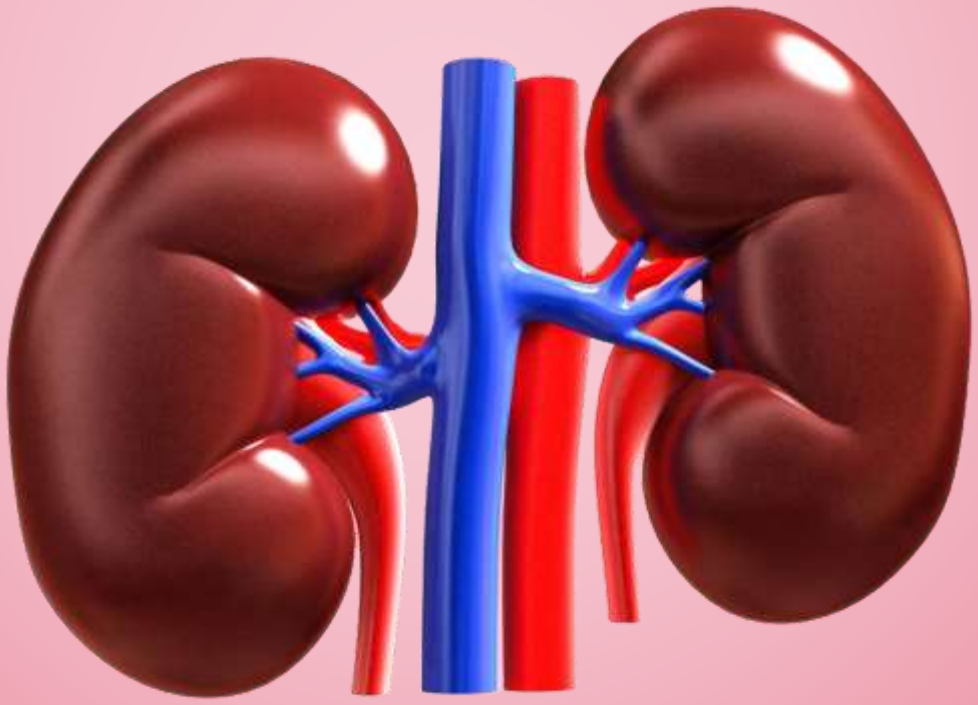
Module on End-Stage Renal Disease (ESRD)

Module 1



UNDERSTANDING THE CAUSES AND PROGRESSION OF ESRD

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I. INTRODUCTION TO END-STAGE RENAL DISEASE (ESRD)

ESRD represents a critical phase of chronic kidney disease (CKD), where the kidneys lose their ability to function effectively, resulting in a life-threatening condition without intervention. This condition is included in stage 5 of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative classification, indicating the most severe form of CKD. ESRD is characterized by an estimated glomerular filtration rate (eGFR) of less than 15 mL per minute per 1.73 m^2 body surface area or the need for dialysis irrespective of eGFR.[1] The disease's progression to this terminal stage involves multiple physiological disruptions, profoundly impacting the patient's quality of life and increasing the risk of premature death.[2]

Patients with ESRD face numerous challenges, including fluid retention, anemia, and disturbances in bone and mineral metabolism. These complications contribute significantly to the high incidence of cardiovascular events observed in this population. Fluid retention can lead to hypertension and ventricular dysfunction, while anemia, primarily due to reduced erythropoietin production by the kidneys, exacerbates the overall health decline. Understanding these complexities is essential for managing ESRD effectively and improving patient outcomes.[1]

1. DEFINITION AND OVERVIEW

ESRD is defined as the irreversible decline in kidney function severe enough to be fatal without dialysis or a kidney transplant. Classified under stage 5 CKD, ESRD is marked by an estimated glomerular filtration rate (eGFR) of less than 15 mL per minute per 1.73 m^2 of body surface area. Regardless of the eGFR value, individuals requiring dialysis to sustain life are also considered to have ESRD. This stage signifies a complete or near-complete loss of kidney function, necessitating renal replacement therapy to maintain health.[1]

