Diabetic Kidney Disease

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Epidemiology

Chronic kidney disease (CKD) is growing at an epidemic rate throughout the world. The major causes are diabetes and hypertension. CKD from both diabetes and hypertension have been increasing for over 20 years, but the increase in diabetic kidney disease (DKD) has been significantly more rapid [1]. The best way to appreciate the epidemic rise is to examine the changes in the numbers of people with end-stage kidney disease (ESKD). The reasons for this are as follows. Chronic kidney disease (CKD) is defined as an estimated glomerular filtration rate (eGFR – as calculated using one of the eGFR formulae) of <60 ml/min and/or an increase in the urine albumin/creatinine ratio of 30 mg/g [1]. By this definition, about 13.6% of the US population has CKD. There is a legitimate argument as to whether everyone at these levels has CKD as, for example, eGFR declines with age. At birth, eGFR ranges from 110 to 140 ml/min. Normal rate of decline is as high as 1 ml/min/year. Hence many people 65 and over may have an eGFR of <60 ml/min/1.73m^2 as a consequence of normal aging. Therefore using the CKD definition, the number of people older than 65 with CKD may be an overestimate. But there is no controversy as to the numbers of people with ESKD (includes all dialysis and transplant) patients. In 1978, there were 41,000 people with ESKD and 307,000 in 1996. By 2015, 700,000 people had ESKD in the United States [1]. This is a 17-fold rise in ESKD patients since 1978. Type 2 diabetes mellitus (DM) is the main cause of ESKD (type 2 DM comprises >90% of all DM cases). In 1996, there were about 99,000 cases of ESKD ascribed to DM, and as of 2015, it was 267, 956 cases in 2015. Forty-five percent of the new cases in 2013 were due to DM, and 28% were due to hypertension.

This dramatic increase in ESKD is especially surprising as it is occurring despite the following facts: (1) Many studies have shown that it is more likely that a person with DM and CKD will die from a cardiovascular event rather than progress to ESKD. For example, decreasing eGFR and/or increasing urine albumin level led to a highly significant increased risk for death from a cardiovascular event [2]. Moreover an important study from 2014 determined that death rates in type 2 DM patients in excess of the age-matched non-DM population were associated with CKD [3]. By analyzing the NHANES database, these researchers found that the presence of albuminuria (>30 mg/g) or a decrease in eGFR led to increased death rates as compared to people with type 2 DM and no evidence of CKD. Furthermore,

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the combination of increased urine albumin and decreased eGFR was associated with the highest death rates. Of most importance though was that those with type 2 DM and no signs of CKD had death rates similar to the age-matched population who did not have type 2 DM. This finding suggested that all excess deaths in type 2 DM patients were associated with the presence of CKD. (2) The death rates for people on dialysis in the United States are as high as 21% per year [4]. Hence when considering that most people with CKD will die before reaching ESKD and that the yearly death rates for people on dialysis are quite high, the CKD number must be in the millions to maintain the high (and increasing) numbers of people with ESKD. Of note, in addition to the personal costs of increased morbidity and mortality, there are tremendous financial costs. In 2013, the US government spent about 6% of the healthcare budget (31 billion dollars) on ESKD (which is about 0.2% of the population) [1].

This increase in CKD and ESKD is occurring worldwide. China and India have the greatest number of cases, and the rise in both countries is continuing. Interestingly, not all ethnic and racial groups share the same risk. According to the data from the United States, African-Americans, Hispanics, American Indians, and Asians have significantly higher rates of CKD and ESKD [1]. Thus, physicians need to be even more vigilant when caring for people from these ethnic and racial groups.

Pathophysiology

There is no definitive explanation as to why people with diabetes develop DKD. Interestingly most people with DM do not develop DKD. Many studies estimate that the percentage of people who develop DKD vary from 20% to 40% depending on whether one has type 1 or type 2 DM. And of those who develop DKD – diagnosed clinically primarily as a combination of eGFR of <60 ml/min/1.73m^2 and/or an increase in urine albumin level that is associated with a bland urine sediment – most will not progress to ESKD. Indeed major research efforts are focused on determining who is at risk to develop DKD and who is going to progress to ESKD [5–7]. A number of potential markers have been found including the tumor necrosis factor alpha receptor and kidney injury molecule 1 (KIM-1). To date, it is not clear whether any of these markers will offer more clinical utility than following changes in eGFR and the urine albumin level. They may become particularly useful for research studies since it is very challenging to do clinical DKD studies. This is because only a subset of DM patients will ever develop DKD and it takes years to develop DKD. Knowing who will develop DKD and knowing who will progress to ESKD will make it possible to use fewer patients in clinical studies for shorter periods of time, greatly increasing research productivity.

