Guidelines for the management of chronic kidney disease

Hypertension

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Guideline 1.1: Treatment of hypertension in association with nondiabetic chronic kidney disease

1.1.1. For patients with proteinuric chronic kidney disease (CKD) (urine albumin-to-creatinine ratio ≥ 30 mg/mmol), anti-hypertensive therapy should include an angiotensin-converting enzyme inhibitor (grade A) or an angiotensin receptor blocker in case of intolerance to angiotensin-converting enzyme inhibitors (grade D).

1.1.2. Blood pressure should be targeted to < 130/80 mmHg (grade C).

1.1.3. For patients with nonproteinuric CKD (albumin-to-creatinine ratio < 30 mg/mmol), anti-hypertensive therapy should include either an angiotensin-converting enzyme inhibitor (grade B), an angiotensin receptor blocker (grade B), a thiazide diuretic (grade B), a beta blocker (in patients younger than age 60) (grade B), or a long-acting calcium channel blocker (grade B).

Background

The target blood pressure in this group of patients is justified on the basis of evidence from both prospective cohort studies and randomized clinical trials. Utilizing data from 332 544 middle-aged men screened for the Multiple Risk Factor Intervention Trial, Klag et al reported an increased risk for end-stage renal disease beginning at the third quintile of systolic (mean 127 mmHg) and diastolic (mean 82 mmHg) blood pressure.[1] In a similar analysis of men and women in the Okinawa mass screening program (n = 98 759), risk for end-stage renal disease increased in a progressive fashion with blood pressure levels above "high normal" (mean blood pressure 131/79 in men and 131/78 in women).[2] This risk persisted after adjusting for proteinuria and excluding patients with diabetes mellitus.

In a pooled analysis from 11 randomized controlled trials involving patients with nondiabetic CKD (n = 1860), Jafar et al[3] reported the lowest risk for CKD progression (doubling of serum creatinine or end-stage renal disease) at an *achieved* follow-up systolic blood pressure of 110–129 mmHg, and an increase in the relative risk for CKD progression at blood pressures above 130 mmHg. The benefit associated with achieved blood pressure levels < 130 mmHg was strongly influenced by patients with proteinuria exceeding 1 g/d.

Four randomized trials have also addressed the issue of blood pressure targets in patients with CKD.[4-7] The Modification of Diet in Renal Disease (MDRD) trial was a multicentre randomized study designed to determine the effect of dietary protein restriction and strict

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blood pressure control on the progression of CKD.[4] Only 3% of the 585 patients enrolled had diabetes. After a follow-up of 48 months, no difference in glomerular filtration rate decline was observed for the subjects randomized to the low blood pressure arm (< 125/75 mmHg) versus those randomized to usual blood pressure control (< 140/90 mmHg). A post hoc analysis demonstrated a benefit of the low blood pressure target in slowing the rate of glomerular filtration loss only in the subgroup of patients with a baseline glomerular filtration rate between 25–55 mL/min and baseline proteinuria exceeding 1g/d.[8] The long-term follow-up of patients enrolled in the MDRD study demonstrated a reduced risk for kidney failure (hazard ratio [HR] 0.66; 95% confidence intervals [CI] 0.53–0.81) in the low target blood pressure group compared with the usual target blood pressure group.[9] However, blood pressure measurements were not recorded during the follow-up period, and it is uncertain whether differences in angiotensin-converting enzyme inhibitor use which occurred within the trial itself (51% use in the subjects assigned to the low blood pressure group versus 32% use in those assigned to usual blood pressure control) persisted throughout the follow-up period.

The African American Study of Kidney Disease and Hypertension (AASK) followed 1094 African Americans with hypertension-induced CKD.[5] Patients were randomized to a usual mean arterial pressure (102–107 mmHg) or to a lower mean arterial pressure (≤ 92 mmHg) and followed for up to 4 years. Compared with the usual blood pressure group (mean achieved blood pressure 141/85 mmHg), the lower blood pressure group (mean achieved blood pressure 128/78 mmHg) did not experience a reduction in either glomerular filtration rate decline or the composite outcome (reduction of glomerular filtration rate by ≥ 50%, end-stage renal disease, or death).

In the second Ramipril Efficacy In Nephropathy (REIN-2) study, 335 patients with nondiabetic CKD and proteinuria exceeding 1 gram per day were randomized to 2 blood pressure targets: conventional control with a diastolic blood pressure < 90 mmHg (irrespective of systolic blood pressure), and intensified control with a blood pressure < 130/80 mmHg.[6] All patients were receiving an angiotensin-converting enzyme inhibitor (ramipril). A dihydropyridine calcium channel blocker (felodipine) was used as the add-on therapy in the intensified blood pressure group. The mean difference in achieved blood pressure between the groups (4 mmHg systolic and 2 mmHg diastolic) was small and no difference in the development of end-stage renal disease between the groups was observed. The validity of these results have been questioned given the small differences in achieved blood pressure, the choice of a dihydropyridine calcium channel blocker as the second line agent in the intensive blood pressure arm, and the wide CIs (0.61–1.64) which fail to rule out a benefit associated with intensive blood pressure control with reasonable certainty.

Finally, the Hypertension Optimal Treatment (HOT) study randomized 18 790 hypertensive patients (less than 10% were diabetic) to 1 of 3 diastolic blood pressure target groups (≤ 90 mmHg, ≤ 85 mmHg, and ≤ 80 mmHg) to determine the impact of these blood pressure targets on incident cardiovascular events.[7] The subjects were followed for an average of 3.8 years. In a nonprespecified, post hoc analysis, the

incidence of major cardiovascular events in patients with a baseline serum creatinine level > 133 μmol/L (n = 470) did not differ between the 3 different target groups. When CKD was defined as a creatinine clearance < 60 mL/min (n = 2821), cardiovascular events tended to be less frequent in patients with lower blood pressure but this trend was not statistically significant.

Therefore, the current recommendation for a target blood pressure of < 130/80 mmHg in nondiabetic CKD patients is largely influenced by observational data reporting renal outcomes.

The evidence supporting angiotensin-converting enzyme inhibitor use as initial therapy in nondiabetic CKD primarily comes from a meta-analysis of patient level data (n = 1860) from 11 randomized controlled trials[10] including 2 landmark studies.[11,12] In an analysis adjusting for baseline characteristics and changes in systolic blood pressure and urinary protein during follow-up, antihypertensive regimens that included angiotensin-converting enzyme inhibitors (compared with non-angiotensin-converting enzyme inhibitor antihypertensive therapy) decreased the development of end-stage renal disease by 31% and the combined outcome of doubling of serum creatinine or end-stage renal disease by 30%. This benefit was significant in patients with baseline proteinuria exceeding 500 mg per day but was not evident in patients with less severe proteinuria.

There is no evidence favouring a specific antihypertensive agent in nondiabetic CKD patients with proteinuria < 500 mg/d (~ albumin-to-creatinine ratio of 30 mg/mmol). In a post hoc analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), 5662 patients (n = 1888 patients with diabetes) were identified to have an estimated glomerular filtration rate < 60 mL/min/m^2.[13] Even though urinary protein excretion was not assessed in the trial, it is likely that patients with proteinuria exceeding 500 mg/d were few in number given the low prevalence of this degree of proteinuria in a hypertensive population and the likely exclusion of such patients from enrollment since the sixth report of the Joint National Committee recommended angiotensin-converting enzyme inhibitor therapy in patients with kidney disease.[14] Over a mean follow-up time of 4.8 years, no differences in the risk of end-stage renal disease or for the composite endpoint (≥ 50% decline in glomerular filtration rate or end-stage renal disease) were observed among the patients randomized to lisinopril, amlodipine, or chlorthalidone.[15] Also, there were no statistically significant differences in risk for coronary heart disease or stroke among the 3 groups. Compared to the lisinopril group, chlorthalidone was superior for the combined cardiovascular disease and heart failure outcomes; however, these results were not presented for the nondiabetic cohort.[13]

Although a post hoc nonprespecified subgroup analysis of the HOPE trial did suggest a cardiovascular benefit associated with angiotensin-converting enzyme inhibitor use in predominantly nonproteinuric CKD patients,[16] several concerns were raised when this trial was reviewed. The trial was not designed as a blood pressure lowering trial even though the majority of patients were hypertensive. The details of blood pressure control have not been presented, and there are legitimate concerns about the blood pressure

lowering benefits within the ramipril arm. Also, in the intervention arm, ramipril was used as add-on therapy. As such, it did not address our specific purpose of developing recommendations around *initial* therapy.