The progression to ESRD involves a range of maladaptive changes in the body. These include fluid retention, leading to extracellular volume overload, anemia due to decreased erythropoietin synthesis, and significant disturbances in bone and mineral metabolism. Patients with ESRD often experience severe secondary hyperparathyroidism, dyslipidemia, and protein-energy malnutrition, all of which compound the disease's complexity. Effective management of ESRD requires a comprehensive understanding of these interconnected issues to mitigate symptoms and enhance patient survival and quality of life.[1]

Table 1. Chronic kidney disease classified into five stages based on GFR level[2]

Stage 1	Kidney damage with normal GFR (greater than 90 ml/min)
Stage 2	Mild reduction in GFR (60-89 mL/min)
Stage 3a Stage 3b	Moderate reduction in GFR (45 to 59 mL/min) Moderate reduction in GFR (30 to 44 mL/min)
Stage 4	Severe reduction in GFR (15 to 29 mL/min)
Stage 5	Renal failure (GFR less than 15 mL/min)

2. EPIDEMIOLOGY AND PREVALENCE

ESRD poses a rapidly increasing global health burden, particularly affecting low- and middle-income countries (LMICs). According to the United States Renal Data System (USRDS), an

estimated 2.6 million people worldwide received kidney replacement therapy (KRT) in 2010. However, it is believed that between 4.9 to 9.7 million people required KRT, highlighting a significant treatment gap. This discrepancy indicates that over 2.3 million individuals might have died due to lack of access to this essential therapy. The impact is most severe in LMICs, where access to KRT is limited, resulting in higher mortality rates among ESRD patients.[3]

The distribution of treated ESKD patients varies globally, with significant disparities in access to care. In high-income countries, about 40% of those needing KRT do not receive it, while in low-income countries, this figure rises dramatically to 96%. Regions like Asia and Africa show the most substantial treatment gaps, with only 17-34% and 9-16% of patients receiving necessary care, respectively. Projections suggest that by 2030, the global demand for KRT will more than double, reaching 5.4 million people, with the highest growth expected in Asia. Addressing these disparities is crucial for reducing the global burden of ESRD and ensuring equitable access to life-saving treatments.[3]

II. RISK FACTORS FOR ESRD

1. DEMOGRAPHIC FACTORS

Age: While renal function naturally declines with age, aging alone may not be a significant risk factor for ESRD. However, elderly individuals often have reduced renal reserves, contributing to a higher prevalence of advanced CKD. The true incidence of ESRD may have been underestimated in previous studies due to the use of dialysis incidence as a surrogate marker, potentially overlooking cases where subjects with low kidney function or advanced age may have died before developing ESRD.[4]

Sex: Men have shown a higher risk of developing ESRD compared to women, even after accounting for age and other factors. Sex differences in disease progression have been observed in various kidney conditions, including diabetic nephropathy. While the mechanisms underlying these differences require further investigation, lifestyle factors and genetic predispositions may play a role.[4]

2. CLINICAL AND PHYSIOLOGICAL FACTORS

Body Mass Index (BMI): Excess body weight, particularly obesity, has been associated with an increased risk of ESRD. Studies have revealed a significant relationship between BMI and the risk of developing ESRD, with higher BMI levels correlating with elevated risk. However, the precise mechanisms linking obesity to ESRD progression require further elucidation.[4]

Proteinuria: Proteinuria, a well-known marker of renal disease, has been identified as a crucial factor in the pathogenesis of chronic renal injury and a predictor of ESRD. Epidemiological evidence supports the use of dipstick urinalysis for proteinuria as a predictor of ESRD, although the costs and benefits of treatment for individuals with proteinuria require further evaluation.[4]

Hematuria: While common in women, hematuria has been identified as a significant predictor of ESRD. Individuals with both proteinuria and hematuria demonstrate the highest risk of ESRD development. However, the clinical significance of isolated hematuria in terms of ESRD risk remains uncertain, warranting further investigation.[4]

