]
<i>Flavonoids and polyphenols of P. niruri</i>		$\uparrow$ SOD $\uparrow$ CAT $\uparrow$ GPx	Animal model; [164]
<i>Allicin</i>		$\downarrow$ AT1R $\downarrow$ Keap1 $\downarrow$ eNOS $\uparrow$ Nrf2 $\uparrow$ SOD $\uparrow$ CAT $\uparrow$ GPx	Animal model; [167,168]
<i>Ursolic acid</i>	$\downarrow$ IL-6 $\downarrow$ NF- κ B $\downarrow$ p-STAT3 $\downarrow$ C/EBP- δ		Human study and animal model; [170] Animal model; [172] Cellular and animal model; [173]
<i>Epigallocatechin-3-gallate</i>	$\downarrow$ NF- κ B $\downarrow$ NLRP3 $\downarrow$ caspase-1 $\downarrow$ IL-1 β and IL-18 $\downarrow$ p-Akt $\downarrow$ p-JNK $\downarrow$ p-ERK1/2 $\downarrow$ p-P38 $\uparrow$ PPAR γ and $\uparrow$ SIRT1 $\downarrow$ MCP-1 $\downarrow$ TGF- β	$\uparrow$ Nrf2 $\uparrow$ GPx $\uparrow$ HO-1 $\downarrow$ AGE and lipid peroxidation $\downarrow$ ROS	Cellular model; [176] Animal model; [177–182]

AGE: advanced glycation end-product; AMPK: 5' AMP-activated protein kinase; AT1R: angiotensin II receptor type 1; C/EBP: CCAAT-enhancer-binding proteins; CAT: catalase; COX-2: cyclooxygenase-2; CTGF: connective tissue growth factor; eNOS: endothelial nitric oxide synthase; FGF23: fibroblast growth factor 23; GCL: glutamate-cysteine ligase; GPx: glutathione peroxidase; GSR: glutathione-disulfide reductase; GST: glutathione S-transferase; H₂O₂: hydrogen peroxide; HO-1: heme oxygenase-1; IL-18: interleukin 18; IL-1 β : interleukin 1 beta; IL-6: interleukin 6; iNOS: inducible nitric oxide synthase; JNK: c-Jun N-terminal kinases; KEAP1: Kelch-like ECH-associated protein 1; LDH: lactate dehydrogenase; MCP-1: monocyte chemoattractant protein-1; NF- κ B: nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3; NO: nitric oxide; NQO1: NAD(P)H dehydrogenase [quinone] 1; Nrf2: nuclear factor erythroid 2-related factor 2; O₂ $\cdot^-$: superoxide; ONOO $\cdot^-$: peroxynitrite; p-Akt: phospho protein kinase B; p-ERK: phospho extracellular signal-related kinase; p-P38: phospho mitogen-activated protein kinases; PPAR: peroxisome proliferator-activated receptor; p-STAT3: phospho signal transducer and activator of transcription 3; PTH: parathyroid hormone; ROS: reactive oxygen species; SIRT-1: sirtuin 1; SOD: superoxide dismutase; TGF- β : transforming growth factor beta; TNF- α : tumor necrosis factor alpha; VEGF: vascular endothelial growth factor.

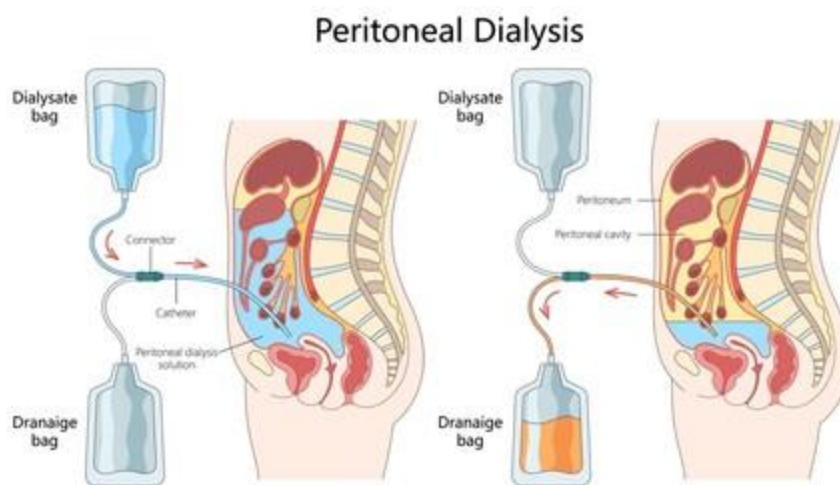
These natural compounds and micronutrients represent promising therapeutic targets to slow CKD progression, improve kidney function, and reduce systemic complications. I can help you turn this summary into an article, presentation, or infographic if you'd like.

Nutritional and Dietary Therapy

Nutritional therapy represents a cornerstone in the management of chronic kidney disease (CKD), acting as a non-pharmacological intervention capable of modulating disease progression and optimizing metabolic homeostasis in affected patients. Low-protein diets (LPD), particularly very-low-protein diets (VLPD), have demonstrated beneficial effects in reducing urea production and uremic symptoms, thereby contributing to a slower decline of renal function. This therapeutic approach also allows for a reduction in pharmacological burden, decreasing the use of antihypertensive agents, phosphate binders (to prevent secondary hyperparathyroidism and vascular calcification), erythropoietin (for anemia management), and diuretics (to control edema), thus providing both clinical and metabolic benefits.⁸⁹ The main objectives of nutritional therapy include maintenance of adequate nutritional status, prevention and correction of metabolic complications, and delay in the initiation of dialysis, through the regulation of protein, sodium, potassium, and phosphorus intake, combined with an appropriate caloric supply.⁹⁰ Recent studies have revealed a functional connection between the kidney and the gut microbiota. Elevated plasma urea levels in CKD patients, together with gut microbiota alterations, increase intestinal permeability and lead to damage of the epithelial barrier. Therefore, preservation of gut microbiome quality through dietary modulation - particularly by balancing protein intake and increasing dietary fiber - is of primary importance.⁹¹ VLPD interventions have been shown to reduce plasma levels of p-cresol sulfate (PCS) by approximately 30–35% after only one week of dietary treatment an effect attributed to lower urea concentrations and the adoption of plant-based nutritional patterns.⁹² In parallel, supplementation with short-chain fatty acids (such as acetic, butyric, and propionic acids) has demonstrated anti-inflammatory effects and beneficial modulation of gut-derived uremic toxins, improving inflammatory markers even in hemodialysis (HD) patients.⁹³

2 PERITONEAL DIALYSIS

Peritoneal Dialysis (PD) represents a significantly more physiological alternative to hemodialysis (HD), offering distinct clinical advantages including lifestyle adaptability, enhanced preservation of residual renal function, and lower economic costs. Despite these benefits and survival rates comparable to HD—or even superior during the initial years of treatment—PD is utilized by only approximately 10% of the end-stage renal disease (ESRD) population.⁹⁴⁻⁹⁶ As a home-based therapy, PD can be administered manually via Continuous Ambulatory Peritoneal Dialysis (CAPD) or through an Automated Peritoneal Dialysis (APD) cycler, providing patients with substantial autonomy.⁹⁷



2.1. Historical Overview

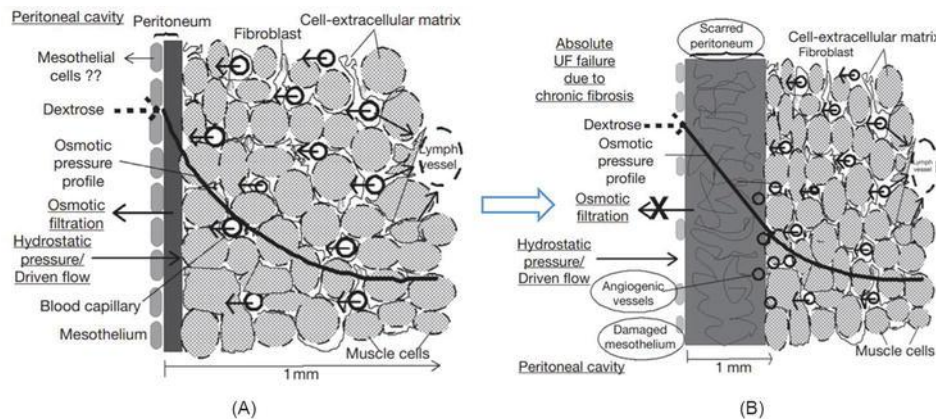
The evolution of Peritoneal Dialysis (PD) has transitioned from early experimental observations of peritoneal permeability to a sophisticated home-based therapy. Initially conceptualized in the early 20th century, the clinical application was hindered by the lack of sustainable access and bio-compatible solutions. The landmark introduction of the Tenckhoff catheter and the development of the "Closed System" were pivotal in mitigating peritonitis, eventually allowing for the transition from intermittent hospital-based treatments to Continuous Ambulatory Peritoneal Dialysis (CAPD) and, subsequently, Automated Peritoneal Dialysis (APD).

2.2. Theoretical and Physical Principles

The efficacy of PD is predicated on the movement of water and solutes across a biological semipermeable membrane, governed by distinct biophysical mechanisms

- Ultrafiltration: This represents the removal of fluid from the intravascular compartment into the peritoneal cavity. In PD, ultrafiltration is primarily driven by an osmotic gradient (generated by glucose or icodextrin) rather than the hydrostatic pressure gradients typical of hemodialysis.

- **Diffusion and Convection:** Diffusion is the primary mechanism for the clearance of small solutes (e.g., urea, creatinine), moving down their concentration gradients. In contrast, convection (solvent drag) occurs when larger middle molecules are "dragged" across the membrane alongside water during ultrafiltration, significantly contributing to the total clearance of uremic toxins.
- **Osmosis:** The movement of water from a region of low solute concentration to high solute concentration. The use of osmotic agents in the dialysate creates a chemical potential difference that facilitates the removal of excess total body water.



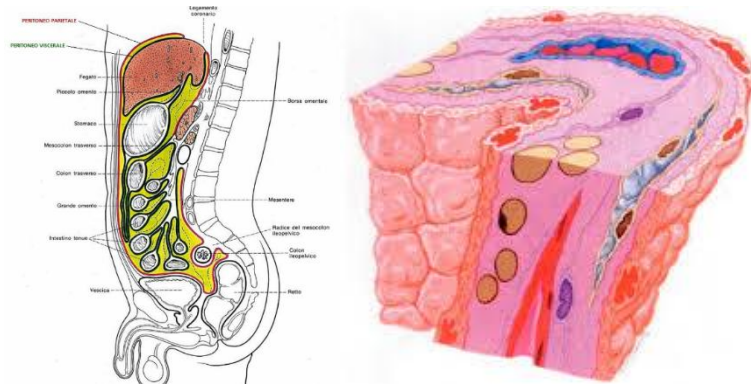
Distributed concept of normal ultrafiltration barrier. Dextrose diffuses from dialysate into tissue and sets up an osmotic pressure profile (thick curved line).⁹⁸

2.3. Anatomy of the Peritoneal Membrane

The peritoneal membrane is not a single anatomical structure but a complex physiological organ system that serves as a multi-layered barrier between the blood in the peritoneal capillaries and the dialysate in the abdominal cavity.

2.3.1. Macroscopic Anatomy

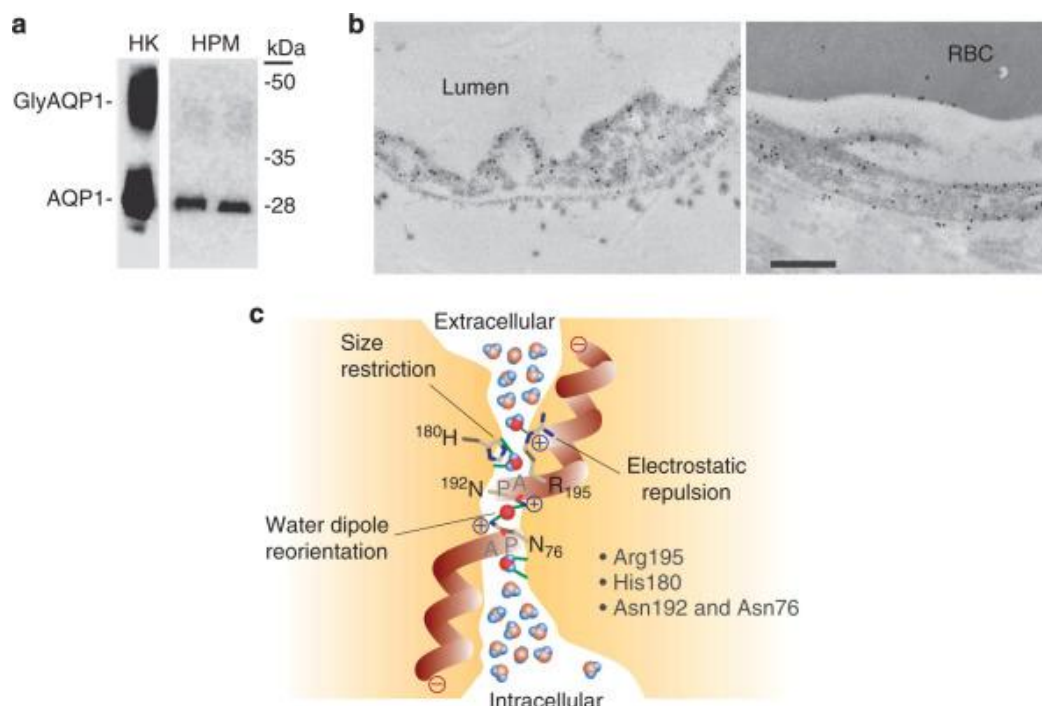
Macroscopically, the peritoneum is the largest serous membrane in the human body, with a surface area approximately equal to the total body surface area (1,7-2,0 m²). It is divided into two continuous layers: the parietal peritoneum, which lines the abdominal wall and is highly vascularized via the systemic circulation, and the visceral peritoneum, which covers the intra-abdominal organs. The space between these layers, the peritoneal cavity, typically contains a minimal amount of lubricating serous fluid (5–100 mL), but in the context of PD, it acts as the reservoir for several liters of dialysate. While the peritoneal cavity is entirely sequestered in males, it communicates with the external environment in females via the uterine tube orifices.



The normal peritoneum.⁹⁹

The dialysis process utilizes the peritoneum as the interface for metabolic exchange. Structurally, the membrane consists of:

- The Mesothelium: A superficial layer of polygonal epithelial cells characterized by numerous microvilli that expand the functional surface area twenty-fold. These cells are metabolically active, featuring a well-developed Golgi apparatus and mitochondria.
- The Interstitium: A layer of loose connective tissue and a mucopolysaccharide matrix containing collagen fibers, fibroblasts, and macrophages.
- The Capillary Endothelium: The primary barrier to transport, consisting of non-fenestrated flat cells resting on a continuous basement membrane. Dialytic exchange is facilitated by a tunneled abdominal catheter, where a sterile, hypertonic solution is instilled to promote the movement of waste products and excess fluid via diffusion (along concentration gradients) and convection (driven by osmotic pressure).



Expression and distribution of aquaporin-1 (AQP1) in the peritoneal membrane; structure of the water pore. (a) Immunoblotting for AQP1 in human kidney (HK) and human peritoneal membrane (HPM) extracts. The signal for the core AQP1 (28 kD) and glycosylated AQP1 (GlyAQP1; 35–50 kD) is detected in the extracts, with lower expression levels in the peritoneal membrane. (b) Immunogold electron microscopy on mouse visceral peritoneum uncryl sections shows a very strong signal for AQP1 in the plasma membrane and plasma membrane infoldings of capillary endothelial cells. Comparison of the labeling density in wild-type mice shows that AQP1 labeling is markedly stronger in endothelial cells than in red blood cells (RBCs). Bar=500 nm. (c) Structure and selectivity of the water pore of AQP1. The channel consists of an extracellular and a cytoplasmic vestibule connected by an extended narrow pore or selectivity filter. Four bound water molecules are localized within the selectivity filter, along three hydrophilic binding sites in the long hydrophobic pore segment. Residues of the constriction region, in particular Arg195, His180, Asn192, and Asn76, are critical in establishing water specificity and proton exclusion.¹⁰⁰

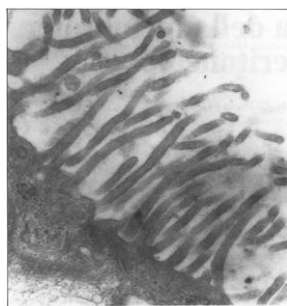
The peritoneal fluid is a complex biological medium derived from a combination of interstitial fluid, originating from the contacted abdominal viscera, and plasma filtrate from the peritoneal microvasculature. Under physiological conditions, this fluid contains water, electrolytes, and proteins, as well as a cellular population consisting of desquamated mesothelial cells, macrophages, lymphocytes, and fibroblasts.

2.3.2. Microscopic Anatomy

The peritoneal membrane is a complex histological barrier with an average thickness of 0.13 ± 0.06 mm. It functions as a multi-layered structure composed of the mesothelium, an underlying interstitium, a dense vascular network, and nerve fibers.

The most superficial layer consists of the mesothelium, a monocouche of flattened, polygonal epithelial cells. These cells have an average thickness of approximately 670 nm and a diameter ranging from 20 to 30 μm , featuring a centrally located oval nucleus. They are anchored to a continuous basement membrane that provides a structural demarcation from the interstitium.

The luminal surface, particularly within the visceral peritoneum, is densely populated with microvilli (1.5 - 4.2 μm in length), which effectively expand the functional mesothelial surface area by twenty-fold. Cellular continuity is maintained through a specialized complex of intercellular junctions - including the *zonula occludens*, *zonula adhaerens*, and desmosomes. This configuration ensures a continuous yet plastic serosa, allowing the membrane to adapt to the shifting shapes and volumes of the intra-abdominal viscera.



Peritoneal mesothelial microvilli visualized via transmission electron microscopy (TEM).¹⁰¹

Internal organelles, such as numerous mitochondria, a prominent Golgi apparatus, and an extensive endoplasmic reticulum, reflect high metabolic activity. Furthermore, the presence of luminal vesicles facilitates active pinocytosis and transcellular transport mechanisms.

Beneath the basement membrane lies the lamina propria, characterized by loose connective tissue interspersed with elastic and collagen fibers oriented parallel to the peritoneal surface. The elastic fibers are organized into two distinct strata: a superficial layer of thin, densely packed fibers adjacent to the mesothelium, and a deeper layer containing coarser fibers. The interstitium itself is composed of a mucopolysaccharide matrix and connective tissue harboring fibroblasts, histiocytes, and macrophages.

The vascular and nerve supply of the peritoneum reflects the distinct embryological origins of its two layers. The visceral peritoneum is an anatomical extension of the viscera, sharing their sympathetic innervation and blood supply. Conversely, the parietal peritoneum is supplied by the systemic arterial, venous, and lymphatic systems of the abdominal wall, with its sensory innervation provided by the spinal nerves

The peritoneal vascular tree is a critical component of dialytic exchange:

- **Arterial Supply:** Vessels with a maximum diameter of 100- 150 μm transition into delicate arterioles. These possess a discontinuous muscular layer, allowing endothelial cells to participate actively in transvascular exchange.
- **Capillaries:** With an average diameter of 7.2 μm , these consist of a continuous, non-fenestrated endothelial layer resting on a basement membrane (0.17 - 0.25 μm thick). Solute transport occurs via both intercellular (paracellular) and intracellular (pinocytic) pathways.
- **Venules:** These exhibit an endothelial structure similar to capillaries but are supported by a smooth muscle cell layer.

The lymphatic system features an endothelium anchored to a fenestrated basement membrane. These vessels play a fundamental role in the reabsorption of fluid from the peritoneal cavity, directly influencing the net ultrafiltration rate achieved during peritoneal dialysis.

2.4. Physiology of the Peritoneal Membrane

The primary physiological role of the peritoneum is to encapsulate the viscera, optimizing the mechanical relationship between the internal organs and the abdominal wall across various postural states - such as the upright or supine positions - and during the contraction of the abdominal musculature. This mechanical harmony is facilitated by the secretion of a specialized lubricating surfactant, primarily composed of phosphatidylcholine, by the mesothelial cells.

The microscopic architecture previously described strategically dictates both the baseline physiology of the peritoneum in healthy individuals and its functional capacity as a dialysis interface. During dialytic exchange, the removal of water and solutes is governed by the cumulative transport resistance

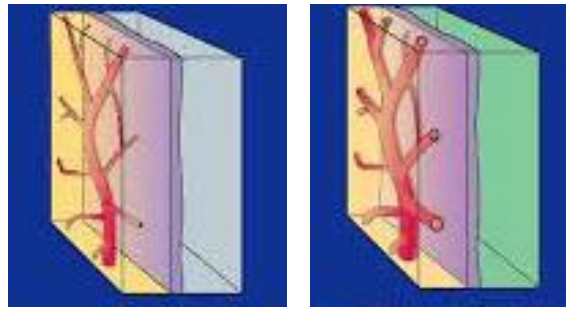
exerted by the distinct structural components of the system: the capillary endothelium, the interstitium, and the mesothelial layer.

In the context of dialysis, the peritoneal membrane should not be viewed merely as the mesothelium, but rather as a complex system of barriers. The "distributed resistance model" identifies six distinct layers arranged in series that solutes must traverse from the intravascular compartment to the dialysate:

- R1: The stagnant fluid film within the capillary lumen.
- R2: The capillary endothelium (the primary transport barrier).
- R3: The endothelial basement membrane.
- R4: The interstitium (extracellular matrix).
- R5: The peritoneal mesothelium.
- R6: The stagnant fluid layer on the peritoneal surface of the mesothelium.

While synthetic membranes allow for a precise estimation of hydraulic permeability and pore density, characterizing the biological peritoneal membrane is inherently more complex due to the continuous interference between diffusion and convection. Empirically, the peritoneum behaves as a structure with low pore density but a wide dispersion of pore diameters, permitting even the passage of larger proteins like albumin. This functional behavior is best described by the "Three-Pore Model." Solute movement occurs through two primary mechanisms: diffusion (the dominant transport mode for low-molecular-weight solutes) and Convection (Solvent Drag - the principal mechanism for high-molecular-weight molecules, occurring alongside water movement).

From a resistance perspective, the mesothelium and its associated stagnant fluid films offer negligible hindrance to transport. The interstitium acts as a partial barrier, contributing approximately one-third of the total diffusive resistance for small solutes. However, the capillary endothelium remains the definitive rate-limiting barrier. Under physiological conditions, in the absence of dialysate, only a limited fraction of the peritoneal microvasculature is perfused, with an estimated blood flow of 50–80 mL/min. The introduction of dialysate promotes recruitment of additional capillaries, thereby expanding the effective surface area for exchange and increasing blood flow to approximately 100–150 mL/min.

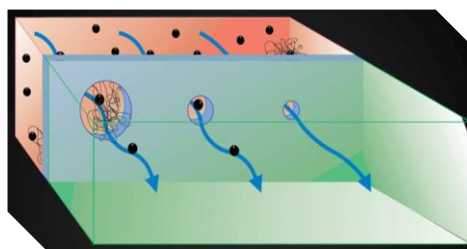


Peritoneal capillary behavior in the presence and absence of dialysate

The specialized pore system on the endothelial surface - comprising large, small, and ultra-small pores - regulates transport based on molecular size, forming the basis of the Three-Pore Theory of Capillary Transport.

The Three-Pore Model of Transport

The functional behavior of the peritoneal membrane as a molecular sieve is most accurately characterized by the Three-Pore Model, which conceptualizes the capillary endothelium as the primary rate-limiting barrier for exchange. Unlike the specialized Glomerular Filtration Barrier (GFB), which discriminates based on molecular shape and deformability, the peritoneal membrane functions as a biological gel filtration matrix. Compared to the classical Pyle-Popovich (P&P) model, the three-pore theory provides superior predictive accuracy for small (2.3–15 Å), intermediate (15–36 Å), and large solutes, utilizing significantly lower reflection coefficients ($\sigma < 0.1$) for small molecules and identifying a tenfold higher ultrafiltration capacity ($L_p S$).¹⁰²



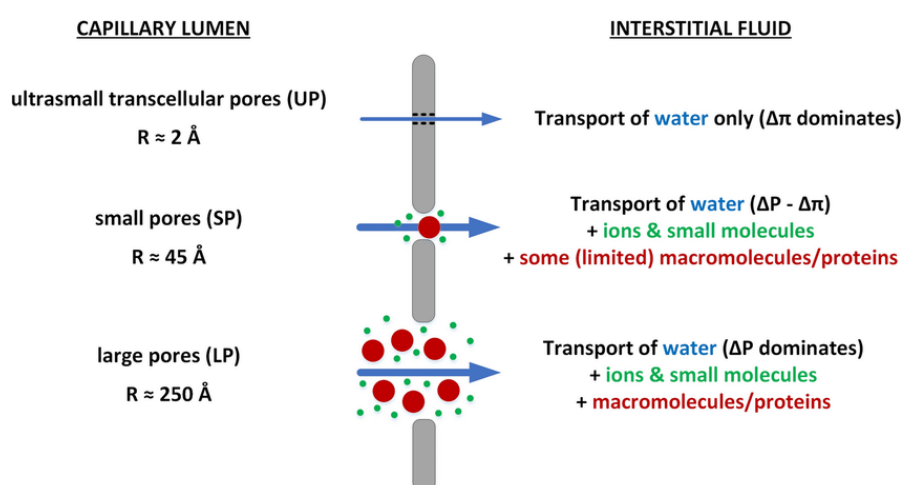
Three-Pore model of transport

According to this model, water and solute movement occur via three distinct pathways:

- Small Pores (Radius 40–55 Å): These account for approximately 99% of the total pore area and 90-95% of the ultrafiltration coefficient. They represent the primary route for the diffusive transport of low-molecular-weight solutes, such as urea and creatinine. While albumin (radius 36 Å) experiences minimal passage through these channels, the transport of larger proteins like immunoglobulins is entirely obstructed.
- Large Pores (Radius 150–500 Å): Comprising less than 0.1% of the total pore population, these rare pathways allow the unrestricted passage of macromolecules and proteins (e.g., albumin).