The PREVEND-IT trial also addressed the impact of angiotensin-converting enzyme inhibitor therapy in nondiabetic CKD patients.[17] In this trial, CKD was defined on the basis of persistent microalbuminuria; glomerular filtration rate was normal in the majority of patients. Blood pressure was under good control at baseline (mean blood pressure 130/76 mmHg). Eight hundred and sixty-four patients were randomized to 20 mg of fosinopril or matching placebo daily. After 4 years of treatment, fosinopril was associated with a trend towards fewer cardiovascular events than placebo, but this effect did not reach statistical significance (HR 0.60; 95% CI 0.33–1.10). These wide CIs are likely a reflection of the limited number of endpoints ($n = 45$) and indicate that the trial was underpowered to detect a difference between fosinopril and placebo.

Therefore, blood pressure lowering therapy which includes an angiotensin-converting enzyme inhibitor slows progression of proteinuric nondiabetic CKD to end-stage renal disease. Whether this translates to improved cardiovascular outcomes remains to be determined. In contrast, beyond the benefit from blood pressure lowering per se, there appears to be no additional benefit from any specific blood pressure lowering drug class with regards to renal and cardiovascular outcomes in nondiabetic patients with CKD and proteinuria < 500 mg/d. The recommended antihypertensive classes for these patients are extrapolated from mortality outcome studies performed in non-CKD patients.[18]

Guideline 1.2: Treatment of hypertension in association with diabetic chronic kidney disease

1.2.1. Antihypertensive therapy should include either an angiotensin-converting enzyme inhibitor (grade A) or an angiotensin receptor blocker (grade A).

1.2.2. Blood pressure should be targeted to < 130 mmHg systolic (grade C) and < 80 mmHg diastolic (grade B).

Background

The target diastolic blood pressure in this group is justified on the basis of extrapolated data from the HOT trial[7] and the UKPDS study.[19] Of the 1501 patients within the HOT study with baseline diabetes mellitus, the risk for subsequent cardiovascular events was halved in those randomized to the diastolic blood pressure of 80 mmHg compared to those randomized to 90 mmHg.[7] In the UKPDS study, 1148 hypertensive diabetic patients were randomized to tight control of blood pressure (< 150/85 mmHg) or less tight control (< 180/105 mmHg). After a median follow up of 8.4 years, subjects assigned to tight control (achieved mean blood pressure 144/82 mmHg) were 32% less likely to experience a diabetes related death and 44% less likely to develop a stroke than subjects assigned to the higher blood pressure arm (achieved mean blood pressure 154/87 mmHg).[19] Given that these analyses did not specifically identify subjects with CKD, the grade of the recommendation has been appropriately reduced.

The evidence for the 130 mmHg systolic target is far less robust and is based upon prospective observational data including results from the MRFIT trial[1] and the Okinawa screening program[2] discussed above. Although results from both the UKPDS study[20] and the Pittsburg Epidemiology of Diabetes Complications Study[21] reported statistically significant associations between cardiovascular complications and systolic blood pressure levels above 120 mmHg, the CKD work group judged that the current evidence lacked the strength to recommend a systolic target lower than 130 mmHg. Recent observational evidence also suggests caution when actively lowering systolic blood pressure to less than 120 mmHg in patients with CKD.[22,23] More definitive evidence for or against a systolic blood pressure target of 130 mmHg awaits completion of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial in which 4733 persons with diabetes are being randomized to systolic blood pressure targets of 120 or 140 mmHg. The results of this trial are not expected until 2010.

The evidence supporting angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy as first-line agents for the treatment of hypertension in diabetic patients with proteinuria is robust and is based primarily on the results of 3 valid randomized controlled trials with clinically relevant renal endpoints.[24-26]

In contrast, the evidence for angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy in diabetic patients without proteinuria is less definitive and must be extrapolated from these studies above[24-26] and from cardiovascular outcomes in non-CKD studies with diabetic subgroups.[16,27] It should also be stated that initial therapy with chorthalidone was superior to lisinopril for the heart failure endpoint in the 1888 subjects in ALLHAT with diabetes and a glomerular filtration rate < 60 mL/min.[13] Other trials, involving subgroups of subjects with diabetes and predominantly normal kidney function, have also shown cardiovascular benefits for additional classes of anti-hypertensives including beta blockers,[28] and nondihydropyridine[29] and dihydropyridine[30] calcium channel blockers. For these reasons, if an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker are contraindicated or cannot be tolerated, a diuretic, a cardioselective beta blocker, or a long acting calcium channel blocker can be substituted as first line therapy in diabetic nonproteinuric CKD patients.

Guideline 1.3: Treatment of hypertension in association with large-vessel renal vascular disease

1.3.1. Renovascular hypertension should be treated in the same manner as nondiabetic, nonproteinuric CKD, with caution in the use of an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker due to the risk of acute renal failure (grade D).

Background

Atherosclerotic renal artery stenosis is a common problem for which there is limited data on diagnosis and therapy. In the absence of data indicating that any 1 class of

antihypertensive therapy is superior to another in the treatment of renovascular hypertension, any of the agents recommended for the treatment of nonproteinuric nondiabetic CKD may be appropriate. Given the risk of acute renal failure, caution should be exercised when using angiotensin-converting enzyme inhibitors or angiotensin receptor blockers particularly in those patients with severe bilateral disease or unilateral disease with a solitary kidney. Although close follow-up and early intervention (angioplasty and stenting or surgery) should be considered for patients with uncontrolled hypertension (despite therapy with 3 or more drugs), deteriorating kidney function, bilateral atherosclerotic renal artery lesions (or tight atherosclerotic stenosis in a single kidney), or recurrent episodes of flash pulmonary edema, the evidence for nonmedical interventions is limited. Completion of the CORAL study, a randomized, multicentre clinical trial (target sample size 1080 subjects) testing the effect of optimal medical therapy alone versus stenting with optimal medical therapy on a composite of cardiovascular and renal endpoints, should provide more definitive data in this area.

Guideline 1.4: Combination therapy

Multiple agents are frequently required to achieve target blood pressure in patients with CKD. For example, the mean number of agents to achieve a systolic blood pressure of 141 mmHg in the RENAAL trial was 2.7;[26] in the IDNT trial, on average 2.6 agents were to used achieve a systolic blood pressure of 138 mmHg.[24] Unfortunately, given the lack of randomized controlled trials identifying the optimal second-line antihypertensive agent in people with diabetes and CKD, Canadian guideline groups have struggled with producing a consistent recommendation as to which agents should be added to angiotensin system medications in this population. Thiazide diuretics are effective in combination with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers and should be considered as additive therapy for control of hypertension, salt and water retention, and serum potassium. Loop diuretics can be used in those patients who fail therapy with thiazide diuretics or in those patients with severe salt and water retention or hyperkalemia, complications which frequently occur with glomerular filtration rate levels < 30 mL/min/1.73m.^{2}

The combination of an angiotensin-converting enzyme inhibitor with an angiotensin receptor blocker has generated significant interest in the last several years. Theoretically, such a combination would offer renin angiotensin system blockade at 2 discrete sites. Unfortunately, most studies examining this combination have used suboptimal doses of one or both agents.[31,32] It has also been difficult to determine if the observed beneficial effects on proteinuria are secondary to more complete renin angiotensin system blockade or just better blood pressure control. Only one study has reported clinically relevant renal endpoints.[33] Although the COOPERATE trial did suggest a renal benefit of combining trandolopril with Cozaar in patients with proteinuric nondiabetic CKD, it is important to recognize that the trial was from a single centre and was relatively small with few endpoints (10 patients in the combination arm, 20 patients in the angiotensin-converting enzyme-inhibitor arm, and 20 patients in the angiotensin receptor blocker arm reached the combined endpoint of doubling of serum creatinine or end-stage renal disease).