Blood Pressure: High blood pressure, both high-normal and hypertensive, has been identified as a strong independent risk factor for ESRD, particularly in men. Subjects with hypertension often present with multiple risk factors associated with ESRD, emphasizing the importance of blood pressure management in ESRD prevention.[4]

3. LABORATORY AND METABOLIC FACTORS:

Serum Creatinine (SCr): Elevated SCr levels have been associated with an increased risk of ESRD, although the relationship between SCr and ESRD development requires further exploration. Changes in SCr measurements over time may provide valuable insights into the progression of renal disease.[4]

Serum Uric Acid: Hyperuricemia has been implicated in the progression of renal failure and the development of ESRD. While evidence supporting chronic hyperuricemia as a causative factor for renal damage is still lacking, hyperuricemia has been associated with a higher cumulative incidence of ESRD.[4]

Dyslipidemia: Dyslipidemia, commonly observed in patients with chronic renal failure, may play a significant role in renal damage progression. Although dyslipidemia has been identified as a risk factor for renal dysfunction, its role in ESRD development remains controversial.[4]

4. LIFESTYLE FACTORS:

Smoking: Cigarette smoking has been linked to renal function impairment and proteinuria development. Smoking-related renal injury mechanisms include increases in blood pressure, heart rate, sympathetic nerve activity, and direct toxic effects on endothelial cells.[4]

Alcohol Intake: Moderate alcohol consumption may have a protective effect on renal function, although the relationship between alcohol intake and ESRD incidence requires further investigation.[4]

Exercise Habits: Physical activity levels may impact cardiovascular health and, potentially, renal function. Exercise has been shown to improve insulin sensitivity and may have protective effects against progressive renal dysfunction.[4]

5. ADDITIONAL FACTORS:

Family History of CKD: A family history of CKD and dialysis is a risk factor for proteinuria and ESRD development. Relatives of ESRD patients often share similar lifestyle habits and may have genetic susceptibility to renal failure initiation or progression. However, further epidemiological evidence is needed to fully understand the impact of familial factors on ESRD risk.[4]

III. ESRD PROGRESSION

Progression to end-stage renal disease (ESRD) typically arises from various underlying conditions, with diabetes mellitus being the most prevalent cause. Other contributing factors include hypertension, renal vascular diseases, primary or secondary glomerulonephritis, cystic kidney diseases, tubulointerstitial nephritis, urinary tract obstructions or dysfunctions, recurrent kidney stone diseases, congenital kidney or bladder defects, acute kidney injuries, autoimmune disorders, nephrotoxic substances, obesity, and certain medications like nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, and antiretroviral drugs.[5]

These conditions manifest as changes in renal function, affecting individual nephrons' contribution to the overall glomerular filtration rate (GFR). Initially, renal dysfunction may be asymptomatic, leading to hyperfiltration in nephrons. Compensatory mechanisms, such as nephron hypertrophy and hyperfiltration, help maintain normal GFR levels, masking mild renal dysfunction and delaying detection. However, over time, these adaptive responses become inadequate, resulting in glomerular damage in remaining nephrons.[5]

The pathological progression towards ESRD involves increased glomerular capillary pressure, leading to focal and segmental glomerulosclerosis, eventually progressing to global glomerulosclerosis. Inflammation plays a pivotal role in renal pathology, contributing to glomerulosclerosis, tubulointerstitial fibrosis, and atrophy. Additionally, ESRD is often associated with endocrine disorders and epigenetic changes.[5]