There are a number of mechanisms that likely play a role in the development and progression of DKD. The exact importance of each of these mechanisms is unclear. A major reason for all of this uncertainty is that the animal models of human DKD are generally not reflective of human DKD and it is difficult to do pathophysiological studies in humans as development and progression of DKD occur over many years. In this section, some of the relevant mechanisms will be discussed.

At the molecular and cellular level, a number of deleterious pathways have been implicated from cell culture and animal studies. The principal inciting cause for these pathways is elevated glucose. For all mechanisms described, drugs have been developed or are being developed:

1. Reactive oxygen species (ROS). ROS have been shown to be elevated in both animals and humans [8–10]. In many studies the elevation of ROS has been shown to be due to a combination of increased ROS production and decreased antioxidant function [8, 10]. Increased ROS leads to oxidation of lipids, proteins, and carbohydrates and deleterious cellular changes that may lead to cellular dysfunction and cell death. To date, antioxidant treatment has not been effective. This is likely due to the lack of specificity of current antioxidant treatments. Drug development aimed at targeting specific enzymes or pathways known to play a role in

the development of ROS is either in development or in clinical trials and will hopefully have significant therapeutic benefits.

2. Transforming growth factor β (TGFβ). TGFβ has a number of normal as well as abnormal functions [11]. In DKD, many studies have shown that increased TGFβ plays a significant role in the fibrosis seen in DKD and in a process called endothelial to mesenchymal transformation that is also part of DKD pathophysiology. There are no specific inhibitors of TGFβ, but studies in animals have demonstrated that blocking TGFβ (e.g., with an antibody) prevents the development of DKD. There have been small studies using a non-specific anti-fibrosis medication (pirfenidone) that have appeared intriguing but to date have not been shown to be useful [12]. There are ongoing efforts to find drugs that specifically block TGFβ.
3. Protein kinase C β (PKCβ). There is a large family of PKC proteins [13]. Although a variety of isoforms have been implicated in the pathogenesis of DKD, in particular, PKCβ has been seen shown to be increased in DKD leading to multiple cellular defects [13]. A specific inhibitor of PKCβ has been developed and studied in human clinical trials [14]. No clear benefit for DKD was observed in these studies.
4. Advanced glycation end products (AGEs). AGEs are proteins that are glycated through nonenzymatic processes [15, 16]. These proteins accumulate as blood sugar levels rise and lead to altered cell membranes, increased ROS, and other pathophysiological processes [15, 16]. Unfortunately, to date trials of drugs designed to prevent AGE formation and to prevent or treat DKD have not been successful in humans [16].

There are a number of other possible mechanisms [17, 18]. To date, drugs targeting these pathways have either not been effective or not yet tried in humans. Some have speculated that perhaps a combination pill or medication cocktail that consists of drugs against all or a combination of these targets would be effective. Others speculate that some of these mechanisms are relevant for development but not progression of DKD such that particular drugs may have not been given at their optimal effective time. Whatever the role these play, more work is needed to define importance, timing, and how these mechanisms interact with each other so that better treatments are developed and delivered at the optimal time.