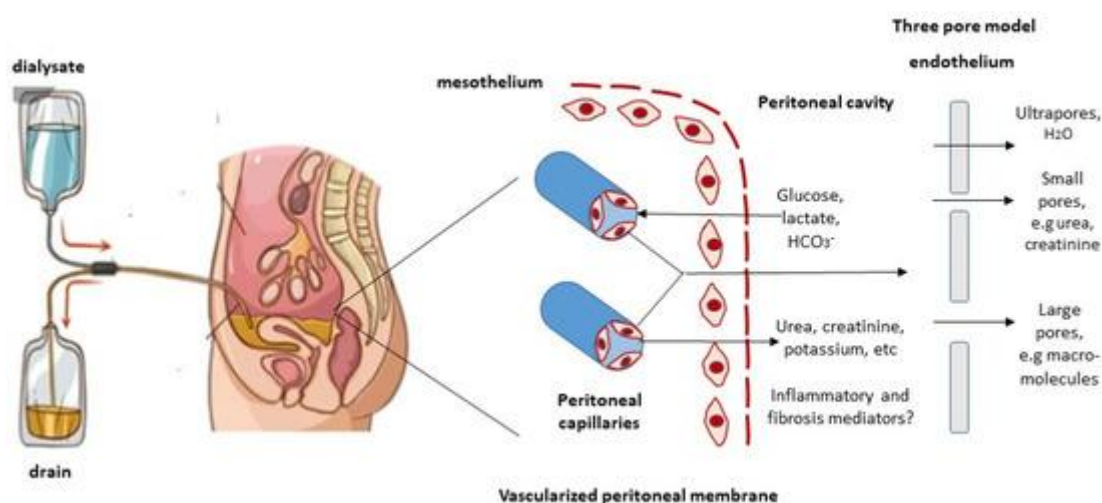
Their exact anatomical nature remains a subject of debate; they may represent wide intercellular gaps, vesicular-vacuolar transport systems, or transcellular pinocytosis, reflecting the dynamic nature of a living biological membrane.

- Ultra-small Pores (Radius 3–5 Å): Identified as Aquaporin-1 (AQP-1), these transcellular water-only channels are identical to those found in the proximal renal tubule and erythrocytes. They contribute approximately 2% of the total L_pS and are exclusively permeable to water, effectively excluding all solutes. These channels are responsible for Free Water Transport (FWT) in response to crystalloid osmotic gradients.



The three-pore model of the transcapillary transport of water, small solutes and macromolecules. The transport of water is driven by the hydraulic-hydrostatic pressure difference between capillary blood and interstitial fluid (ΔP) counteracted by the osmotic pressure difference between plasma and interstitial fluid ($\Delta\pi$).¹⁰³

Maintaining the integrity of this pore system is clinically vital. Chronic exposure to conventional, bio-incompatible dialysates can trigger neoangiogenesis and interstitial fibrosis. These structural alterations eventually culminate in ultrafiltration failure (UFF), which remains the leading cause of technique dropout in long-term peritoneal dialysis patients. .¹⁰³



Peritoneal membrane transport in PD. During peritoneal dialysis exchanges, dialysate is instilled into the peritoneal cavity, and is later drained. During dwells, transport of water, solutes, and molecules occurs across the peritoneal membrane through

diffusion and convection. According to the three-pore model, transport depends on the relative abundance of large and small pores (endothelial clefts) and ultrapores (aquaporins). It is not known whether macromolecules such as cytokines or fibrosis mediators are cleared by the peritoneal membrane.¹⁰⁴

A comparative analysis of the Glomerular Filtration Barrier (GFB) and the peritoneal transport barrier reveals fundamental differences in transendothelial exchange mechanisms. While the GFB operates as a highly specialized molecular sieve - discriminating molecules by size, charge, shape, and deformability - the peritoneal capillaries function more like a biological gel filtration matrix. Key distinctions between these two systems include:

- **Selectivity and Pore Architecture:** The GFB exhibits significantly higher selectivity for macromolecules like albumin. Although the large pores in the GFB are smaller in radius than those in the peritoneum, its fractional ultrafiltration coefficient (ω_0) is approximately three orders of magnitude lower - a disparity only partially attributed to electrostatic charge.
- **Resistance Distribution:** In the GFB, resistances to diffusion and ultrafiltration converge morphologically. Conversely, in the peritoneal membrane, these resistances are spatially distinct, with the interstitium playing a decisive role in defining overall transport properties.
- **Systemic Reflection:** Unlike the specialized GFB, the peritoneal membrane more closely mirrors the systemic capillary-endothelial barrier. This makes peritoneal protein leakage a significant, independent predictor of patient survival and a marker of underlying cardiovascular pathology and systemic endothelial dysfunction.

The dissociation between small-solute diffusion and ultrafiltration capacity often serves as an early clinical marker of membrane failure. In long-term PD, the integrity of these barriers is compromised by neoangiogenesis and fibrosis, leading to Ultrafiltration Failure (UFF). Advanced modelling - integrating pore theory with fiber-matrix frameworks - is essential to accurately characterize these progressive alterations and optimize therapeutic adequacy.¹⁰⁵

2.4.1. Peritoneum Equilibrium Test

The Peritoneal Equilibration Test (PET) is the gold-standard diagnostic procedure for the functional characterization of the peritoneal membrane. By evaluating the individual transport kinetics of solutes and water, the PET allows clinicians to personalize dialysis prescriptions and monitor the long-term integrity of the peritoneal tissue.¹⁰⁶

 The Test Works by instilling a standardized glucose-based solution (usually 2.27%, 2.5% or 3.86% glucose) into the peritoneal cavity. Then samples of dialysate and blood are collected at intervals (typically 0, 2, and 4 hours). The dialysate-to-plasma ratio of creatinine and the concentration of glucose in the dialysate are analyzed to determine membrane efficiency.

 Purpose of the PET is to:

- Assess the diffusive capacity of the peritoneal membrane. D/P Creatinine: The ratio between the concentration of creatinine in the dialysate (D) and plasma (P) at 240 minutes).
- Measure solute transport rates (especially creatinine and glucose). D/D₀ Glucose: The ratio of the glucose concentration in the dialysate at the end of the dwell compared to the initial concentration, reflecting the rate of osmotic gradient dissipation.
- Classify patients into transport categories: high, high-average, low-average, or low transporters.
- Optimize PD regimen (e.g., dwell time, solution type)

 Data interpretation allows to categorize patients into four transport categories: High (Fast), High-Average, Low-Average, or Low (Slow) transporters.

Transport Type	D/P Creatinine at 4h	Glucose Absorption	Clinical Implication
High	>0.81	Rapid	Short dwell times preferred
High-average	0.65–0.81	Moderate	Flexible prescription
Low-average	0.50–0.65	Slow	Longer dwell times may be needed
Low	<0.50	Very slow	Risk of inadequate solute clearance

High transporters absorb glucose rapidly, leading to a quick loss of the osmotic gradient; they generally benefit from shorter dwell times (APD).

Conversely, low transporters maintain the osmotic gradient longer but have slower solute clearance, often requiring extended dwell periods (CAPD).

 The clinical relevance of PET results lies in guiding the customization of dialysis prescriptions, monitoring changes in peritoneal membrane function over time, and detecting early signs of ultrafiltration failure or membrane deterioration.

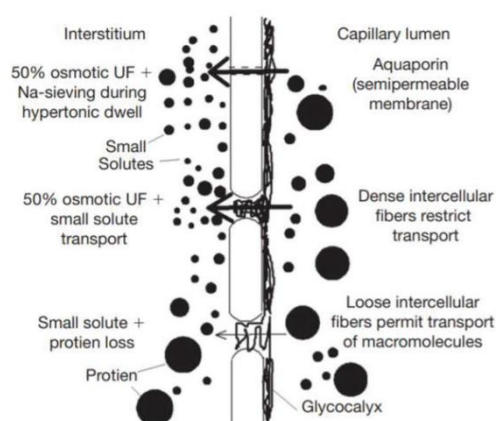
- PET results help tailor PD regimens to individual patient needs.
- Detects early signs of ultrafiltration failure or membrane deterioration.
- Supports long-term monitoring of peritoneal membrane health.

While the standard PET focuses on small solute diffusion, the Mini-PET (a 1-hour test using a 3.86% glucose solution) has been developed to specifically quantify Free Water Transport (FWT) through the ultra-small transcellular pores (Aquaporin-1).¹⁰⁷ A critical parameter derived from this assessment is Sodium Sieving (ΔNa), defined as the reduction in dialysate sodium concentration after 60 minutes due to the dilution caused by solute-free water movement.

- Conserved FWT: $\Delta Na \geq 5$ mmol/L.
- Reduced FWT: $\Delta Na < 5$ mmol/L.

The PET should ideally be performed within the first 3 months of treatment (4 - 8 weeks post-initiation) to establish a baseline. It must be repeated annually or whenever clinical issues—such as inadequate clearance or Ultrafiltration Failure (UFF) - arise.

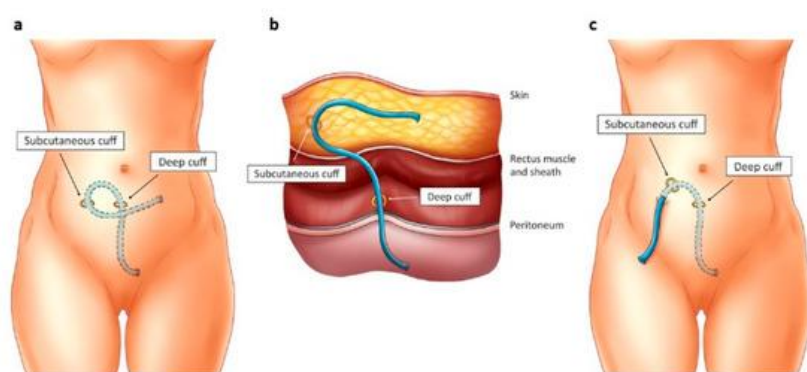
Monitoring these parameters over time is essential, as the peritoneal membrane is a dynamic tissue. A significant reduction or loss of sodium sieving is a severe clinical warning sign; it not only contributes to UFF (which accounts for approximately 50% of ultrafiltration in the early phase of a hypertonic exchange) but may also serve as a predictive marker for serious complications, such as Encapsulating Peritoneal Sclerosis (EPS).¹⁰⁸



Pore-matrix concept of endothelial barrier incorporating the luminal glycocalyx

2.5. Peritoneal catheter

The peritoneal catheter is a medical device used in peritoneal dialysis to introduce and remove dialysis solution from the peritoneal cavity. Its structure is designed to ensure both functionality and protection against infection. One of its key components is the Dacron cuff, which acts as a protective barrier against bacterial infiltration into the peritoneal cavity. While it helps prevent infection, it can also become a site of irritation and, if colonized, a potential reservoir for bacteria. The exit-site refers to the point where the catheter emerges through the skin. This area requires careful monitoring and hygiene, as it represents a direct pathway from the external environment to the internal system. Connected to the exit-site is the sinus tract, a small invagination of skin that follows the catheter inward. This tract forms naturally and can influence the healing process and infection risk. The catheter also passes through a subcutaneous tunnel, which lies between the two Dacron cuffs. This tunnel provides additional protection by distancing the external exit-site from the internal peritoneal cavity, reducing the likelihood of infection traveling along the catheter. Together, these components form a system that balances effective dialysis delivery with safeguards against complications, particularly infections. Proper placement, maintenance, and monitoring of the catheter are essential for the success of peritoneal dialysis therapy.



A laparoscopically inserted buried Tenckhoff catheter. (b). Illustration of the position of the subcutaneous and deep cuffs. (c). A laparoscopically inserted catheter ready for use.¹⁰⁹

2.6. Composition of Dialysis Bags and Biocompatibility

Peritoneal dialysis (PD) fluids are pharmaceutical solutions containing essential electrolytes (Na, Cl, Ca, Mg), buffers (lactate or bicarbonate), and an osmotic agent (glucose, amino acids, or icodextrin).

2.6.1. Electrolytes

Calcium: The optimal calcium concentration in PD solutions remains a subject of debate. Commercial solutions typically provide calcium levels ranging between 1.25 and 1.75 mmol/L. Historically, 1.75 mmol/L was the standard; however, this concentration is frequently associated with hypercalcemia, particularly in patients receiving calcium-based phosphate binders or vitamin D analogues. Consequently, many centers have transitioned to low-calcium solutions (1.25 mmol/L) to allow for more aggressive hyperphosphatemia management. Conversely, 1.75 mmol/L solutions may still be indicated for patients on Cinacalcet to counteract its hypocalcemic effects.

Sodium: Sodium concentrations in PD fluids generally range from 132 to 134 mmol/L. In the absence of ultrafiltration (UF), diffusive sodium removal is negligible due to the minimal concentration gradient between plasma and dialysate. While UF should theoretically enhance sodium removal via convection, the use of hypertonic glucose solutions causes a transient drop in dialysate sodium concentration during the first two hours of a dwell. This "sodium dipping" is the result of free water transport through aquaporins (functional sieving) and a modest Donnan effect.

Although 7.5% icodextrin utilizes small pores for transport, its effect on systemic sodium levels may be more related to osmotic water shifts from the intracellular to the intravascular space rather than true induced natriuresis. To address chronic sodium overload, low-sodium solutions (102–120 mmol/L) have been proposed to enhance diffusive clearance, though they are not yet widely available.

Buffers: To correct metabolic acidosis, early PD used bicarbonate, which unfortunately caused calcium carbonate precipitation in single-bag systems. Acetate was briefly utilized but abandoned due to its association with peritoneal sclerosis. Today, lactate remains the most common buffer worldwide due to its stability and metabolic conversion to pyruvate and subsequently bicarbonate via

the Krebs cycle or gluconeogenesis. However, concerns regarding lactate's peripheral vasodilatory effects and potential myocardial depression have led to the development of physiological bicarbonate buffers. Technical hurdles - specifically calcium precipitation and glucose caramelization at high pH - were overcome by dual-chamber bag technology. This system separates the ingredients during sterilization and storage, allowing for a final physiological pH only at the moment of infusion. In APD, CO₂ buildup in large 5-liter bags remains a challenge, often managed by using bicarbonate/lactate mixtures or reducing bag volume to 3 liters.

2.6.2. Osmotic Agents

The ultrafiltration (UF) process and the maintenance of fluid balance in peritoneal dialysis are strictly dependent on the concentration and biophysical properties of the osmotic agent utilized.

An ideal osmotic agent for PD should possess the following characteristics:

- Rapid metabolism into non-toxic degradation products;
- Low absorption rate from the peritoneal cavity;
- Inert and non-toxic profile regarding the peritoneal membrane;
- Cost-effectiveness and ease of industrial production;
- High osmotic efficacy at low concentrations;
- Minimal generation of undesirable systemic metabolites upon absorption;
- Potential nutritional value;
- Preservation of the peritoneum's physiological defense mechanisms.

To date, no single agent fulfills all these criteria. However, three distinct osmotic agents are currently available, each with unique structural and functional characteristics.

Glucose: Remains the most widely used osmotic agent globally. While Ganter's initial 1923 experiments used physiological saline - which cleared urea and creatinine but failed to remove water - Abbot and Shea introduced hypertonic glucose solutions in 1946 to drive ultrafiltration.

Industrial production provides glucose concentrations for both CAPD and APD, typically classified by their anhydrous concentration: 1.36%, 2.27%, and 3.86% (corresponding to 1.5, 2.5, and 4.25 g/dL of glucose monohydrate). Glucose is highly effective, non-foreign to the body, and inexpensive. By maintaining an osmolarity 12 to 45 times higher than that of plasma, it promotes unidirectional ultrafiltration from the vasculature to the peritoneal cavity.

However, glucose presents significant physiological challenges:

1. **Osmotic Dissipation:** During a dwell, glucose is gradually absorbed into the bloodstream. This reduces the osmotic gradient over time, eventually leading to a cessation of UF or even fluid reabsorption (negative ultrafiltration).

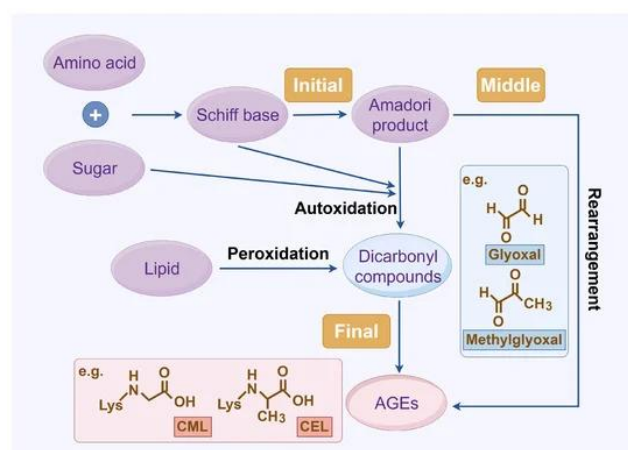
2. Transport Phenotypes: In "high (fast) transporters," glucose absorption is accelerated, rapidly neutralizing the osmotic delta. These patients often require shorter dwell times, typically managed via Automated Peritoneal Dialysis (APD) cyclers.
3. Glucose Degradation Products (GDPs): During heat sterilization, glucose tends to caramelize if the environment is not sufficiently acidic, forming harmful GDPs such as 3,4-Dideoxyglucosone-3-ene (3,4-DGE), 5-hydroxymethyl-furfural (5-HMF), acetaldehyde, and formaldehyde.

GDPs react with protein amino groups to generate Advanced Glycation End-products (AGEs). Together, GDPs and AGEs trigger neoangiogenesis, fibroblast activation, and mesothelial cell depletion. These structural changes increase peritoneal thickness and connective tissue components, ultimately compromising the long-term viability of the dialysis method.

To mitigate these damages, the dual-chamber bag system (pioneered in Vicenza in 1985) was developed.

- Compartment A: Contains glucose, calcium, and magnesium at a very low pH to prevent caramelization during sterilization.
- Compartment B: Contains sodium and buffers (lactate and/or bicarbonate) at a more physiological pH.

The two compartments are mixed immediately prior to infusion, resulting in a final solution with a physiological pH and a significantly lower concentration of GDPs. This setup also allows for the use of bicarbonate as a buffer, preventing the precipitation of calcium or magnesium carbonates that would occur in single-chamber systems.



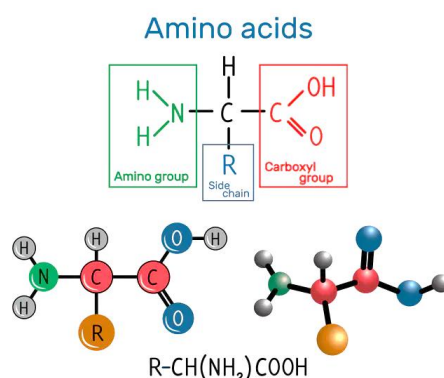
AGE formation. Abbreviations: AGEs, advanced glycation end products; CEL, carboxyl ethyl lysine; CML, carboxyl methyl lysine.¹¹⁰

Amino acids: As early as the 1980s, the development of dialysis solutions utilizing a mixture of essential and non-essential amino acids as an alternative osmotic agent to glucose was proposed. The rationale for employing amino acids stems from the clinical observation that many uremic patients exhibit signs of protein-energy wasting (PEW), likely exacerbated by the continuous loss of amino

acids and proteins into the dialysate. In addition to their nutritional potential, amino acids provide the necessary hyperosmolarity to drive ultrafiltration. In the early 1990s, research conducted at the Karolinska Institutet led to the industrial production of a dialysis solution containing a specific blend of 9 essential amino acids (Valine, Leucine, Isoleucine, Methionine, Lysine, Histidine, Threonine, Phenylalanine, and Tryptophan) and 6 non-essential amino acids (Serine, Alanine, Arginine, Proline, Glycine, and Tyrosine), with a total concentration of 1.1%. This solution, commercially known as Nutrineal®, provides an osmotic effect substantially comparable to that of a 1.36% glucose solution (1.5% monohydrate). The primary advantages of this formulation include:

- Elimination of GDP-related risks, as the solution is glucose-free;
- Reduction of the cumulative daily glucose load, improving metabolic profiles;
- Nutritional supplementation, partially compensating for peritoneal protein losses.

Despite these theoretical benefits, current clinical evidence has not yet conclusively demonstrated a significant improvement in the overall protein status of patients managed with a single daily exchange of amino-acid-based solution.



Icodextrin: The introduction of icodextrin-based solutions in the mid-1990s represents one of the most significant technological advancements in peritoneal dialysis. Marketed under the trade name Extraneal®, this solution contains 7.5% icodextrin and is typically used for the "long dwell"—the overnight exchange in CAPD or the daytime dwell in Automated Peritoneal Dialysis (CCPD).

Icodextrin is a high-molecular-weight glucose polymer (13–19 kDa) derived from the hydrolysis of starch. Unlike glucose, which creates a crystalloid osmotic gradient, icodextrin exerts a colloid-osmotic (oncotic) pressure similar to that of albumin.

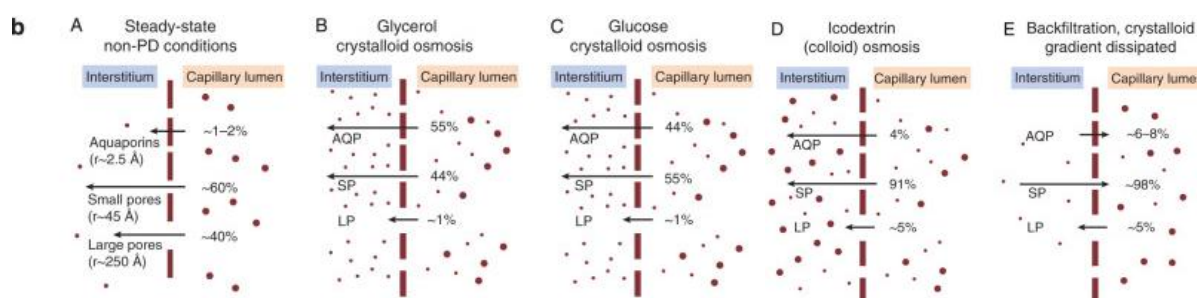
The primary biophysical distinction lies in the transport pathway:

- **Pathway:** Water transport occurs exclusively through small pores and is aquaporin-independent.
- **Duration:** Due to its large molecular size, icodextrin is minimally absorbed by the peritoneum (only slowly via the lymphatic system), allowing for sustained ultrafiltration for up to 10–16 hours.

- **Biocompatibility:** The solution is iso-osmolar to plasma (≈ 282 mOsm/kg), significantly reducing the aggressive metabolic stress on the mesothelium, and contains minimal levels of GDPs.

Despite its benefits, specific clinical precautions are required:

- **Glycemic Interference:** Icodextrin metabolites (maltose) can interfere with specific glucose monitoring systems, particularly those using GDH-PQQ or glucose dye-oxidoreductase methods, leading to falsely elevated readings. This poses a severe risk of masked hypoglycemia.
- **Metabolic Impact:** Icodextrin is degraded by serum amylase into maltose. In patients using this solution, serum amylase levels appear falsely low; therefore, serum lipase must be used to diagnose potential pancreatitis.
- **Dosing:** To prevent excessive maltose accumulation and potential neurological side effects, its use is strictly limited to one exchange per 24 hours.
- **Sterile Peritonitis:** Some patients may develop an aseptic inflammatory reaction characterized by eosinophilia in the peritoneal effluent.



Transcapillary UF in the TPM. (A) Fractional fluid flows across the peritoneum under normal conditions with no dialysis. In the absence of an osmotic agent, $\sim 60\%$ of the transcapillary fluid flow occurs through small pores, where the Starling forces are close to equilibrium. Approximately 40% of the capillary UF occurs across large pores where there is hardly any colloid osmotic pressure counteracting the transcapillary hydrostatic pressure gradient. (B) With glycerol (Stokes–Einstein (SE)-radius ~ 3 Å) as the osmotic agent, $\sim 55\%$ of the transperitoneal water flow will occur through water-only, ultrasmall pores and 45% through small pores. This is due to the relative inefficiency of glycerol as an osmotic agent across the small-pore pathway ($\sigma \sim 0.02$). LP, large pore; SP, small pore. (C) With glucose (SE-radius ~ 3.7 Å) as the osmotic agent, $\sim 45\%$ of the transperitoneal water flow will occur through water-only pores and 55% through small pores. Although glucose is a relatively inefficient osmotic agent in the small pore pathway ($\sigma \sim 0.03$), it is 50% more efficient than glycerol. (D) In a conventional icodextrin PD solution, ~ 25 – 30% of the molecules (~ 3 nm) act as a colloid, implying a reflection coefficient close to unity. It should be noted that 3 mm of high-molecular-weight (MW) icodextrin will produce a colloid osmotic pressure of ~ 58 mm Hg (3×19.3 mm Hg), which is sufficient to counteract the plasma colloid osmotic pressure (22 – 26 mm Hg) exerted by ~ 1 mm of negatively charged plasma proteins. Note that the partitioning of fluid flows among the different porous pathways in the TPM is now almost identical to that in the peritoneum occurring during high net UF conditions in the absence of crystalloid osmotic forces. (E) Reabsorption of fluid across the small pores occurs when the crystalloid (glucose) osmotic gradient has totally dissipated (usually after 4 h). The net Starling fluid balance is biased toward reabsorption across the small pores in PD. Some fluid reabsorption will also occur across AQP1. Minute UF still occurs across the large pores.¹¹¹

2.6.3. Dialysis Bag Materials and Biocompatibility

The materials used for dialysis fluid containers also play a critical role in biocompatibility. Historically, Polyvinyl Chloride (PVC) was the standard polymer. However, PVC requires plasticizers like DEHP (di-2-ethylhexyl phthalate) to remain flexible. DEHP is associated with cardiotoxicity, hepatotoxicity, and potential endocrine disruption. Furthermore, the incineration of PVC releases toxic dioxins.