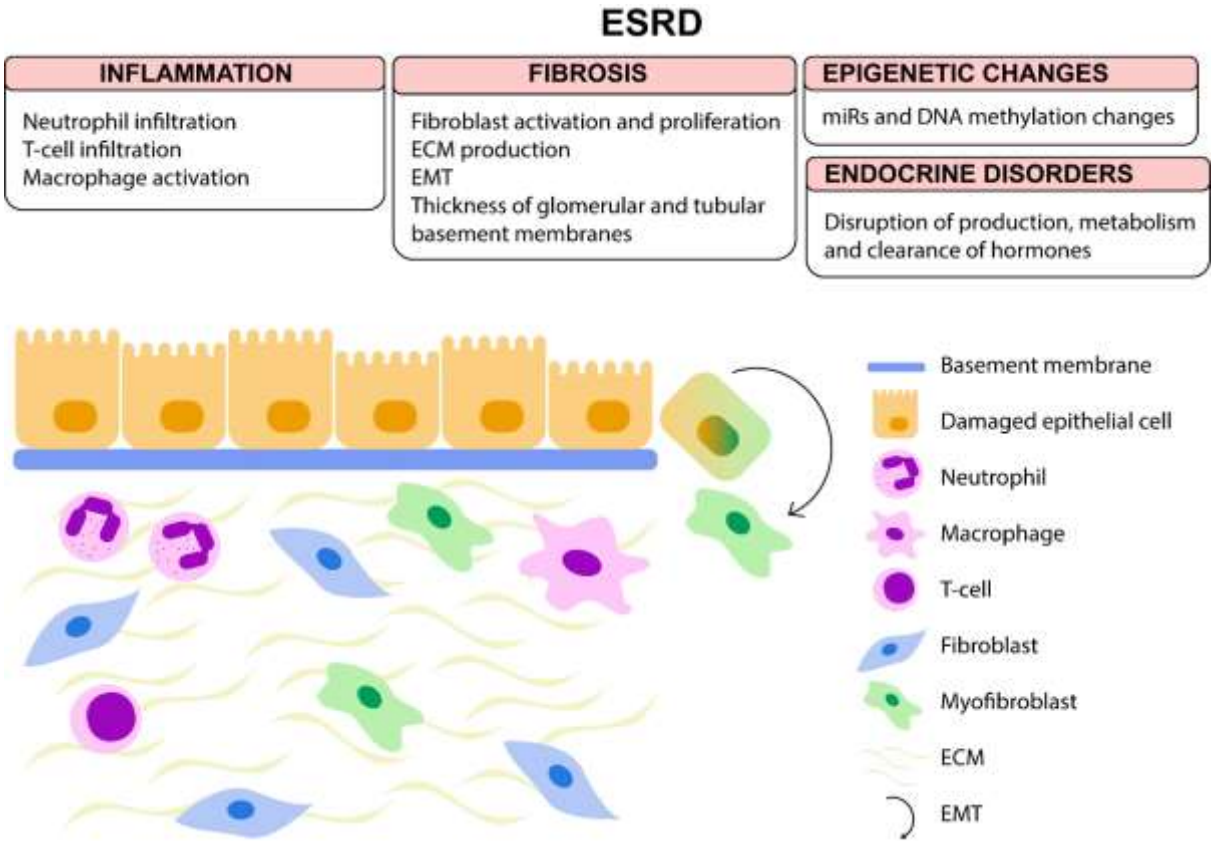

Figure 1.Pathological mechanisms of CKD-to-ESRD progression[5]

In summary, the development of ESRD stems from a complex interplay of underlying conditions, renal dysfunction, compensatory mechanisms, and pathological changes, underscoring the multifaceted nature of renal disease progression.[5]

6. INFLAMMATORY MARKERS

Inflammation plays a crucial role in the progression of renal diseases, serving as a prognostic factor for all-cause and cardiovascular mortality in hemodialysis patients. The inflammatory response involves a multitude of molecules, including pro-inflammatory cytokines, chemokines, cell adhesion molecules, and growth factors.[5]

Numerous studies have investigated the utility of inflammatory markers in assessing declining kidney function. Combining inflammatory and prothrombotic markers with creatinine

evaluation has shown promise in predicting changes in renal function, particularly in elderly patients. However, associations between specific inflammatory and procoagulant markers and rapid decline in renal function have been inconsistent. Notably, a decrease in baseline serum albumin levels has consistently correlated with estimated GFR decline.[5]

