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Chapter 3: Innovations in kidney disease: Diagnostic breakthroughs and cutting-edge treatment protocols

3.1. Introduction to Kidney Disease

Kidney diseases have a diverse global impact on public health, comprising an array of disorders that affect the kidneys and their surrounding tissues, and serve to disrupt the normal functions of the organ. The kidneys are two highly specialized and vascularized organs, whose functions primarily serve the removal of metabolic waste, via the filtration of blood. Other important kidney functions are the regulation of fluid balance, control of electrolytes, regulation of acid-base homeostasis, maintenance of normal blood pressure, and endocrine functions, such as the regulation of calcium and vitamin D homeostasis, and the stimulation of erythropoiesis. The disruption of normal kidney function can lead to a wide range of clinical consequences, including acute kidney injury, chronic kidney disease, metabolic bone disease, electrolyte derangements, hypertension, fluid overload, and anemia (Badura et al., 2023; Dąbek et al., 2023; Coimbra & Santos-Silva, 2025).

Kidney disorders are, however, often asymptomatic for long. As such, patients are exposed to increased risks for them to end up with acute kidney injury or progressing to the requirement for renal replacement therapy at later stages; these represent unwanted outcomes that can lead to an economic burden to healthcare systems and a non-negligible risk of morbidity and mortality on behalf of the patients. Hence, in the present era, the need is to achieve the early identification of patients at risk of, or already showing, decreased kidney function, and to effectively implement novel therapeutic strategies, and patient-centered options, to halt or delay disease progression, thus preventing unwanted short and long-term outcomes of kidney diseases. This work summarizes some of the most promising innovative diagnostic strategies and therapeutic options, which

healthcare professionals should be aware of shortly, to effectively deal with kidney diseases in a multidisciplinary manner (Lee et al., 2023; Sharaby et al., 2023).

3.1.1. Understanding the Fundamentals of Kidney Disease

Kidney disease refers to a group of disorders in which the kidneys lose their normal function. The kidneys are responsible for removing waste and excess fluid from the blood, balancing electrolyte levels, and producing hormones that regulate blood pressure. There are many types of kidney disease, including acute kidney injury, chronic kidney disease, kidney stones, kidney infections, and kidney failure. Worldwide, chronic kidney disease is among the top 20 leading causes of death. Programs that assess and manage chronic kidney disease not only reduce the need for dialysis and transplantation but will also improve the patient's overall health and well-being. However, care for patients with chronic kidney disease is inconsistent and often does not follow evidence-based guidelines.

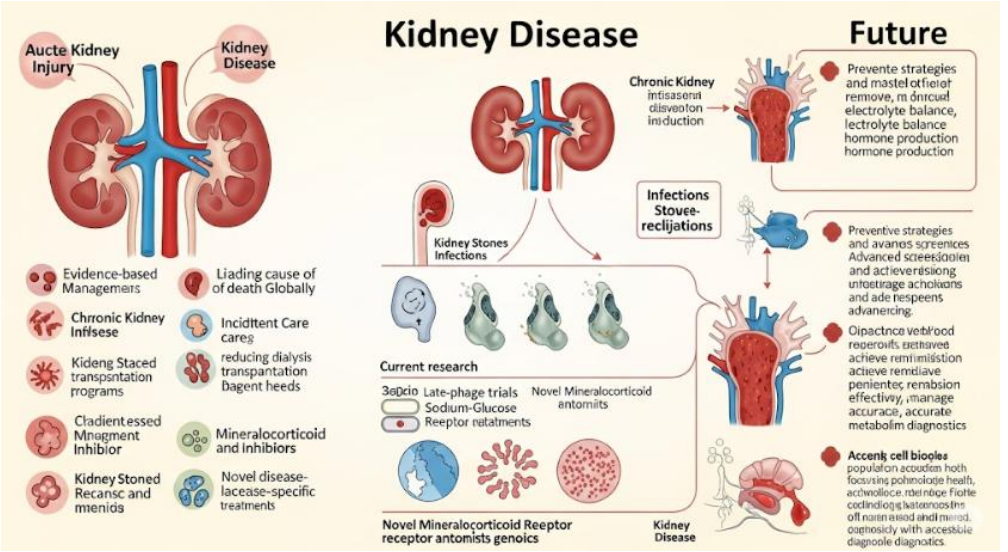

Fig 3 . 1 : Kidney Disease

Currently, there are no medications that specifically target the mechanisms involved in the initiation and progression of chronic kidney disease. The recognition of chronic kidney disease as a clinical and public health problem has resulted in an outpouring of research and development efforts to identify novel treatments. A number of late-phase clinical trials are underway, focusing on glucose- and sodium-glucose transport inhibitors, incretin-based medications, and novel mineralocorticoid receptor antagonists. Advances in our understanding of kidney cell biology, as well as the increased use of big data and genomics, have helped advance the kidney research field. Shortly, efforts

to prevent chronic kidney disease through population health and technology will come together to enable more patients to enter remission. Tools to screen for patients with chronic kidney disease and metabolism errors will be accurate, efficient, and widely available.