To improve safety, industry leaders have developed PVC-free and phthalate-free systems:

- ClearFlex® (Baxter): A multi-layered co-extruded material. The inner polyethylene layer is non-toxic and inert; the middle nylon (polyamide) layer acts as a gas barrier (preventing CO₂ loss from bicarbonate solutions); and the outer polypropylene layer ensures water impermeability.
- Biofine® (Fresenius): A biocompatible material based on polyolefins (polyethylene and polypropylene). These polymers exhibit excellent chemical inertness and do not require harmful solvents or plasticizers for polymerization.

BIOINCOMPATIBILITY remains a fundamental limiting factor in the longevity of peritoneal dialysis. Chronic exposure to non-physiological pH, GDPs, and toxic plasticizers triggers a cascade of inflammation, neoangiogenesis, and fibrosis. These anatomical changes eventually render the membrane incapable of functioning as a dialytic filter, leading to technique failure.

The pursuit of superior biocompatibility standards is the central focus of current medical research and forms the core objective of the present study.¹¹²

3. COMPLICATIONS OF PERITONEAL DIALYSIS TREATMENT

While Peritoneal Dialysis (PD) is a highly effective treatment for End-Stage Renal Disease (ESRD), its application is often limited to a minority of the dialysis population due to critical constraints regarding long-term efficacy and sustainability.¹¹³ The success of this therapeutic modality is inextricably linked to the integrity of the peritoneal catheter, which utilizes Dacron cuffs to establish a mechanical and biological barrier against bacterial infiltration. Maintaining the health of the subcutaneous tunnel and exit-site is paramount, as infections remain a significant risk that can jeopardize the peritoneal cavity; these complications, along with non-infectious issues, are typically categorized by their onset as short-, medium-, or long-term.¹¹⁴ Beyond physical access, the primary obstacle to long-term sustainability is the bioincompatibility of conventional dialysis solutions. Biocompatibility - defined as the ability of a solution to maintain the anatomical and functional characteristics of the peritoneum both locally and systemically - is frequently compromised by prolonged exposure to non-physiological fluids.¹¹⁵ This exposure triggers a pathological cascade of neoangiogenesis, chronic inflammation, and fibrosis, which manifests clinically as a progressive decline in ultrafiltration capacity.¹¹⁶ Such structural degradation eventually culminates in ultrafiltration failure, the leading cause of technique dropout. Furthermore, the management of these patients requires rigorous drug stewardship to address the altered pharmacokinetics inherent to PD, necessitating precise dose adjustments that account for both peritoneal removal and residual renal clearance to ensure therapeutic safety and effectiveness.^{117–119}

3.1. Infectious Complications

In the clinical management of peritoneal dialysis (PD), infectious complications represent a formidable challenge, serving as a primary driver of both patient morbidity and the premature cessation of the therapeutic technique. These pathologies are broadly classified into the following categories:

- Exit-site Infections: These typically present with localized inflammatory markers such as erythema, pruritus, and tenderness at the catheter entry point, often accompanied by granulation tissue or seropurulent discharge.
- Tunnel Infections: Often manifesting as an extension of exit-site pathologies, these involve pain along the subcutaneous tract and indurated pericatheter edema (commonly referred to as a "plastron"). They are implicated in the development of peritonitis in up to 75% of cases.
- Peritonitis: The most severe complication, characterized by acute abdominal pain, fever, and a macroscopic shift of the peritoneal effluent from clear to turbid or overtly purulent.

The microbiological landscape is predominantly dominated by the following causative pathogens:

- *Staphylococcus aureus* (50–75%): Frequently associated with both exit-site and tunnel involvement.
- Coagulase-negative Staphylococci ($\approx 20\%$): Primarily *Staphylococcus epidermidis*, often linked to touch contamination.
- *Pseudomonas aeruginosa* ($\approx 8\%$): Known for being particularly recalcitrant and often requiring aggressive intervention.
- Other Gram-negative bacteria (10%): Including *Escherichia coli* and other enteric organisms.
- Fungal organisms (4%): Though less common, these often necessitate immediate catheter removal.

Upon clinical suspicion of peritonitis, immediate laboratory analysis and dialysate cultures are mandatory. Peritonitis itself remains the most severe complication, identified by the clinical triad of acute abdominal pain, fever, and a distinct macroscopic alteration of the peritoneal effluent, which shifts from its usual clarity to a turbid or overtly purulent appearance. Upon clinical suspicion, immediate laboratory analysis and dialysate cultures are mandatory.

The therapeutic strategy necessitates the prompt initiation of empiric broad-spectrum antibiotic therapy to minimize irreversible damage to the peritoneal membrane. Once specific culture results and sensitivities are available, treatment is transitioned to a targeted regimen. In recalcitrant cases—particularly those involving relapsing or persistent infections—the surgical removal of the tunneled catheter may be required to eradicate the infectious nidus. While catheter replacement can sometimes be attempted later, severe or recurrent episodes frequently necessitate a permanent transition to

hemodialysis, highlighting the critical impact of infectious morbidity on the long-term viability of the PD program.

3.2. Non-Infectious Complications

Beyond infectious risks, the sustainability of peritoneal dialysis (PD) is often challenged by a variety of non-infectious complications, which can be categorized into mechanical, metabolic, and functional disorders. Mechanical issues frequently involve catheter dysfunction, typically arising from physical obstructions such as omental wrapping, catheter migration (malposition), or the accumulation of fibrin within the lumen. Additionally, the chronic elevation of intra-abdominal pressure inherent to the therapy commonly predisposes patients to the formation of abdominal wall hernias and dialysate leakage. On a metabolic level, the continuous exchange process can lead to systemic imbalances. These include hypoproteinemia due to peritoneal protein loss, hypertriglyceridemia driven by the glucose load, and various electrolyte disturbances. Furthermore, patients may experience functional symptoms such as abdominal pain and respiratory distress associated with the dwell volume. Over the long term, the most severe functional concern remains the development of peritoneal sclerosis, which fundamentally alters the membrane's structural integrity across different stages of the treatment.

3.2.1. Short-Term Complications

In the immediate period following the initiation of peritoneal dialysis (PD), several short-term complications may manifest, many of which are directly related to the surgical catheter insertion and the initial introduction of fluid into the abdominal cavity. These post-surgical events typically emerge within the first few weeks and are largely influenced by the patient's clinical history and the surgical technique employed. Early mechanical issues often involve catheter malfunction, which can present as malpositioning or obstruction. Common causes include the formation of fibrin plugs that block the lumen or poor initial channeling. Furthermore, patients may experience transient discomfort in the perineal, bladder, or rectal regions; however, this pain usually resolves as the body adapts to the catheter's presence. Meticulous surgical hemostasis is required to prevent early bleeding, which may occasionally manifest as blood-tinged dialysate during the first exchanges. Additionally, some patients may experience reflex ileus - a temporary cessation of intestinal motility - within 24 to 36 hours post-placement. Fluid-related complications, such as peri-catheter leakage, are frequently observed, particularly in patients with specific risk factors like obesity, diabetes, or a history of prior abdominal surgeries. These leaks occur when the catheter seal is insufficient to withstand the increased intra-abdominal pressure. This pressure can also trigger other secondary issues, including genital edema, the development or exacerbation of hemorrhoids, and, in rarer cases, hydrothorax or

vagal reflex symptoms. Preventative management of these early complications relies on precise surgical insertion techniques, rigorous early monitoring, and the careful titration of initial dialysate volumes to ensure the long-term viability of the peritoneal access.

3.2.2. Medium-Term Complications

In the clinical progression of peritoneal dialysis (PD), medium-term complications typically manifest within the first few months of treatment. These issues often arise from the persistent mechanical stress of increased intra-abdominal pressure or specific catheter-related failures.

The following non-infective complications are frequently observed:

- **Dacron Cuff Extrusion:** This occurs when the internal cuff is displaced toward the skin surface, often due to improper surgical placement, accidental trauma, or chronic exit-site inflammation leading to tissue erosion.
- **Abdominal Wall and Structural Issues:** The continuous presence of dialysate elevates intra-abdominal pressure, predisposing patients to umbilical or inguinal hernias. Furthermore, dialysate may infiltrate the abdominal wall or leak into genital and scrotal areas, a condition often confirmed via CT imaging.
- **Catheter Dislocation and Malfunction:** Mechanical failure may result from omental entrapment, fibrin obstruction, or displacement. This complication manifests as incomplete or slow drainage, drainage that improves with position changes, and a "pseudo-drop" in ultrafiltration. The suspicion is confirmed through abdominal X-ray or catheterography. Management ranges from conservative measures (stimulating peristalsis) to non-invasive repositioning using a pre-shaped metallic guide wire. In severe cases, video laparoscopy or surgical replacement is required.
- **Hydrothorax:** This involves the translocation of dialysate into the pleural cavity (usually the right side) through peritoneo-pleural communications. It presents as dyspnea and reduced ultrafiltration. Diagnosis is confirmed by analyzing pleural fluid glucose levels or via lung scintigraphy using technetium-labeled dialysate.
- **Hemoperitoneum:** Blood-stained effluent can stem from various etiologies, including gynecological events (ovulation, endometriosis), acute abdominal pathologies (pancreatitis, splenic rupture), or membrane abnormalities (sclerosis, calcification). It may also follow intense physical activity or the rupture of hepatic/renal cysts.
- **Metabolic Disturbances:** The absorption of glucose from the dialysate over several months frequently triggers systemic effects such as hyperglycemia and hyperlipidemia.

Surgical intervention becomes necessary when medical management fails to preserve the access or the membrane.

- Catheter Replacement: Indicated for irreversible mechanical obstructions, subcutaneous tunnel abscesses, or catheter-related recurrent peritonitis that does not respond to antimicrobial therapy.
- Catheter Removal: This is mandatory in cases of fungal or fecal peritonitis, infections failing to resolve after seven days of targeted antibiotics, or persistent dialysate leaks. Removal is also performed upon elective discontinuation of PD due to successful renal transplantation, recovery of native kidney function, or a permanent switch to hemodialysis.

3.3. Long-Term Complications

In the advanced stages of therapy, prolonged exposure to the dialysis environment can induce profound structural and functional transformations within the peritoneal membrane. These long-term alterations represent a significant challenge to the continued viability of the technique.

The most critical chronic complications include:

- Ultrafiltration Failure (UFF) and Altered Permeability: Over time, the membrane often exhibits a progressive increase in solute permeability and a concomitant loss of ultrafiltration capacity. This functional decline is frequently driven by neoangiogenesis and the expansion of the interstitial collagen matrix.
- Encapsulating Peritoneal Sclerosis (EPS): Although rare, EPS is the most devastating long-term complication. It is characterized by severe fibrotic thickening of the peritoneum, which eventually leads to intestinal "cocooning," resulting in bowel obstruction, chronic pain, and severe malnutrition.
- Protein-Energy Wasting (PEW) and Cardiovascular Risk: The chronic loss of proteins and amino acids into the dialysate, combined with the systemic inflammatory state and glucose-mediated metabolic stress, heightens the risk of malnutrition and accelerated cardiovascular disease.

The prevention of these irreversible changes relies on a proactive management strategy. This involves the systematic and regular monitoring of peritoneal function through tests like the PET to detect early signs of membrane failure. Furthermore, the clinical transition toward the use of biocompatible, glucose-lowering solutions is essential to minimize chronic peritoneal injury and extend the lifespan of the dialysis therapy.

Recent clinical evidence suggests that the use of peritoneal dialysis (PD) solutions with a mildly reduced sodium content can significantly improve blood pressure (BP) management in end-stage kidney disease (ESKD) patients. Standard PD solutions, typically containing sodium concentrations between 132 and 134 mmol/L, often face challenges in effective sodium removal, contributing to hypertension through sodium retention. A case-report study demonstrating the transition to a novel, uncompensated 130 mmol/L sodium PD solution (e.g., DextroCore LS) showed a substantial

reduction in both diurnal and nocturnal arterial blood pressure, even restoring the physiological circadian rhythm in cases of resistant hypertension. Notably, these clinical improvements were achieved without significant alterations in ultrafiltration, residual diuresis, or systemic serum sodium levels, suggesting that mild sodium lowering in the dialysate may effectively reduce the total body sodium burden and interstitial sodium stores. This approach represents a promising "right compromise" to enhance cardiovascular outcomes while avoiding the risks of hyponatremia or increased glucose load associated with ultra-low sodium solutions.¹²⁰

3.3.1. Bioincompatibility

A pivotal factor regarding the long-term sustainability of this therapy is the biological impact of dialysis solutions on the peritoneal membrane. This phenomenon, known as bioincompatibility, inevitably imposes a temporal limit on the treatment's duration. The chronic exposure to non-physiological fluids accelerates the aging of the peritoneal surface, triggering a pathological sequence of inflammation, neoangiogenesis, and fibrosis. These alterations eventually compromise the membrane's emunctory function, leading to the cessation of the therapy.¹²¹

The primary driver of this damage is the high concentration of glucose (MW 180 Da), which is typically 10 to 50 times higher than physiological serum levels.¹¹⁴ While glucose is utilized for its efficiency, low cost, and safety profile in creating the osmotic gradient necessary for ultrafiltration (UF) and toxin clearance, it induces severe detrimental effects:

- **Local Pathogenesis:** High glucose levels trigger the Epithelial-to-Mesenchymal Transition (EMT) of mesothelial cells, promoting angiogenesis and fibrosis. Advanced technologies, such as multi-photon microscopy, are currently being utilized by researchers like D'Apolito et al. to study these physiological changes in real-time during dialytic exchanges.
- **Systemic Metabolic Impact:** Beyond local membrane damage, excessive glucose absorption contributes to systemic issues, including insulin resistance, new-onset diabetes, and increased cardiovascular morbidity.
- **Functional Deterioration:** The resulting structural changes lead to a progressive loss of UF capacity and small solute clearance, ultimately resulting in technique failure.¹²²

The clinical outcomes of PD are determined by the interplay between the dialysis prescription and individual patient characteristics, such as body size, residual glomerular filtration rate (GFR), and peritoneal permeability. Given that permeability is highly variable and deteriorates over time, systematic monitoring through the study of solute concentration equilibrium between dialysate and plasma is essential. This evaluation allows clinicians to optimize treatment and monitor the health of the peritoneum.

To address these limitations, modern research focuses on enhancing biocompatibility through the development of solutions with neutral pH, reduced glucose degradation products (GDPs), and alternative osmotic agents like icodextrin or amino acids. Furthermore, the integration of remote patient monitoring in Automated Peritoneal Dialysis (APD) now allows clinicians to analyze real-time data and implement timely interventions to improve clinical outcomes and extend the lifespan of the peritoneal membrane.^{123,124}

3.3.2. Remodeling

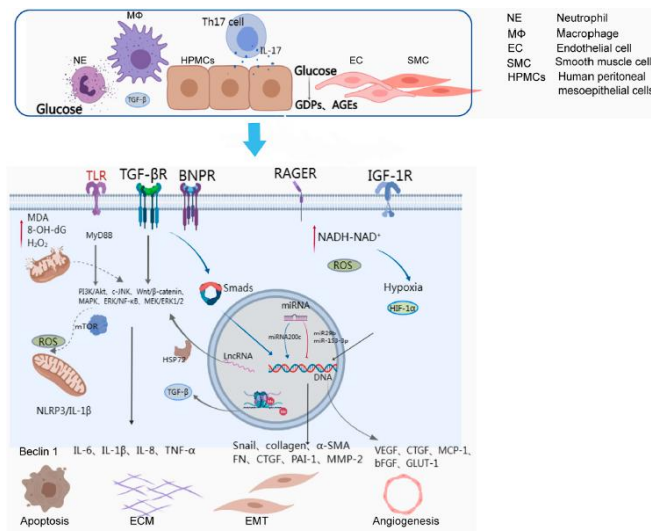
Upon initial contact with dialysate, the peritoneal membrane undergoes profound structural alterations that, combined with hemodynamic factors, define individual solute and water transport characteristics and their evolution over time. The utilization of the peritoneum as a dialysis interface induces anatomical effects categorized into short-term acute inflammatory responses and medium-to-long-term thickening and fibrosis.

At the cellular level, mesothelial cells exhibit a progressive loss of microvilli and an increase in basal vesicles, eventually detaching from the lamina propria. This process triggers interstitial edema and the subsequent deposition of collagen fibers. Concurrent with this gradual thickening, a specific hyalinizing vasculopathy develops, marked by subendothelial hyaline deposition. This leads to the distortion and eventual obliteration of the peritoneal capillary network. In rare but severe instances, this remodeling culminates in encapsulating peritoneal sclerosis (EPS), a condition where the membrane becomes a fibrotic cocoon around the visceral organs, causing catastrophic functional failure.

The progression toward this sclerotic state is exacerbated by several key factors:

- **Prolonged Uremia:** The chronic presence of uremic toxins serves as a persistent stimulus for tissue degradation.
- **Bioincompatibility of Dialysate:** The use of fluids characterized by high osmolarity, acidic pH, and elevated glucose concentrations facilitates the accumulation of Advanced Glycation End-products (AGEs), which are potent drivers of fibrosis.
- **Recurrent Peritonitis:** Repeated infectious episodes fuel a continuous inflammatory cycle that accelerates membrane deterioration.

Furthermore, clinical outcomes can be improved by addressing these long-term criticalities through optimized solutions. For example, implementing uncompensated, mildly reduced sodium PD solutions (130 mmol/L) has been shown to improve hypertension and restore circadian blood pressure rhythms in ESKD patients without compromising ultrafiltration or residual renal function.^{125,126}



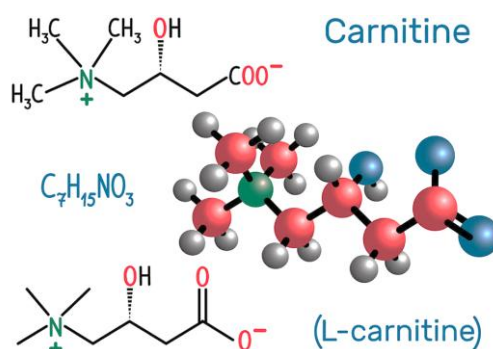
Cells and activated molecular pathways involved in peritoneal ultrafiltration failure.¹²⁷

4. OSMO-METABOLIC APPROACH AND GLUCOSE-SPARRING STRATEGIES – THE STUDIES

One of the primary goals of current research in peritoneal dialysis (PD) is to develop strategies that reduce or eliminate glucose-associated toxicity (glucose sparing) without compromising patient safety or treatment efficacy. However, identifying alternative osmotic agents that are both effective and biocompatible remains a significant challenge. At present, only two alternative osmotic agents are clinically available for PD: icodextrin, a glucose polymer, and amino acids. These formulations, used individually or in combination, have demonstrated clinical benefits and are well tolerated by patients.^{128 129 130} Nevertheless, icodextrin and amino acids typically replace only 30–50% of the daily absorbed glucose and are generally limited to a single exchange per day.^{131 132 133} Two recent randomized controlled trials have shown that the combined use of icodextrin and amino acids can improve metabolic parameters. However, in some patients, this combination was associated with an increase in extracellular fluid volume, underscoring the importance of effective ultrafiltration (UF) and the need for close clinical monitoring of fluid status when implementing glucose-sparing strategies.¹³⁴

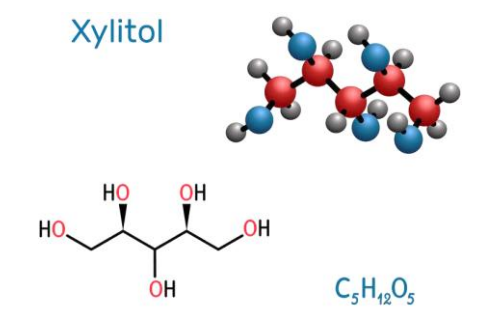
The future of PD will largely depend on the clinical outcomes and published evidence surrounding currently available glucose-sparing solutions, as well as the development of novel osmotic agents that enhance biocompatibility, fluid balance, and metabolic safety. In this context, the use of **osmometabolic agents** in PD solutions represents a promising innovation.^{135(p)} Osmometabolites are compounds with both osmotic and favorable metabolic properties.^{136 137} This approach offers a form of *bioactive glucose sparing* by reducing the intraperitoneal glucose load without impairing UF, while also mitigating the underlying adverse metabolic effects of glucose exposure.

Among the most promising candidates currently under investigation are **L-carnitine** and **xylitol**, both of which exhibit potential to improve the safety and efficacy of peritoneal dialysis solutions.



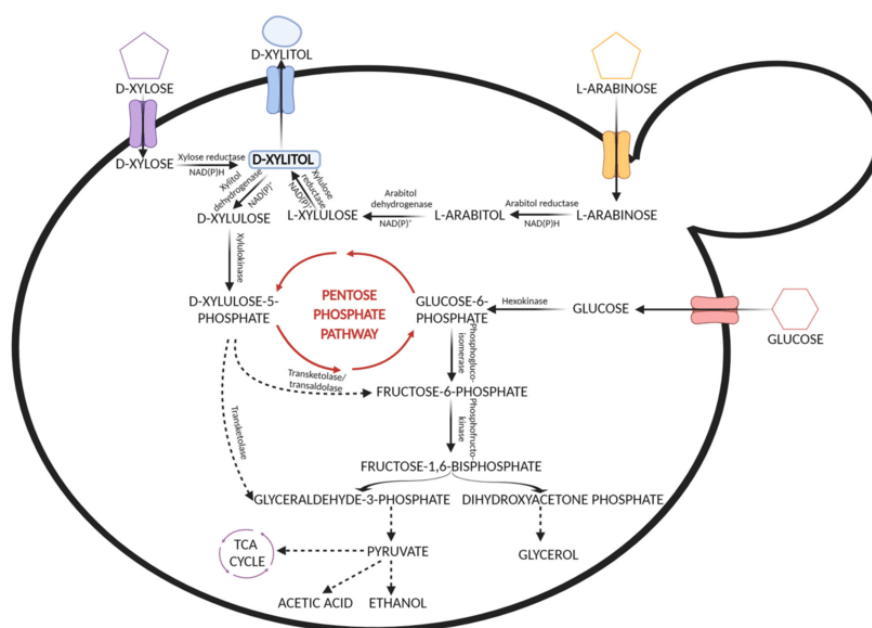
L-Carnitine (LC), a highly water-soluble and chemically stable compound with a molecular weight of 161.2 Da, is a promising candidate for inclusion in peritoneal dialysis (PD) fluids due to its osmotic properties and metabolic benefits.¹³⁸⁻¹³⁹ Beyond its role as an osmotic agent, LC contributes to the regulation of mitochondrial fatty acid transport and oxidation, ketogenesis, and cellular energy production. It facilitates the translocation of long-chain fatty acids into mitochondria via the carnitine shuttle system, involving carnitine palmitoyltransferases (CPT I and II) and carnitine-acylcarnitine translocase (CACT).¹⁴⁰ LC also modulates the intramitochondrial acetyl-CoA/CoA ratio through carnitine acetyltransferase (CAT), influencing pyruvate dehydrogenase (PDH) activity and glucose metabolism. Experimental evidence indicates that pharmacological concentrations of LC (low millimolar range) exert metabolic effects not achievable at physiological levels due to its poor bioavailability and rapid renal clearance.¹⁴¹ PD patients, who typically exhibit LC deficiency and altered acyl/free carnitine ratios, may benefit from LC supplementation both to restore physiological levels and to achieve therapeutic effects. Intravenous LC administration in hemodialysis (HD) patients has been shown to significantly elevate plasma LC concentrations, unlike oral supplementation in individuals with normal renal function.¹⁴² Clinical studies in healthy volunteers and diabetic subjects have demonstrated that LC enhances whole-body glucose utilization, primarily by increasing non-oxidative glucose disposal. This effect is attributed to LC's ability to relieve acetyl-CoA-mediated inhibition of PDH, thereby improving insulin sensitivity and overcoming metabolic inflexibility in insulin-resistant skeletal muscle.¹⁴³ In ESRD patients, LC has been shown to improve insulin tolerance and reduce protein catabolism, with greater efficacy observed in individuals with baseline insulin resistance. Preclinical studies further support LC's role in modulating hepatic glucose production.¹⁴⁴ In diabetic rodent models, LC administration reduced hyperglycemia, glucosuria, and polydipsia, suggesting an inhibitory effect on gluconeogenesis. In fructose-fed rats, LC normalized plasma glucose and insulin levels, as well as hepatic triglyceride and free fatty acid content, likely by correcting LC depletion and restoring fatty acid oxidation. Similar improvements in glucose disposal

and hepatic insulin sensitivity were observed in obese diabetic transgenic mice following dietary LC supplementation. Additionally, LC has shown potential in lowering lipoprotein(a) [Lp(a)] levels in hypercholesterolemic and newly diagnosed diabetic patients, indicating broader metabolic benefits. Collectively, these findings suggest that pharmacological LC administration may offer a multifaceted therapeutic approach to improving glucose and lipid homeostasis in PD patients. L-Carnitine has demonstrated a favorable safety profile across a range of preclinical and clinical studies. Toxicological evaluations in rodents revealed high tolerability, with LD₅₀ values of 12 g/kg in mice and 8 g/kg in rats. No adverse effects were observed at doses up to 7 g/kg. Subsequent studies in Sprague Dawley rats confirmed systemic and peritoneal safety following both single and repeated intraperitoneal administrations of LC at concentrations up to 15% (300 mg/kg). Local tolerability was also validated in rabbits receiving subcutaneous LC injections at equivalent doses. Clinical investigations in CAPD patients further support LC's safety. In early trials, intraperitoneal administration of 2 g LC during the nocturnal exchange was well tolerated and improved lipid profiles. Additional studies using doses of 20 mg/kg over 14 days showed enhanced nitrogen balance without adverse events. In HD patients, intravenous LC at doses of 2 g and 40 mg/kg administered thrice weekly for up to 12 months resulted in plasma carnitine levels up to 100-fold above physiological concentrations, with no reported toxicity. A recent study in CAPD patients compared the osmotic performance of a 2.27% glucose solution with a 1.36% glucose solution supplemented with 5 g LC (0.25% w/v). Ultrafiltration volumes remained stable or improved (5–13% increase), with no significant changes in body weight or diuresis. Plasma LC levels reached a steady state within four days, remaining within a pharmacologically acceptable range. Over 75% of the administered LC was eliminated via urine and peritoneal effluent. Notably, the LC concentration proposed for current clinical trials (0.02% w/v) is substantially lower than previously tested doses. No adverse reactions have been reported in any of the completed or ongoing clinical trials, including those registered under ClinicalTrials.gov (NCT00755404 and NCT00755456), confirming the excellent tolerability of LC in PD applications.¹⁴⁵