In addition to the cellular pathophysiology, there are very important hemodynamic mechanisms. First, systemic high blood pressure is a clear factor both in the development and progression of DKD [19–22]. As vascular damage occurs in DKD (due to the effects of hyperglycemia on endothelial cells), hypertension likely leads to more damage of already susceptible endothelial cells leading to loss of nephrons. Many studies have demonstrated that control of hypertension is important for both prevention and progression of DKD [19–22]. Second, glomerular hyperfiltration has been shown to play a likely central role in the progression of DKD [23]. Glomerular hyperfiltration, which was mechanistically delineated using micropuncture studies in rats, is manifested as increased GFR [24]. Treating glomerular hyperfiltration in animal models of DKD has been demonstrated to prevent development and slow progression of DKD [25]. There are two approaches to decreasing glomerular hyperfiltration in animals, using medications that block the action of angiotensin II and low-protein diets [26]. Both approaches appear to work by decreasing glomerular hyperfiltration. Angiotensin II regulates glomerular filtration by causing vasoconstriction of the efferent arteriole and because of the increased resistance to outflow from the glomerulus, increased glomerular pressures, and, as a result, increased GFR [26]. Hence blocking the actions of angiotensin II leads to lower glomerular pressures. Low-protein diets also lower glomerular hyperfiltration via changes in renal blood flow. These diets are effective treatment in animals with DKD. On the other hand, high-protein diets in animals greatly accelerate DKD. In humans drugs that decrease the actions (via decreasing production or blocking action) of angiotensin II appear to be most beneficial for slowing progression in people with increased

albumin levels in the urine but do not appear to be beneficial for preventing the development of DKD. In humans the benefit of a low protein diet is much less clear and most nephrologists are not recommending a low protein diet [27–31]. But there may well be a risk for progression of DKD from high-protein diets in humans.

Natural History

Natural history studies for DKD are difficult for already mentioned reasons: only a subset of DM patients will develop DKD, and it takes years to develop DKD (typically 5–15 years after the onset of type 1 diabetes). It is even more difficult to study the natural history of DKD in type 2 DM patients as the typical person with type 2 DM has it for years before it is diagnosed. Nevertheless, the classic view of the natural history of DKD is as follows [32]. The earliest sign is glomerular hyperfiltration (eGFR >140 ml/min/1.73m^2), followed by an elevated urine albumin level, followed by a progressive increase in the urine albumin level, and followed by a progressive decline in GFR. It is clear now that even though this construct does fit a subset of patients with DKD (at least in people with DKD due to type 1 DM), there are many variations for the majority of patients whether they have type 1 or type 2 DM [32]. For example, the decline in eGFR that has been thought to occur in following the development of increased urine albumin level does not always occur. Indeed, there are a variety of patterns that occur after developing an increased urine albumin level. Some people revert to normal urine albumin levels, some stay at the same level, and some have increases in the urine albumin level [5, 33–35]. And the association of GFR decline with albuminuria is variable as well. GFR may stay stable or decline completely independent of the urine albumin level [5, 33–35]. In general, the higher the urine albumin level, the more likely the GFR will decrease. And the best current marker of future decline in GFR is a continuously rising urine albumin level. Of note though GFR may decline even in the absence of elevated urine albumin [5, 33–35]. Hence the development of increased urine albumin should raise the concern that the GFR might decline in the future, but it is not definite that GFR will decline. Also the absence of an increase in urine albumin should not lead to complacency that there is no DKD in a particular patient. One should be following eGFR as well as the urine albumin level. Hence health-care professionals should be vigilant in searching for DKD and not assume that there is a clear pattern that any particular patient will follow.

Diagnosis

Diagnosis of DKD is done by measuring the urine albumin levels and by measuring the serum creatinine and calculating eGFR (the formulae are accurate within 10–20% of true GFR). The diagnostic signs for DKD in a person with DM are an elevated urine albumin and/or decreased eGFR associated with a relatively bland urinalysis (Table 2.1). The urine albumin level should be measured at least once per year using the albumin/creatinine ratio preferably by collecting a spot urine and measuring the ratio of albumin/creatinine as this method has been shown to closely reflect the

Table 2.1 Diagnosis of diabetic kidney disease

1. Either increased urine albumin/creatinine ratio (>30 mg/g) or decreased eGFR (<60 ml/min/1.73m^2) in a person with diabetes
2. Relatively unremarkable urine sediment analysis. None to few red blood cells or white blood cells
3. Pathology: increased glomerular basement membrane thickening, tubular basement membrane thickening, and mesangial expansion
4. Reasons to consider kidney diseases other than DKD:
   (a) Development of kidney disease in a person with type 1 DM of less than 5-year duration
   (b) Active urinary sediment (e.g., many white or red blood cells or many casts)
   (c) Lack of diabetic retinopathy especially in a person with type 1 DM
   (d) Rapidly declining eGFR or a change in pattern from a slow rate of decline to a rapid rate of decline in eGFR
   (e) Normal urine albumin level in a person with decreased eGFR
   (f) Long-term well-controlled blood sugar