3.2. Epidemiology of Kidney Disease

Because kidney disease is associated with various comorbidities, including cardiovascular disease and diabetes, it is recognized as a global public health issue. Most renal symptoms and signs are often overlooked until the clinical condition is advanced; hence, current estimates reveal that more than half of the global population living with CKD are still undiagnosed and unaware of their condition. Chronic kidney disease is considered a "silent epidemic" as it is asymptomatic even in its late stages, and the diagnosis depends on the measurement of kidney function that is usually performed by estimating the eGFR, during investigations for other conditions or through systematic screening when population-based screening for the disease is implemented. CKD prevalence rates increase with age, resulting in important implications for the health care management of this complex geriatric syndrome, with consequences for both the individual and for health care systems. Due to various risk factors including an increasingly aging population, growing prevalence of diabetes and hypertension, and changing diet, lifestyle, and habit patterns, CKD prevalence has been rising in the last three decades. The global burden of disease data showed that an estimated 750 million people in the world are living with CKD, and among those, 294.4 million are diagnosed with CKD stage 2 and above. Furthermore, it was reported that CKD is linked to 1.5 million deaths per year. Screening strategies, targeting high-risk groups such as patients with diabetes, hypertension, and a family history of kidney disease, can detect kidney disease at early stages, when intervention is more beneficial and may prevent or delay the progression to advanced kidney disease that is associated with increased morbidity, mortality, and costs.

3.2.1. Global Prevalence and Risk Factors of Kidney Disease

Chronic kidney disease (CKD) affects approximately 10%–15% of the population worldwide, including 2.5% of the United States adult population, with an increasing prevalence in Eastern European and Asian countries. Epidemiological studies show a global increase in the number of patients with end-stage kidney disease (ESKD), both on renal replacement therapy and not, with a disproportionately higher prevalence in diabetic and hypertensive patients. Aging, diabetes, hypertension, obesity, and smoking

are the leading risk factors for CKD. A better understanding of CKD epidemiology is important to identify and improve patients' clinical outcomes at the population level.

Kidney disease and its consequences present major global health concerns. Kidney diseases such as chronic kidney disease (CKD) and end-stage kidney disease (ESKD) increase the risk of other diseases, such as cardiovascular disease, with accompanying mortality and morbidity. The global burden of CKD diagnosis is increasing largely due to an aging population and a higher occurrence of diabetes and hypertension. CKD has an impact on quality of life, both directly and indirectly. CKD can affect the quality of life of both patients and their caregivers; moreover, the loss of productivity of patients with CKD results in an economic burden for society. CKD affects nearly all countries, regardless of whether they are high-, middle-, or low-income countries. Furthermore, the costs of kidney disease are considerable and increasing. Diabetes and hypertension, the most well-known risk factors for CKD and ESKD, have been previously investigated in a variety of populations, but few have focused on Japan, Taiwan, the Philippines, and other Asian countries.

3.3. Traditional Diagnostic Methods

Despite the advent of artificial intelligence and deep learning in radiology, most AI systems aimed at the detection of kidney disease have been focused on incorporating kidney ultrasound scans, computed tomography studies, and magnetic resonance imaging data. Given the well-described and ubiquitous associations between the kidneys, vascular supply, and urinary outflow system and the establishment of diagnosis-planning protocols, these modalities serve an important role in the evaluation of kidney abnormalities. However, imaging alone may not be sufficient, and traditional laboratory studies remain pivotal in the evaluation of kidney disease. The pathologist’s examination of renal biopsies has long informed on challenging clinical questions as to whether the glomerular injury is hypertensive, diabetic, vascular, infectious, immune-mediated, or genetic in origin; whether transplant allograph dysfunction represents acute rejection or delayed graft function; and whether urinary tract obstruction is a result of schistosomiasis, foreign body disease, or malignancy.