Xylitol is a five-carbon sugar alcohol (pentitol) with a molecular weight of 151.2 Da, produced through the reduction of D-xylulose. Naturally occurring in various fruits and vegetables—such as

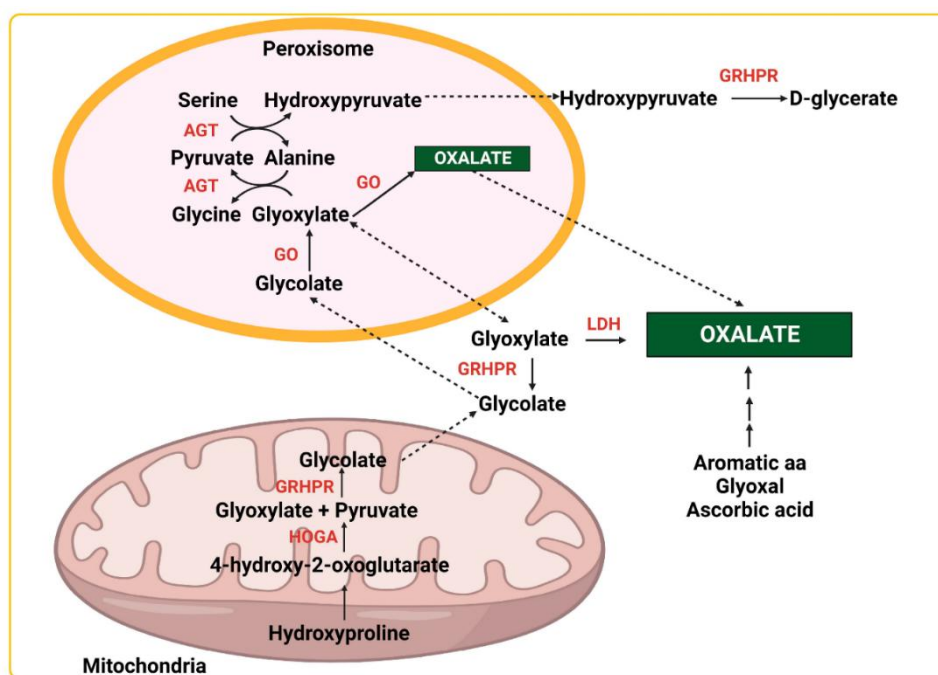
plums, strawberries, raspberries, and cauliflower—it is also endogenously synthesized in small quantities in humans, with estimated daily production ranging from 5 to 15 grams. Xylitol has long been used as a non-cariogenic sweetener and as a glucose substitute in parenteral nutrition, particularly in patients with impaired glucose metabolism, such as those with diabetes, sepsis, or trauma. From a metabolic standpoint, xylitol is absorbed more slowly than glucose via passive or facilitated diffusion in the intestine. Once in circulation, it is primarily metabolized in the liver (accounting for 50–80% of its clearance), where it is first oxidized to D-xylulose by NAD-dependent xylitol dehydrogenase, increasing the NADH/NAD⁺ ratio. D-xylulose is then phosphorylated to D-xylulose-5-phosphate, entering the pentose phosphate pathway and subsequently yielding fructose-6-phosphate and glyceraldehyde-3-phosphate. These intermediates are further metabolized into glucose, glycogen, or lactate. Importantly, xylitol uptake and metabolism are insulin-independent, making it particularly advantageous in insulin-resistant states. Its pharmacokinetics follow first-order elimination, with a plasma half-life of approximately 20 minutes in non-adapted adults, and it is excreted unchanged via glomerular filtration without tubular reabsorption.



The metabolic fate of Xylitol

Xylitol has been evaluated and approved by several international regulatory agencies. In 1986, the Federation of American Societies for Experimental Biology (FASEB), under commission from the U.S. FDA, concluded that xylitol is safe for human consumption and suitable for use in foods for special dietary purposes. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) later assigned xylitol an Acceptable Daily Intake (ADI) of “not specified,” the most favorable safety classification, indicating no toxicological concern at typical intake levels. Similarly, the European Union’s Scientific Committee for Food recognized xylitol as acceptable for dietary use.

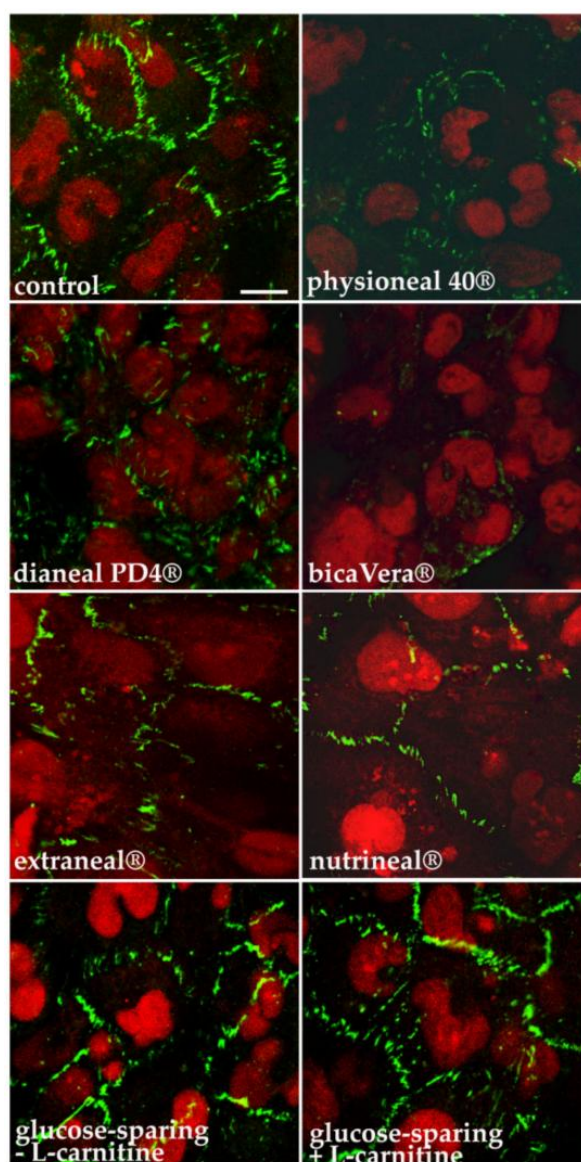
In the context of peritoneal dialysis (PD), xylitol has been investigated as an alternative osmotic agent to glucose.¹⁴⁶ Its use has been associated with improved glycemic control, reduced insulin requirements, and favorable effects on lipid metabolism. A clinical study involving six insulin-dependent diabetic patients undergoing CAPD for at least five months employed a regimen of three daily exchanges with 1.5% xylitol and one with 3% xylitol. The treatment was well tolerated, maintained effective ultrafiltration, halved exogenous insulin needs, and significantly reduced HbA1c levels.¹⁴⁷ Further studies, including those by Bazzato and Buoncristiani, confirmed the safety and metabolic benefits of xylitol-based PD solutions. In Bazzato's study, patients received up to 150 g/day of xylitol intraperitoneally, with stable ultrafiltration and improved lipid profiles. Although serum lactate levels increased slightly (from 12.6 to 17.5 mg/dL), they remained within the normal physiological range. Buoncristiani's long-term experience with lower xylitol doses (55 g/day) showed no significant changes in lactate levels compared to glucose-based PD, supporting the metabolic safety of xylitol at clinically relevant doses. Regarding urate metabolism, high-dose xylitol administration may lead to modest increases in serum uric acid, likely due to enhanced purine biosynthesis via the pentose phosphate pathway. In Bazzato's cohort, urate levels rose from 5.6 to 9.1 mg/dL, slightly exceeding the upper normal limit. However, in Buoncristiani's experience, urate levels remained within the normal range. Given that planned xylitol doses in current protocols are significantly lower, the risk of hyperuricemia appears minimal. Concerns about oxalate accumulation have also been addressed. Although rare cases of oxalate-related toxicity have been reported in patients receiving high-dose sugar infusions, these are typically confounded by underlying metabolic disorders such as primary hyperoxaluria.^{148–150} Studies have shown that xylitol contributes minimally to oxalate production. In both Bazzato's and Buoncristiani's studies, no clinical signs of calcium oxalate deposition were observed, and plasma oxalate levels remained within normal limits. Large-scale clinical use of xylitol-containing parenteral nutrition products, such as Tutofusin OP X, has not been associated with oxalate-related adverse events, further supporting its safety.^{123,151}



Pathways of endogenous production of oxalate.

In summary, xylitol is a metabolically active, insulin-independent osmotic agent with a well-established safety profile. Regulatory authorities have endorsed its use in both dietary and clinical settings. Clinical and preclinical data support its tolerability and efficacy in PD, particularly at doses well below those associated with metabolic disturbances. When used appropriately, xylitol offers a valuable alternative to glucose in PD solutions, with potential benefits for glycemic control, lipid metabolism, and overall biocompatibility.

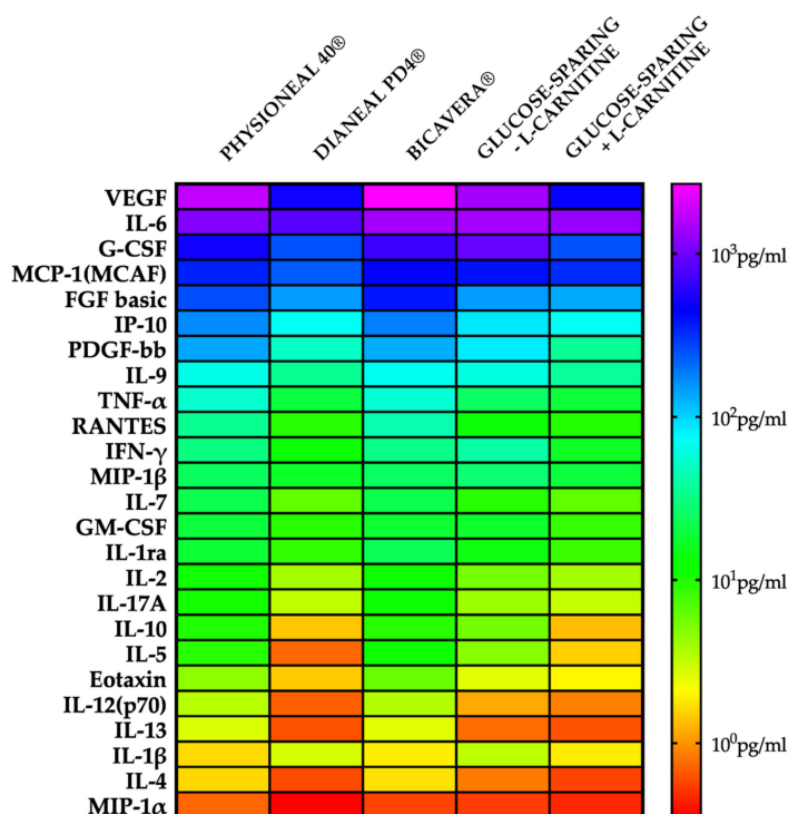
Osmometabolic agents such as xylitol and L-carnitine can be used individually or in combination to enhance their therapeutic potential. A novel PD solution has recently been developed, incorporating L-carnitine, xylitol, and a low concentration of glucose. Its effects were tested on human umbilical vein endothelial cells (HUVECs) derived from healthy mothers with gestational diabetes. This experimental solution demonstrated a favorable safety profile, showing no evidence of cytotoxicity, inflammation, or nitro-oxidative stress—adverse effects commonly observed with glucose-based PD solutions, even those formulated with neutral pH and low concentrations of glucose degradation products (GDPs), which are typically considered "biocompatible".^{136 152}



Immunofluorescence analysis of tight junction marker ZO-1 in HMC, grown on permeable supports and exposed for 8 h to different PD solutions at the apical side. HMC monolayers grown on permeable supports were incubated for 8 h at the apical side with high osmolarity glucose-based PD solutions (Physioneal 40®, Dianeal PD4® and BicaVera®), glucose-free Extraneal®/Nutrineal® and high osmolarity glucose-sparing PD solutions ($\pm$ L-carnitine). Cells were immunostained with anti ZO-1 antibodies (green) and scanned by laser confocal microscopy. Nuclei were stained with propidium iodide (red). Scale bars = 10 μ m.¹⁵³

This innovative formulation of peritoneal dialysis (PD) solution was compared against a broad range of commercially available PD solutions, including several marketed as “biocompatible.” The evaluation was conducted using cultured human mesothelial cells grown on membrane inserts and exposed to the PD solution exclusively on the apical side, simulating the conditions of a dwell phase in clinical PD.¹⁵⁴

The novel PD solutions demonstrated superior performance in several key parameters: enhanced cell viability, improved preservation of mesothelial layer integrity, and a reduced release of proinflammatory cytotoxic mediators. These findings suggest a promising biocompatibility profile and support the potential of osmometabolic formulations to mitigate cellular stress commonly associated with glucose-based PD fluids.



Cytokines, chemokines and growth factors released from the apical side by HMC incubated with high osmolarity PD solutions. A heatmap shows the result of a quantitative 27-plex Luminex assay. The concentration (pg/ml) increases as the color changes from red to violet.¹⁵³

The use of osmo-metabolic agents such as L-carnitine and xylitol in peritoneal dialysis (PD) fluids—whether formulated with or without low doses of glucose—represents a promising strategy to mitigate glucose-related toxicity while preserving ultrafiltration efficiency and improving metabolic outcomes. These agents have demonstrated favorable effects on insulin sensitivity and glycemic control, offering a dual benefit as both osmotic and metabolically active compounds.

A newly formulated PD solution combining L-carnitine, xylitol, and minimal glucose has shown superior biocompatibility compared to standard glucose-based solutions. In vitro studies revealed reduced cytotoxicity and inflammatory response, alongside improved cell viability and preservation of mesothelial integrity. These findings align with the broader body of research that has, over the years, explored alternative PD formulations aimed at enhancing biocompatibility, reducing glucose-associated toxicity, and optimizing both fluid management and metabolic parameters.

Recent investigations have further emphasized that retaining small amounts of glucose in PD fluid can be beneficial, particularly in malnourished patients, by leveraging its osmotic capacity and energetic contribution. Importantly, the experimental solutions used in these studies contained glucose at significantly lower concentrations, which did not appear to elicit the adverse effects typically associated with higher glucose loads.

Building on this evidence, the FIRST trial (Efficacy and Safety Assessments of a Peritoneal Dialysis Solution Containing Glucose, Xylitol, and L-Carnitine Compared to Standard PD Solutions in CAPD) was initiated and approved. In this thesis, I will present the results from the first cohort of patients who completed the full study period. Additionally, I will report interim findings from the ongoing Elixir and Pure studies, and introduce the design of the EXCITE study, which is currently pending approval by the ethics committee.

4.1. Description of the studies

FIRST is a study to evaluate "efficacy and safety assessments of a peritoneal dialysis solution containing glucose, xylitol and l-carnitine compared to standard PD Solutions in CAPD." The study was designed to evaluate the clinical effects of an experimental peritoneal dialysis (PD) solution in patients with End-Stage Renal Disease (ESRD) undergoing Continuous Ambulatory Peritoneal Dialysis (CAPD). The study aimed to compare the safety, efficacy, and metabolic outcomes of novel osmometabolic formulations against conventional PD protocols. Specifically, it investigated the use of the experimental solution IPX15, containing 0.5% glucose, 1.5% xylitol, and 0.02% L-carnitine as osmotic agents, administered during the nocturnal exchange, and compared it to a standard nocturnal exchange solution containing 2.5% glucose. Additionally, the study assessed the impact of IPX07, formulated for one to three daytime exchanges and composed of 0.5% glucose, 0.7% xylitol, and 0.02% L-carnitine, in combination with a nocturnal exchange using icodextrin. This regimen was evaluated against a conventional PD protocol consisting of 1.5% glucose for daytime exchanges and icodextrin for the nocturnal exchange, with the goal of determining whether the incorporation of osmo-metabolic agents could improve ultrafiltration performance, reduce glucose-related toxicity, and enhance metabolic control in CAPD patients.¹²¹

Elixir is "A Study to Evaluate the Efficacy and Safety of XyloCore, a Glucose Sparing Experimental Solution, for Peritoneal Dialysis". Literature data from various clinical studies clearly suggest the possibility of using peritoneal dialysis solutions containing osmotic agents such as Xylitol and L-carnitine. These solutions would not only significantly reduce the amount of glucose present in currently available peritoneal dialysis solutions but also take advantage of the metabolic properties of L-carnitine and Xylitol, potentially correcting any L-carnitine deficiency. A synergistic effect of these two compounds could also improve glycemic and lipid homeostasis. The phase III ELIXIR study was designed to confirm the efficacy and tolerability of the osmo-metabolic PD solution (XyloCore) in a larger population and for a longer period.

The PURE study (Peritoneal Ultrafiltration in Cardio Renal Syndrome to Prevent Heart Failure Exacerbation) is a Phase II/III randomized, controlled, open-label trial evaluating the safety and

efficacy of PolyCore, an investigational peritoneal ultrafiltration (PUF) solution containing icodextrin, L-carnitine, and D-xylitol. It targets patients with advanced heart failure (NYHA III–IV) and diuretic resistance. Participants are randomized to receive either standard care or adjunctive home-based PUF with PolyCore for six months, followed by a five-month follow-up. The primary endpoint is a composite of mortality or clinical worsening, including cardiovascular hospitalization, increased diuretic need, or renal decline. Secondary outcomes assess functional capacity, natriuretic biomarkers, renal preservation, and healthcare utilization. An independent adjudication committee and data safety monitoring board oversee endpoint validation and interim analysis. The study aims to determine whether PolyCore PUF can improve outcomes in a high-risk heart failure population.

The EXCITE study is a Phase II, single-arm, multicenter pilot trial evaluating the safety and efficacy of PolyCore—a peritoneal dialysis solution containing polydextrin, xylitol, and L-carnitine—in adult patients with end-stage kidney disease undergoing incremental peritoneal dialysis. Following a 28-day run-in phase, patients receive PolyCore for 28 days in one or two daily exchanges, tailored to maintain adequate dialysis performance ($Kt/V \text{ urea} \geq 1.7$). The primary endpoint is safety, assessed through adverse events, vital signs, lab tests, and dialysis metrics. Efficacy endpoints include depuration adequacy, ultrafiltration, sodium removal, and quality of life. Safety analyses will summarize treatment-emergent adverse events using MedDRA coding, including frequency, severity, and relation to the investigational product. Physical exams, lab values, and dialysis parameters will be tracked over time, with changes from baseline reported. Efficacy will be evaluated descriptively, focusing on weekly Kt/V , residual kidney function, and peritoneal performance. Exploratory analyses include oxalate levels and quality of life in genetically predisposed subgroups. No formal hypothesis testing is planned; statistical outputs will include means, standard deviations, and confidence intervals. The study will conclude at the last patient's final visit.

4.1.1. Studies design

The FIRST study (NCT04001036) was a Phase II, prospective, open-label, multicenter clinical trial conducted to assess the tolerability and efficacy of a novel peritoneal dialysis (PD) solution containing L-carnitine and xylitol in patients with End-Stage Renal Disease (ESRD) undergoing Continuous Ambulatory Peritoneal Dialysis (CAPD). The study spanned approximately 84 days and was divided into three distinct phases: screening, intervention, and follow-up. Following a four-week run-in screening period to identify eligible participants, patients entered a four-week intervention phase. Group A received the experimental solution IPX15 for the overnight dwell, while Group B underwent one to three daytime exchanges with the experimental solution IPX07, supplemented by a nocturnal exchange using icodextrin. In the subsequent four-week follow-up phase, patients reverted

to their standard PD regimens, with Group A resuming a 2.5% glucose solution for overnight exchanges and Group B using 1.5% glucose for daytime exchanges alongside icodextrin overnight. Safety and tolerability were evaluated through multiple parameters, including patient withdrawal, incidence and severity of adverse events, use of concomitant medications, abnormal hematological and biochemical findings, clinical indicators of fluid overload, and changes in patient-reported well-being questionnaires. As an exploratory study, no predefined primary or secondary efficacy endpoints were established; however, several efficacy indicators were monitored, such as daily ultrafiltration volume, weekly total urea Kt/V, weekly total creatinine clearance, and results from the peritoneal equilibration test (PET). Additionally, 24-hour urine output was recorded to support the overall assessment of treatment impact.¹²¹

Elixir is a Phase III, multicentric, randomized, controlled, parallel groups, open label, blinded end-point assessment clinical trial. Its purpose is to compare XyloCore, an experimental peritoneal dialysis (PD) solution containing Xylitol, L-Carnitine and low Glucose as active ingredients, to standard glucose-only PD regimens in patients with ESKD receiving CAPD over a 6-month study period. This study is designed as a randomized, controlled, parallel-group, open-label, multicenter clinical trial with blinded end-point assessment. Its primary objective is to compare the clinical effects of a novel low-glucose peritoneal dialysis (PD) solution, XyloCore®, with those of standard glucose-only PD regimens in patients with end-stage renal disease (ESRD) undergoing continuous ambulatory peritoneal dialysis (CAPD). The intervention period spans six months.

Eligible participants are those receiving two or three daytime exchanges with one of the following commercially available PD solutions: Physioneal® 35 or 40 (including Clear-Flex bags), Fixioneal® 35 or 40, Dianeal® or Dianeal® Low Calcium (glucose concentrations of 1.36%, 2.27%, or 3.86%), or Balance®, Bicavera®, Bicanova®, or Equibalance® (glucose concentrations of 1.5%, 2.3%, or 4.25%). All patients must also be prescribed one bag of Extraneal® (7.5% icodextrin) for the long nocturnal dwell. Participants are centrally randomized to receive either the investigational product XyloCore® or continue with their standard glucose-based PD regimen. Those assigned to the control group will maintain their existing prescription of two to three short-dwell exchanges per day using the aforementioned glucose-based solutions. Patients randomized to the XyloCore® arm will receive one of three formulations—Low, Medium, or High Strength—corresponding to the osmotic strength of their pre-randomization PD prescription. All patients will continue to receive Extraneal® for the overnight exchange. Throughout the study, PD prescriptions may be adjusted by the investigator based on clinical requirements, with the goal of maintaining a minimum total weekly Kt/V of greater than 1.7. A stratified randomization approach is employed to ensure balanced distribution of diabetic

patients across both treatment arms. Randomization is conducted centrally using a secure web-based system and a computer-generated allocation sequence. Given the constraints imposed by the COVID-19 pandemic, the study protocol allows investigators to choose between on-site or home-based patient management, depending on local public health conditions. This flexibility ensures continuity of care and data collection while maintaining patient safety. The ELIXIR study follows a structured schedule consisting of five key visits over a six-month period, designed to monitor patient safety, treatment efficacy, and metabolic outcomes.

Screening (Visit 1): Conducted up to 3 months prior to randomization, this visit includes informed consent, eligibility assessment, comprehensive clinical and biochemical evaluations, and baseline data collection. Multiple screening visits are permitted within this window.

Randomization (Visit 2, Day 0): Occurs within 14 days of the final screening visit. Patients are randomized to either the investigational (XyloCore®) or control group. Baseline fatigue assessment is performed, and investigational product instructions are provided. For patients randomized to XyloCore® and identified as heterozygous for primary hyperoxaluria, baseline oxalate levels are collected.

First Follow-Up (Visit 3): Scheduled at 30 days $\pm$ 5 days after initiation of PD treatment. This visit includes reassessment of clinical parameters, dialysis adequacy (Kt/V), peritoneal ultrafiltration, residual kidney function, metabolic markers, and patient-reported fatigue. Blood samples are collected for centralized oxalate analysis (if applicable), and patient diaries are reviewed.

Second Follow-Up (Visit 4): Conducted at 120 days $\pm$ 15 days post-treatment initiation. Evaluations include physical examination, vital signs, dialysis adequacy, ultrafiltration, diuresis, and adverse events. Patient diaries are again reviewed to assess adherence and treatment consistency.