Furthermore, the trial design allowed the combination of an angiotensin-converting enzyme inhibitor with an angiotensin receptor blocker only after blood pressure was controlled, which typically required the use of 3 other antihypertensive drugs.[33] Therefore, it seems reasonable to state that in nondiabetic patients who reach target blood pressure and continue to have proteinuria > 1 g/d despite therapy with an angiotensin-converting enzyme-inhibitor, the addition of an angiotensin receptor blocker to the antihypertensive regimen can be tried.

Use of aldosterone antagonists, direct renin inhibitors, or supramaximal doses (doses exceeding that recommended by the *Compendium of Pharmaceuticals and Specialties*) of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers also offer the possibility of more complete renin angiotensin system blockade and perhaps improved patient outcomes. However, no trials have assessed the impact of these approaches on hard clinical endpoints in any hypertensive population.

Guideline 1.5. Safety

For the majority of patients with CKD, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are either recommended as first-line antihypertensive agents or are an integral part of the antihypertensive regimen. Episodes of hyperkalemia or acute renal failure are infrequent in clinical trials but such side effects are a real concern outside the controlled setting of a trial environment.[34] For this reason, serum creatinine should be checked within 1 to 2 weeks of initiation or titration of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker,[35] and consideration should be given to withholding these agents during times of acute illness, especially when intravascular volume contraction is present or suspected. As the use of angiotensin system medications has been associated with adverse fetal outcomes, women should avoid becoming pregnant when receiving angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy.[36]

Background and Methods

In patients with CKD, hypertension is treated to slow progression of kidney disease and to reduce cardiovascular risk. Unlike many other sections of this Appendix, the treatment of hypertension in CKD is frequently guided by clinical trials designed specifically for this population. In certain subgroups of patients, recommendations are made using evidence extrapolated from non-CKD populations. This chapter reviews the evidence for target blood pressure and the pharmacological management of hypertension. The reader is referred to the chapter "Lifestyle management" and the Canadian Hypertension Education Program's publication for recommendations on the nonpharmacological management of hypertension,[37] which are paramount in the management of all hypertensive individuals.

For the first time, hypertension treatment recommendations from the Canadian Hypertension Education Program process, the Canadian Diabetes Association Guidelines process, and the guidelines process of Canadian Society of Nephrology have been

harmonized to provide a consistent unambiguous message to health care providers and patients in Canada. A literature search for clinical trials and systematic reviews was performed by a librarian employed by the Canadian Hypertension Education Program. This literature search was supplemented using 3 methods. First, the bibliography supplied in the Kidney Disease Outcomes Quality Initiative Hypertension Guidelines publication[38] was utilized. Second, the Workgroup members used their content expertise to identify new or missing evidence. Finally, a focused literature search of English language nephrology and general medical journals was performed by the Workgroup members to search topics not covered by the Canadian Hypertension Education Program librarian.

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Diabetes

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Disclaimer: The purpose of this chapter is to provide key aspects of management of blood glucose control *for patients with non-dialysis-dependent chronic kidney disease* (CKD). Currently there is limited evidence to guide recommendations in this area specific to the non-dialysis-dependent CKD population**,** and thus statements are limited in scope due to the need for evidentiary base. These recommendations are not intended to replace the Canadian Diabetes Association Guidelines,[1] but rather to focus on aspects of care specific for the CKD population. The reader is encouraged to refer to the Canadian Diabetes Association Guidelines[1] for additional information.

Guideline 1.4: Glycemic control as part of a multifactorial intervention strategy

1.4.1. Targets for glycemic control, where they can be achieved safely, should follow standard Canadian Diabetes Association Guidelines (hemoglobin $A_{1c} < 7.0\%$, fasting plasma glucose 4–7 mmol/L) (grade B).

1.4.2. Glycemic control should be part of a multifactorial intervention strategy addressing blood pressure control and cardiovascular risk and promoting the use of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, statins, and aspirin (grade A).

Background

Tight glycemic control can prevent or delay progression of microvascular and macrovascular complications. The absolute benefits will be greatest in those starting with higher hemoglobin A_{1c}. The risk of hypoglycemia increases with tight glycemic control and is increased in CKD.

Most deaths in diabetes are due to cardiovascular disease. Multifactorial interventions clearly prevent macrovascular disease. The benefits of a glucose-centric approach will primarily be for microvascular complications.

Although renal impairment was a common exclusion for many intervention trials, it seems reasonable to extrapolate the general recommendations of the Canadian Diabetes Assocation clinical practice guidelines[1] to people with CKD (particularly stage 1 and 2). Current recommendations are largely based on data from the DCCT trial in type 1 diabetes mellitus[2] and the UKPDS in type 2 diabetes mellitus.[3,4] The former trial included some type 1 subjects with microalbuminuria in the secondary prevention arm. In the UKPDS study of newly diagnosed type 2 subjects, those with renal impairment (creatinine > 175 µmol/L) were excluded.

Tight or intensive glycemic control has been shown to reduce the incidence and progression of microvascular complications in the DCCT[2] (type 1 diabetes mellitus) and the UKPDS[3,4] (type 2 diabetes mellitus) studies compared with conventional therapy. The benefit of tight glycemia control in these trials was largely in the reduction of

microvascular complications, and particularly retinopathy. Furthermore, the benefits of superior glycemic control with intensive insulin therapy over 6.5 years in type 1 diabetes mellitus persist in terms of reduction in both retinopathy[5] and nephropathy[6] but also with a reduction in cardiovascular events.[7] Although it is clear that hyperglycemia is a risk factor for cardiovascular disease, there is less evidence that tight glycemic control (alone) reduces cardiovascular events in type 2 diabetes mellitus except for the use of metformin in obese type 2 diabetes mellitus.[3]

Nevertheless, tight glycemic control, as part of a multifactorial intervention strategy addressing blood pressure control and cardiovascular risk and promoting the use of renin-angiotensin blocking drugs, statins, and aspirin, has been shown to reduce macrovascular complications by 50% and microvacscular complications by 60%.[8]

Numerous trials clearly demonstrate that good glycemic control is associated with reduced development of microalbuminuria and progression to macroalbuminuria in both type 1 diabetes mellitus and type 2 diabetes mellitus.[2,4,9-12] The benefits of tight glycemic control in reducing the decline in glomerular filtration rate is less compelling, largely because of the small number of subjects and low event rates.[2,4,10,11,13] The trend toward benefit is consistent across these small intervention trials.

Although there is little direct evidence to support tight glycemic control to prevent progression in stage 3–5 CKD, good glycemic control has important benefits for preventing other microvascular complications[14] and will reduce risk of infection and promote wound healing. Even in end-stage renal disease, hemodialysis patients with good or moderate glycemic control had a survival advantage,[15] although this has not been apparent in short-term studies (12 months).[16]

Other aspects of diabetes care such as regular screening for retinopathy and assessment of risk for foot ulceration, with education and intervention as required, should continue as recommended in current clinical practice guidelines.[1]

Guideline 1.5: Use of metformin in type 2 diabetes mellitus

1.5.1. Metformin is recommended for most type 2 diabetic patients with stage 1 and 2 CKD who have *stable renal function unchanged over the prior 3 months* (grade A).

1.5.2. Metformin may be continued in individuals with *stable* stage 3 CKD (grade B).

Clinical practice recommendations

Metformin should be held if there are acute changes in renal function or during intercurrent illnesses that could precipitate such changes (e.g., gastrointestinal upset or dehydration) or cause hypoxia (e.g., cardiac or respiratory failure). Particular care should be taken in patients in whom angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, or diuretics are

used, or after intravenous contrast administration; the risk of acute renal failure—and thus accumulation of lactic acid—is greatest in these individuals.

