REVIEW ARTICLE

Changes in Renal Disease: A Vascular Perspective

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Abstract

This paper aims to review and discuss important advances in renal medicine that have occurred in the last 50 years. This has shaped the way that patients with end-stage renal failure (ESRF) are managed, with emphasis on renal replacement therapy (RRT), and has resulted in wide-reaching improvements in each patient's journey. These changes have been summarized in an easily accessible form and addressed from the perspective of the United Kingdom.

Keywords: Renal disease, Renal replacement therapy, Vascular access.

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Introduction

Renal disease is estimated to affect 6.1% of the UK population aged over 16 years.[1] The most recent renal registry report shows a continued rise in the incidence of renal replacement therapy (RRT) across the UK.[2] Over the last 50 years, huge advances have been made in managing renal disease. This has been instrumental in the management of these patients who historically have a poor prognosis.[3] The influences of calculating estimated glomerular filtration rate (eGFR), classifying renal failure and the introduction of population screening, have impacted how disease is detected and investigated, a key step in its effective management. From a surgical perspective, the guidance on vascular access was also developed, providing clear and evidence-based advice. This has encouraged a surge in both the recognition of chronic kidney disease (CKD) and improvements in primary and secondary care management.

The aim of this study was to review the changes in clinical practice that have occurred in the management of the patient with CKD, from the perspective of a vascular surgeon, and present them in an easily accessible format. Specifically, the review will provide a summary of the key changes in the diagnosis, monitoring, and management of CKD.

Materials and Methods

A literature search was performed using the terms "chronic kidney disease" OR "end-stage renal failure (ESRF)" AND "diagnosis" OR "treatment" OR "management." Articles written in the English language and published in the last 50 years were included for review. Articles based on adults (ages >18 years) only were included and both Medline and Embase were searched. The reference lists of included articles were also searched for further articles worthy of inclusion. The following review is based on the results of this literature review together with the authors' personal knowledge on this subject area.

The databases were accessed on August 7, 2018, which resulted in 481 papers. In all, 417 articles were excluded based on the abstract and title alone. The remaining 64 were formally reviewed and a further 31 papers were excluded on this basis, leaving a total of 33 papers for inclusion.

Results

The results of the literature search can largely be grouped into three key areas, namely, those affecting (1) the diagnosis, (2) the investigation, and (3) the treatment of patients with CKD. Within each subsection, data are presented chronologically where possible.

The introduction of the National Kidney Foundation (NKF) guidelines consolidated all of these areas into a single set of guidelines, which form the foundation of CKD management throughout the United Kingdom and National Health Service (NHS).

The NKF Guidelines

When we consider vascular access in renal disease, one of the key advances in the last quarter century is the introduction of the NKF's Kidney Disease Outcomes Quality Initiative (NKF DOQI), a set of guidelines covering almost all aspects of renal disease. Perhaps most importantly for this review, they have also published definitive and thorough guidance regarding vascular access. Along with these guidelines, the UK Renal Association have provided national audit aims for both the incidence and prevalence of "permanent" access. In these guidelines, arteriovenous (AV) fistulas, along with AV grafts and peritoneal dialysis (PD) catheters, are considered as a permanent form of access.[4] Since the introduction of the NKF DOQI guidelines in 1997, there has been a shift toward promoting the use of AV fistulas over other forms of renal vascular access. These guidelines advise clinicians that AV fistula access should be planned and put in place in advance of patients being commenced on hemodialysis (HD) and also provide guidance on AV fistula maintenance.[5,6]

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Changes in the Diagnosis of Patients with CKD

Estimated GFR

Kidney function is determined by GFR. The introduction of eGFR was a significant advancement on the previously used creatinine clearance method of measuring GFR principally owing to its simplicity. Unlike creatinine clearance measurements of GFR which require both the patient's age and weight, per the original description by Cockcroft and Gault in 1976 (see Formula 1A), eGFR measurements are based on the serum creatinine and patient's age alone (as well as the patient's gender and ethnicity) (Formula 1A). Furthermore, eGFR measurements negate the need for 24 hours of urine collection.[7]

- Formula 1A. The Cockcroft–Gault equation to calculate creatinine clearance was adapted from (7)

$$\text{Creatinine clearance (mL/minute)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{815 \times \text{serum creatinine (mmol/L)}}$$

- Formula 1B. The modification of diet in renal disease (MDRD) equation for GFR was adapted from (7). SCR, serum creatinine

$$\text{GFR} = 186 \times (\text{SCR} \div 88.4) - 1.154 \times \text{age} - 0.203$$

(Female : multiply result by **0**.742; African - Caribbean's : multiply result by 1.212)
Note : ethnicity factors have not yet been calculated for other ethnic groups.