Elevated plasma levels of interleukin-6 (IL-6) have been observed in CKD, particularly in stage 5, and serve as predictors of all-cause and cardiovascular mortality in pre-dialysis patients. In fact, IL-6 levels have demonstrated superior predictive ability compared to other major inflammatory biomarkers such as C-reactive protein and TNF-α. Additionally, tumor necrosis factor receptors (TNFRs) have shown promise as predictors of end-stage renal disease (ESRD) progression, especially in diabetic kidney disease and IgA nephropathy.[5]

A range of systemic inflammatory biomarkers has been associated with CKD progression, including proinflammatory cytokines (TNF-α, IL-6, IL-18), chemokines (IL-8, IL-34, SDF1α, MCP-1, MIP-1β), growth factors (GM-CSF, FGF-23, HGF), soluble receptors (sTNFR1, sTNFR2, sCD40L, sCD163), and cyclophilin A. However, the relationship between these markers, GFR levels, and ESRD development across different CKD stages remains poorly understood.[5]

In addition to soluble markers, in situ inflammatory status and lymphocyte immune phenotype have shown promise in distinguishing ESRD patients from healthy controls. Reductions in regulatory T cells (Tregs) and alterations in cytokine profiles have been observed in ESRD patients, particularly those with systemic lupus erythematosus. Furthermore, differences in T- and B-cell populations have been noted between ESRD patients and healthy controls, suggesting a potential role for immune phenotyping in ESRD diagnosis and prognosis.[5]

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have emerged as diagnostic markers of inflammation in ESRD patients, with associations observed with inflammation and mortality. However, the use of inflammatory markers in renal failure diagnosis must be complemented with other diagnostic approaches due to the complex nature of ESRD development across different pathologies.[5]

7. FIBROSIS MARKERS

In healthy tissues, a delicate balance between extracellular matrix (ECM) synthesis and proteolysis maintains organ integrity. Disruption of this balance can lead to excessive deposition of ECM components, causing fibrosis and eventual organ dysfunction. Renal fibrosis, characterized by the accumulation of ECM in the kidney, is a hallmark of chronic kidney disease (CKD) and end-stage renal disease (ESRD), contributing significantly to morbidity and mortality worldwide.[5]

The prevalence of CKD, often accompanied by renal fibrosis, has risen steadily since the 1990s, resulting in a substantial burden on healthcare systems globally. Renal fibrosis can affect various renal compartments, including glomeruli, tubulointerstitium, and vasculature, ultimately leading to kidney failure.[5]

Collagens are among the most common markers of fibrosis, with different types of collagens accumulating in renal fibrous tissue. Techniques such as Masson's trichrome and Picrosirius Red staining are commonly used to identify fibrosis in clinical and experimental settings, although they have limitations in specificity. Immunohistochemical assays offer a more direct and specific approach to detecting and quantifying collagens in renal tissue.[5]

Biochemical analysis of hydroxyproline, a constituent of collagen, provides another method for evaluating collagen content. Collagen or its fragments can also be assessed in serum and urine samples, offering noninvasive biomarkers for renal fibrosis diagnosis and monitoring. Studies have shown associations between collagen fragments and CKD progression, providing insights into the dynamics of renal failure development.[5]

Besides collagens, other ECM proteins and intermediate filament proteins such as fibronectin, thrombospondin 1, vimentin, and nestin are associated with kidney fibrosis and can serve as biomarkers for renal failure diagnosis. Non-ECM proteins like transforming growth factor-β1 (TGF-β1), galectin 3, and chemokine ligands are also implicated in renal fibrosis and have prognostic value in predicting ESRD development and mortality.[5]

Combining multiple biomarkers, including ECM components and non-ECM proteins, may enhance the prediction of CKD progression and renal outcome compared to traditional clinical parameters alone. These biomarkers offer valuable insights into the severity of CKD, progression to ESRD, and potential outcomes post-kidney transplantation.[5]

In summary, kidney fibrosis biomarkers play a crucial role in diagnosing, monitoring, and predicting the progression of CKD and ESRD. Their use in clinical practice can improve risk stratification, guide treatment decisions, and ultimately improve patient outcomes.