Background

Metformin is an inexpensive and effective oral hypoglycemic agent which is recommended as first-line therapy in obese patients with type 2 diabetes mellitus[1] but is also at least as effective in nonobese patients.[17] It is generally well tolerated, particularly if the dose is titrated up gradually [e.g., 500 mg once daily, increasing the daily dose by 500 mg each week towards 1 g twice daily with meals]. In contrast to other oral agents, it is associated with weight loss, rather than weight gain.[18] It may have additional benefits over other glucose lowering therapies as it appears to protect from cardiovascular disease[3,19,20] and cancer.[21,22]

There is much concern regarding the safety of metformin in renal failure, particularly the risk for lactic acidosis. A recent Cochrane review of 206 trials including 47 846 patient-years of exposure to metformin found no cases of fatal or nonfatal lactic acidosis.[23] Others have observed that rates of lactic acidosis were similar before and after the introduction of metformin in the United States and that in all cases a potential cause other than metformin use was present.[24] Other data suggests that the risk of death from lactic acidosis with metformin therapy is equivalent to the risk of death from hypoglycemia with sulphonylureas.[25,26]

Metformin acts, at least in part, by inhibiting gluconeogenesis, but unlike phenformin does not enhance peripheral lactate production or inhibit peripheral lactate oxidation.[25] However, in the same Cochrane review there was no evidence that metformin was associated with increased lactate levels.[23] Metformin has a short half-life (1.5–5 hours) and is excreted unchanged by the kidney.[25] Although metformin can accumulate in renal failure, there is no evidence of a correlation between metformin levels and either circulating lactate levels or prognosis of lactic acidosis.[27]

Reviews of case reports of metformin associated lactic acidosis actually suggest that metformin alone is rarely a cause of lactic acidosis and never a cause of fatal lactic acidosis but rather metformin may be viewed as a co-precipitant along with an underlying disease.[28] Cases of lactic acidosis were most commonly seen in acute (or acute on chronic) renal failure (often precipitated by angiotensin-converting enzyme inhibitors or nonsteroidal anti-inflammatory drugs), and also observed in dialysis patients or were associated with another major illness: hepatic failure, sepsis, bowel obstruction, and shock.[28] The prognosis of lactic acidosis seems most related to the severity of the underlying disease and comorbidity.[28-31]

While the benefits of metformin therapy are clear, the risks appear to be overstated. Some commentators feel that the net effect of the list of contraindications to metformin actually has a negative effect on health.[32,33] The contraindications seek to avoid metformin or lactate accumulation and emphasize conditions where lactate production is increased or lactate clearance is decreased. It has been noted that the definitions are often vague,[32] that

there is substantial variation between guidelines,[32] and that contraindications are frequently ignored without any apparent excess of lactic acidosis.[34-36]

Discontinuation of metformin is not a neutral decision, even if well intended. Metformin withdrawal in patients with stage 3 and 4 CKD (creatinine levels between 130 and 220 μmol/L) was associated with poorer glycemic control despite increased use of other oral agents and insulin, as well as more weight gain, an adverse lipid profile, and higher blood pressure.[37] The authors draw a distinction between continuation of metformin versus its initiation in subjects with traditional contraindications and emphasize the need for caution in high-risk situations (e.g., use of intravenous contrast agents).[37]

The CKD work group believes that, with care, the benefits of metformin can be safely extended to patients with stage 3, and possibly stage 4, CKD, but whose ***clinical state is stable***. The absence of data precludes any recommendation regarding the risks or benefits of initiating metformin in patients with stage 3–4 CKD. Clearly such a decision should be carefully considered by the physician, discussed with the patient, and include close monitoring of renal function and clear instructions relating to intercurrent illness. The work group would not recommend that metformin be started or continued in stage 5 CKD.

Guideline 1.6: Choice of other glucose-lowering agents

1.6.1. Tailor the choice of other glucose-lowering agent(s) (including insulin) to the individual, the level of renal function, and comorbidity (grade D, opinion).

1.6.2. Risk of hypoglycemia should be assessed regularly in individuals taking insulin or insulin secretagogues, and these patients should be taught how to recognize, detect, and treat hypoglycemia (grade D, opinion).

Clinical practice recommendation

Short-acting sulfonylureas (e.g., gliclazide) are preferred over long-acting agents in CKD.

Background

In general, the choice of glucose-lowering agents should follow conventional guidelines.[1] Hypoglycemia is a potential complication for anyone using insulin, sulphonylureas, or meglitinides. However, altered pharmacokinetics and pharmacodynamics of some oral agents and insulin increases the risk of hypoglycemia in CKD. Thus, agents with a low risk of hypoglycemia are indicated in people with CKD.

The risk of hypoglycemia is increased in CKD, particularly in stage 3–5, for several reasons.

- Reduced gluconeogenesis:

The kidney plays a role in glucose homeostasis making a small but significant contribution to gluconeogenesis, which decreases as renal disease advances, thus providing less and less protection from hypoglycemia.

- Reduced clearance of insulin:

  Normally, the kidney is responsible for up to one-third of insulin clearance. The reduction of insulin clearance as renal function declines leads to an increase in the effect and duration of action of both exogenous and endogenous insulin.

- Increased insulin sensitivity:

  The weight loss associated with advancing renal dysfunction and uremia may lead to an improvement in insulin sensitivity or reflect a relative increase in dose per unit of body weight.

In non-CKD populations, the risk of hypoglycemia with glyburide is greater than with other sulphonylureas, and indeed similar to insulin.[38] Sulphonylureas undergo hepatic metabolism to water-soluble metabolites, which are excreted by the kidney. The metabolites of glyburide and glimepiride retain clinically significant hypoglycemic effects.[39] These metabolites may accumulate in renal failure, increasing the risk of hypoglycemia. In contrast, gliclazide's metabolites do not have any hypoglycemic action and its half-life is relatively short.[40] Tolbutamide is a sulphonylurea with a short half-life. However, adherence may be more challenging since the tablets are very large and generally require 3-times-daily dosing. In contrast, gliclazide tablets are small and relatively inexpensive, and can be taken once or twice daily.

Repaglinide, a short-acting, nonsulphonylurea secretagogue which undergoes hepatic metabolism, can be used safely in CKD. Acarbose, an intestinal alpha glucosidase inhibitor, is associated with intolerance and lower efficacy than other oral hypoglycemic agents. The safety of acarbose in renal impairment has not been studied directly and opinions differ regarding its use.

If hypoglycemia is present, doses of oral hypoglycemic agents or insulin may need to be reduced. Since the usual time-action curves of insulin preparations may not apply in advanced CKD, the choice of insulin preparations may need to be reviewed and adjusted. The duration of action of insulins tends to be prolonged. Thus regular (Toronto) insulin may act more like intermediate-acting insulin causing late hypoglycemia. A switch to a rapid-acting insulin analogue may be effective in this case. In other cases, the frequency of NPH insulin injection may need to be reduced from twice daily to once daily.

Note on assessing and monitoring glycemic control in chronic kidney disease

Self blood glucose monitoring and regular measurements of HbA_{1c} can both be used to assess and monitor glycemic control.[1] However, HbA_{1c} may be less reliable in some

circumstances. Since HbA_{1c} depends on erythrocyte half-life, blood glucose levels will be underestimated if red cell lifespan is reduced (e.g., hemolytic anemia) or after blood transfusions. Intermittent use of erythropoietin can also lead to fluctuations in A_{1c} levels.[41]

The performance of some point of care methods for measuring A_{1c} (e.g., DCA 2000) may be inferior in CKD, particularly in stage 5 CKD.[42] The use of modern high performance liquid chromatography based A_{1c} assays has largely overcome the unreliability of older methods in CKD patients. Nevertheless, some concern continues since the slope of the regression line relating A_{1c} and self blood glucose monitoring seems to differ in those with end-stage renal disease[43] – although self blood glucose monitoring does not seem to be an appropriate gold standard. Self blood glucose monitoring is a useful tool, which generally performs well. Some brands of test strips may give false readings for some patients using dialysis fluids containing icodextrin for continuous ambulatory peritoneal dialysis.[44,45] In stage 1–4 of CKD, this is not a concern.