Final Study Visit (Visit 5): Takes place at 180 days $\pm$ 15 days from the start of PD treatment. This comprehensive assessment includes all prior evaluations, with additional focus on final metabolic profiles, residual kidney function, and fatigue. Final blood and urine samples are collected, and patient diaries are reviewed for the full study period.

This timeline ensures consistent monitoring of both short- and long-term effects of the investigational PD solution, while allowing flexibility to accommodate patient needs and clinical logistics.

The PURE study is a randomized, controlled, open-label clinical trial with adaptive design, aimed at evaluating the safety and efficacy of PolyCore, an investigational peritoneal ultrafiltration (PUF) solution, in patients with advanced heart failure (NYHA class III–IV) and confirmed diuretic resistance. Eligible participants are adults who remain congested despite guideline-directed medical therapy, including high-dose loop diuretics and low urinary sodium excretion. Participants are randomly assigned to either standard care or adjunctive PUF therapy with PolyCore for six months.

Those in the treatment arm undergo catheter implantation and receive training before initiating nightly exchanges with 2 liters of PolyCore solution, lasting 12–14 hours. The intervention begins within 30 days of enrollment and is followed by a five-month observation period. Continued PUF treatment during follow-up is permitted based on clinical judgment. The primary endpoint is a composite of mortality or clinical deterioration, including cardiovascular hospitalization, increased diuretic requirement, or renal decline (eGFR <10 ml/min/1.73 m²). Secondary outcomes include improvements in functional capacity, quality of life, natriuretic peptide levels, NYHA class, renal function, and reduced hospital resource use. An independent adjudication committee will validate primary outcomes, while a data safety monitoring board will oversee trial integrity and interim analyses. The visit schedule includes:

Visit 1 (Screening): Baseline assessments include medical history, physical examination, ECG, echocardiography, laboratory tests, natriuresis evaluation, and quality of life. Eligibility is confirmed, and informed consent is obtained. Visit 2 (Catheter Implant): Patients randomized to the PUF group undergo surgical catheter placement and receive training for home-based ultrafiltration. Visit 3 (Day 30 ±5): Follow-up includes physical examination, NYHA classification, biomarker analysis, ultrafiltrate sampling, and review of patient diaries documenting daily blood pressure, weight, and UF volume. Visit 4 (Day 60 ±7): Continued monitoring includes clinical assessments, laboratory tests, ultrafiltration parameters, and evaluation of treatment adherence and adverse events. Visit 5: conducted at approximately 90 days, marks a comprehensive mid-treatment evaluation. Patients undergo physical examination, cardiac monitoring via ECG and echocardiography, and assessment of heart failure severity using NYHA classification and natriuretic biomarkers. Renal function is evaluated through both estimated and measured GFR, alongside 24-hour urine analysis. Quality of life is reassessed, and hospital resource use is reviewed. Laboratory testing includes a broad metabolic and hematologic panel, and patients complete the 6-minute walk test. Peritoneal ultrafiltrate is collected for future analysis, and daily self-monitoring data are reviewed to assess fluid status and treatment adherence. Visit 6 at 120 days focuses on ongoing safety and efficacy monitoring. Clinical assessments include physical examination, diuretic dosage adjustments, and evaluation of ultrafiltration parameters. Laboratory tests and eGFR are repeated, and patient diaries are reviewed to monitor congestion and treatment response. Visit 7 at 150 days continues the same protocol, maintaining consistency in clinical and biochemical evaluations, ultrafiltrate analysis, and diary review. This visit ensures longitudinal tracking of patient stability and treatment impact. Visit 8 at 180 days concludes the six-month treatment phase. Key assessments include NYHA classification, natriuretic biomarkers, quality of life, renal function, and hospital resource utilization. Adverse events and treatment adherence are documented, and patients' diaries are reviewed to confirm daily

monitoring compliance. Visit 9 at 210 days initiates the follow-up phase. It includes a full clinical reassessment, cardiac imaging, ECG, and laboratory testing. Renal function is measured, and functional capacity is reassessed. Peritoneal ultrafiltrate samples are collected for metabolic studies. Patients may continue PolyCore PUF treatment during follow-up based on the investigator's discretion. Long-term follow-up visits at day 270 and 360 provide final evaluations of safety and clinical status. These include physical examination, NYHA classification, laboratory testing, and adverse event reporting. Female patients treated with PolyCore undergo pregnancy testing. Additional visits may be scheduled if clinically indicated, ensuring patient safety and responsiveness to emerging concerns. Monthly assessments continue through the treatment phase, with additional visits at day 270 and 360 during follow-up. This structured schedule ensures comprehensive monitoring of safety, efficacy, and patient outcomes throughout the study.

The EXCITE study is a Phase II, single-arm, prospective, multicenter pilot trial designed to evaluate the safety and efficacy of PolyCore, a novel peritoneal dialysis solution composed of polydextrin, xylitol, and L-carnitine, in adult patients with end-stage kidney disease undergoing incremental peritoneal dialysis. Eligible patients must have a residual glomerular filtration rate of at least 5 ml/min/1.73m² and be within six months of initiating dialysis, either already receiving two daily exchanges—one icodextrin-based and one glucose-based—or newly implanted with a peritoneal catheter and starting such a regimen. All participants begin with a 28-day run-in phase continuing their standard-of-care prescription, which allows verification of dialysis adequacy and genetic screening for primary hyperoxaluria types 1 and 2. Following this, patients transition to a 28-day treatment period with PolyCore, administered as either two extended-duration exchanges or one extended and one short dwell exchange, with dosing individualized to maintain a weekly Kt/V urea of at least 1.7. Patients requiring escalation to full-dose dialysis during the study will be withdrawn. The study schedule includes four key visits: informed consent up to day -14, screening on day 0, end of run-in on day 28, intermediate evaluation on day 42, and end-of-treatment on day 56. Each visit involves fasting assessments, collection of 24-hour urine and dialysate samples, physical examinations, vital signs, comprehensive blood chemistry and hematology, glycemic and lipid profiles, dialysis performance metrics, and patient-reported outcomes including the KDQOL-SF questionnaire. Plasma samples are collected for central metabolic and oxalate analyses, and all concomitant treatments and adverse events are monitored throughout. This structured approach ensures consistent evaluation of safety, efficacy, and patient experience across the study timeline.

4.1.2. Studies population

In the FIRST study, clinically stable patients aged 18 years or older with End-Stage Renal Disease (ESRD) undergoing Continuous Ambulatory Peritoneal Dialysis (CAPD) for a minimum of three months were enrolled following the provision of written informed consent. The study protocol received approval from the Ethics Committee of the G. d'Annunzio University of Chieti-Pescara. Prior to enrollment, participants were required to have been consistently treated with CAPD using either a standard dialysis solution containing 2.5% glucose monohydrate (126.1 mmol/L, Dianeal; Baxter Healthcare, McGaw Park, IL, USA) for the overnight dwell (Group A), or with one to three daytime exchanges using standard solutions containing 1.5% glucose monohydrate (75.5 mmol/L, Dianeal), combined with a nocturnal exchange using icodextrin (Extraneal; Baxter Healthcare) (Group B), based on individual clinical requirements. Eligibility criteria included clinical stability for at least four weeks prior to screening, confirmed through medical history, physical examination, and laboratory evaluations. Key exclusion criteria comprised prior use of L-carnitine or its derivatives within the preceding month, previous exposure to dialysis bags containing L-carnitine, or any episode of peritonitis within the last three months. Additional exclusion criteria included hemoglobin levels below 9 g/dL, presence of severe illness or acute infection, a history of major cardiovascular events such as stroke, acute myocardial infarction, or coronary/arterial revascularization procedures within the past three months, pregnancy or lactation, and an estimated life expectancy of less than 12 months.¹²¹

Participants eligible for the ELIXIR trial were required to demonstrate clinical stability during the three months preceding screening, as evidenced by the absence of non-elective hospitalizations and major cardiovascular events. Stable patients aged 18 years or older, male and female. Additional inclusion criteria included the absence of peritonitis episodes within the same timeframe, ongoing treatment with Extraneal® (7.5% icodextrin) for the nocturnal long-dwell exchange for at least one month, and a prescribed regimen of one, two or three short-dwell exchanges using commercially available glucose-based PD solutions such as Physioneal® (including Clear-Flex bags), Fixioneal®, Dianeal® or Dianeal® Low Calcium (1.36%, 2.27%, or 3.86% glucose), or Balance®, Bicavera®, Bicanova®, or Equibalance® (1.5%, 2.3%, or 4.25% glucose). A minimum weekly Kt/V_{urea} value of >1.7 was required to ensure adequate dialysis. Patients also had to be under regular follow-up by the participating clinical center for at least three months and capable of understanding the study protocol and providing informed consent. Exclusion criteria encompassed a range of clinical and pharmacological conditions. Patients were excluded if they had a history of drug or alcohol abuse within the previous six months, were receiving androgen therapy, or exhibited clinically significant liver dysfunction (Gamma-GT > 4× upper normal limit). Acute infectious diseases—including pulmonary infections, hepatitis, urinary tract infections, renal parenchymal infections, and

pericarditis—were grounds for exclusion, as was a projected life expectancy shorter than the study duration. Additional exclusions included prior L-carnitine therapy within one month, use of investigational drugs within three months, pregnancy or breastfeeding, and inadequate contraception in women of childbearing potential (defined as within 24 months of last menstruation). Patients diagnosed with primary hyperoxaluria, those with elevated serum uric acid levels (>7.2 mg/dL in males and postmenopausal women; >6.0 mg/dL in premenopausal women), recent major cardiovascular events, or advanced heart failure (NYHA Class IV) were also excluded.

Patients are centrally randomized to the glucose-only PD solution active comparator or to the investigational product XyloCore (Low, Medium or High Strength according to the glucose osmotic strength of their pre-randomization prescribed PD solution). All patients continue with Extraneal (7.5% Icodextrin) for the nocturnal (long-dwell) exchange. PD prescriptions in both treatment arms should be tailored to reach the minimum target of a total Kt/V of > 1.7 per week throughout the study. The study is open-label with blinded evaluator (primary endpoint), without blinding of patients or clinical staff.

Patient eligibility for the PURE trial is determined through a structured screening process, with each center maintaining a log of all individuals assessed, enrolled, or excluded, including reasons for exclusion. Multiple screening visits are permitted to ensure thorough evaluation. To qualify, patients must be adults (≥ 18 years) with advanced heart failure (NYHA class III–IV) and reduced left ventricular ejection fraction ($\leq 60\%$), despite optimal medical therapy. Inclusion also requires evidence of persistent right ventricular failure, confirmed by hemodynamic imbalance (RAP/CWP ratio >0.65), moderate or greater tricuspid regurgitation, and loop diuretic resistance verified through standardized natriuresis testing. Additional criteria include signs of fluid overload (e.g., dilated inferior vena cava), impaired renal function (GFR between 15–60 ml/min/1.73 m²), elevated natriuretic peptides (BNP or NT-proBNP), and a history of decompensation requiring intravenous diuretics. Candidates must be suitable for peritoneal ultrafiltration and provide informed consent. Exclusion criteria include recent cardiac surgery or device implantation, severe valvular or coronary disease, active myocarditis, end-stage renal disease (GFR <15 ml/min/1.73 m²), organ transplantation, pulmonary embolism, fibrotic lung disease, liver cirrhosis, malignancy, and contraindications to catheter placement. Women who are pregnant, breastfeeding, or not using effective contraception are excluded, as are individuals unable to consent or those participating in other interventional trials. Patients with hypersensitivity to PolyCore components or any condition deemed unsafe or incompatible with study participation by the investigator are also excluded. This rigorous selection framework ensures that enrolled patients represent a clinically appropriate and homogeneous population for evaluating the safety and efficacy of PolyCore PUF therapy.

The study population comprises adult male and female patients diagnosed with End-Stage Kidney Disease (ESKD) who are undergoing incremental Continuous Ambulatory Peritoneal Dialysis (CAPD). To ensure the appropriateness of incremental dialysis, all participants must retain sufficient residual kidney function, defined by a glomerular filtration rate (GFR) ≥ 5 ml/min/1.73m² at screening. Additionally, patients must have initiated peritoneal dialysis within the previous six months to minimize the likelihood of transitioning to full-dose regimens during the study period, which would necessitate withdrawal. Inclusion criteria are assessed during screening and baseline visits and require patients to be adults with ESKD, maintain a GFR ≥ 5 , be clinically stable, and currently treated with one daily exchange of icodextrin (7.5%) and one of glucose ($\leq 1.5\%$) in accordance with the study's incremental PD protocol. Participants must understand the study and provide informed consent, and demonstrate dialysis adequacy with a weekly Kt/V urea ≥ 1.7 at baseline. Exclusion criteria include recent peritonitis, participation in other investigational trials within the past month, substance abuse history, severe organ dysfunction, abnormal liver function tests, active malignancies (except excised basal cell carcinoma), pregnancy or breastfeeding, lack of adequate contraception in women of childbearing potential, hypersensitivity to study compounds, history of primary hyperoxaluria or clinically significant oxalate/lactate abnormalities, and any condition deemed by the investigator to pose undue risk or interfere with study assessments. Patients with acute renal failure, contraindications to polydextrin-based solutions, compromised peritoneal function due to adhesions or recent abdominal surgery, and uncorrectable mechanical defects that impair PD efficacy or increase infection risk are also excluded. Women of childbearing age must use approved contraceptive methods throughout the study duration, with postmenopausal status confirmed by clinical criteria or hormonal testing where applicable. All enrolled patients will begin with a 28-day run-in period during which they will continue their pre-study peritoneal dialysis regimen, consisting of one daily exchange with icodextrin (7.5%) and one with glucose (up to 1.5%), representing the standard of care. Following this phase, patients will transition to the investigational treatment with PolyCore, administered over 28 days in two daily exchanges: one extended-duration exchange and one either extended or short dwell exchange. Prescriptions will be individualized by the nephrologist based on clinical needs, with the goal of maintaining a weekly Kt/V urea of at least 1.7 throughout the treatment period.

4.1.3. Studies solutions

In the FIRST study, the peritoneal dialysis (PD) solutions were provided in sterile, single-use 2-liter bags manufactured by Galenica Senese (Monteroni d'Arbia, Siena, Italy), each with a pH of 5.5 and containing sodium 134 mmol/L, calcium 1.75 mmol/L, magnesium 0.5 mmol/L, chloride 103.5

mmol/L, lactate 35 mmol/L, glucose 27.7 mM, and L-carnitine 1.24 mM. The two formulations differed in their xylitol concentrations, with the IPX15 solution containing 98.6 mM and the IPX07 solution containing 46 mM. The osmotic strength of these experimental PD solutions was comparable to that of the glucose-based PD solutions administered during the intervention and follow-up phases. All solutions used in the study were manufactured in compliance with Good Manufacturing Practice (GMP) standards.¹²¹

In ELIXIR, is under evaluation the XyloCore®, an investigational peritoneal dialysis (PD) solution formulated to reduce glucose exposure by incorporating osmo-metabolic agents—xylitol and L-carnitine—while maintaining effective osmotic strength. The solution is packaged in a hermetically sealed, two-chambered bag composed of medical-grade plasticized polyvinyl chloride (PVC). This primary container is enclosed within a transparent overpouch made of multilayer copolymers, sealed through thermal fusion to ensure sterility and stability. Previously, the XyloCore® solution was packaged in dual-chambered bags requiring manual mixing prior to administration. These have now been replaced by single-chambered bags, which simplify the preparation process and eliminate the need for reconstitution before infusion. XyloCore® is available in three osmotic strengths—Low, Medium, and High—corresponding to the glucose concentrations of standard PD solutions such as Physioneal®, Fixioneal®, Dianeal®, Balance®, Bicavera®, and Equibalance®. The composition of the reconstituted solution is summarized in Table below.

Component	Low Strength (a)	Medium Strength (b)	High Strength (c)
Xylitol (mmol/L)	46 (0.7% w/v)	98.6 (1.5% w/v)	125 (2.0% w/v)
Glucose (mmol/L)	27.7 (0.5% w/v)	83 (1.5% w/v)	—
L-Carnitine (mmol/L)	1.24 (0.02% w/v)	1.24	1.24
Sodium (mmol/L)	132	132	132
Calcium (mmol/L)	1.3	1.3	1.3
Magnesium (mmol/L)	0.5	0.5	0.5
Chloride (mmol/L)	101	101	101
Lactate (mmol/L)	35	35	35
pH	6.5–7.5	6.5–7.5	6.5–7.5
Osmolarity (mosmol/L)	346.5	399.1	480.8

The osmotic strength of each formulation is designed to match that of conventional glucose-based PD solutions with glucose concentrations of 1.36%, 2.27%, and 3.86% (w/v) or 1.5%, 2.3%, and 4.25% (w/v), respectively. Variations within each osmotic category are maintained within a 3%

margin. Patients randomized to the XyloCore® arm receive the formulation that corresponds to the osmotic strength of their pre-enrollment PD prescription, ensuring continuity in ultrafiltration efficacy while reducing glucose exposure. The study solutions were provided in sterile, single-use 2-liter bags.

The experimental bags had a pH of 6.5-7.5 and the following composition: sodium 132 mmol/L; calcium 1.3 mmol/L; magnesium 0.5 mmol/L; chloride 101 mmol/L; lactate 35 mmol/L; glucose 27.7 mM/l in the Low and Medium Strength and 83 mM/L in the High Strength; L-carnitine 1.24 mM/L. The bags differed in xylitol content: Xylitol 46 mM/L (Low Strength), 98.6 mM/L (Medium Strength) and 125 mM/L (High Strength). Osmolarity: 346.5 mosmol/L (Low Strength), 399.1 mosmol/L (Medium Strength) and 480.8 mosmol/L (High Strength). The Active Comparator (standard treatment), for patients randomized to the control group remain on their prescribed PD solutions with the same dosing schedule for the duration of the study unless investigators determine medically necessary to change the prescription.

In the PURE study, patients assigned to the treatment arm receive PolyCore, a peritoneal ultrafiltration (PUF) solution administered through nightly exchanges. Each session typically involves 2 liters of solution over 12–14 hours, with the option for an additional daily exchange if further fluid removal is needed. The frequency of exchanges, ranging from four to seven per week, is tailored by the investigator based on the patient's fluid status. Adjustments may be made in cases of compromised perfusion, reducing the frequency to alternate days. Catheter implantation is performed using an open surgical technique with a self-locating device to minimize displacement. The procedure involves abdominal access under general anesthesia, careful placement of the catheter, and post-operative testing to ensure proper function and absence of complications. A two-week break-in period is required before initiating PUF therapy. Patients are advised to continue beta-blockers and aspirin perioperatively, while other antihypertensive medications may be withheld. PolyCore is formulated as a 2-liter solution. Initial dosing may begin with 1.5 liters, especially in smaller patients, with gradual volume increase over one to two weeks.

Component	Concentration (mmol/L)	Strength (% w/v)
Xylitol (mmol/l)	98.6	1.5%
Polydextrine (mmol/l)	3.1	4.0%
L-Carnitine (mmol/l)	1.24	0.02%
Sodium (mmol/l)	133	—
Calcium (mmol/l)	1.75	—
Magnesium (mmol/l)	0.25	—

Chloride (mmol/l)	96	—
Lactate (mmol/l)	40	—
pH	5.5	—
Osmolarity (mosmol/L)	376	—

Treatment duration is set at 180 days, accounting for one month of catheter implantation and training, followed by six months of active therapy. After this period, all participants enter a five-month follow-up phase for continued monitoring. Patients in the PolyCore group may continue PUF during follow-up and beyond, based on clinical judgment and investigator prescription.

The investigational peritoneal dialysis solution designed for the EXCITE study is PolyCore, a formulation developed to replace conventional incremental peritoneal dialysis (PD) regimens. PolyCore is formulated to mimic the osmolarity of Extraneal (Baxter), with a nominal volume of 2000 mL per exchange, packaged in a polypropylene bag connected to a 3000 mL drain bag. The system uses a Luer-lock connection and must be stored above 4°C; any temperature excursion below this threshold for more than 30 minutes renders the product unusable. Storage temperature monitoring is not required during on-site or home storage, provided local procedures for PD fluids are followed. Labeling includes three components: a plastic-stamped label with batch and expiry data on the primary bag, a primary label on the over-pouch, and a secondary label on the outer packaging. These components are intended to remain together throughout the product lifecycle. Treatment with PolyCore begins after a 28-day run-in period and confirmation of genetic screening for primary hyperoxaluria. It replaces both extended-duration exchanges (previously with icodextrin 7.5%) and short-dwell exchanges (glucose-based solutions 1.36–2.30%). The solution is administered twice daily, either as two extended exchanges or one extended and one short dwell, with durations tailored to clinical needs and aimed at maintaining a weekly Kt/V urea ≥ 1.7 . In specific cases, such as low body surface area patients, volumes below 2L may be used per exchange. The following table summarizes the treatment regimens across study periods:

Study Period	Regimen	Product	Exchange Duration
Run-in (Standard of Care)	2 Dwells per day	1× Extraneal (7.5%)	Extended (8–12 hours)
		1× Glucose-based PDS	Short (4–6 hours)
Intervention (PolyCore)	2 Dwells per day	2× PolyCore	Extended (8–12 hours)

Intervention (PolyCore)	2 Dwells per day	2× PolyCore	1× Extended (8–12 hours), 1× Short (4–6 hours)
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PolyCore treatment continues until Visit 4 (Day 56 ± 6), after which patients revert to their pre-intervention commercial PD solutions. Compliance is monitored through patient diaries, documenting each dose, including missed or delayed exchanges. At each clinic visit, compliance is reviewed with the patient and cross-checked against the number of bags delivered, returned unused, and expected usage based on prescription. This structured approach ensures accurate tracking of adherence and supports robust data collection for efficacy and safety analysis.

4.1.4. Objectives and endpoints

The purpose of the FIRST study was to evaluate and compare the clinical effects of two experimental peritoneal dialysis solutions in patients with end-stage renal disease undergoing continuous ambulatory peritoneal dialysis. The first solution, referred to as IPX15, contained low concentrations of glucose, xylitol, and L-carnitine, and was intended for use during the nocturnal exchange. Its osmotic profile was designed to be comparable to that of the conventional 2.5% glucose solution. This formulation was administered to a group of twenty patients, designated as Group A. The second solution, named IPX07, also included glucose, xylitol, and L-carnitine, but at different concentrations, and was used for one to three daytime exchanges. It was combined with icodextrin for the overnight dwell, mimicking the standard regimen that employed 1.5% glucose during the day and icodextrin at night. This treatment was evaluated in another group of twenty patients, referred to as Group B. The study was primarily focused on assessing the safety and tolerability of these experimental solutions. This was achieved by observing the occurrence and severity of any adverse events, evaluating patients' subjective perceptions of well-being, and monitoring variations in standard biochemical and hematological parameters throughout the treatment period. In addition to safety, the study aimed to explore the impact of the experimental solutions on dialysis efficacy and peritoneal membrane function. This included analyzing solute clearance and transport characteristics over time, as well as measuring changes in specific biomarkers such as CA 125 and protein concentrations in the peritoneal effluent, which could reflect alterations in membrane integrity and cellular response. Through this comparative approach, the study sought to determine whether the incorporation of xylitol and L-carnitine into PD fluids offered advantages over traditional glucose-based solutions in terms of biocompatibility, metabolic outcomes, and overall patient experience.

About the ELIXIR study, the primary objective of this randomized clinical trial is to demonstrate the non-inferiority of the glucose-sparing peritoneal dialysis (PD) solution, XyloCore®, compared to

conventional glucose-based PD solutions in patients with end-stage renal disease (ESRD) undergoing continuous ambulatory peritoneal dialysis (CAPD). The primary efficacy endpoint is the total weekly Kt/V_{urea}, a validated measure of dialysis adequacy, assessed after 24 weeks of treatment using the assigned PD solution. This parameter will be determined through a standardized peritoneal function test (Keen, 1994), which involves the collection of blood, 24-hour urine, and spent dialysate to calculate both peritoneal and renal contributions to total Kt/V. Secondary endpoints include changes from baseline in lipid profile parameters (LDL, HDL, total cholesterol, and serum triglycerides), glycemic control markers (HbA1c and insulin), and hematologic indices (hemoglobin levels and erythropoietin requirements). Additional clinical outcomes include patient-reported fatigue, assessed using the Chalder Fatigue Scale, as well as objective measures of fluid management such as daily peritoneal ultrafiltration, 24-hour urine volume, and residual kidney function. The latter will be calculated as the arithmetic mean of urinary urea and creatinine clearance, as described by Steubl et al. (2019).

Exploratory endpoints are also incorporated to support future mechanistic and translational research. These include the measurement of plasma oxalate levels in patients from the intervention group who are heterozygous for primary hyperoxaluria. Furthermore, biological samples (plasma, urine, and peritoneal effluent) will be collected and biobanked for subsequent analyses aimed at exploring insulin sensitivity, glucose and carnitine metabolism, and broader metabolomic profiles in both plasma and dialysate. These investigations are intended to uncover potential pathophysiological mechanisms and biomarkers that may inform future therapeutic strategies.

The primary objective of the PURE study is to determine whether treatment with PolyCore peritoneal ultrafiltration (PUF) influences the composite outcome of patient mortality or clinical deterioration. This includes assessing whether the intervention can prevent worsening heart failure in patients with cardiorenal syndrome. Secondary objectives focus on evaluating broader clinical benefits, such as improvements in patient condition and quality of life, reduction in hospital resource utilization, and changes in NYHA functional class. The study also aims to assess kidney function preservation, maintenance of urine output and sodium excretion, and reduction in sympathetic nerve activity. Additionally, it investigates whether PolyCore PUF can reduce the need for increased loop diuretic dosage and prevent hospitalizations requiring intravenous diuretic therapy.