The ability to estimate the GFR from a simple blood test has enabled more rapid measurement and therefore wider diagnosis of derangement in renal function. Furthermore, eGFR measurements are used to grade the severity of CKD: stage 1 represented by an eGFR > 90 mL/minute/1.73 m^2, stage 2 by an eGFR of 60 to 89, stage 3a by an eGFR of 45 to 59, stage 3b by an eGFR 30 to 44, stage 4 by an eGFR of 15 to 29, and stage 5 (end stage) by an eGFR <15mL/minute/1.73 m^2.[8] Important to note is that using eGFR to diagnose CKD stage 1 or 2 requires another feature of CKD, such as small kidneys on imaging, to also be present.[9] There are a few limitations to the widespread use of eGFR over creatinine clearance (acute changes in renal function, consumption of a high creatinine/protein diet, extreme body size, and presence of severe liver disease); however, since its introduction nearly 20 years ago, its measurement has become part of a routine clinical practice and is now often provided as part of the urea and electrolyte profile in most UK centers.[10,11]

Population Screening and Risk Factor Modification

In 2009, a further step was taken in order to identify those patients at risk of developing CKD. The NHS Health Check, run in general practice, allows patients to present to their general practitioner (GP) once every 5 years between the ages of 40 years and 74 years. The main aim of this checkup is to evaluate each patient's cardiovascular risk and therefore reduce the associated morbidity. As part of this assessment, those who are identified at high risk of cardiovascular disease will have to be screened for diabetes and CKD. Again, this aims to pick those patients who are at risk of occult or early stage renal disease.[12]

Currently there is no national screening program specifically for CKD in the UK.[13] In determining whether to offer screening for a particular disease, the UK National Screening Committee uses the principles commonly known as Wilson's criteria to evaluate whether a proposed screening program is beneficial for a specific population.[13]

These principles include the following:

- There is a defined target population
- Intervening early improves patient outcome
- The test is safe and feasible in the population and healthcare system
- There is an effective treatment
- There is a cost–benefit in identifying patients early

They must then weigh up the risks and benefits of the screening and treatment of disease and evaluate whether such a program would be cost-effective.[14]

The NHS Health Check, though not specifically directed at identifying renal disease, does screen for many of the known cardiovascular risk factors. Cardiovascular disease and CKD are strongly linked, a phenomenon that is becoming increasingly supported by the literature. The principal mechanism by which these two entities are linked is blood pressure (BP) management.[15,16] The importance of optimum BP control in patients with CKD is now well recognized and the methods to do so remain an active area of medical research.[16,17] The effect of HD or PD on total body fluid volume as well as the interaction on serum electrolytes must be considered. Guidelines across the world (including the UK, France, and the USA) advocate varied targets for BP that are also dependent on comorbidities such as diabetes mellitus. The European guidelines give a variety of options for first line treatments, whereas the UK guidelines provide much more specific guidelines based on age and race.[18,19] The general consensus, however, is that medical management of patients with CKD should take into account the effect of RRT, comorbidities, and any other factors which may affect their BP, e.g., pregnancy.[16–19]

Hypertension and ESRF have a well-established relationship with a demonstrable inverse relationship between falling eGFR and cardiovascular risk. Together with his, microalbuminuria is a consistent sign of those patients with CKD at increased cardiovascular risk. It was found that those patients with microalbuminuria, there was an increased incidence of cardiovascular events and may be an early clinical indicator of declining renal function. The exact mechanism for this is not yet known.[20] In normotensive patients with microalbuminuria and type 1 diabetes mellitus, evidence shows angiotensin-converting enzyme inhibitors (ACEIs) can slow the descent into CKD; whereas those with type 2 diabetes mellitus, ACEI or angiotensin-II type 1 receptor antagonists may be used for the same effect.[21,22]

Management of dyslipidemia is also a key part of CKD management. The use of statins to reduce serum cholesterol levels is again well established in the literature, however, there is evidence that the use of statins in dialysis patients is of negligible benefit.[23] Therefore, clear and specific guidance as to when and what should be used to manage dyslipidemia in patients with CKD of all stages has not yet been defined.[23–25]

An underappreciated risk factor for renal disease is smoking. In the last 20 years, the link between smoking and CKD has been established with evidence suggesting that cigarette smoking increases the rate of decline in renal function nearly twofold. Education and smoking cessation advice now play an integral role in renal patient management.[26]

Changes in the Investigation of Patients with CKD

In many regards, the investigation of CKD may well overlap with its diagnosis. In addition, the well-recognized complications of CKD

are also preempted and steps taken to prevent their manifestation. However, few distinct areas are discussed subsequently.