In clinical practice, where many patients with diabetes have suboptimal control, concerns about the performance of the A_{1c} assay seem academic. An elevated A_{1c} is generally consistent with poor diabetes control.

However, in those with A_{1c} levels at, or close to, target, the performance of the A_{1c} assay should be considered in case glucose levels are underestimated. Self blood glucose monitoring results should be reviewed to provide supplementary information regarding the level of glycemic control.

In addition, symptoms of hypoglycemia should be sought in those whose A_{1c} is at or close to target. Swings in blood glucose, with episodes of hypoglycemia, may be overlooked if only the A_{1c} is considered. Particular care should be taken to consider hypoglycemia unawareness (reduction or absence of symptoms) in those with autonomic neuropathy or those who have very tight control.[46]

General information

The prevalence of diabetes is increasing rapidly worldwide,[47] particularly type 2 diabetes, due to increasing obesity and urbanization.[48] Diabetes is associated with reduced life expectancy largely due to a 2- to 4-fold increased risk for cardiovascular disease.[49] Cardiovascular risk is higher still in diabetic patients with renal impairment.[50] Microvascular complications (retinopathy, nephropathy, and neuropathy) resulting from chronic hyperglycemia are associated with reduced quality of life[51,52] as well as mortality.[53,54] Treatment of diabetes and its complications consumes a large proportion of health care costs.[55-57]

Diabetic nephropathy is an important cause of CKD. Diabetes is also a common comorbid condition in people with CKD due to other causes. These guidelines make recommendations for blood glucose control in people who have both diabetes and CKD irrespective of the underlying cause of their kidney disease.

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Dyslipidemia

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Guideline 1.7: Screening for dyslipidemia

1.7.1. A fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) should be measured in adults with stage 1–3 chronic kidney disease (CKD) (grade A).

1.7.2. A fasting lipid profile should be measured in adults with stage 4 CKD only if the results would influence the decision to initiate or alter lipid-modifying treatment (grade D).

Background

Patients at every stage of CKD have an increased prevalence of dyslipidemia as traditionally defined (i.e., elevated triglycerides, low high density lipoprotein [HDL] cholesterol), compared to those with normal renal function.[1-4] Chronic kidney disease is also frequently associated with qualitative lipid abnormalities that are potentially atherogenic (i.e., small dense low density lipoprotein [LDL] cholesterol, oxidized LDL cholesterol, increased apolipoprotein B [ApoB], elevated lipoprotein (a) [Lp(a)]) (reviewed in [5]. Specific subsets of CKD patients (such as those with the nephrotic syndrome or treated with peritoneal dialysis) have a particularly atherogenic lipid profile.[2,6-11] Thus, the fasting lipid profile is more likely to be abnormal in patients with CKD compared to people with normal renal function. However, screening for dyslipidemia should be performed only if the results would influence decisions about treatment.

Therapy with an HMG-CoA reductase inhibitor (statin) reduces cardiovascular risk in patients with or at high risk for coronary disease and concomitant stage 1–3 CKD (see guideline 1.9). Current guidelines for the general population suggest screening for dyslipidemia only in persons with elevated cardiovascular risk (conferred by age, gender, smoking status, or comorbidity).[12] The CKD work group believes that all patients with mild to moderate CKD (stage 1–3) should be screened, irrespective of age or comorbidity, given the increased cardiovascular risk associated with impaired kidney function. Although the absolute risk of cardiovascular events in people with stage 1–3 CKD and no other cardiovascular risk factors is unknown, lower levels of glomerular filtration rate in patients with nondialysis dependent CKD are independently associated with increased (relative) risk of cardiovascular events compared to those with normal kidney function.[13,14] Furthermore, the magnitude of the cardiovascular risk due to dyslipidemia is similar among patients with normal renal function compared to those with any stage of CKD, [15-17] and treatment of dyslipidemia may similarly reduce cardiovascular events in both groups (see guideline 4.3). Therefore, screening for dyslipidemia is recommended in all patients with stage 1–3 CKD.

The absolute risk of a future cardiovascular event in the setting of stage 4 CKD appears to be similar to that associated with established coronary disease.[13] A definitive

recommendation cannot be made regarding screening for dyslipidemia in patients with stage 4 CKD since the benefits of treatment are less well established in this subgroup.[18]

Guideline 1.8: Frequency of lipid profile measurement

1.8.1. Lipid profile should be measured after an overnight fast (ideally ≥ 12 hours in duration) (grade A).
1.8.2. Total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides should be measured (grade A).
1.8.3. Fasting lipid profile should be measured no sooner than 6 weeks after initiation or change in pharmacologic therapy. Thereafter, lipid profile should be monitored every 6–12 months if the results could influence subsequent therapeutic decisions (grade D).

Background

Few data guide the optimal timing of lipid measurement in patients with CKD specifically. Therefore, the CKD work group recommends that existing guidelines for the general population be followed in the setting of CKD.[12] Specifically, lipid profile should be measured after an overnight fast, as cardiovascular risk and treatment targets are more closely associated with fasting rather than postprandial lipids in the general population.

The majority of data in both unselected and CKD populations support measurement of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides since these are the strongest determinants of cardiovascular risk.[12] Treatment with statins aimed at reducing total cholesterol and LDL cholesterol has been repeatedly shown to directly reduce the risk of cardiovascular events.[19-26] Despite data in both dialysis- and nondialysis-dependent CKD demonstrating qualitative lipid abnormalities such as increased Lp(a), C-reactive peptide, small-dense LDL cholesterol, oxidized LDL cholesterol, and non-HDL cholesterol (total cholesterol minus HDL, representing "remnant" particles),[5] at present no prospective trials demonstrate that treatment of these abnormalities specifically (in the absence of other indications for treatment) improves clinical outcomes. Therefore, measurement of these nontraditional indices of dyslipidemia is not currently recommended.

Other secondary causes of dyslipidemia (besides CKD) should be screened for if clinically suspected. These include nephrotic syndrome, hypothyroidism (with a thyroid stimulating hormone assay), diabetes, liver disease, excess alcohol consumption, and specific medications.

Guideline 1.9: Treatment of dyslipidemia

1.9.1. Statin therapy should be initiated in patients with stage 1–3 CKD according to existing lipid guidelines for the general population (grade A).
1.9.2. In patients with stage 1–3 CKD, clinicians should consider titrating statin dose according to lipid guidelines for the general population (grade B).

1.9.3. Clinicians should consider initiating statin therapy in patients with stage 4 CKD and titrating the dose to target LDL cholesterol < 2.0 mmol/L and total cholesterol to HDL cholesterol ratio < 4.0 mmol/L (grade B).

1.9.4. Gemfibrozil 1200 mg daily may be considered as an alternative to statin treatment in patients with stage 1–3 CKD who are at intermediate or high cardiovascular risk with concomitant low levels of HDL cholesterol (< 1.0 mmol/L) (grade B).

1.9.5. Fasting triglycerides > 10 mmol/L at any stage of CKD should be treated by recommending lifestyle changes and adding gemfibrozil or niacin, as required, to reduce the risk of acute pancreatitis (grade D). Current data do not support treating hypertriglyceridemia per se as a cardiovascular risk reduction strategy (grade A).

Background

Dyslipidemia clearly increases the risk of cardiovascular events in unselected populations, and the magnitude of cardiovascular risk conferred by dyslipidemia appears to be similar in patients with normal renal function versus those with nondialysis-dependent CKD.[15] Data from multiple trials including a total of more than 100 000 participants indicate that statin treatment reduces the risk of first[20,25,26] or recurrent[21-24] cardiovascular events by approximately one-third and that the absolute magnitude of benefit is driven by baseline cardiovascular risk and the extent of on-therapy LDL cholesterol reduction rather than pre-treatment LDL cholesterol levels.[19] Subgroup analyses of 5 landmark statin trials demonstrate that statin therapy leads to a similar relative reduction in the risk of cardiovascular events in patients with stage 1–3 CKD, compared to those with normal kidney function,[19,26,27] and indicate that the absolute benefit of treatment is greater in people with CKD due to their higher baseline risk.