Moreover, traditional laboratory data provide the clinical context when interpreting imaging results. Mildly increased kidney echogenicity may suggest amyloidosis or possible amyloidosis due to its association with multiple myeloma, but laboratory findings demonstrating a lack of monoclonal gammopathy would favor a diagnosis of fatty metamorphosis. Contrast-enhanced CT imaging may expose a small renal collision tumor that is a transitional cell carcinoma arising in the pelvis and having associated obstruction and upper tract debris; yet, loss of function of the affected renal unit justifies nephron-sparing. Thus, the prudent interpretation of imaging studies by any involved

specialist, whether a radiologist, nephrologist, or urologist, relies on a culmination of clinical context and basic laboratory knowledge, in juxtaposition to a deeper understanding of disease pathophysiology and the full portfolio of imaging modalities.

3.3.1. Key Techniques in Kidney Disease Diagnosis

Reduced filtration efficiency, severe metabolic imbalance, and deregulated homeostasis of various compounds correlate with established kidney disease. To assess these parameters, health practitioners may have used many traditional diagnostic methods, including physical examination-based approaches, blood sampling-based biomarker assessment, urine analysis, and imaging of the kidneys. Physical examination-assisted techniques generally rely on the detection of clinical signs during a routine physical exam. These clinical signs reflect deranged system bodily functions and are indicators of potential kidney involvement. Blood and urine sample-based assaying are popular among health professionals due to their ease and safety. Blood test-based biomarkers, including creatinine, urea, cystatin-C, and creatine clearance/filtration rate, and urine test-based biomarkers, including microalbuminuria/proteinuria or urinary protein-to-creatinine ratio, radiologic imaging-assisted markers, and physical-examination-based accessibility markers, have documented utility in the diagnosis of kidney diseases. Ultrasound-based imaging is commonly the first and least invasive imaging modality used. Computed tomography and magnetic resonance imaging have a very limited utility in kidney disease; compared to ultrasound, their higher cost and lack of feasibility in patients with compromised renal function considerably reduce their practicality, especially since ultrasound detection of kidney disease generally has similar or better sensitivity/specificity than the other imaging modalities. Histochemistry-based immunohistochemical labeling for specific innate and adaptive immune cell populations alongside a battery of protein markers to assess tubular injury, inflammation, and fibrosis is essential for improved diagnostic understanding of kidney disease. The potential unsuitability of the current traditional approaches to detect the developing burden of kidney disease at an early asymptomatic stage or compromised function at a higher functional stage necessitates the continuous and comprehensive assessment of the kidneys using new-generation biomarkers that provide complementary and sensitive data at various functional stages.

3.4. Emerging Biomarkers in Kidney Disease

In recent decades, the use of serum kidney function biomarkers in clinical practice has made substantial contributions to CKD prevention and management. However, these traditional biomarkers, especially creatinine, have limitations related to their low

sensitivity, low specificity, and late increase when kidney injury is already established. In addition, both serum creatinine and urea concentrations depend not only on kidney function but also on variables such as muscle mass, protein intake, acute-phase response, and hydration status. Moreover, creatinine and urea do not provide information on the specific mechanisms underlying the kidney injury. Therefore, there is currently much interest in the identification and validation of novel non-invasive urinary or serum biomarkers that could be used in clinical practice to facilitate the early diagnosis, prognosis assessments, and differential diagnosis of the diverse histological entities underlying the clinical syndrome of kidney injury, as well as monitor therapeutic efficacy. The ideal markers should be sensitive, specific, and cost-effective and reflect kidney damage not influenced by glomerular filtration rate alterations. In addition, urinary markers should provide information on the altered pathways of kidney injury. Although validating biomarkers is an expensive and time-consuming process, many promising urinary and serum biomarkers have been identified in explorative studies for several kidney diseases.

Urinary Biomarkers

The combination of specific urinary markers reflecting tubular, glomerular, or interstitial damage helps with the differential diagnosis of acute kidney injury mechanisms, such as the differentiation of prerenal azotemia from acute tubular necrosis and the differentiation of ischemic from nephrotoxic tubular necrosis; the detection of acute tubular injury after exposure to nephrotoxins; the prediction of acute kidney injury after kidney surgery; disease progression assessment; and the prediction of long-term chronic kidney disease progression, the prognosis of end-stage renal disease, or mortality in patients with either acute or chronic kidney injury. However, to date, other than albumin, cleaved interleukin-18, neutrophil gelatinase-associated lipocalin, and kidney injury molecule-1 have not become established clinical tools.