24-hour urine albumin level [36]. Normal is <30 mg/g. If the level is elevated, it should be repeated in about 1 month as there are reasons for transient elevations such as exercise, pregnancy, urinary tract infection, congestive heart failure, sudden rise in blood pressure, and high blood sugar (Table 2.2). It is important to remember that measuring urine albumin level by urine dipstick is not an adequate screening test as it is a qualitative (not quantitative) test, and it is not sensitive enough to detect a low-level increase in the urine albumin level. One should always use the urine albumin/creatinine ratio test. It is also critical to calculate eGFR using one of the GFR formulae. Of note the Chronic Kidney Disease Epidemiology Collaboration eGFR formula (CKD-EPI) has been shown to predict cardiovascular and renal outcomes better than other formulae [37].

It is important to remember that just because a person has DM and kidney disease does not mean that they have diabetic kidney disease (Table 2.1). Reasons to consider other causes of kidney disease in diabetic patients include:

1. Short duration of DM. Kidney disease in a person with type 1 DM of less than 5 years duration.
2. No diabetic retinopathy. In general (especially in people with type 1 diabetes), diabetic retinopathy is diagnosed prior to the development of DKD. Although there are many patients with DKD and no retinopathy, it should raise a concern for another kidney disease if there is no retinopathy.
3. Active urinary sediment. Usually DKD has a bland urinary sediment or just a few red blood cells. If there are many red blood cells, white blood cells, or other substances in the urine, there should be concern that there is another cause of the kidney disease.
4. Rapidly declining eGFR or rapidly rising urine albumin level. The usual rate of decline in eGFR for DKD patients is 2–5 ml/min/year, so if there is a very rapid rate, there may be another etiology of kidney disease. Similarly, urine albumin levels usually rise gradually in DKD patients and do not get to very high levels.
5. Normal urine albumin level. Most patients with DKD have increased urine albumin level. But, as previously noted, this is not always seen, and people may have very advanced disease with low or normal urine albumin levels [33, 38].
6. Excellent blood sugar control. If a DM patient has had long-term excellent blood sugar control (hemoglobin A1c of 6–8%), then that should raise the concern that there is another cause of kidney disease.

Table 2.2 Screening and monitoring of DKD

1. Measurement of urine albumin level with spot urine albumin/creatinine ratio (normal <30 mg/g) at least yearly for screening. Repeat 1 month later if abnormal. Reasons for transient change in urine albumin level:
(a) Strenuous exercise
(b) Pregnancy
(c) Urinary tract infection
(d) Congestive heart failure
(e) Rapid elevation in blood pressure
(f) Hyperglycemia
2. At least yearly measurement of serum creatinine and calculation of eGFR using preferably the CKD-EPI equation to screen for DKD
3. Monitoring of DKD includes checking the urine albumin/creatinine ratio and calculating eGFR at each visit

When should a patient see a nephrologist for diagnosis and possible kidney biopsy? A referral to a nephrologist for diagnosis need only be done if the primary care doctor or endocrinologist are concerned that a diagnosis other than DKD is responsible for the kidney disease. Hence there needs to be a clear understanding of the signs as noted above that would alert the physician to these other causes. The nephrologist would likely do a detailed history, urinary sediment analysis, possibly a kidney ultrasound, and possibly a number of serologic and other lab tests. The nephrologist will also consider whether a kidney biopsy should be done. Hypertension is the most common cause of kidney disease other than diabetes in people with DM, but studies have shown that all types of kidney disease have been diagnosed in people with DM [39]. Classic findings on biopsy for DKD are glomerular basement membrane thickening, mesangial expansion, and tubular basement membrane thickening followed

by glomerulosclerosis and tubular-interstitial fibrosis [40].