Epidemiological data show an association of dyslipidemia with accelerated glomerular filtration rate decline,[28,29] and some data suggest this decline may be attenuated with statin therapy.[30] However, this evidence is not strong enough to support treatment of dyslipidemia solely for the purpose of renoprotection.

Therefore, statin treatment in patients with stage 1–3 CKD should be aimed at reducing cardiovascular risk in accordance with lipid guidelines for the general population.[12] Patients at low risk of cardiovascular events (10-year Framingham risk score ≤ 10%) should be initiated on statin therapy if LDL cholesterol > 5.0 mmol/L or total cholesterol/HDL cholesterol > 6.0 mmol/L, while those at moderate cardiovascular risk (10-year Framingham risk 10%–19%) should be initiated on treatment if LDL cholesterol > 3.5 mmol/L or total cholesterol/HDL cholesterol > 5.0 mmol/L. Patients with stage 1–3 CKD who are at high risk of cardiovascular events (10-year Framingham risk score ≥ 20%), including all patients with diabetes or established atherosclerotic disease, should be treated with a statin.

The optimal statin dose in patients with CKD is unknown, although existing trials[19,26,27] have demonstrated cardiovascular benefit at low to moderate doses (see Table 1:

pravastatin 40 mg; simvastatin 40 mg; atorvastatin 10 mg). Although no data examine the cardiovascular benefits of high *versus* low dose statin therapy in CKD patients specifically, higher doses of statins lead to better clinical outcomes in the general population. In addition, preliminary data indicate that the increased risk of adverse events due to higher dose statin therapy is similar in people with and without a glomerular filtration rate < 60 mL/min/1.73m^2.[31] Therefore, moderate to high dose statin therapy (pravastatin or simvastatin 40 mg, or atorvastatin 40–80 mg, regardless of baseline LDL cholesterol) would represent reasonable initial therapy in patients with stage 1–3 CKD in whom statin therapy is indicated based on guideline 1.9. Alternatively, consideration could be given to titrating the dose of statin to achieve specific LDL cholesterol targets in people with CKD, recognizing that this strategy has not been shown to improve outcomes even in the general population. Based on recommendations from the general population, reasonable LDL cholesterol targets for dose titration in stage 1–3 CKD would be at least a 40% reduction for patients at low to moderate cardiovascular risk, or < 2.0 mmol/L for those at high risk or with diabetes or established atherosclerosis.

There are no prospective, randomized controlled trials demonstrating that statin therapy improves cardiovascular outcome in patients with stage 4 CKD, and such patients were generally excluded from existing trials.[19,26,27] One small open-label randomized trial in stage 4 CKD (n = 33) demonstrated a trend towards a reduced risk of cardiovascular events (myocardial infarction, coronary revascularization, or death) in nondialysis dependent patients with stage 4–5 CKD who received atorvastatin 10 mg daily rather than placebo (odds ratio 0.41; 95% confidence interval 0.16–1.07).[18] In addition, among those with stage 3 CKD, there is no evidence of declining statin efficacy at lower levels of kidney function. Finally, the absolute risk of cardiovascular events is markedly higher in patients with stage 4 CKD (as compared to those with stage 3 CKD), indicating greater potential clinical benefit if statins are indeed effective in this population. Although these data are not conclusive, clinicians may consider the use of statins in patients with stage 4 CKD to reduce cardiovascular risk. While guidelines for the general population would suggest an aggressive LDL cholesterol target for such patients (LDL< 2.0 mmol/L, given their high baseline cardiovascular risk), no data demonstrate the safety or efficacy of this strategy. If statin therapy is selected, empiric prescription of a moderate dose (simvastatin or pravastatin 40 mg; atorvastatin 10–20 mg) would be reasonable. Higher dose therapy could also be considered in patients at lower risk of toxicity (see guideline 1.10) acknowledging the lack of supporting evidence. Conversely, until results are available from randomized controlled trials evaluating statin therapy on cardiovascular risk reduction in stage 4 CKD,[32,33] clinicians may wish to forego statin treatment.

Fibrate treatment (which tends to lower triglycerides and increase HDL cholesterol) appears to reduce the risk of cardiovascular events in certain populations (including those with stage 1–3 CKD and concomitant low HDL cholesterol.[34] However, the cardiovascular benefits of fibrates (or other treatments targeting triglycerides and HDL cholesterol) are less well established than those attributable to statins.[35] Therefore, treatment with a fibrate should be considered only if statins are not tolerated or if HDL cholesterol remains persistently low despite statin treatment. Gemfibrozil has been shown

to be well tolerated in patients with stage 1–3 CKD, with no significant persistent effect on renal function.[36] There are no data to support treatment of elevated triglycerides as a cardiovascular risk reduction strategy. The primary indication for triglycerides reduction (with a fibrate or niacin) is to reduce the risk of acute pancreatitis.[37]

Guideline 1.10: Monitoring for medication adverse effects

1.10.1. Serial monitoring of creatinine kinase and alanine aminotransferase is not required in asymptomatic patients with CKD (any stage) treated with a low to moderate dose of statin (≤ 20 mg/d of simvastatin or atorvastatin, or equivalent dose of another statin) (grade A).

1.10.2. Serial creatinine kinase and alanine aminotransferase should be measured every 3 months in patients with stage 4 CKD who are treated with a moderate to high dose of a statin (≥ 40 mg/d of simvastatin or atorvastatin, or equivalent dose of another statin) (grade D).

1.10.3. A statin and fibrate should not be coadministered in patients with stage 4 CKD due to the risk of rhabdomyolysis (grade D).

1.10.4. Gemfibrozil is safe to use in patients with CKD. Other fibrate preparations (e.g., fenofibrate) should be avoided or the dose significantly reduced in patients with stage 2–4 CKD due to an increased risk of toxicity (grade D).

Background

The largest randomized controlled trial of statin therapy in unselected patients (serum creatinine < 200 μmol/L) showed that a moderate dose statin (simvastatin 40 mg/d) did not result in any significant increase in adverse events, including increased creatinine kinase, alanine aminotransferase, or myalgias.[19] Similarly, 7 randomized controlled trials in patients with dialysis-dependent CKD suggest that *low to moderate dose* statin treatment (generally ≤ 20 mg/d of simvastatin or atorvastatin) does not increase the rate of serious adverse events, although a small but clinically significant risk in toxicity cannot be ruled out.[38-44]. Thus, (similar to recommendations for the general population), there is no evidence to support routine serial monitoring of creatinine kinase and alanine aminotransferase in patients with CKD on low to moderate dose statin therapy.

Statin related toxicity (alanine aminotransferase and creatinine kinase elevation) directly relates to the dose of a given statin, as opposed to the on-therapy LDL cholesterol reduction achieved.[45] Thus, the maximal recommended dose of a low potency statin (e.g., fluvastatin) is associated with a greater risk of toxicity than a low to moderate dose of a high potency statin (e.g., rosuvastatin), even if the latter reduces LDL cholesterol to a greater extent. Thus, as illustrated in Table 1, our definition of low, moderate, and high dose statin applies to a given statin dose relative to its maximal recommended dose.

Manufacturer pharmacokinetic data suggest minimal renal metabolism of many statins (atorvastatin, simvastatin, fluvastatin). However, there are no specific trials confirming the safety of moderate to high dose statin therapy in patients with CKD. For this reason, it is reasonable to monitor creatinine kinase and alanine aminotransferase levels in patients

with stage 4 CKD treated with moderate to high dose statins, given the potentially increased risk of adverse events.