3.4.1. Urinary Biomarkers

Emerging Biomarkers in Kidney Disease

Kidney diagnostic testing has seen limited innovation over recent years, particularly in the development of non-invasive and point-of-care testing, essential for early detection of kidney dysfunction. The existing gold standard for kidney disease diagnosis, serum creatinine, is a relatively insensitive marker of early kidney injury and has a poor prognostic value for future risk of adverse kidney disease-related outcomes. Most kidney disease-related systemic testing relies on risk or prognostic modeling rather than risk stratification by identifying or characterizing the affected cohort. This is mainly because systemic serum creatinine-based testing is ineffective for stratifying very early disease

and patients with largely asymptomatic disease. Such patients often present at an advanced stage of disease for which treatment options are limited and expensive, associated with significant morbidity, and do not provide good prognostic outcomes. Therefore, early detection of kidney disease is key to reducing the resulting burden of morbidity and mortality.

Functional tests of the kidney disease extension spectrum predict changes relative to historic normal values rather than quantifying the presence of ongoing injury. By comparison, urinary biomarkers provide a characterization of the ongoing pathophysiological processes within the kidney during injury. On the one hand, predicting residual function and elucidating the pathology of mild or attenuated anomalies with impaired function are valuable uses of urine biomarkers. On the other hand, also detecting and quantifying markers of active ongoing pathophysiological processes can be informative if the value represents a transition point relative to normality incorporated into a risk predictor. The compelling need for non-invasive quantitative tests at the level of ongoing infection, inflammation, repair, ischemia, and scarring has given rise to unprecedented recent interest in urinary biomarkers.

3.4.2. Serum Biomarkers

Novel approaches to improve early diagnosis and prognostic prediction of kidney disease have focused primarily on urinary diagnostics due to the direct exposure of urine to the nephron microenvironment. However, serum biomarkers remain a primary focus of ongoing research, propelled by the desire for greater accessibility, lower costs, and the ability to detect systemic and metabolic changes that affect multiple organs. In addition to the traditional parameters of kidney function, urea, creatinine, and electrolytes, the growing field of metabolomics has revealed numerous novel serum metabolites associated with different causes and complications of kidney disease. A wide array of metabolomic studies in CKD associated with DM and hypertension, kidney stones, AKI, ADPKD, kidney transplant rejection and survival, and cardiovascular disease have revealed numerous metabolites with diagnostic and prognostic utility. Moreover, inflammatory and immune responses also play a role in kidney injury and loss of function. In patients with kidney disease, systemic inflammation has been characterized by the enhanced expression of proinflammatory cytokines and a persistent increase in inflammatory mediators such as C-reactive protein, pentraxin, and vascular adhesion protein 1, which are secreted mainly by the liver and vascular endothelium. Due to their ease of access and cadence of collection, circulating inflammatory cytokines like TNF-α, IL-6, IL-10, TGF-β1, and macrophage inflammatory protein-1α have been touted as potential serum biomarkers. However, these data must be interpreted with caution since they represent the balance between proinflammatory and anti-

inflammatory activities, and some may also be associated with renal reserve. The use of serum protein arrays has advanced the ability to probe thousands of candidate proteins involved in kidney function and could point to novel therapeutic targets. Multiplex assays are continually refined to detect soluble factors with biological importance.

3.5. Advanced Imaging Techniques

New and advanced imaging techniques are developing into powerful disease diagnostics and prognostics in KD. Though ultrasound has been a long-utilized cornerstone imaging modality in kidney disease evaluation, MRI and CT are exciting LMWD modalities that are poised to revolutionize KD imaging. Both have seen increasing usage thanks to more widespread availability and advancements in field strength and scanner speed. Both modalities have high resolution and high contrast potential. However, both are more expensive than ultrasound, are less available in secluded clinical care settings, and usually require transporting bedridden patients. They also have potential adverse effects from ionizing radiation and gadolinium-based contrast agents. These innovations in MRI and CT scanning modalities have changed their effectiveness in diagnosing, prognosticating, and planning KD surgical intervention.

MRI Innovations

MRI has long been known for its high anatomical resolution. In recent years, novel soft-tissue characterization techniques have pushed forward the potential diagnosis of KD, including lymphoma, acute cellular rejection, denervation injury, tuberculous infection, renal ablation injury, and acute pyelonephritis. It was found that diffusion-weighted MRI was superior to CT, non-contrast MRI, and gadolinium-contrast generating techniques for detecting early acute rejection in renal transplant patients. In a follow-up study of the same patient group, it was found that non-gadolinium-enhanced diffusion-MRI had 100% sensitivity and 86% specificity in detecting acute rejection but required a high field strength.