Classification of CKD

In 2002, one of the most significant developments in renal disease management occurred when the NKF produced guidelines for the classification on CKD based on the estimated GFR. This was set out with the aim of improving how renal disease is discussed between clinicians, patients, families, and other professionals. It was also assumed that providing a framework for this group of conditions would help to improve estimations of the magnitude of the problem and identify those patients in the early stages of disease.[8]

Prior to the publication of this guidance, renal disease was categorized by pathology, despite most complications remaining almost independent of the cause. It was also noted that many patients would present already in ESRF which is classed as an eGFR <15 mL/minute/1.73 m^2. Classifications with regard to renal failure have not only improved our awareness of the extent of the problem but also stimulated further study into the complications it produces and therefore how to minimize and manage these comorbidities.[8,27]

The stages of renal disease are outlined earlier in this report.

The propagation of research from this one piece of guidance has led to a further revision of this classification and guidelines on the clinical management of patients with CKD. These recommendations include tight regulation of BP, safeguarding against AKI, monitoring hemoglobin, and tight glycemic control in diabetic patients.[28]

Changes in the Treatment of Patients with CKD

The treatment of patients with CKD encompasses a wide range of pathophysiologies. As discussed, clinicians must preempt the development of comorbidities, manage them in a timely manner as well as reduce the overall cardiovascular risk in this patient population. The management of renal dysfunction itself largely varies according to the stage of dysfunction; however, from the vascular surgeon's perspective, a number of advancements have been made in the care of patients with pre-ESRF and ESRF requiring RRT.

Access Coordinators

The role of the access coordinator is not necessarily a new idea, but this role has gained traction in the last 10 years, driven by the increasingly recognized economic and clinical benefits of having a specialized healthcare professional employed specifically to help plan vascular access, preserve venous real estate, and monitor and maintain this vascular access.[29]

Vascular access coordinators also serve as a vital link between the medical and surgical teams in those centers where it is the surgeons who create more definitive access in the form of AV fistulae and surgically placed Tenckhoff catheters.[29]

AV Grafts

In 2016, a systematic review of 200 studies by Almasri et al. concluded that autogenous fistulas provided the best patency rates at 2 years, being favored over both AV grafts and central venous catheters. This was a landmark study since it provided unequivocal high-quality evidence of the benefits of AV fistulas over all other forms of vascular access in ESRF patients.[30]

Basilic Vein Transposition

As the evidence that autogenous AV fistulas were superior to grafts and lines gained momentum, an increasing number of studies began to look at the option of using the basilic vein as an alternative to forearm fistulas.[30] This involves mobilizing the basilic vein within the upper arm, anastomosing it to the brachial artery and tunneling it in a more superficial plane in order to provide its use as an AV fistula. This can be done as a one- or two-stage procedure.[31–33]

As the evidence emerged that these fistulas were able to provide acceptable patency rates (68% primary patency at 16 ± 7 months), the advantages of using these fistulas also became clear.[30,31,34–36] They provide a further option within the ipsilateral (usually nondominant) arm before needing to look for suitable vein in the contralateral (usually dominant) arm.[32]

Unfortunately, basilic vein transposition fistulas have shown poor maturation rates in the population over 60 years of age. They should therefore be used with caution in this patient demographic and not until proper venous duplex assessment has excluded all other ipsilateral upper limb options.[36]

Needling Techniques

Not only have the NKF guidelines changed how vascular access is created in CKD patients, but they have also given an insight into the techniques used to cannulate AV fistulas.[37] Two main techniques are recognized: the buttonhole technique and the rope ladder technique.