The risk of myositis with statin-fibrate combination therapy is well described in unselected patients, although more recent data suggest the risk may be less than reported in early studies.[46] Statin-fibrate combination should be avoided in the CKD population given the lack of safety data. Many fibrates acutely increase serum creatinine, possibly due to inhibited tubular secretion of creatinine or intra-renal vasoconstriction.[47,48] Although no comparative randomized trials have been performed, gemfibrozil may be better tolerated than other fibrates since the incidence of such transient serum creatinine appears to be lower than with other agents.[36,47] Furthermore, many fibrates (e.g., fenofibrate) are renally excreted and should be avoided or significantly dose-reduced in patients with stage 2–4 CKD. If fibrate monotherapy is instituted, consideration could be given to selecting gemfibrozil in preference to other agents.

From the University of Alberta, Edmonton AB

Table 1: Statin dose equivalence

	Atorvastatin	Simvastatin	Pravastatin	Fluvastatin	Rosuvastatin	Lovastatin
Equipotent dose to reduce LDL-C ~ 27%	---	5 mg*	10 mg*	20 mg*	---	10 mg*
	5 mg*	10 mg*	20 mg*	40 mg†	---	20 mg*
	10 mg*	20 mg†	40 mg†	80 mg‡	---	40 mg†
	20 mg†	40 mg†	80 mg‡	---	5 mg*	80 mg‡
	40 mg†	80 mg‡	---	---	10 mg*	
	80 mg‡	---	---	---	20 mg†	
	---		---	---	40 mg‡	

Note: LDL-C = low density lipoprotein cholesterol.
*Dose-related toxicity: Low Dose
†Dose-related toxicity: Moderate Dose
‡Dose-related toxicity: High Dose

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Lifestyle management

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Guideline 1.11: Smoking cessation

1.11.1. Smoking cessation should be encouraged to reduce the risk of developing chronic kidney disease (CKD) and end-stage renal disease, and for reduction of cardiovascular risk (grade D).

Background

The association between smoking and development of CKD and end-stage renal disease has been explored in several cohort studies (Table 2). In one of the largest studies Haroun et al[1] followed 23 534 community-dwelling subjects in the United States over 20 years and showed a greater than 2-fold increased risk for the composite outcome of CKD, end-stage renal disease, or renal-related death for current smokers compared to nonsmokers. Heavy smokers may have an even greater risk of developing end-stage renal disease. Results from the NHANES II study, which included 6341 subjects followed for a mean of 13 years, reported a greater than 2-fold increase in the risk of end-stage renal disease or CKD related death for smokers of > 20 cigarettes per day compared to nonsmokers, but no increased risk for those who smoked < 20 cigarettes per day.[2]

Smoking has also been shown to be an independent risk factor for the development of CKD or worsening renal function among subjects with normal kidney function at baseline[3-6] and has been associated with an increased risk of end-stage renal disease among a cohort of subjects with lupus nephritis.[7] The evidence supporting smoking as a risk factor for worsening kidney function is limited to observational data alone as randomized controlled trials have not been conducted in this area. Therefore, it is impossible to establish whether smoking accelerates progression of kidney dysfunction or whether smoking is associated with other factors that promote kidney disease, such as hypertension and vascular disease. However, the consistency of the evidence in these prospective cohort studies supporting smoking as a risk factor warrants a recommendation for smoking cessation.

Guideline 1.12: Weight reduction

1.12.1. Obese (BMI > 30 kg/m^2) and overweight (BMI of 25.0–29.9 kg/m^2) individuals should be encouraged to reduce their BMI to lower their risk of developing CKD and end-stage renal disease (grade D).

1.12.2. Maintenance of a health body weight (BMI of 18.5–24.9 kg/m^2; waist circumference < 102 cm for men and < 88 cm for women) is recommended for nonhypertensive individuals to prevent hypertension (grade C), and for hypertensive patients to reduce blood pressure (grade B). All overweight hypertensive individuals should be advised to lose weight (grade B).

Background

An increasing number of large cohort studies are available to support the association between obesity and the development of CKD or end-stage renal disease. These cohort studies are summarized in Table 3. The largest cohort study to date included over 320 000 adults with normal kidney function at baseline and over 8 million person-years of follow-up, and demonstrated a dose-response effect between increasing body mass index (BMI) and risk of developing end-stage renal disease.[8] After adjusting for demographic characteristics, cardiovascular risk factors, and baseline serum creatinine, compared to normal BMI (18.5–24.9 kg/m^2), there was an increased risk of end-stage renal disease with each increasing class of obesity. Similar results were demonstrated in a cohort study of Japanese subjects, where each unit increase in BMI was associated with an 11% increased risk of developing end-stage renal disease (odds ratio [OR] 1.11; 95% confidence interval [CI] 1.01–1.22).

Obesity has also been shown to be associated with an increased risk of developing CKD. The Framingham Offspring Study included 2585 participants who were followed for an average of 18.5 years.[6] In this study, 1 standard deviation above the mean BMI was associated with a 23% increased risk of developing CKD (OR 1.23; 95% CI 1.08–1.41). Results of other studies have shown a similar relationship between obesity and development of CKD.[9-11] The association between obesity and risk of CKD has not been demonstrated in all studies, however. Results of the NHANES II study suggested an increased risk of CKD with increasing BMI, although the risk was no longer increased after adjustment of diabetes and hypertension.[2]

The majority of available evidence, albeit based on observational data alone, supports an increased risk of developing CKD and end-stage renal disease with increasing levels of BMI. However, all studies included patients with normal kidney function at baseline, therefore recommendations regarding obesity and *progression* of CKD cannot be made. Based on this evidence, the CKD work group would recommend that obese and overweight individuals be encouraged to reduce their BMI to normal (18.5–24.9 kg/m^2) to reduce the risk of developing CKD and end-stage renal disease. Further research is required regarding the association between obesity and progression of CKD. Maintenance of a healthy body weight for prevention of hypertension, and for reduction of blood pressure among hypertensive patients, is based on the Canadian Hypertension Education Program's recommendations for lifestyle management,[12] which have been generalized to the CKD population for the purposes of these recommendations.

Guideline 1.13: Dietary protein control

1.13.1. A protein-controlled diet (0.80–1.0 g/kg/d) is recommended for adults with CKD (grade D).

1.13.2. Dietary protein restriction of < 0.70 g/kg/d should include careful monitoring for clinical and biochemical markers of nutritional deficiencies (grade D).

Background

The effects of dietary protein restriction on progression of kidney dysfunction are controversial, and individual randomized controlled trials of dietary protein restriction have not provided compelling evidence to adopt this intervention for management of CKD. An earlier randomized controlled trial of 456 Italian patients[13] found that a low protein diet (0.4 g/kg/d compared to 1.0 g/kg/d) produced a small nonsignificant trend toward slowing progression of kidney dysfunction, although concerns regarding noncompliance with the low protein diet have been raised. The largest randomized controlled trial to date, the Modification of Diet in Renal Disease (MDRD) study,[14] showed little overall benefit with a low protein diet (actual protein intake of 0.7 g/kg/d compared to 1.1 g/kg/d; mean glomerular filtration rate 39 mL/min). Even among subjects with more advanced kidney disease (mean glomerular filtration rate 19 mL/min) randomized to a low protein diet or a very low protein diet (0.3 g/kg/d) with supplements, the overall benefit was minimal, and no significant differences in glomerular filtration rate decline were evident.

Four meta-analyses have been conducted over the past 10 years examining the relationship between dietary protein restriction and progression of kidney dysfunction (Table 4). The largest and most recent meta-analysis[15] included 8 randomized controlled trials (n = 1524) and compared severely or moderately reduced protein intake (0.3–0.6 g/kg/d) with standard protein intake. The requirement for renal replacement therapy or death was reduced in the low protein intake group (OR 0.69; 95% CI 0.56–0.86). However, this degree of protein restriction would require supplements to prevent protein malnutrition and therefore is considered an intensive intervention that requires Registered Dietitian consultation and monitoring. The relevance of the outcomes chosen in these studies (end-stage renal disease or death) has been questioned. The only meta-analysis[16] that used estimated glomerular filtration rate as an outcome found only a small benefit of dietary protein restriction (0.53 mL/min/year).