3.5.1. MRI Innovations

Despite the ease with which MRI can capture multiparametric renal data, its clinical utilization in kidney disorders is limited by its high operational cost, time-consuming nature, and limited access. Standard MRI is not sensitive to abnormalities in microstructural details, the presence of small tumors, and certain renal conditions such as stone disease. Current advances aim to resolve these limitations and explore innovative applications. Magnetization transfer contrast imaging represents a new mode of MRI contrast enabling quantitative assessment of microstructural features and has

found application in kidney transplant patients and those with chronic kidney disease. By exploiting T2-weighted signal changes, T2 mapping allows the estimation of T2 values over the kidney, helping differentiate cystic from solid tumors and detect renal iron overload.

Researchers recently described high-resolution T2 mapping at 3.0T with a T2 value of 60 ms at the renal cortex compared to a T2 value of 209 ms in the renal medulla, enabling better discrimination of anatomical segments and microstructure. Morphologic patterns of cortical ischemia compared to congestive hyperemia in rodent models were studied with T2 mapping. Newer ultrashort echo time imaging exploits multiple gradient sequences to capture both T1- and T2-weighted contrasts providing an improved depiction of renal structures in significantly shorter periods, including in patients with renal failure. Quantification of renal perfusion is another exciting innovation with demonstrated association with and predictive capability for results in transplant patients.

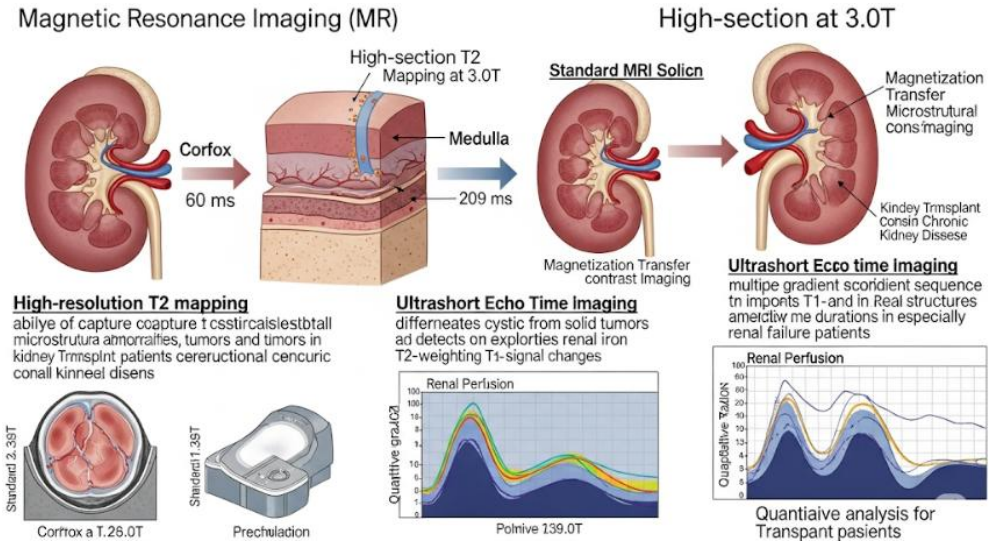

Fig 3 . 2 : MRI: From Limitations to Innovation in Kidney Imaging

3.5.2. CT Scan Developments

CT imaging has undergone significant advances as summarized in this section. The use of dual-energy CT has grown in recent years for detecting both hypervascular renal tumors and renal stone disease. The applications of perfusion imaging techniques that can evaluate and quantify renal blood flow have also advanced. Perfusion CT and contrast-enhanced ultrasound can provide information on tumor vascularity, a key consideration for determining the risk of renal tumor growth. The advances in spectral imaging using single-source dual-energy CT have increased the clinical utilization of

renal perfusion imaging, with relatively short acquisition time and low radiation dose. Virtual non-contrast imaging and dual-layer detector spectral imaging have further reduced the obstacles to adopting perfusion CT for clinical practice. These advances, combined with new biomarkers, can help in delineating indolent renal tumors from those needing intervention. The trends toward high-spatial and temporal resolution CT, utilized with low or ultra-low radiation dose, noise smoothing algorithms, high-radiation dose efficiency, and use of low-energy speckle noise canceling and more advanced tensor-based denoising techniques. In addition to the advances in CT hardware, breakthrough CT applications, such as spectral Doppler, are available to assess renal function. These advances in CT imaging are also combined with novel biomarkers, which can help in improving diagnostic accuracy, prognostic stratification, and therapy response assessment for various renal diseases.