Prevention and Treatment

Proven treatments for primary prevention of DKD are glucose control and blood pressure control (Table 2.3). Many studies have clearly demonstrated a lower incidence of the development of DKD in people with better glucose control. The Diabetes Control and Complications Trial (DCCT) study [41] followed 1441 patients for a mean of 6.5 years who were assigned to conventional or intensive treatment. Conventionally treated people had an average hemoglobin A1c of 9.1%, and intensively treated people had an average hemoglobin A1c of 7.2%. Intensive treatment decreased the development of microalbuminuria by 39%. The original cohort has been followed since then, and the 25-year follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study was reported recently [42]. After the original 6.5 years, both groups were treated the same with an average hemoglobin A1c of 7.9%. Thus in the EDIC study, the only difference between the two groups occurred during the first 6.5 years. The original intensively treated group had 50% less development of microalbuminuria and 50% less development of an eGFR of <60 ml/min/1.73m^2 as compared to the original conventional group 25 years later. Hence tight control of blood glucose as early as possible has long-term benefits for the prevention of DKD in people with type 1 DM. Similar findings have been found for people with type 2 DM in studies such as the United Kingdom Prospective of Diabetes Study (UKPDS) [43].

Table 2.3 Prevention and treatment of diabetic kidney disease

1. Prevention
(a) Blood glucose control – aim for a hemoglobin A1c of <7%
(b) Blood pressure control – aim for 130/80
(c) No clear unique role for RAAS inhibitors
2. Treatment
(a) Blood glucose control – goal for hemoglobin A1c of 7%
(b) Blood pressure control – goal is 130/80
(c) Use RAAS inhibitors if urine albumin level is elevated. Goal is to lower urine albumin level to at least <300 mg/g
(d) Consider using combination of ACE-I with aldosterone antagonist or ARB with aldosterone antagonist
(e) Routine use of low-protein diets has unclear benefit (<0.8 g/kg/day)
(f) Avoid high-protein diets (>1.5–2.0 g/kg/day)
(g) Smoking cessation and weight loss also may slow progression of DKD

Blood pressure control is also very important for the primary prevention of DKD. As has been well documented, hypertension alone causes kidney disease [44]. At the time of writing of this chapter, there is much debate as to the best blood pressure levels for prevention and for treatment of DKD. Since 2008, influential, large hypertension and diabetes studies have been published. The Action to Control Cardiovascular Risk in Diabetes study is typical of these studies in that they were primarily focused on cardiovascular risk in people already at high risk for cardiovascular disease [45]. In ACCORD and other studies, it appeared that a systolic blood pressure of 120 mm Hg was not better than 135 mm Hg for reducing cardiovascular outcomes. Moreover a systolic blood pressure of <115 mm Hg appeared to lead to worse cardiovascular outcomes in some of the studies [46]. Hence many guideline committees changed their recommendations for optimal blood pressure control from <130/80 to <140/80 or <140/90, but these studies were not DKD studies. Studies in DKD suggest that lower blood pressure is better both for prevention and treatment [20, 47, 48]. Hence, 130/80 seems to be a better goal than 140/80 as it is possibly more protective for the development of DKD. Moreover in ACCORD and other studies, although there was not a cardiovascular benefit for lower blood pressures, there was a significant stroke prevention benefit. So it seems that 130/80 is an excellent blood pressure goal that can prevent many diabetic complications in addition to providing cardiovascular protection and stroke protection. In the future, it is likely that the guideline committees will be again recommending a blood pressure of 130/80 for prevention of DKD.

Some have proposed that blockers of angiotensin II, specifically ACE inhibitors (ACE-I) or angiotensin receptor blockers (ARBs), should be used to prevent the development of DKD. Although there is very clear evidence for activation of the renin-angiotensin-aldosterone system (RAAS) in people with DM, there is little to no evidence that using these medications prevents the development of DKD. An excellent study on type 1 DM patients (where ACE-Is and ARBs were compared to placebo for prevention of DKD over 5 years) observed no benefit for ACE-Is or ARBs for the either the development of albuminuria but more importantly for the prevention of pathological changes in the kidney as determined by kidney biopsy at the start of the study and at the end of the study [49]. In type 2 DM, some studies reported prevention of DKD using an ACE-I or ARB [50, 51]. But the studies that seemed to show prevention using RAAS inhibition had higher starting blood pressures than large studies that showed no benefit [52]. Thus the studies reporting a beneficial effect may have been due more to a blood pressure lowering effect rather than due to a unique effect of the RAAS inhibitors. At this time, the main treatments to prevent development of DKD are blood glucose control (aim for a hemoglobin A1c of 7%) and blood pressure control (aim for 130/80), and there is no unique role for RAAS inhibitors for the primary prevention of DKD.