The primary objective of the EXCITE study is to evaluate the safety profile of PolyCore in patients undergoing incremental peritoneal dialysis, through continuous monitoring of adverse events, vital signs, and laboratory parameters. Primary endpoints include the incidence and nature of adverse events, physical examination findings, vital signs and body weight, blood chemistry and hematology,

24-hour urine and dialysate analyses, weekly Kt/V urea, and residual kidney function, all assessed at each study visit. The secondary objective is to assess the efficacy of PolyCore in maintaining adequate dialysis performance, including solute clearance, ultrafiltration, and sodium removal. Secondary endpoints encompass the post-baseline profile of weekly Kt/V urea, peritoneal ultrafiltration (also recorded daily in patient diaries), peritoneal and total sodium removal, glycemic and lipid parameters, peritoneal clearances of creatinine, phosphate, and beta-2 microglobulin, quality of life via the KDQOL-SF questionnaire (administered at visits 2 and 4), and the number of patients who discontinue the study due to safety or efficacy concerns. Exploratory endpoints include plasma oxalate levels in patients with heterozygous pathogenic mutations associated with primary hyperoxaluria types 1 or 2, and centralized metabolic analyses of plasma, 24-hour dialysate, and urine samples. Intercurrent events such as progression to full-dose peritoneal dialysis, switch to alternative renal replacement therapies, death, kidney transplantation, loss to follow-up, or withdrawal of consent will result in study discontinuation and exclusion from the per-protocol analysis, following the Principal Stratum strategy. Discontinuation may also occur due to serious adverse events, medical conditions, or non-compliance, and must be thoroughly documented by the investigator. Participants are considered lost to follow-up if they repeatedly miss scheduled visits and cannot be contacted despite documented efforts. In such cases, the last completed visit will be recorded as the end-of-study date for that patient.

4.1.5. Safety

In FIRST the safety and tolerability of the experimental peritoneal dialysis solutions were assessed through clinical evaluations, laboratory tests, and patient-reported outcomes. Both L-carnitine and xylitol have demonstrated good tolerability in humans, with adverse effects only observed at high doses exceeding those used in the study. Patients underwent regular monitoring of vital signs, physical examinations, and electrocardiograms. Laboratory analyses included blood chemistry, hematology, and specific markers such as uric, lactic, and oxalic acids to detect potential metabolic effects. CA 125 and protein levels in the peritoneal effluent were measured to evaluate peritoneal membrane integrity and biocompatibility. Adverse events were documented and classified according to standard definitions, with any clinically relevant abnormalities investigated and followed until resolution. Overall, the study applied a comprehensive safety protocol to ensure accurate assessment of the investigational solutions' tolerability.

Safety in the ELIXIR study is rigorously monitored through the documentation of adverse events (AEs), serious adverse events (SAEs), and suspected unexpected serious adverse drug reactions (SUSARs). Any medical occurrence after informed consent—whether or not related to the

investigational product—is recorded as an AE. These include new symptoms, worsening of pre-existing conditions, or clinically significant lab abnormalities requiring treatment. AEs are classified by severity (mild, moderate, severe) and assessed for causality. SAEs are defined as events resulting in death, life-threatening conditions, hospitalization, disability, or congenital anomalies. SUSARs are serious, unexpected reactions not listed in the product’s safety documentation and must be reported promptly to regulatory authorities—within 7 days for fatal/life-threatening events and 15 days for others. All SAEs must be reported within 24 hours of investigator awareness, regardless of causality. Follow-up information must be submitted as it becomes available. AEs and SAEs are monitored until resolution or stabilization, including up to 30 days after the final study visit if related to the investigational product. Pregnancies occurring during the study or within 90 days post-treatment must be reported immediately. Affected participants are withdrawn from the study and monitored for maternal and fetal outcomes. This safety framework ensures comprehensive pharmacovigilance throughout the study and follow-up period.

In the PURE study, the assessment of efficacy and safety is designed to capture both the clinical impact of PolyCore therapy and its tolerability in patients with advanced heart failure. The primary efficacy endpoint focuses on a composite of critical outcomes: mortality, cardiovascular hospitalization, escalation in diuretic therapy, and significant renal deterioration. These events are carefully adjudicated by an independent committee of cardiologists and nephrologists to ensure objectivity and consistency. Beyond these core outcomes, the study also explores a range of secondary parameters that reflect the broader clinical picture. These include changes in physical capacity, quality of life, heart failure severity, and renal function over time. Biomarkers such as NT-proBNP and BNP are monitored to track disease progression and therapeutic response. Hospital resource utilization and the need for alternative treatments like hemodialysis are also considered, offering insight into the real-world burden of disease and care. Safety monitoring is equally rigorous. From the moment a patient signs the informed consent until the final follow-up visit, every adverse event is documented and evaluated. These events range from mild symptoms to serious complications, and their severity is classified using standardized criteria. Particular attention is given to serious adverse events—those that result in death, are life-threatening, require hospitalization, or cause lasting disability. Even events that do not immediately meet these thresholds but pose a potential risk to the patient are treated with caution and reported accordingly. Unexpected serious reactions to the investigational product, known as SUSARs, are subject to expedited reporting. The sponsor is responsible for notifying ethics committees and investigators in compliance with regulatory timelines, ensuring transparency and patient safety. The protocol also outlines procedures for managing and reporting pregnancies during the study. Female participants are instructed to inform

investigators immediately if they become pregnant, and any such cases are followed closely to monitor outcomes for both mother and child. Pregnant participants are withdrawn from the study and informed of their treatment allocation if requested. All adverse events, whether mild or severe, are followed until resolution or stabilization. This commitment extends beyond the study period, especially for events deemed related to the investigational product. Investigators are required to document the course of each event thoroughly, including any medical interventions, outcomes, and relevant clinical data. Together, these measures form a comprehensive framework for evaluating the therapeutic potential of PolyCore while safeguarding the well-being of every participant. The study's design reflects a deep commitment to scientific rigor, ethical responsibility, and patient-centered care.

Safety and exploratory assessments in the EXCITE study ensure thorough monitoring of patient health and treatment response to PolyCore. Safety evaluations include local blood chemistry and hematology covering complete blood count, electrolytes, liver and kidney markers, coagulation, inflammation, and β 2-microglobulin. Diuresis and dialysate are collected over 24 hours to assess volume and solute levels, including urea, creatinine, sodium, phosphate, and ultrafiltration. Dialysis adequacy is measured weekly via Kt/V urea, calculated from peritoneal and residual renal clearance, adjusted for body surface area. For patients with minimal urine output, only peritoneal Kt/V is used. Body weight is recorded after the morning exchange using the “flush before fill” method, and residual kidney function is calculated by averaging urea and creatinine clearance. Adverse events (AEs) are any unfavorable medical occurrences post-consent, regardless of causality. Severity follows CTCAE grading from mild (Grade 1) to death (Grade 5). Serious adverse events (SAEs) include death, actual life-threatening conditions, unplanned hospitalization, disability, or important medical events requiring intervention. Planned hospitalizations, elective procedures, and routine monitoring are not considered SAEs. SAEs must be reported within 24 hours and followed until resolution or stabilization, including up to 30 days post-study if related to the investigational product. Reports must include full clinical and administrative details, and deaths require autopsy findings and medical history. Peritonitis is classified as an expected SAE and must meet ISPD criteria: clinical symptoms, elevated effluent white cell count, and positive culture. Cases linked to known organisms, enteric sources, or catheter infections are not considered related to PolyCore. Culture-negative peritonitis may be considered related if responsive to antibiotics. Investigators should repeat cultures and test for atypical pathogens. Treatment follows standard hospital protocols. Pregnancies during or within 90 days after treatment must be reported within one working day. Affected participants are withdrawn and monitored for maternal and fetal outcomes. All pregnancy outcomes are documented. SUSARs are unexpected serious reactions not listed in the product's safety profile and require expedited reporting by the sponsor under EU regulations. Exploratory endpoints include plasma oxalate levels

in heterozygous PH1/PH2 carriers, analyzed centrally at the University of Padova using samples collected at Visit 2. Metabolic profiling of plasma, urine, and dialysate is conducted at Visits 2 and 4, with patients following a standardized exchange schedule. All materials and procedures are sponsor-provided and centrally managed. Routine lab assessments are performed locally under hospital SOPs. Participating labs must maintain updated reference ranges and certification to ensure data quality. This framework supports robust safety and exploratory evaluation of PolyCore in incremental peritoneal dialysis.

4.1.6. Statistical methods and data analysis

The safety and tolerability of the investigational peritoneal dialysis solution in FIRST were evaluated through a comprehensive protocol incorporating clinical, biochemical, and patient-reported parameters. L-carnitine and xylitol, the key osmo-metabolic agents, are known to be well tolerated in humans, with adverse effects reported only at doses significantly exceeding those used in this study. Safety monitoring included medical history, physical examination, vital signs, electrocardiography, and laboratory assessments such as serum uric, lactic, and oxalic acid levels. Additional laboratory analyses encompassed clinical chemistry, hematology, and biomarkers of peritoneal membrane integrity, including CA 125 and protein concentrations in the peritoneal effluent. Subjective tolerability was assessed via a standardized well-being questionnaire administered at baseline and follow-up visits. Adverse events were systematically recorded and classified according to international standards (MedDRA, CTCAE), with serious adverse events subject to expedited reporting procedures. All data were documented in electronic case report forms (eCRFs) and reviewed for clinical relevance. This structured safety framework ensures rigorous pharmacovigilance and supports the evaluation of biocompatibility and systemic tolerability of the experimental solution.

In ELIXIR all collected data are entered into an online platform (eCRF) from where all data will be analysed and statistical analysis will be carried out. The ELIXIR study employs a randomized, controlled, open-label design with blinded end-point assessment, comparing the effects of the glucose-sparing PD solution XyloCore® to conventional glucose-based regimens in patients with ESRD undergoing CAPD over a six-month period. Statistical analysis is structured around three populations: intent-to-treat, per-protocol, and safety. The primary efficacy endpoint—weekly Kt/V_{urea} at 24 weeks—is evaluated using a two-sided 95% confidence interval for the difference in least-square means between treatment groups. Non-inferiority is confirmed if the lower bound of this interval exceeds -0.25 . This analysis is conducted across both ITT and per-protocol datasets. Patient disposition, baseline characteristics, and concomitant therapies are analyzed using descriptive

statistics, with adjustments made if baseline imbalances are detected. Safety and efficacy outcomes are explored through descriptive methods, without interim analysis. The study design ensures robust comparison while maintaining methodological rigor and regulatory compliance.

The PURE study is a randomized, controlled, open-label clinical trial with adaptive design, aimed at evaluating the safety and efficacy of PolyCore peritoneal ultrafiltration in patients with advanced heart failure across all ejection fraction categories. The trial includes both an intention-to-treat population for efficacy analysis and a safety population comprising all patients who received at least one dose of the investigational treatment. The primary efficacy endpoint is a composite measure that includes mortality, cardiovascular hospitalization, escalation in loop diuretic therapy, and renal deterioration, adjudicated by an independent committee. Secondary endpoints assess functional capacity, NYHA classification, natriuretic peptide levels, renal function, quality of life, and healthcare utilization, while exploratory parameters include catecholamine levels, urinary electrolytes, echocardiographic measurements, and ultrafiltrate composition. Safety is monitored from randomization through the final follow-up visit and includes treatment-emergent adverse events, vital signs, physical exams, ECGs, urinalysis, and laboratory tests. Adverse events are classified using MedDRA terminology and CTCAE grading, with serious adverse events defined by outcomes such as death, life-threatening conditions, hospitalization, or significant disability. Unexpected serious reactions are subject to expedited reporting, and pregnancies occurring during or shortly after the study are documented and followed. Statistical analysis employs standard methods for binary, continuous, and time-to-event data, with sensitivity analyses addressing informative dropouts. An interim analysis is planned once 20 patients per group complete seven months of follow-up; if conditional power exceeds 80%, the study proceeds unchanged, otherwise the sample size is recalculated. Advanced techniques will assess multiple events per patient, including cumulative event count curves and area-under-the-curve comparisons. Secondary analyses will isolate post-implantation data, excluding the first month. Additional endpoints include the need for supplementary diuretics, hospital resource use, and escalation in furosemide dosage. Safety data are presented descriptively, and final analysis occurs after all patients complete the study. Sample size estimation assumes a 50% event rate in the control group and 20% in the PolyCore group, yielding a target of 84 patients with a 10% dropout margin. This comprehensive framework ensures methodological rigor and patient safety while capturing the clinical impact of PolyCore therapy.

The statistical framework of the EXCITE study is designed to support its exploratory nature as a single-arm pilot trial evaluating the safety and efficacy of PolyCore in patients undergoing incremental peritoneal dialysis. With no formal hypothesis testing, the analysis is entirely descriptive.

The sample size of 28 patients accounts for an expected 20% dropout rate, ensuring at least 22 evaluable subjects. This number was justified using Kt/V urea as the primary adequacy endpoint, a robust and quantifiable marker widely accepted in dialysis research. Supporting data from the ELIXIR trial and a large cohort study by Rocco et al. confirmed that the expected mean Kt/V values exceed the clinical adequacy threshold of 1.7, with confidence intervals demonstrating sufficient precision for pilot-level conclusions and future study planning. All analyses will be conducted on three predefined populations: the Safety Analysis Set (SAF), including all patients who received at least one dose of PolyCore; the Full Analysis Set (FAS), comprising patients without major protocol violations; and the Per Protocol (PP) population, which includes those who completed the study without significant deviations affecting efficacy assessment. Categorical data will be summarized using counts and percentages, while continuous variables will be described using mean, standard deviation, standard error, median, minimum, and maximum. Baseline is defined at Visit 2, and changes from baseline will be calculated for Visits 3 and 4. No imputation for missing data will be applied, and all results are considered exploratory without correction for multiplicity. Safety assessments will include coding of adverse events using MedDRA, with summaries of treatment-emergent events, serious adverse events, withdrawals, and deaths. Physical examinations will be tabulated by body system and time point, including shifts from baseline. Vital signs and body weight will be reported with changes over time. Blood biochemistry and hematology will be analyzed with flagged abnormal values and reference ranges. Diuresis and dialysate parameters, including volume, solute concentrations, and ultrafiltration, will be evaluated at each time point. Weekly Kt/V urea values—peritoneal, renal, and system-calculated—along with residual kidney function metrics will be presented with 95% confidence intervals for mean changes. Efficacy endpoints will include post-baseline profiles of weekly Kt/V urea, peritoneal ultrafiltration, and sodium removal, all analyzed with summary statistics and confidence intervals. Glycemic and lipidic parameters such as HbA1c, fasting glucose, insulin, LDL, HDL, total cholesterol, and triglycerides will be assessed, along with peritoneal clearances for creatinine, phosphate, and β 2-microglobulin. Exploratory analyses will focus on plasma oxalate levels in heterozygous carriers of PH1/PH2 mutations, measured at visits 2, 3, and 4. Metabolic profiling of plasma, urine, and dialysate samples will be conducted at visits 2 and 4, with summary statistics and changes from baseline. Quality of life will be evaluated using the KDQOL-SF 1.3 questionnaire, with scores across multiple subscales—including physical and emotional well-being, social function, sleep, cognitive function, and patient satisfaction—reported at visits 2 and 4 and analyzed for changes over time. This integrated statistical approach ensures a comprehensive and nuanced evaluation of PolyCore’s clinical performance, patient safety, and overall treatment impact.

4.2. Results

The FIRST study presents preliminary clinical data from CAPD patients treated with these experimental solutions over a four-week intervention period. Group A received IPX15 (0.5% glucose, 1.5% xylitol, 0.02% L-carnitine) for the nocturnal exchange, while Group B received IPX07 (0.5% glucose, 0.7% xylitol, 0.02% L-carnitine) for two daytime exchanges, combined with icodextrin overnight. Both solutions were well tolerated, with no infusion-related discomfort or safety concerns reported. Vital signs, body weight, ECGs, and biochemical parameters remained stable, and patient-reported well-being scores showed no significant variation. Dialysis efficacy was assessed through weekly urea Kt/V, creatinine clearance (CrCL), residual kidney function (RKF), PET parameters, daily UF, and urine output. Both Kt/V and CrCL improved modestly at the end of the intervention, particularly in Group B, while RKF followed a similar trend. These findings are clinically relevant, as recent evidence suggests that urea may exert toxic effects at concentrations typical of ESRD. Preservation of RKF could therefore enhance uremic toxin clearance and improve long-term outcomes. PET results indicated average PM transport profiles, with PET-creatinine mirroring the trend of Kt/V and PET-glucose remaining stable. These observations suggest that the glucose-sparing solutions may enhance small-solute clearance without increasing glucose absorption, aligning with theoretical predictions. Daily UF remained unchanged in Group B but increased progressively in Group A, indicating a potential carry-over effect. Urine output remained stable across both groups, albeit with differing trajectories. Importantly, the experimental solutions significantly reduced the daily glucose load. Group A patients received only 20% of the glucose typically delivered by a standard 2.5% solution (10 g vs. 50 g), while Group B patients received 30% compared to conventional 1.5% regimens (20 g vs. 60 g), without compromising osmotic strength. This reduction may contribute to improved metabolic profiles and reduced long-term complications. Taken together, these findings support the non-inferiority of the osmo-metabolic solutions compared to standard glucose-based PD fluids in terms of dialysis adequacy and PM transport characteristics. However, the results are preliminary, derived from a small cohort treated over a short duration, and recruitment was hindered by the COVID-19 pandemic. Despite these limitations, the favorable safety profile and promising efficacy outcomes warrant further investigation. Larger, longer-term studies are underway, including the ongoing FIRST trial and the upcoming ELIXIR trial—a six-month randomized study evaluating the efficacy and safety of XyloCore, a glucose-sparing PD solution—which will help define the clinical role of these novel formulations in routine PD practice.

Since the study is still ongoing, definitive data on the endpoints are not yet available. However, based on the current reporting phase, the ELIXIR study is being conducted across 34 active clinical centers, with an additional 13 sites in the startup phase. These centers are distributed across several European

countries, including Sweden, Germany, Denmark, the United Kingdom, Spain, and Italy, with notable participation from Padua and Bologna. A total of 88 patients have been randomized, with 69 having provided informed consent. Approximately half of the randomized participants have been assigned to receive the investigational glucose-sparing PD solution, XyloCore®. Among the enrolled cohort, there is a broad age distribution, with a mean age of approximately 70 years and a slight predominance of male participants. Notably, one participating center authorized the off-label use of XyloCore® for compassionate purposes following the study, based on observed clinical benefits compared to the patient's prior PD regimen. This decision underscores the potential therapeutic value of the investigational solution and supports further evaluation in larger, long-term studies. Preliminary observations suggest encouraging trends, although definitive conclusions regarding the study endpoints cannot yet be drawn.

The PURE study is currently undergoing a phase of structural reorganization aimed at optimizing its operational framework. At present, five clinical centers are actively participating: Policlinico in Milan, Vanvitelli in Naples, Santissima Annunziata in Chieti, Vito Fazzi in Lecce, and Maggiore Hospital in Bologna. As the study has only recently commenced, patient enrollment is still in its early stages, with two participants recruited to date.

The EXCITE study is currently in its initiation phase and is set to be launched across X centers nationwide. This multicenter project represents a significant research initiative aimed at collecting robust data and fostering innovation within its field of investigation. The simultaneous activation in multiple sites will ensure broader sample representation and enhance the generalizability of the findings.

5. CYCLER PROTOTYPE FOR APD

The development of a new cyclor prototype for peritoneal dialysis represents a significant advancement in home-based renal replacement therapy. This thesis explores the design, engineering, and clinical validation of a compact, user-friendly, and cost-effective device aimed at improving patient autonomy and treatment outcomes. The project integrates additive manufacturing techniques, modular architecture, and smart control systems to enable personalized dialysis cycles and remote monitoring capabilities.

The prototype was conceived through a multidisciplinary approach involving nephrologists, biomedical engineers, and end-users, ensuring ergonomic and clinical compatibility. Initial bench testing and simulated clinical scenarios demonstrated reliable performance in fluid exchange, ultrafiltration control, and alarm management. Subsequent pilot trials confirmed its feasibility in real-world settings, highlighting improvements in patient comfort, adherence, and quality of life.

Compared to traditional cyclers, the new device offers enhanced portability, reduced noise levels, and simplified maintenance. Its integration into assisted peritoneal dialysis programs supports decentralized care models and aligns with current trends in telemedicine and digital health. This work contributes to the ongoing innovation in dialysis technology and proposes a scalable solution for expanding access to peritoneal dialysis, particularly in underserved or remote populations.

5.1. Description of the cycler prototypes

A distinctive feature of the device at the core of my research is its unique capability to continuously monitor intra-peritoneal pressure (IPP) throughout the entire dialysis session—something no existing cycler currently offers. This real-time tracking of IPP is crucial for managing the fluid dynamics involved in the infusion and drainage of dialysate, ensuring these processes remain within safe and predefined operational thresholds. By doing so, the system can actively regulate pressure—whether positive or negative—to avoid overfilling and mitigate discomfort or pain caused by negative pressure during drainage.

To grasp the significance of this parameter, it's important to understand that IPP reflects the pressure exerted by the dialysate and ultrafiltrate within the peritoneal cavity, which behaves like a rigid, non-elastic container. In conventional cyclers, fluctuations in IPP—both increases and decreases—are common. These variations not only contribute to patient discomfort, such as pain from excessive cavity distension or during fluid withdrawal, but can also trigger serious complications and interfere with the ultrafiltration process itself.

Moreover, pressure overload in the peritoneal cavity can induce significant hemodynamic alterations in the cardiovascular system, which in some cases has resulted in patient death during automated peritoneal dialysis (APD). Elevated IPP also compromises ultrafiltration efficiency and is associated with gastrointestinal complications such as hernias, membrane damage, and an increased risk of peritonitis. In pediatric patients, IPP measurement is considered the gold standard for optimizing peritoneal fill volumes, ensuring both safety and therapeutic efficacy.

5.2. The “old” new cycler prototype

In the previous years, my doctoral work focused on developing and testing a prototype cycler for APD. Laboratory tests had shown the cycler's ability to perform the following automated operations: IPD, CCPD, NPD, Tidal PD & Enhanced PD, customizable modality. Also an automated and quantitative measurement of peritoneal cavity volume in order to prevent volume overfill during the

Fill phase and optimize Dwell duration. This is in order to maintain constant volume and pressure during the rest phase.



Figure 1. The “old” new cyclor prototype.

The device’s continuous intra-peritoneal pressure monitoring, combined with self-regulation and automated tracking of ultrafiltration kinetics during the dwell phase, was designed to prevent drainage-related pain. A piston-driven mechanism ensured complete evacuation of the infused dialysate at the end of each cycle, depending on the selected final state - wet or dry.

The prototype supported the mixing and delivery of any approved dialysate formulation, including premixed solutions with both traditional and non-traditional osmotic agents. It also accommodated medicated bags pre-fortified with additives or drugs. Additionally, it featured the ability to adjust non-physiological pH solutions to physiological levels at the point of use. Integrated heating plates enabled in-line warming of solutions to ensure patient comfort.

Therapy prescriptions were configured by the clinician and transferred to the cyclor via a patient-specific USB stick. Treatment data were stored on a mass storage device, allowing for easy retrieval and review of therapy history. A multilingual, color touchscreen interface provided intuitive patient interaction, supported by a user-friendly graphical alarm system with self-correcting capabilities. To enhance safety, the system automatically detected and managed accidental disconnections, as well as kinks and blockages in the fluid lines throughout the dialysis session.

In vivo testing to date has demonstrated that the cyclor is non-inferior to existing devices in terms of dialysis adequacy. However, the patented infusion and drainage system - engineered to minimize drainage pain and prevent overfilling - relied on real-time, proactive control of the fill and drain phases. This approach occasionally led to discrepancies between the programmed and actual treatment durations. Moreover, the acoustic alarms were insufficiently audible, limiting the patient’s ability to respond when the machine encountered an unresolved issue.

These limitations, coupled with the impact of therapy schedule disruptions on patient well-being and treatment efficacy, led us to redesign the prototype and develop a new version.

5.3. The “first” new cyclor prototype

The New Cyclor Project was launched in 2019 and successfully completed its initial phases of analysis, conceptual design, and proof-of-concept validation through prototype development. During this stage, the general mechanical design and preliminary control electronics architecture were defined, and a regulatory pre-assessment was conducted, including the setup of the Technical File with a particular focus on Risk Analysis.

The new cyclor prototype was designed as an evolution of the previous model, aiming to address the main issues encountered during patient testing: noise levels and optimization of therapy times.

In preparation for subsequent development activities, the technical working group, suppliers, and consultants were identified to ensure rapid and efficient execution of the project.

The first prototype was aimed at verifying basic functionality and usability. The new cyclor model introduces several enhancements aimed at improving patient interaction, safety, comfort, and connectivity.

A key improvement is the monitor placement, now positioned at the front of the device. This configuration ensures continuous visibility of the screen, even during the setup phase when the cyclor is open. Upon each access, the patient is prompted to identify themselves by entering their first and last name, the prescribed treatment plan, and the initial abdominal condition (wet or dry status). The interface supports multiple languages and includes step-by-step educational animations to guide the patient through kit setup and the connection of fluid bags and the catheter. A voice-guided assistant further enhances accessibility and ease of use.