3.6. Genetic Testing in Kidney Disease

The past few decades have seen significant advances in understanding the underlying genetic basis of many renal disease processes, which have resulted in an explosion of novel genetic diagnostic tests. Over two hundred kidney disease-associated monogenic variants have been identified in genes primarily associated with the renal epithelium, for which genetic testing is clinically available. While the majority of genetic tests for kidney disease are currently focused on syndromic conditions that can present in childhood, such as Alport syndrome and Bartter syndrome, an increasing number of non-syndromic variants in kidney disease genes are also being reported in adults with conditions such as just ESKD, hypertension, or glomerular disease. With the increased accessibility of genetic testing, in this chapter, we summarize the utility of genetic testing in the clinical management of kidney diseases.

Clinical genetic testing can be performed using both single-gene tests and multi-gene panel tests. Single-gene tests might be more useful when dealing with a specific renal disease, such as a mutation in pontocerebellar hypoplasia type 8 with renal manifestations, while multi-gene panel tests are better suited for patients with syndromic or adult-onset conditions who may have broader phenotypic heterogeneity, such as those with autosomal dominant ESKD due to mutations in certain genes. In addition, it is increasingly common for clinicians to send broad genomic sequencing tests that may include all kidney disease-associated gene panels or more generalized variant detection tests to arbitrate between overlapping phenotypes for syndromic or non-syndromic conditions with renal manifestations.

3.7. Artificial Intelligence in Diagnosis

The application of artificial intelligence (AI) for human health can be broadly categorized into two groups: diagnostic and therapeutic. Here, we focus primarily on the diagnostic aspect of AI. The diagnostic applications utilize two AI tools–machine learning (ML) and predictive analytics (PA). Machine learning is the study of algorithms and statistical models that generalize to new data when trained on known data. It can be broadly divided into supervised ML or unsupervised ML, with supervised ML further divided into classification, regression, and deep-learning models. Predictive analytics, on the other hand, is a subfield of data mining, analytics, and statistical and mathematical modeling that uses known data to predict future outcomes using a wide variety of techniques, including data mining methods and statistical methods.

Machine learning has gained traction for various applications in nephrology–from predicting the future onset of kidney disease to estimating the risk for poor outcomes and disease complications to automating and expediting clinical processes, and so on. Beyond nephrology, there is growing interest in the use of diagnostic ML algorithms for imaging tests, laboratory assays, and patient data. A few examples are computer-aided detection algorithms for radiological interpretations, including chest X-rays, mammograms, CT imaging, and chest CT interpretative aids; hematology-based algorithms like those that triage basic laboratory tests; algorithms that classify medical images from dermatology, gastroenterology, ophthalmology, pathology; vocal cord evaluation and screening; and those applied on ECG interpretations. However, the adoption of diagnostic AI algorithms for patient care has been slower than anticipated.

3.7.1. Machine Learning Applications

Machine learning has exploded in popularity across all directions of healthcare due to its applications in clinical decision-making. There has been a wealth of machine learning applications in kidney disease detection, treatment prediction, risk stratification, prognosis, and clinical decision support. In this section, we explore the development and application of machine learning in the field of nephrology, specifically in kidney disease risk prediction, kidney disease detection, differential diagnosis, treatment prediction, prognosis and complications, and machine learning-decision support systems.

In general, the ability of a machine learning algorithm to perform well in a particular task strongly relies on how the model is set up and how the data is processed and curated. Successful implementations of machine learning in clinical care, therefore, require upfront careful planning, which includes defining the clinical mission and scope of the project, selecting and curating data, processing features, setting up a machine learning model, validating the model, and designing model deployment and clinical integration.

Despite the potential, not many clinical machine learning projects up until now have successfully transitioned from research to daily clinical practice of decision support tools. Among different steps, model validation is one of the most cited hurdles in the mission of translating machine learning into clinical care. A validated decision support tool should generalize well on unseen data from a patient population different from the one that the training and development of the model were based on. Broad validity of machine learning in clinical care is vital, considering the number of parameters that can affect clinical data during the patient journey, which is the foundation of a supervised learning problem.

3.7.2. Predictive Analytics

Predictive analytics is an area of statistical analysis that uses machine learning, predictive modeling, and other advanced analytics methods to predict future events. Predictive analytics techniques try to predict future habits and behaviors through supervised machine learning methods that utilize training data sets. Predictive analytics methods are commonly applied to analyze data sets of past events to identify patterns of behavior that can lead to significant probabilities of occurrence of future events whenever similar situations arise. In particular, predictive analytics enables a clearer understanding of how current events may lead to specific forecasted patient outcomes.