The rope ladder technique is the traditional technique. This describes when both cannula sites are rotated moving up and down the length of the fistula but, carries concerns that it may lead to whole vessel stenosis.[38,39] However, there it is thought to have a reduced risk of infection and can be used in patients with PTFE grafts where the buttonhole technique would lead to problems with bleeding.[38,40]

The buttonhole technique was first described in 1977 in Poland by Twardoski. This method involves repeatedly using the same puncture sites for both needles, creating an epithelialized tract for their passage. The benefits of this technique include less discomfort for the patient, a reduced failure rate, and no increase or even a reduced number of complications from needling.[40] However, this technique is associated with a significant risk of aneurysm or stenosis development within the fistula.[41]

Peritoneal Dialysis

Peritoneal dialysis is now a well-established and economical method of providing RRT. It has a number of key advantages that are likely to have contributed to its growing popularity in the developing countries; however, it still has low uptake in many areas of the developed world.[42] Not only does PD provide freedom from regular hospital attendance for patients compared with HD, recent studies have also shown that patient outcomes are comparable to patients on other forms of RRT.[43]

The increasing prevalence of PD in developing countries provides an economical and accessible treatment of patients who suffer ESRF and acute kidney injury who would otherwise have suffered poor prognosis. This has allowed for improvement in worldwide treatment of patients with renal disease.[42]

Hemodialysis at Home

Over the last 10 years, the provision of HD in the patient's own home has become very topical within the HD community. Performing HD

at home requires a complex adaptation to the patients home, often requiring a large team to assess and coordinate therapy; however, in an era when patient autonomy and independence are key priorities, such a therapy can be life changing.[44]

Clinically, one particular study was able to show home HD provided an improved patient survival benefit when compared with PD (HR 0.61, 95% CI 0.40–0.93).[45] Not only this, but it is demonstrated that home HD can reduce the cost burden of dialysis on the NHS is reduced, though satellite HD was found to be cheaper than home HD (£1660 and £1490 cheaper at 5 and 10 years), as the effectiveness of home HD meant the cost per quality adjusted life year was superior in home HD. Both modalities were more cost-effective than hospital-led HD.[46] However, there are many clinicians who hold apprehension about the introduction of home HD, which is noticeably reduced in those clinicians who have firsthand experience of home HD.[47]

Perioperative Management

As patients with established renal failure continue to live longer, they are requiring operative intervention for numerous indications, including vascular access and transplantation, at an increasingly senior age. As such, the provision of anesthesia to these patients is becoming increasingly complex. The altered physiology seen in CKD patients mandates that the mechanism of action of many routine anesthetic agents including their excretion pathways be considered carefully. For example, the action of bupivacaine for local anesthetic may be propagated by metabolic acidosis, whereas the action of propofol is unchanged in renal disease. Furthermore, the increased risks of both surgery and anesthesia in patients with CKD should be weighed against the clinical benefit of any potential operation.[48]

Anemia in CKD

Anemia is a well-established complication of CKD. Chronic anemia not only carries a risk to the patient physiologically but can cause debilitating symptoms such as shortness of breath, cardiac failure, and fatigue. Erythropoietin-stimulating agents, such as Aranesp® or Epogen®, stimulate the bone marrow to increase the production of red blood cells and are now routinely used as a treatment for anemia in CKD patients. Good evidence shows that their use is associated with a decreased transfusion requirement in CKD patients; however, a benefit in terms of mortality is yet to be shown.[49,50]

Multidisciplinary Team

Multidisciplinary working has become more prevalent among clinicians from all specialties and the management of the CKD patient is no exception to this. For the renal patients, this involves close working with renal physicians, transplant physicians, transplant surgeons, vascular surgeons, interventional radiologists, access coordinators, dialysis nurses, and technicians just to name a few. Systematic reviews have shown that taking a multidisciplinary approach while managing patients with CKD not only prolongs time to dialysis but also reduces all-cause mortality. While this evidence is limited and further work is to be done as to exactly who should be included in these multidisciplinary discussions, which is good evidence to support their continuation as a key element to the CKD patient's care.[51,52]

Physical Activity

Evidence is emerging to strengthen the argument that more should be done to encourage CKD patients to increase or maintain their levels of physical activity. Now a strong established association can be observed between low levels of physical activity and increased morbidity and even mortality.[53] This has led to increasing emphasis on education about exercise and its role in the management of these patients.[53]

Interventional Radiology and Nephrology

Interventional nephrology with radiology represents a specialty that has emerged over the last few decades with a vital role in the provision and salvage of vascular access as well as PD catheters among renal patients. Since their establishment as a defined specialty, evidence has cemented their role as an effective and cost-effective addition to the vascular access team.[54,55]

Conclusion

This review has identified a number of areas in which the management of patients with CKD has advanced over the last five decades. Technological advancements have not only improved the overall patient care but also been particularly useful for clinicians, both medical and surgical, treating these patients. The introduction of national guidelines and frameworks for managing patients with CKD support these technological advancements by providing minimum acceptable standards of care. Together, these changes serve to drive the quality initiative among this comorbid group of patients who historically have had poor outcomes.

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