To reduce the risk of connection errors, a color-coded system will be implemented for the fluid bags, allowing patients to match each line and bag with the corresponding colored LEDs on the cyclor. Additionally, a dedicated support structure will be provided to facilitate proper dialyzer positioning and establish a defined dialysis zone. This controlled environment minimizes exposure to external contaminants, thereby lowering the risk of infection.

The cyclor also incorporates a self-adjusting time system, which adapts the filling speed and pressure based on the treatment duration prescribed by the clinician. When the peritoneal cavity is empty, the system accelerates the infusion process, conserving time that can be used to slow down during the final phase—an added safety feature for the patient.

Regarding filling time, the cyclor typically infuses 0.5 liters of dialysate in approximately 5 minutes, equating to 10 minutes for 1 liter and 20 minutes for a standard 2-liter bag. However, the infusion rate is adjustable according to clinical requirements, with a maximum capacity of up to 8 liters per hour.

To ensure patient comfort, particularly during nighttime use, the system has been engineered with a strong focus on noiselessness. Sound-absorbing materials have been strategically integrated both

within the internal structure and on external surfaces, including vibration-dampening rubber feet that minimize mechanical resonance. These design choices enable the device to operate at a noise level of just 38 decibels—comparable to the gentle rustling of leaves—making it suitable for use in quiet environments without disrupting rest or sleep.

Advanced connectivity features ensure secure, bidirectional communication between the patient and the machine, as well as between the dialysis center and the patient. An integrated modem enables remote access even for patients without home internet service. This allows the cyclor to download the prescribed dialysis protocol and apply any updates made by the nephrologist in real time. The system supports telemedicine by facilitating direct communication with caregivers and dialysis centers when needed.

Each cyclor will be equipped with mass storage memory for data logging . A dedicated reader will be provided to dialysis centers to ensure secure access and maintain patient privacy. During routine check-ups, clinicians can retrieve and analyze stored data to optimize therapy. Furthermore, the connectivity system enables the transmission of alarm signals to caregivers in case of urgent intervention.

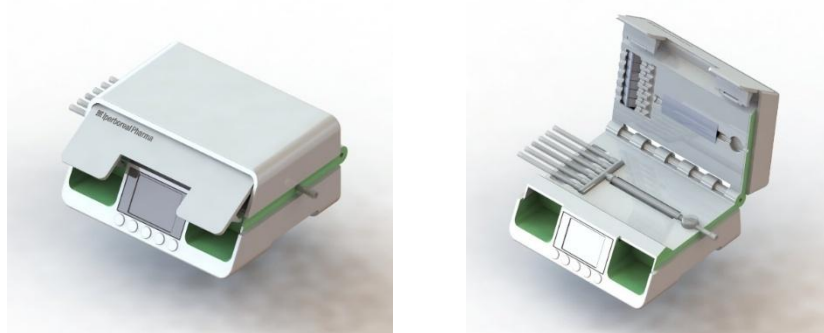


Figure 2. The “first” new cyclor prototype.

5.4. The “second” new cyclor prototype

The second prototype was refined to meet regulatory specifications and medical requirements, with a focus on mechanical performance.

Key updates included:

- Implementation of a simplified mechanical system
- Dimensional adjustments, including a 7" display
- Introduction of a new valve system and linear peristaltic mechanism

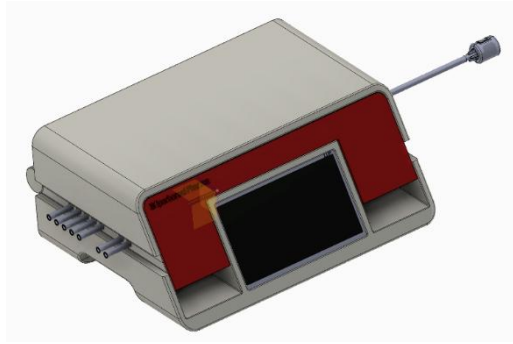


Figure 3. The “second” new cyclor prototype.

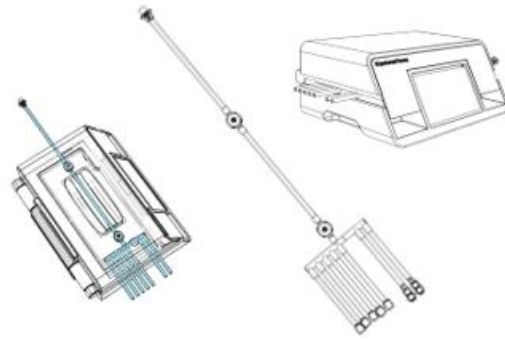


Figure 4. The linear peristaltic mechanism.

The Executive Mechanical Design of the Cyclor

The executive mechanical design of the Cyclor adopted a development strategy aimed at prototype realization and validation. Initially, the system was divided into "functional subgroups" that were developed in parallel and later integrated into a complete assembly.

External and Internal Layout

The function of the chassis is to house the disposable kit, creating a dedicated compartment for its placement. This configuration is essential for securely positioning the inflow and outflow lines so that they can be clamped by profiles descending from the valve subsystem (SV), and so that the designated line can be engaged by the peristaltic action of the rollers in the pumping system (SP).

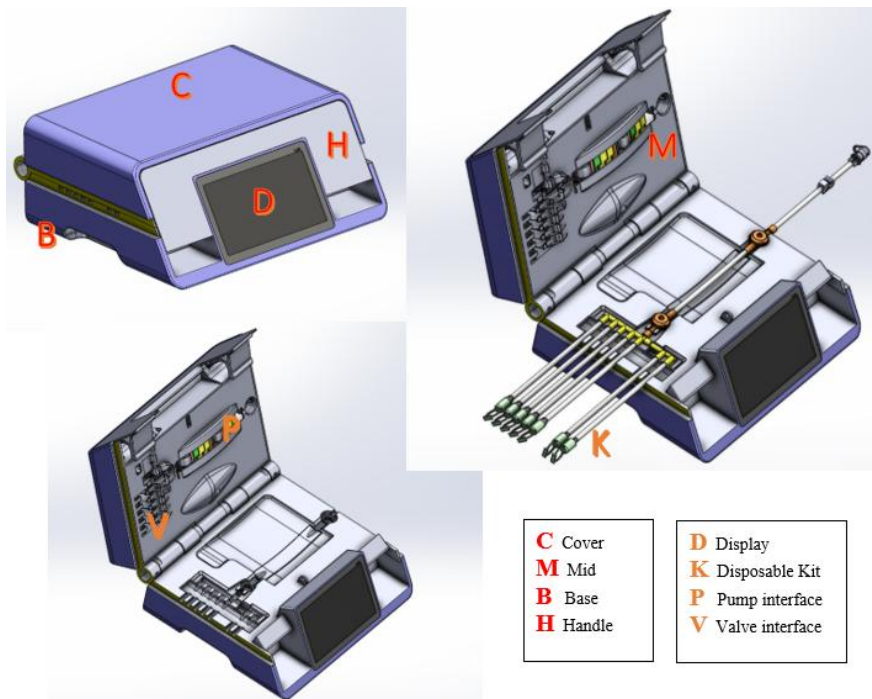


Figure 5. External and Internal Layout.

Mechanical Interface and Anchoring System

A critical aspect of the cyclor's design was ensuring precise coupling tolerances to prevent mechanical play that could compromise the long-term stability and functionality of the valve (SV) and peristaltic (SP) subsystems. The active components were positioned on the upper section of the

machine to allow easy placement of the disposable kit on the top surface. This layout required the integration of elastic coupling systems to maintain consistent contact pressure within predefined ranges, tailored to each functional requirement.

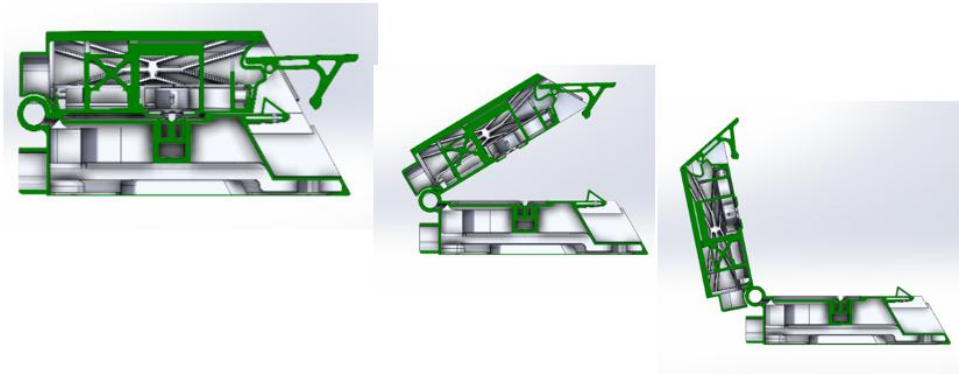


Figure 6. Mechanical Interface and Anchoring System.

The anchoring mechanism was implemented via a hinged handle (H) attached to the lid. When closed, the handle locked the base to the lid. During opening, the handle rotated using two symmetrical grips, disengaging from a profile on both sides of the base (B) and allowing the lid (C) to pivot. An optical sensor tracked the handle's position, while a bistable solenoid interlock secured the machine during treatment.

✂ Valve Subsystem (SV)

The propulsion system represents a key strength of the new cyclor, as it introduces a redesigned mechanism for fluid delivery and management. In the previous prototype, fluid propulsion was achieved through a constant push piston mechanism, which often resulted in pressure spikes during operation. In contrast, the new prototype adopts a peristaltic pumping system—similar to those employed in hemodialysis machines—which enables smoother and more controlled fluid handling. This improvement is clearly reflected in the pressure-over-time graphs, where the transition to a peristaltic approach results in a significantly more stable and gentle pressure profile.

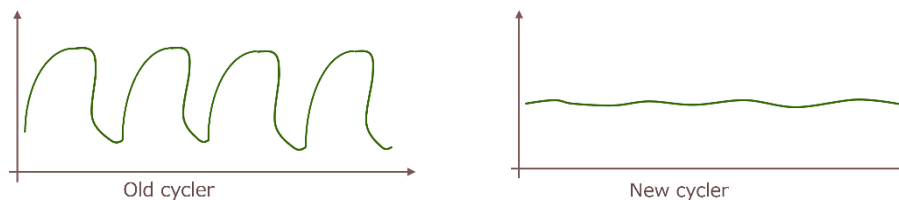


Figure 7. PRESSURE/TIME GRAPHS. Fluid management – comparison of cyclor prototypes.

Based on the disposable kit's structural layout, the clamping system was housed within the machine and stabilized by a dedicated coupling geometry. Cam-driven profiles extended from the lid to occlude each line against the base surface. The central component (MID), shown in Figure below, contained all active elements, with the clamp actuation system highlighted.

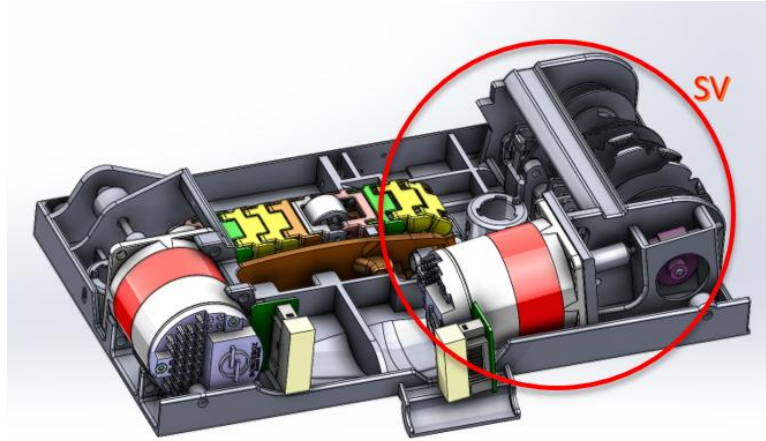


Figure 8. The Valve Subsystem (SV).

The internal arrangement minimized the distance between the lid/base rotation axis and the MID's center of mass, reducing inertial resistance during opening and closing. As shown in Figure below, the valve system included a multi-profile cam (C) controlling seven clamp “keys” (T), actuated by a stepper motor via a worm gear and pinion (VP). Each key ended in a V-shaped profile suitable for line clamping. Each key consisted of two rotating components (T1 and T2, Figure below) mounted on a shared axis (Fa), connected to limit switches via a spiral spring. The cam featured seven profiles offset by 40°, allowing sequential activation of each clamp.



Figure 9. Details of the Valve System and Buttons.

Figure below illustrates the longitudinal section, showing the cam profile (PF), bearing (Cp), and V-profile clamp. A compression spring (Mc) and a flat spring (MP) ensured continuous contact between the bearing and cam.

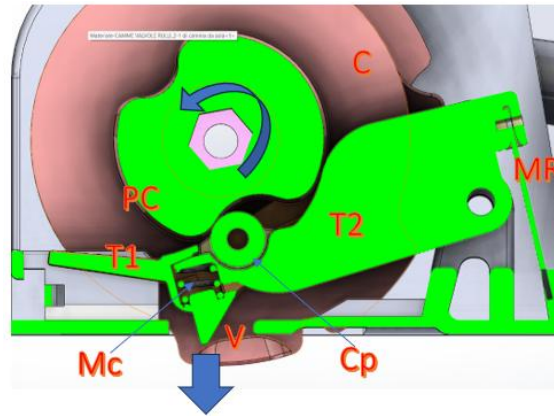


Figure 10. Longitudinal Section of the Valve System.

Cam rotation forced the V-profile downward, with elastic coupling providing an “overstroke” to maintain adequate clamping force. The system defaulted to closing all lines, selectively opening one based on the cam’s angular position. After static load calculations and resistance testing, functional prototypes were built. Iterative design-prototype cycles optimized cam profiles and overall valve performance. A contrast plate was added to test PVC line clamping.



Figure 11. First Prototype of the Valve System.

Peristaltic Subsystem (SP)

According to the principles of fluid dynamics, pressure is directly related to flow rate. The volume of fluid delivered through the tubing depends on the energy imparted to the fluid—specifically, the delivery speed of the pump.

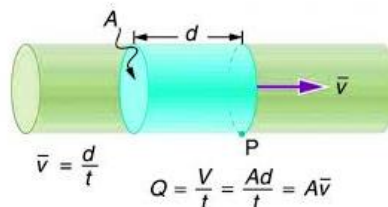


Figure 12. Fluid dynamics.

Poiseuille’s law, a fundamental equation in fluid dynamics, describes the relationship between pressure drop and flow rate in conduits. Originally developed to model blood flow in vessels, it was later extended to laminar flow in incompressible fluids. The law states that “flow rate is directly

proportional to the pressure gradient and the square of the radius, and inversely proportional to the length of the conduit and the fluid's viscosity.” In the cyclor system, flow generation is governed by the energy transferred to the fluid, which is controlled by the pump's operating speed. The system continuously monitors pressure via a manometer located inside the dome, approximately one meter from the peritoneal cavity. If the detected pressure exceeds the optimal range, the pump does not stop immediately but instead reduces its speed to maintain a stable pressure. Should the pressure continue to rise—suggesting that the peritoneum is not absorbing the fluid energy—the system will further slow or halt the flow to ensure patient safety. At this point, diagnostic routines are triggered to identify the underlying issue. The software analyzes pressure values and their trends to correlate them with potential causes. These safety mechanisms are essential. For instance, if counterpressure is present due to a full peritoneal cavity and the machine fails to detect it, continued pumping could lead to overfilling and potential damage to the peritoneal membrane. Conversely, if a kink occurs along the tubing, the system will detect an overpressure condition, resulting in a pressure drop within the sensor and triggering an alarm to alert the patient. In tidal dialysis scenarios, a rise in pressure may indicate excessive filling; after several verification steps, the system will interrupt the fill phase and issue an alert.

Under normal operating conditions, the system maintains a pressure range of 80–90 cmH₂O, comparable to that of CAPD. If pressure exceeds 110 cmH₂O, the pump reduces its speed in an attempt to restore baseline pressure. If unsuccessful, the system halts and reverses the flow to bring pressure down to safer levels (around 50 cmH₂O). This cycle is repeated two to three times; if the issue persists, the system generates an alarm to notify the patient.

The peristaltic subsystem was mounted opposite the valve system on the central chassis component. As shown in Figure below, it consisted of a roller chain (Ca) guided along an arc-shaped profile (Pa), with rollers (R) rotating via coaxial bearings (Cc). A rotary motor powered the system through a pulley-belt transmission (Pg), a dual pinion (Pm) engaging each chain link, and a floating pulley (Pf) mounted on a sliding shaft (Ss) for tensioning via a TPU damping element (Sm).

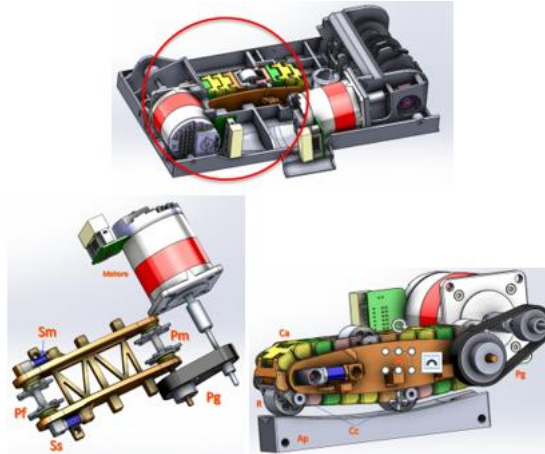


Figure 13. Position of the Pumping System and Peristaltic Subsystem.

This assembly was fixed to the MID, while an additional arc-shaped profile (Ap) on the base housed the peristaltic line. When the machine was closed, the rollers, line, and profile formed a sealed interface. The geometry ensured line occlusion at least one point, preventing flow unless the motor was active. The system supported bidirectional flow.

Initial sizing and prototype testing confirmed key specifications:

- Minimum flow rate: 8 L/h
- Flow stability: ≥ 12 hours
- Flow symmetry: maintained across cycles

Motor speed-flow correlations and system noise characteristics were also evaluated.



Figure 14. First Prototype of the Valve System.

Disposable Kit Design

The disposable kit evolved alongside SV and SP prototype development. It included commercial components and five custom injection-molded parts.

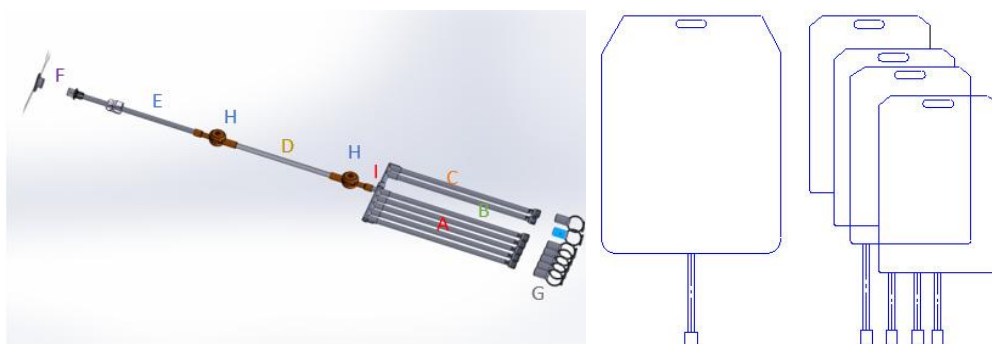


Figure 15. Disposable Kit.

Materials used included:

- ☐ A: 5 loading lines (PVC 4.8/6.8 mm, 40 cm)
- ☐ B: Drain line (PVC 4.8/6.8 mm, 1.2 m)
- ☐ C: Service line (PVC 4.8/6.8 mm, 40 cm)
- ☐ D: Peristaltic line (PVC 4.8/6.8 mm, 17 cm)
- ☐ E: Patient line (PVC 4.8/6.8 mm, 2.5 m)
- ☐ F: Pset connector with TPU cap
- ☐ G: 7 loading bag connectors with ETO-sterilizable caps

Custom components:

- ☐ H: Dome (lid, base, silicone membrane) – 2 per kit
- ☐ I: 5-way and 2-way rails

Assembly steps:

- ☐ 12 tube/component joints (using cyclohexanone)
- ☐ 8 connector insertions onto lines
- ☐ 2 pressure-sensing Dome assemblies using a press, each composed of 3 components (lid + base + central silicone membrane)
- ☐ Connection to a thermoformed tube holder and arrangement of tubes for packaging
- ☐ Packaging in paper/polyethylene
- ☐ Labeling
- ☐ ETO sterilization

The components to be manufactured (H and I) refer to two main elements: the 7-way distributor (Rail), which connects the loading and drainage lines, and the coupling sleeve between the peristaltic line, the Rail, and the line leading to the peritoneum (referred to as the Dome).

To enable plastic injection molding, the 7-way Rail was split into two subcomponents - one with 2 ports and the other with 5. Its primary function is to interconnect all loading and drainage lines with the peristaltic line and align them with the clamping system developed in the SV subgroup.

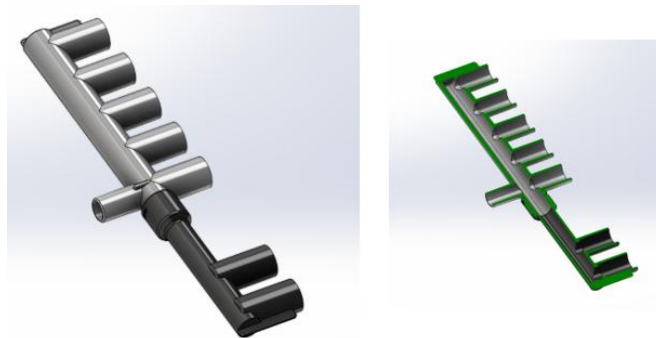


Figure 16. The 7-way Rail and Its Cross-Section.

The Dome is designed to measure pressure and temperature within the circuit. Two Domes are included in the kit -one upstream and one downstream of the peristaltic line. This duplication ensures pressure monitoring both during the pre-treatment verification phase and toward the peritoneum, and provides sensor redundancy for data reliability, as required by applicable standards. The Dome consists of three parts: a lid (Dc), a two-way sleeve (Dm), and a silicone membrane (Ms) placed between them. These components are assembled into a single unit, where the fluid path is isolated from the external environment by the membrane. A hole at the top (F) of the lid allows pressure detection above the membrane. Assembly is achieved through interlocking profiles: tooth-shaped profiles (Pd) on the sleeve and slot-shaped profiles (Ac) on the lid, evenly spaced around the contact circumference. The silicone membrane also ensures a hermetic seal between the two components.

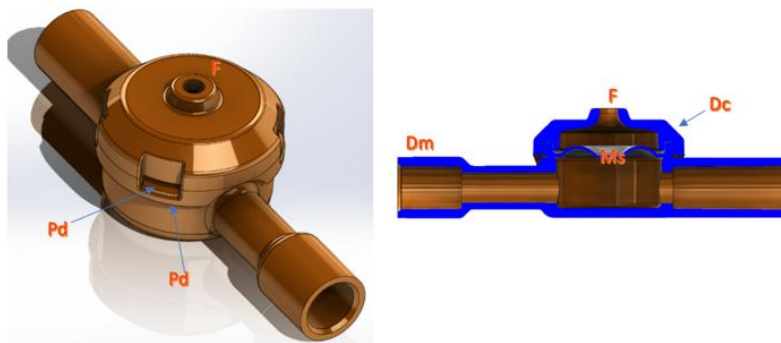


Figure 17. The Dome and Its Cross-Section.

The pressure detection system includes a dedicated “Pick-up” mechanism that creates a stable seal between the Dome’s internal volume and the pressure sensors. The pick-up is fixed but elastically connected to the central chassis (MID), and pushes a cylindrical gasket (G) vertically against the top of the Dome using a spiral spring (M). The Dome contains a communication hole leading to the silicone membrane. A tube inside (Tb) connects the gasket directly to the pressure sensor.

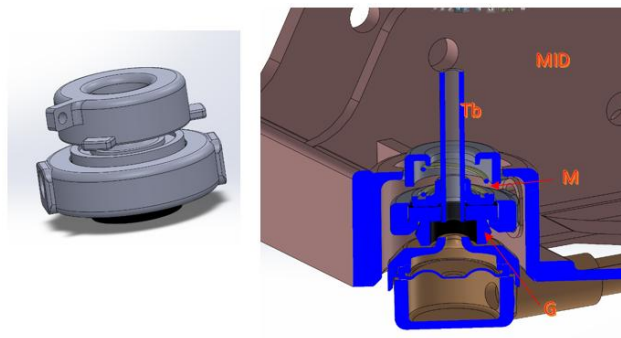


Figure 18. Dome / Pick-up Coupling.

The pick-up’s movement is guided by a slot-pin coupling, making the system geometrically self-adjusting with respect to the gasket–Dome interface.

When engaged, this configuration creates a sealed volume between the membrane and the pressure sensor, allowing calibrated pressure readings of the fluid inside the line without risk of external contamination.

The disposable kit was prototyped to validate its functionality through targeted testing. These components were produced using rapid prototyping techniques (stereolithography) with materials of lower mechanical performance than the final versions. Nevertheless, the tests confirmed the system's mechanical strength and fluid-tight integrity.

The disposable kit design was then refined according to the selected manufacturing methods, leading to the precise definition of geometries and the design of injection molds required for production.



Figure 19. Prototype of the Disposable Kit.

Final components are currently in production. The necessary prototype molds have been designed and are under construction. These will enable the use of certified medical-grade materials suitable for mass production:

- Lines: PVC Nakan – FEA 618 N N S
- Dome: ABS Terluc 2802
- Silicone membrane: Silopren HV 3/622

Machine Prototypes

To verify the integrated functionality of the valve (SV) and peristaltic (SP) subsystems, an initial full prototype was developed using commercial electronics. The goal was to assess the mechanical coordination between SV and SP.