Numerous studies have validated the utility of predictive analytics in nephrology. Steep declines in kidney function are associated with adverse medical outcomes including an increase in mortality, hospitalization for acute kidney injury, and need for renal replacement therapy. Cumulative short-term change in estimated glomerular filtration rate over 6 months is well used in clinical practice to predict worsening of kidney function and associated outcomes. Integrating larger patient cohort data, such as eGFR trajectory, blood urea nitrogen, and serum creatinine use in a support vector machine model has improved predictive abilities using diagnostic modeling. Other patient physiological factors such as albuminuria, hypertension, diabetes mellitus, glomerular hypertension, hyperfiltration, and clinical risk factors such as age, sex, ethnicity, obesity, cardiovascular disease, and smoking history have also enhanced predictive performance in estimating the development of progression to KDOQI stages 4 and 5.

3.8. Novel Treatment Protocols

The pandemic disruption of transplantation services has generated an interest in nonimmunosuppressive treatment protocols that delay ESRD as opposed to invasive modalities that escape ESRD. These protocols address the role of inflammation in promoting ESRD. Two such protocols incorporate early use of some combination of

glucocorticoids, antibiotics with anti-inflammatory properties, statins, and drugs with immunosuppressive qualities that inhibit IL-6/signaling, TNF blockade, IL-23 blockade, IL-17 blockade, and JAK-1 inhibition. These protocols aim to inflate the dynamic renal reserve by stabilizing the glomerular filtration rate before progression is detected.

A second generation of alternative therapies may then be considered if these efforts fail. Early piloting results using the glucagon-like peptide 1 receptor agonist liraglutide in humans with DKD showed initial success in promoting GFR recovery or diffusion despite inducing renal hyperperfusion through the putative effect of GLP-1 on upregulation COX-2 and subsequent prostaglandin synthesis. Future trials with more encouraging semaglutide focusing on stage 3 DKD should clarify uncertainty if it did either reduce the incidence of endpoint ESRD or the risk of kidney failure events in the more advanced stages of DKD because it failed to prolong the effects of liraglutide in DKD. GLP-1RA offers an innovative alternative therapeutic option for high-risk patients wishing to escape the frustratingly stagnant waitlist for renal transplantation. Conventionally approved glucose-lowering medications do not simply delay progression down the nephron evolutive slope from nephronogenesis through the neoepithelization wave at the glomerular level passing through developmental multistage nephron dystrophies before terminus nephrosclerosis.

3.8.1. Innovative Therapeutic Approaches

Various innovative therapeutic approaches for the treatment of progressing chronic kidney disease or complications of progressive chronic kidney disease are under investigation. Of note is the D-Blocker, a new and innovative approach to addressing the dysregulation of glucose and energy metabolism. Accumulation of dicarbonyls such as methylglyoxal can lead to excess formation of advanced glycation endproducts, dysregulation of cellular calcium ions homeostasis, and increased nitric oxide formation by the inducible nitric oxide synthase. Next to structural cellular damage, such cellular stress response can lead to the excess expression of proinflammatory cytokines, malfunctioning of the antioxidant defense system, and eventually cell death and organ dysfunction. Targeting accumulation and formation can rescue cells from stress-induced cell death and organ dysfunction.

A chronic inflammatory state as developed after solid organ transplantation impairs early recovery of kidney function and prolongs delayed graft function after transplantation. Excess accumulation of glucose and polyol pathway metabolites in tissues leads to the formation, and induction of hypoxia-inducible factor 1 alpha and begins from this cytokine production. The possible pathogenic involvement of the cytosolic and mitochondrial glycerol-3-phosphate dehydrogenases in this inflammatory response suggests that the blockade of these two enzymes are useful treatment approach in

transplantation. Several drugs are in development for clinical application. Overproduction can also lead to p53-dependent programmed cell death via central ataxia-telangiectasia mutated and Chk2-dependent signaling and results in chronic graft dysfunction and malfunction. Inhibition of p53 can reduce programmed cell death and inflammation in transplant rejection and may be beneficial for future kidney transplant patients. However, clinical translation of these novel approaches has yet to be done. Thus, further experimental validation of targets that are novel in the field of CKD therapy will be needed before translation to clinical application.