8. EPIGENETIC MARKERS

Epigenetic mechanisms play a significant role in the development of renal fibrosis, as evidenced by studies in cell cultures, animal models, and patients with various kidney pathologies such as diabetic nephropathy, ischemia, and lupus nephritis. These epigenetic changes can directly mediate the transition from acute kidney injury to chronic kidney disease (CKD), highlighting their potential as prognostic factors for CKD severity and end-stage renal disease (ESRD) risk assessment.[5]

MicroRNAs (miRs) and DNA methylation are among the most promising epigenetic markers of renal fibrosis, commonly analyzed in blood cells or urine samples. miRs are small non-coding RNAs that regulate gene expression through RNA interference. Many miRs have been implicated in the development of renal fibrosis, with miR-21, miR-92, and miR-122 showing promise as markers for evaluating CKD stages and ESRD risks. For example, miR-21 is involved in cellular metabolism regulation and can enhance cell viability during acute stress by downregulating various genes associated with metabolic pathways.[5]

DNA methylation, another epigenetic modification, has been linked to kidney pathologies and can serve as a biomarker for CKD severity and ESRD risk. Increased levels of 5-methyl-2'-deoxycytidine (5-Me-dC) in urine predict late-stage CKD when accompanied by macroalbuminuria or α 1-microglobulin appearance. Methylation status of the p66Shc

promoter in blood is associated with cardiovascular risk in ESRD patients, indicating a potential link between epigenetic modifications and comorbidities.[5]

Several genomic sites with altered methylation levels have been identified in association with ESRD, suggesting the complexity of epigenetic regulation in kidney diseases. Methylation of genes like methylenetetrahydrofolate reductase (MTHFR) is upregulated in ESRD patients and correlates with renal function decline and metabolic abnormalities.[5]

The use of epigenetic clocks, which assess epigenetic age based on DNA methylation patterns, holds scientific interest in evaluating kidney health. Epigenetic age correlates with renal function markers and mortality risk, providing insights into the aging process of renal tissue and its implications for kidney disease progression.[5]

9. CHANGES IN THE ENDOCRINE SYSTEM

The endocrine system undergoes significant changes in chronic kidney disease (CKD) and end-stage renal disease (ESRD), impacting hormonal regulation and contributing to disease progression. Hormones involved in water-salt balance, blood pressure regulation, and other physiological processes can serve as biomarkers for CKD and ESRD.[5]

The renin-angiotensin-aldosterone system (RAAS) plays a crucial role in regulating vascular tone, blood pressure, and sodium balance. Angiotensin II (AngII), a key component of RAAS, promotes kidney fibrosis and is associated with CKD progression. Intrarenal RAAS activation is particularly relevant in the transition to ESRD, with increased renal expression of angiotensinogen (AGT) serving as a biomarker for intrarenal RAAS activation. Urinary AGT levels are associated with adverse renal outcomes in CKD patients and are used to assess intrarenal RAAS activity.[5]

Natriuretic peptides, which antagonize RAAS, are also implicated in CKD and ESRD. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels are elevated in CKD patients, reflecting cardiovascular stress and contributing to heart failure risk. C-type

natriuretic peptide (CNP) plays a role in preventing kidney tissue remodeling, with urinary CNP levels potentially serving as an early marker of tubulointerstitial fibrosis.[5]

Erythropoietin, synthesized in the kidney, regulates erythropoiesis and is disrupted in CKD and ESRD, leading to anemia. Anemia is prevalent in CKD patients and is associated with disease severity, highlighting the potential of erythropoietin as a biomarker for renal dysfunction.[5]

Prolactin levels are elevated in CKD and ESRD due to reduced clearance, with hyperprolactinemia serving as an indirect indication for kidney transplantation. The kallikrein-kinin system, involved in blood pressure regulation, shows altered activity in CKD, with urinary kallikrein levels correlating with renal function decline and progression of diabetic nephropathy.[5]

Overall, changes in hormone levels reflect the pathophysiology of CKD and ESRD and can serve as biomarkers for disease severity, progression, and associated complications, aiding in patient management and therapeutic decision-making.

IV. REFERENCES

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