The testing phase involved step-by-step functional verification, where each state of the valve system was tested to confirm flow rates across different paths matched the specified values. This marked the conclusion of the project's feasibility assessment.

Subsequent development phases focused on refining the entire machine, introducing improvements to the mechanical assemblies. These included increased structural rigidity of external components and supports for SV and SP, optimized couplings and moving contacts, and adjustments to roller-peristaltic line dynamics to reduce pump noise.

The final prototype also incorporated:

- ❖ Custom control electronics
- ❖ Backup battery
- ❖ Touch display
- ❖ System-on-Module (SOM)



Figure 20. Prototype Overview and Component Breakdown.

At this stage, all components for both the machine and the disposable kit were finalized.

The Mechanical Components include:

- ❖ Chassis (Top–Mid–Base), SP support and full chain, cam and keys: made of nylon using HP FusionJet technology
- ❖ Special components (shafts, plates, etc.): CNC-machined metal
- ❖ Commercial parts: standard hardware (bearings, screws, etc.)
- ❖ SOM and display: Variscite – VAR-SOM-MX8M-P

Custom Electronics Board Design

The electronics board was designed according to the “first-fault safety” principle, as required by EN 60601-1. This was achieved through CPU and critical sensor redundancy. The core hardware safety concept ensures the system is safe when powered off.

Control, communication, and sensing specifications:

- Dual microprocessors (control and protective), supporting Class B and C firmware, with a dedicated communication channel
- Microcontrollers: STM32F373 (indicative)
- Sensors: temperature, pressure, air, position
- Position sensors: optical forks
- Air sensor: optical detection of refractive index change between air and water
- Pressure sensors: Honeywell MPR series, I2C output, temperature-compensated

- Temperature sensors: PT1000 with analog front-end and Sigma-Delta ADC for $\sim 0.05^{\circ}\text{C}$ resolution
- Communication: UART between processors and with SOM

Power Supply Design:

- Input: 24V medical-grade power supply
- Integrated UPS with lead-acid battery, charged while connected to mains
- Battery charges even when the system is off; however, the system remains on to display charging status
- Battery tests on startup, short-circuit and overload protection, inrush current protection

The system architecture is divided into two independent sections: control and protective, with a shared central area. Each section includes:

- Independent CPU
- Independent sensor array

The protective system can immediately shut off the +24SAFE power line in case of patient risk. This line powers the motors.

Sensor Implementation

The Pressure Sensors require no additional electronics beyond direct I2C acquisition.

The Temperature Sensors are configured so that the measurement element is connected between the TS-RTD-IN and TS-RTD-OUT terminals. A Digital-to-Analog Converter (DAC) is linked to the TS-WRITE point, while a differential Analog-to-Digital Converter (ADC) is connected to the TS-READ-P and TS-READ-N terminals.

The DAC output regulates the current flowing through the PT1000 sensor, and the ADC reads the voltage developed across it. This setup allows precise control of the sensor's operation: by managing the current via the DAC, the sensor can be switched on and off at appropriate times, effectively reducing self-heating effects and improving measurement accuracy.

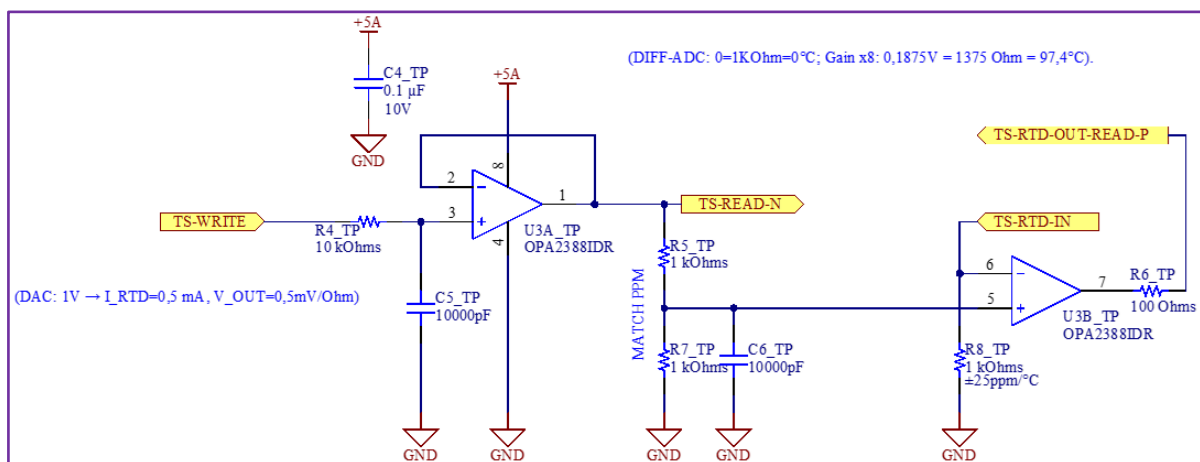


Figure 21. Operating Principle of the Temperature Sensors.

The Air Presence Sensor operates by generating a bias in the LED drive circuit through the DAC. This bias is calibrated so that, upon insertion of the disposable kit—before water begins to flow—the receiving side detects a specific voltage level that indicates the presence of air. During the subsequent flushing phase, the sensor’s correct functionality is verified by observing a voltage variation caused by the expected passage of water. This change confirms that the sensor is responding appropriately to the transition from air to liquid.

Figure 22. Operating Principle of the Air Presence Sensors.

The Power Supply System is designed with independent step-down stages dedicated to the control and protective subsystems. However, some components are shared, such as the in-rush current limiter and the UPS, which serve both areas. A key safety feature is the protective subsystem's ability to operate switch U2, allowing it to immediately shut off the +24SAFE power line in case of any risk to the patient. This safety-controlled voltage also powers the motors, ensuring that critical components can be disabled swiftly when necessary.

Figure 23. Operating Principle of the Power Supply System.

The UPS and Battery Charging System provides a constant 0.2 A charge to the battery until it reaches the float voltage of 13.5 ± 0.13 V. This is achieved through a dual feedback mechanism directed to the switching regulator. Additionally, the system enables monitoring of the charging current—useful

for detecting the end-of-charge condition—and allows both the control and protective subsystems to manage power shutdown or maintenance as needed.

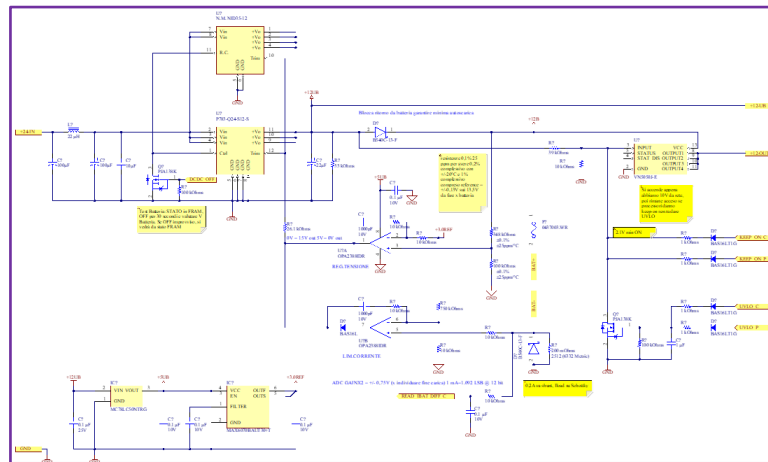


Figure 24. Operating Principle of the UPS and Battery Charging System.

The Inrush Current Limitation System restricts the power-on transient to a controlled rate of 93 V/s, to safeguard downstream capacitive components. This ensures a smooth and safe startup phase for the entire system.

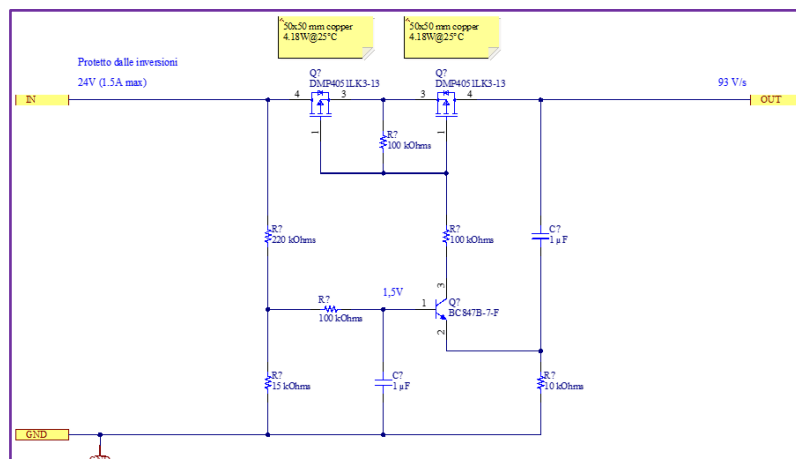


Figure 25. Operating Principle of the Inrush Current Limitation System.



Firmware

Initial firmware development was based on OR1 analysis and implemented on a commercial hardware platform (Arduino Zero). Core control routines were developed for:

- Valve positioning
- Peristaltic actuation with PID control based on pressure sensors on the peritoneal line
- Absolute encoder for valve clamp positioning

The firmware was written in Visual Studio Code, a lightweight yet powerful source code editor supporting JavaScript, TypeScript, Node.js, and extensions for C++, C#, Java, Python, PHP, Go, and .NET. The codebase is modular, organized into functional libraries for readability and debugging.

In line with the software risk analysis, diagnostic and alarm handling specifications were defined. The Cyclor firmware logs anomalies and errors in two types of files:

- Machine event log
- Treatment-related alarm log

Each log entry includes:

- LEVEL: Severity of the message ("TRACE", "DEBUG", "INFO", "WARN", "ERROR", "FATAL")
- SOURCE: Code line or module where the log was generated
- DATA: Comma-separated list of context-specific values

These logs are transmitted to the ITC platform, which hosts two diagnostic dashboards:

- 1) Technical Error Panel – for technical/operational staff
- 2) Clinical Error Panel – for clinical personnel

The Technical Error Dashboard provides an overview of machine-detected errors, including:

- Timestamp of the error
- Error code
- Error description
- Machine status (operational, paused, error)

The dashboard allows filtering by error code, description, or machine status, with key sections including:

- General summary
- Current machine status: OK, Warning, Error
- Timestamp of last log
- Software version
- Serial number
- Assigned patient
- Pending updates

The Patient-Related Error Panel for Clinical Staff is designed for clinical personnel and provides detailed information about system errors that may impact patient safety. It includes:

- Alarm dashboard
- Date and time of the alarm: Indicates when the alarm occurred
- Alarm code: Identifies the specific alarm
- Alarm description: Explains the nature of the alarm

The cyclor will carry out a series of Pre-Treatment Diagnostic Procedures to ensure the integrity of both the machine and the disposable kit. Therefore, a diagnostic check must be performed before each treatment and prior to inserting the disposable kit, following this checklist:

- ❖ Initial tests: The machine verifies that all electronic and electrical components are functioning
- ❖ Temperature consistency check: Verifies coherence among the three temperature sensors
- ❖ Pressure consistency check: Verifies coherence among the three pressure sensors

- ❖ Pump system movement test: Confirms correct initial position, activates the pump motor for a set number of rotations, and verifies motor control via the SP chain position sensor
- ❖ Valve subsystem test: Executes one full rotation of the control cam, verifies motor steps via absolute encoder (control), and checks valve opening positions (protection) using individual optical position sensors
- ❖ Air presence sensor test: Verifies consistency of readings in open air from the optical air sensor within the circuit

Based on all machine operating conditions, a comprehensive list of alarms to be managed by the firmware has been compiled. This list will be subject to revision during the final development phase of the Cyclor.

Graphical User Interface (GUI) Software

The monitor is positioned at the front, allowing the patient to have constant visibility of the screen even during the machine setup phase with the cyclor open.

In alignment with the Software Risk Management Plan, the core functions of the graphical user interface were implemented and made accessible via the touchscreen display. Communication between the SOM and the control electronics was established through UART connections.

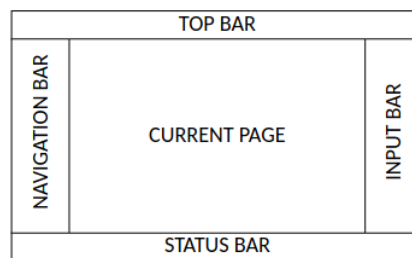


Figure 26. Top Bar.

The General layout of SOM pages includes:

- **Top bar:** Includes navigation to the home page (when available), device shutdown (when permitted), and the current page title
- **Navigation bar:** Allows movement within input fields
- **Input bar:** Enables interaction with input widgets
- **Status bar:** Displays date and time, hardware component status, and alerts for potential issues
- **Current page:** Shows contextual content such as menus (e.g., Prescription, Archive) or specific data (e.g., total UF volume)

The main page appears after hardware status checks (e.g., power connection, battery charge). An additional check retrieves patient and prescription data. If found, a confirmation screen displays the patient's identity. If not, an error screen is shown.

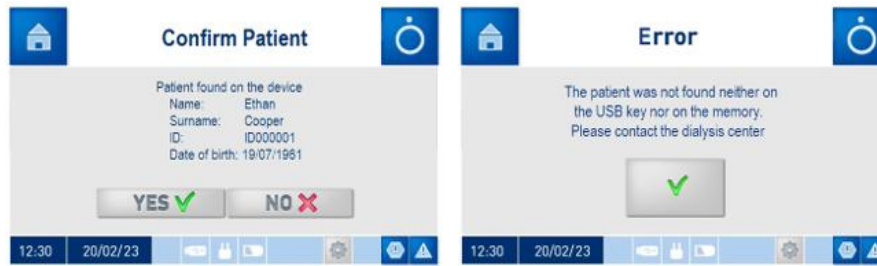


Figure 27. User Interface – Confirm Patient and Error.

Once all checks are passed, the user is directed to the main menu.



Figure 28. User Interface - Menu.

The interface includes the following options:

1. **Treatment** – Perform a complete treatment
2. **Prescription** – Create or modify a prescription (accessible only to nephrologists)
3. **Archive** – View and analyze past treatments
4. **Service** – Maintenance (accessible only to technicians)
5. **Factory** – Modify factory settings (accessible only to technicians)
6. **User Tests** – Display and buzzer tests



Figure 29. User Interface - Treatment.

Before initiating a prescription, the system performs several safety checks:

- Confirmation of the last treatment status (wet or dry)
- Validation of key treatment parameters (total duration, number of cycles, minimum and maximum fill volumes)
- Verification of correct disposable kit connection
- Confirmation of treatment start

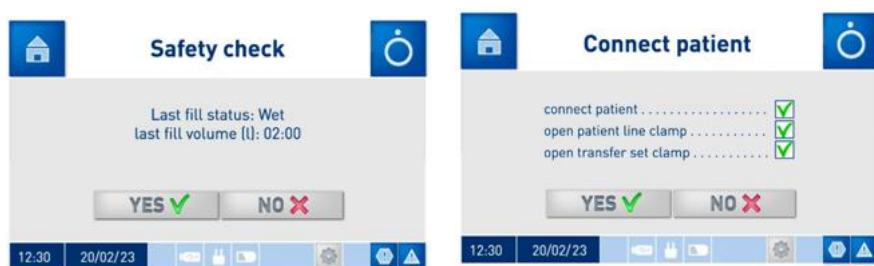


Figure 30. User Interface – Safety check and Connect patient.

Upon patient confirmation, the treatment activation screen is displayed.

A screensaver is activated during nighttime therapy, turning off the display to reduce light. It reactivates with any screen tap. Treatment can be paused or stopped using buttons on the right side. If paused, a suspension screen is shown.

At the end of the treatment, a guided procedure assists the patient in removing the disposable kit and shutting down the system.

Pre-series Prototypes

By September 2024, the general mechanical development phase concludes, along with the electronics phase through the production of custom boards specific to the project. The machine's firmware is capable of controlling all actuation and sensing devices, and the graphical interface has been developed to include all necessary controls for executing a therapy.



Figure 31. The Final Prototype.

From September 2024 onward, the project has undergone continuous refinements aimed at stabilizing and ensuring the reliability of mechanical components. These adjustments were driven by ongoing regulatory checks, particularly based on feedback from certified laboratories conducting tests required for CE product marking. These updates also targeted industrial manufacturability, especially for components produced using the innovative 3D printing technique (HP FusionJet). For example, certain aspects of the chassis were modified to meet the IP classification of the medical device, such as the addition of a protective door to prevent accidental liquid spills when the machine is open.



Figure 32. Details of the Final Prototype.

Continuous operation verification tests have helped identify optimal production tolerances and introduced improvements that ensure easier assembly and optimized noise levels.

⚙️ **Electronic Hardware Verification**

The designed electronic hardware has been verified and updated to ensure proper functionality. As required by regulations, the corresponding documentation has been produced and included in the Technical File (see file: HVR – Hardware Verification Report). As an example, a full-load operational test of the motherboard is provided.

🔧 **Firmware and User Interface (GUI) Development**

From an initial development stage implementing basic functions such as actuator and sensor drivers, the firmware has evolved to support verification phases for CE certification. In summary, programming focused on the following aspects:

- Implementation of dual programming for safety verification – Control / Protective (where the two independent CPUs on the control electronics perform essentially the same operations and continuously verify the consistency of their respective results)
- Management of the pump system states and control of the valve calibration systems
- Programming of routines for therapy management based on the prescription stored in the “PD card” managed by the nephrologist
- Programming of safety alarms through sensor management for valve and pump system positions, pressure, temperature, and air presence in the circuit
- Management of power outages via conditional activation of the internal UPS
- Optimization of PID control systems for the pump system in relation to the pressure delivered to the patient.

In parallel, the graphical control interface was completed by introducing new screens aligned with technical specifications, enabling safe guided therapy execution by the patient. Additionally, SOM communication protocols (control board) were optimized, and a general debugging was performed.

As an additional request from physicians—who are the only ones authorized to define dialysis therapy parameters—a prescription editing section was introduced onboard the machine, protected by a password.



Figure 33. User Interface - Latest layout of the interface.

The certification process for Class IIb medical devices under EU Regulation 2017/745 requires compliance with electrical safety standards, electromagnetic emissions, and specific standards for Peritoneal Dialysis. These requirements must be certified by a laboratory accredited by the Ministry of Health. Testing began in March 2025, and the Electromagnetic Emission and Immunity (EMC) tests have already yielded positive results according to CEI EN 60601-1-2 standards (Medical electrical equipment – Part 1: General requirements for basic safety and essential performance – Collateral standard: Electromagnetic compatibility – Requirements and tests). Ongoing tests include CEI EN 60601-1-11/A1 (Medical electrical equipment – Part 1: General requirements for basic safety and essential performance – Collateral standard: Requirements for medical electrical equipment and systems used in the home healthcare environment) and CEI EN IEC 60601-2-39 (Medical electrical equipment – Part 2: Particular requirements for the basic safety and essential performance of peritoneal dialysis equipment).

The project includes the drafting of documentation required for CE product marking, contained in the repeatedly mentioned Technical File of the Cyclor. As per standard practice, this file is continuously updated based on the progress of certification procedures and will be subject to review by the Notified Body responsible for product certification for market release of medical devices.

The disposable component, through an agreement with a medical device manufacturer (SELLMED S.r.l – Via A. Avogadro, 19 – 10121 Turin), of the same type as the Iperboreal peritoneal dialysis kit, is currently authorized for market release with CE marking: CE 0425-MED-004383-00. Activities carried out included assistance, supervision, and control of production, testing, and quality assurance of the disposable component itself.

Software in Development for Clinical Analysis and Data Intelligence

A dedicated software platform is currently under development to support advanced data processing and optimize the management of dialysis treatments. In addition to graphical visualization, the

software will be capable of performing sophisticated analyses based on sensor-acquired data, enabling clinicians to refine therapeutic strategies.

Among its planned features is the generation of a "Graph Fill" sheet, illustrating pressure trends during the cavity filling phase, and a "Graph Dwell" sheet, which will display pressure evolution throughout the dwell phase. These visual tools will help characterize ultrafiltration (UF) kinetics and membrane transport dynamics.

The system will include a "Technicallog", designed to record all technical and clinical data from the sensors, including both patient-managed and machine-managed alarms. From this dataset, a "Clinicallog" will be extracted to highlight clinically relevant information. The software will also analyze "Fill-Dwell-Drain" sequences and transposed data to generate a "Composite Graph", presenting key clinical indicators such as pressure profiles, infusion and drainage volumes, optical signals, and fluid temperatures.

A "Summary" page will provide a structured overview of treatment phases and any alarms acknowledged by the patient. By integrating additional metrics—such as average peritoneal pressure, peak and minimum pressure values, delivery timing, and bag weight variations—the system will progressively learn to optimize the dialysis cycle and identify potential anomalies or inefficiencies.

Auxiliary Systems Under Development: Heating, Monitoring, and Patient Support Infrastructure

To enhance the functionality and usability of the cyclor, several auxiliary systems are currently under development:

☐ External Enclosed Box Heater

☐ A multi-shelf enclosed heating unit will be positioned adjacent to the cyclor, with each shelf accommodating a dialysis fluid bag. Heating will be achieved via convection, a method that offers superior energy efficiency compared to traditional plate heaters. This approach is favored over inline heating systems, as it reduces overall system complexity and weight, eliminating the need for extensive thermal management components such as insulation and control circuitry. Nonetheless, an inline heater will be available as an optional module, utilizing a coil integrated through a dedicated connection kit. This feature is designed to support patients requiring portable solutions during travel.

☐ Temperature Monitoring

Each shelf within the heating unit will be equipped with an infrared sensor to continuously monitor the temperature of the corresponding fluid bag, ensuring optimal thermal conditions prior to infusion.

□ Ultrafiltration (UF) Calculation

At the base of the heating unit, a precision scale will measure weight variations of the fluid bags throughout the loading and unloading phases. This enables accurate quantification of both infused and drained volumes, with a resolution of 5 grams. Unlike current market solutions - which rely on manual weighing via dynamometers and are prone to parallax errors - this integrated system provides automated, reliable measurements.

□ Utility Shelf

A dedicated tray will be installed beneath the cyclor to accommodate the sterile drape and all necessary instruments for connection and disconnection procedures. The presence of this organized workspace is intended to improve sterility and procedural efficiency.

- Lower Trolley for Drainage Positioned beneath the heating unit, a mobile cart will house the drainage bag. Equipped with wheels and a rear-mounted electric pump, the trolley facilitates effortless transport and disposal of the collected fluid directly into a toilet, eliminating the need for manual lifting and reducing physical strain on the patient.

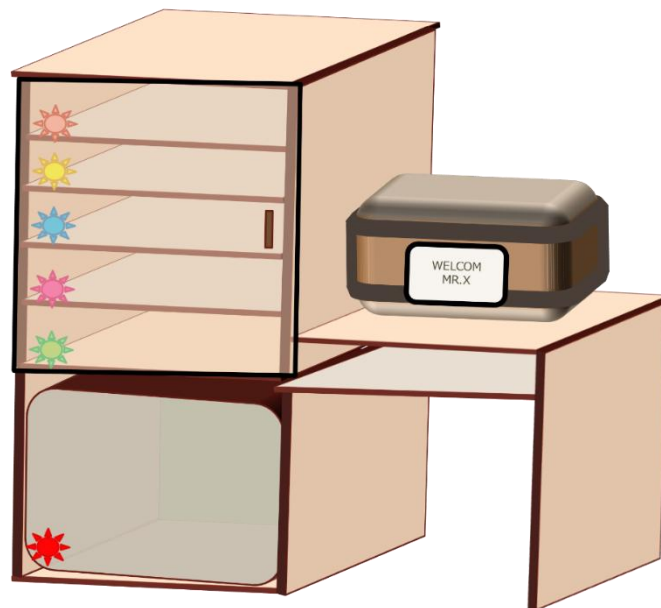


Figure 34. Representation of the support system for the cyclor.

5.5. Cyclor training and initial findings

By the end of the year, the prototype will be prepared for in vivo testing on patients. The initial patient trials scheduled for early next year are expected to generate new clinical data that will support further evaluation and development.

6. TRAINING ACTIVITIES

During the final year of my doctoral program, I actively participated in training activities organized by the school, including conferences and seminars. Additionally, I attended both national and

international congresses related to nephrology. As soon as further data from my research projects become available, I intend to submit two scientific articles: one focused on innovative solutions for peritoneal dialysis, and the other presenting data on the new cyclers prototype.

7. CONCLUSIONS

In conclusion, peritoneal dialysis (PD) represents a versatile home-based therapeutic modality that utilizes the patient's own semi-permeable membrane to achieve metabolic homeostasis through the use of electrolyte-balanced solutions containing specific osmotic agents. While standard regimens involving 2-liter exchanges in CAPD or overnight APD cycles effectively manage uremic toxins and fluid removal, the long-term viability of the technique remains contingent upon mitigating the chronic bioincompatibility of conventional dialysates. Future advancements must focus on the widespread implementation of biocompatible solutions characterized by neutral pH, low glucose degradation products, and alternative osmotic agents to preserve mesothelial integrity and prevent the onset of encapsulating peritoneal sclerosis. Furthermore, the integration of increasingly sophisticated automated cyclers equipped with remote monitoring capabilities offers a significant technological leap, allowing for real-time prescription adjustments and improved clinical outcomes. Emerging strategies, such as the use of uncompensated low-sodium solutions (130 mmol/L), also demonstrate the potential to address persistent challenges like resistant hypertension without the adverse effects of higher glucose loads. Ultimately, the synergy between innovative pharmacological formulations and advanced digital health tools will be paramount in extending the lifespan of the peritoneal membrane and enhancing the quality of life for ESKD patients.

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