For treatment of DKD, there are three major goals: blood sugar control, blood pressure control, and lowering of the urine albumin level (Table 2.3). Many studies have validated the importance of blood sugar control for people with DKD [42, 53]. In general the hemoglobin A1c goal is 7%. Although there are no specific medications that lower blood sugar that are uniquely beneficial for treating DKD, there are trials of newer agents being done. Studies are ongoing for DPP-4 inhibitors (CARMELINA study – Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus) and for SGLT-2 inhibitors (CREDENCE study – Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy) to determine if these classes of medications slow progression of DKD that are likely to be reported on in the years 2018–2020. Recently the EMPA-REG trial reported dramatic reductions in cardiovascular mortality in participants taking the SGLT-2 inhibitor, empagliflozin [54]. Intriguingly analysis of the kidney data from the same study showed significant decreases in rate of decline of eGFR in the participants [55]. Most of the participants in this study had normal eGFR so this may indicate that empagliflozin may have a role in prevention, but it is not clear yet if empagliflozin has a role in treatment of established DKD. The CREDENCE study is a combined renal and cardiovascular study and includes patients with lower eGFRs.

As with primary prevention of DKD, blood pressure control is of great importance for the treatment of DKD. As previously noted for primary prevention, the blood pressure goal is controversial and based on studies primarily designed to assess cardiovascular risk. But some recent analyses have offered new insights on the best blood pressure for DKD. For example, the VA NEPHRON-D (Diabetes in Nephropathy Study) study suggests that at least <140 mm Hg and likely <130/80 mm Hg lead to better outcomes for DKD patients [47]. Analysis of the slope of decline in eGFR as a factor of the blood pressure showed that rate of eGFR declined as systolic blood pressure declined. Clearly 130–139 mm Hg was better than >140 mm Hg, but there was also a clear trend for slowing of eGFR decline below 130 mm Hg. Although current recommendations are to aim for <140/80 mm Hg if there are low levels of urine albumin/creatinine ratio (<300 mg/g) and <125/75 mm Hg if there are higher levels of the urine albumin/creatinine ratio, it seems that 130/80 mm Hg or better is the more appropriate target for DKD patients.

Although RAAS inhibitors do not have a unique role for prevention of DKD, there are many studies showing a major benefit for slowing progression if the patient has high levels of urine

albumin/creatinine ratio (>300 mg/g) [56]. Lowering urine albumin appears to not only slow progression of DKD but is likely to lower the risk of cardiovascular events [2]. Indeed all patients with increased urine albumin level may well benefit from being on an RAAS inhibitor. In addition to ACE-Is and ARBs, the renin inhibitor, aliskiren, has been shown to be effective in lowering urine albumin level [57]. Of great interest is aldosterone blockade, as elevated aldosterone has many deleterious side effects [58] and blocking aldosterone has both cardiovascular and kidney benefits. There is an ongoing trial with a new aldosterone blocker called finerenone that will determine whether the addition of finerenone to ACE-I or ARB will improve cardiovascular and/or kidney outcomes in people with diabetes [59]. This trial is likely to be reported in 2019 or 2020.

There has also been much interest in combining RAAS agents for greater effect. Large studies have suggested that the combination is not more effective than these agents alone and may be more dangerous in combination [60, 61]. But there are questions about the inclusion criteria in these studies, and there still may be a role for combining these medications to help treat DKD. For example, a recent meta-analysis determined that the combination of ACE-I and ARB was more protective than either agent alone with respect to progression to end-stage kidney disease [62]. And there is also a study called Preventing ESRD in Overt Nephropathy of Type 2 Diabetes (VALID), which is evaluating benazepril and valsartan in combination that is to be reported on in 2017. At this time it is not clear what recommendation to make with regard to combining ACE-Is and ARBs. Hopefully VALID and other studies will provide more insight. One other class of antihypertensives that have been shown to have a modest albumin-lowering effect is the non-dihydropyridine medications diltiazem and verapamil [63]. Hence if a patient cannot take a RAAS inhibitor (e.g., high potassium, allergy, etc.), one of these agents may be considered.