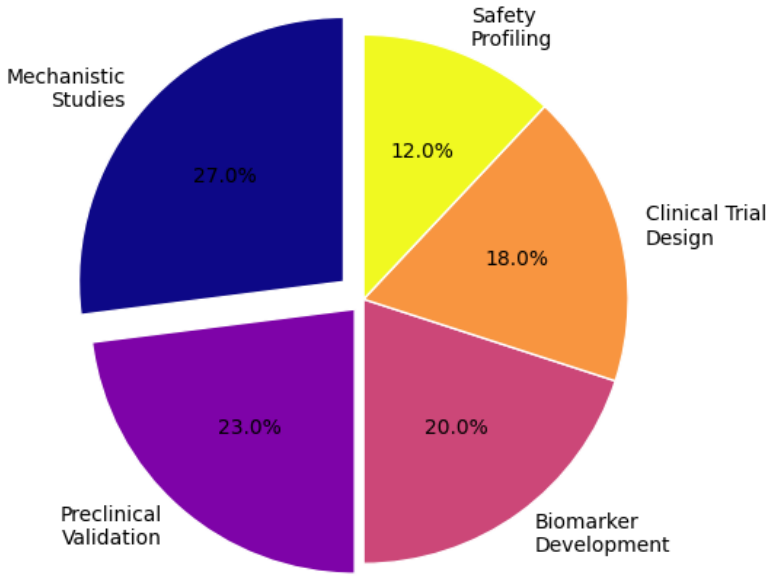

Fig 3 . 3 : Key Research Focus Areas

3.9. Conclusion

Chronic kidney disease (CKD) represents an increasingly prevalent medical condition predicted to affect 14% of the world's population within the next 10 years and is currently the 14th leading cause of mortality. In light of screening recommendations, the majority of CKD patients will not incur end-stage kidney disease necessitating dialysis or kidney transplant in their lifetime. However, cardiovascular events largely driven by coronary artery disease are the most common cause of death overall in CKD patients and within those at earlier stages of the disease. Heavily burdened by heart failure, diabetes, and limited life expectancy, there remains a heightened need for treatment and screening efforts in this population. Recently, three SGLT2 inhibitors for patients with renal indication, empagliflozin, canagliflozin, and dapagliflozin, have been approved, adding to the medical arsenal for CKD management.

As the understanding of the pathophysiological mechanisms underlying renal injury continues to progress, novel therapeutics designed to target key pathways using innovative strategies are expected to improve the management of kidney disease and lower the incidence of cardiocontractility and sudden cardiac death. The present work emphasizes the growing knowledge that cardiac disease and CKD coexist in a bidirectional manner, strengthening the importance of multi-organ system research. Collaborative prevention and treatment modalities designed to benefit the ailing heart while simultaneously protecting kidney function are paramount in the future. As this thin line thickens, educating the non-specialist is key in ameliorating clinical outcomes. For the general population, lowering the incidence of heart and kidney disease focuses heavily on dietary and lifestyle modification. For those at higher risk, it is important that physicians work to educate patients on the severity of both conditions to encourage compliance. Preventive measures warrant the use of agents that have demonstrated favorable renal outcomes including SGLT2 inhibitors.

3.9.1. Future Directions and Implications for Kidney Disease Management

Technological advancements in multiple fields have opened new avenues for therapeutic development and application in all areas of kidney disease. As described throughout this text, ongoing research in kidney disease discovery, basic science, diagnostic, and mutant-phenotype rescue advancements are poised to change the way we screen and diagnose inherited kidney diseases, reduce the impact that known disease alleles have on kidney function, and what conditions or factors result in patients — both those with genetic disease-causing alleles and those at risk of developing age-related kidney diseases — developing relevant kidney dysfunction. Many questions remain to be answered, particularly: What are the normal kidney functions that age-related diseases impact? How might gene editing alleviate the effects of age-related decline in kidney function that varies from patient to patient and what is the best timing for potential intervention, if any? How can innate and adaptive immune responses to injury be mapped together to provide targeted interventions — both physical, such as implantable bioengineered organs or rehabilitation strategies to improve fitness and immune proper response, and chemical, such as antibody or small molecule interventions — against very precise elements of age-related kidney dysfunction? What role for co-existing conditions, such as hypertension, diabetes, and neurodegenerative disorders, play in the relative decline of any specific individual's kidney function? We hope that this collection of reviews will give the reader a snapshot of the current state of the field and inspire greater collaboration between basic scientists, diagnostic laboratories, and any healthcare provider in the kidney disease management space.

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