Many have suggested that low-protein diets are of use in slowing progression of DKD based on the animal studies. A low-protein diet is often defined as <0.8 g/kg/day. Studies in humans have not been impressive or compelling, and often there is another explanation for the positive effect such as lowering salt intake and lowering blood pressure [30]. Hence routine use of a low-protein diet cannot be recommended. Studies will never be done on the possible risks of a high-protein diet, but there is enough evidence from animal studies and from very few human studies that a high-protein diet in people with DKD may accelerate decline in eGFR [64]. Thus it is best to avoid a high-protein diet which may be defined as >1.5–2.0 g/kg/day although the exact level of what constitutes a high-protein diet is not clearly defined.

Complications of Chronic Kidney Disease

Chronic kidney disease including DKD has a number of associated co-morbidities. The presence of chronic kidney disease and DM leads to even higher prevalence of these comorbidities. As previously noted, there is a very strong association between the development of DKD and cardiovascular disease [2]. Many studies have shown that even a small increase in the urine albumin level leads to increased cardiovascular events and cardiovascular mortality. In addition, decreasing eGFR is also associated with highly significant increases in cardiovascular events and death [3]. The combination of increased urine albumin level and decreased eGFR has an additive and possibly synergistic effect leading to even a higher incidence of cardiovascular events. As previously noted, most CKD patients (even more so in DKD patients) have a much higher chance of dying a cardiovascular death than getting to dialysis.

Anemia [65] and possibly secondary hyperparathyroidism occur at higher eGFRs in DKD patients as compared to nondiabetic CKD patients (Table 2.4). This is likely due to the combined effect in people with DM of loss of kidney tissue (primary cause of these complications seen in all CKD patients) and the deleterious effect of hyperglycemia on the enzymes in the remaining cells that impairs these metabolic processes.

Table 2.4 Complications of diabetic kidney disease

These may occur at higher eGFR levels in patients with DKD as compared to those with other types of chronic kidney disease
1. Anemia
(a) Caused, in part, by decreased production of erythropoietin and increased levels of hepcidin leading to decreased iron absorption
(b) Treated by increasing iron stores, controlling blood sugar, and possibly giving erythropoietin
2. Secondary hyperparathyroidism
(a) Caused mainly by decreased activity of the 1-a hydroxylase enzyme in the proximal tubular cell. In later-stage chronic kidney disease, increasing serum phosphate level plays a significant role
(b) Treated primarily by increasing vitamin D levels (goal is >30 ng/ml) using precursors to 1,25 dihydroxyvitamin D (such as vitamin D2 or D3). Use 1,25 dihydroxyvitamin D or analogs if vitamin D levels are >30 ng/ml and parathyroid hormone levels are still elevated. Limit phosphate in diet and/or use phosphate binders if elevated phosphate

Anemia occurs due to a combination of less production of erythropoietin (red blood cell growth factor that is produced in the kidney) and to decreased absorption of iron in part due to increased hepcidin levels [66]. Secondary hyperparathyroidism occurs for a variety of reasons, but a major one is decreased number and function of the 1-α-hydroxylase proteins in the kidney proximal tubule cells that activate vitamin D and regulate parathyroid hormone [67]. The decreased number of 1-α-hydroxylase is due to loss of kidney tissue and decreased function due to the effects of hyperglycemia [67]. Hence in a patient with DKD, it is very important to screen for cardiovascular disease, anemia, and hyperparathyroidism and treat as indicated.

Conclusions

There is an epidemic rise in the number of people with DKD. All physicians caring for diabetic patients need to understand how to optimally manage these patients to help prevent the development of DKD. It is also critical to screen for DKD and to aggressively implement treatments. Early and aggressive treatments do not cure DKD, but current treatments can significantly slow both the development of DKD and slow progression of DKD.

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