There are several limitations to the prior meta-analyses. First, the majority of the studies included were undertaken prior to implementation of current standards of blood pressure control and use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers. The impact of dietary protein restriction in the setting of these well established interventions is likely to be reduced. Second, the majority of the studies included patients with moderate-to-severe renal insufficiency, many of whom were proteinuric. Generalizability of these results to patients with minimal proteinuria and lesser degrees of kidney dysfunction is debatable. Finally, the appropriateness of the outcome measures has been questioned.

In summary, there is a lack of convincing evidence that long-term protein restriction delays progression of CKD. In addition, the possibility of a modest benefit of low protein diets (0.4–0.7 g/kg/d) on progression of CKD must be weighed against the declines in clinical and biochemical parameters of nutrition.[14,17] Therefore, a protein "controlled" diet consisting of 0.80–1.0 g/kg/d is recommended for adults with CKD, regardless of the presence of diabetes and/or proteinuria. The majority of these studies included subjects

with stage 3 or higher CKD; therefore, the recommendation applies to this patient population.

Guideline 1.14: Alcohol intake

1.14.1. To reduce blood pressure, alcohol consumption in both normotensive and hypertensive individuals should be in accordance with Canadian guidelines for low-risk drinking. Healthy adults should limit alcohol consumption to 2 drinks or less per day, and consumption should not exceed 14 standard drinks per week for men, and 9 standard drinks per week for women (grade B).

Background

The association between alcohol intake and development/progression of CKD is unclear (Table 5). The Physicians Health Study followed a cohort of 11 023 healthy male subjects over 14 years for development of CKD (defined as a glomerular filtration rate < 55 mL/min).[18] After adjustment for demographics and comorbidities, there was no association between alcohol consumption (based on self-report) and risk of CKD. In fact, for subjects in the 2 highest categories of alcohol consumption (5–6 and > 7 drinks per week), there was evidence of a statistically significant reduction in the risk of developing CKD, compared to < 1 drink per week. Lack of an association between alcohol intake and CKD development was also evident in other studies.[5] The work group did not identify any studies evaluating the association between alcohol intake and progression of CKD. Given the limited evidence available, recommendations regarding alcohol consumption to reduce the risk of CKD progression cannot be made. However, there is evidence to support low-risk alcohol consumption for blood pressure reduction in the general population based on the Canadian Hypertensive Education Program guidelines,[12,19] which have been generalized to the CKD population. In these recommendations 1 standard drink is considered to be 13.6 g or 17.2 mL of ethanol, or approximately 1.5 oz of 80 proof (40%) spirits, 5 oz of 12% wine, or 12 oz of 5% beer.

Guideline 1.15: Physical exercise

1.15.1. For nonhypertensive individuals (to reduce the possibility of becoming hypertensive) or for hypertensive patients (to lower their blood pressure), rescribe the accumulation of 30 to 60 minutes of moderate intensity dynamic exercise (walking, jogging, cycling or swimming) 4–7 days per week (grade D). Higher intensities of exercise are no more effective.

Background

There has been a paucity of research in the area of exercise and CKD. In the single randomized controlled trial in this area, 30 patients with nondiabetic CKD and a median glomerular filtration rate of 25 mL/min/1.73 m^2 were assigned to regular exercise or none[20] (Table 6). The exercise goal was to increase energy consumption by 2000 kcal/wk. After a median follow-up of 18 and 20 months in the exercise and control group, respectively, maximal aerobic work capacity (measured by oxygen consumption) was

significantly increased in the exercise group but unchanged in the control group. The median loss of glomerular filtration rate was 0.27 mL/min/month and 0.28 mL/min/month in the exercise and control groups, respectively (NS). Although the follow-up period in this study was short, there was no evidence that exercise prevented or slowed progression of CKD. Based on this evidence, exercise cannot be recommended as an intervention to slow the progression of CKD. However, the benefit of exercise in prevention and treatment of hypertension has been established for the general population, based on the Canadian Hypertension Education Program,[12,19] and is generalized to the CKD population for the purpose of these recommendations.

Guideline 1.16: Dietary salt intake

1.16.1. For prevention of hypertension, a dietary sodium intake of < 100 mmol/d is recommended, in addition to a well-balanced diet (grade B).

1.16.2. For hypertensive patients, dietary sodium intake should be limited to 65–100 mmol/d (grade B).

Background

There were no studies regarding dietary salt restriction and development or progression of CKD that met our inclusion criteria. Although recommendations regarding salt restriction specific for CKD management cannot be provided, the related benefits of salt reduction as they pertain to the development and control of hypertension are available, and the recommendations provided are those based on the Canadian Hypertension Education Program recommendations.[12,19]

Methods

The majority of research regarding risk factors for development and progression of CKD has focused on medical conditions including hypertension and diabetes. More recently, however, emphasis has shifted to examining the association between lifestyle factors and CKD development and progression. The evidence regarding the effect of smoking, obesity, alcohol, exercise, dietary protein restriction, and salt restriction on development and/or progression of CKD, has been reviewed in this chapter, with recommendations provided accordingly. Eligible studies were identified by searching electronic databases (1966 to 2006) and included randomized controlled trials, cohort studies, or meta-analyses which explored the association between the lifestyle factors of interest and the outcomes of development and/or progression of CKD. Studies with proteinuria only as an outcome or that had fewer than 50 subjects were not included. Two reviewers assessed studies for inclusion and abstracted relevant data. A total of 1554 abstracts were reviewed. Data were abstracted from the following number of articles that met the eligibility criteria: smoking (7), obesity (6), alcohol (2), exercise (1), protein restriction (6), and salt restriction (0). For areas in which limited evidence was available, the recommendations from the Canadian Hypertension Education Program were followed, and generalized to the CKD population.

From the University of Calgary, Calgary AB

Table 2: Characteristics and results of included studies of the association between smoking and development and/or progression of chronic kidney disease

Study	N	Study design	Participants	Exposure definition	Duration of follow-up	Outcome definition	Results
Regalado M et al[3]	51	Cohort	Patients referred for hypertension	Nonsmokers Current smokers	Mean 35.4 months	Change in GFR (mL/min/month)	Change in GFR (mL/min/month) • Nonsmokers: - 0.09 • Smokers: - 0.41 ($p < 0.001$)
Baggio B et al[4]	1906	Cohort	Italian population with no renal impairment aged 65–84	Mild (5–10 cig/d) Moderate (11–20 cig/d) Heavy (> 20 cig/d)	Mean 3.6 years	sCr increase > 26.5 umol/L	OR (95%CI) Nonsmoker Ref > 20 cig/d 2.29 (1.00–5.25) Adjusted for age, DM, HTN, fibrinogen
Stengel B et al[2]	6341	Cohort	NHANES II participants	Smokers: < 20 cig/ > 20 cig/	Mean 13.2 years	ESRD- or CKD-related death	RR (95% CI) Never Ref 1–20 cig/d 0.9 (0.5–1.9) > 20 cig/d 2.6 (1.4–4.7) Adjusted for age, sex, race, education, smoking, history of MI, cholesterol, proteinuria, hematuria, creatinine
Shankar A et al[5]	3392	Cohort	CKD free	Nonsmoker Former smoker Current smoker	5 years	CKD (GFR <60 mL/min/1.73m^2	OR (95% CI) Never Ref Former 1.12 (0.63–2.01) Current 1.97 (1.15–3.36) Adjusted for age, sex, education, BMI, DM, CVD, ETOH
Ward M et al[7]	160	Cohort	Patients with lupus nephritis	Nonsmokers Smokers	Median 6.4 years	ESRD (dialysis or Cr Cl < 10mL/min)	HR (95% CI) Nonsmoker Ref Smoker 2.5 (1.1–3.9) Adjusted for BP, biopsy, immunosuppression

Haroun MK et al[1]	23 534	Cohort	Community-based population in United States	Nonsmokers Smokers	20 years	CKD (noted on d/c summary or consult note), dialysis, transplant or death due to kidney disease		HR (95% CI)
							Nonsmokers	Ref
							Smokers	2.6 (1.8–3.7)
							Adjusted for age, DM, gender, BP	
Fox C et al[6]	2585	Cohort	Framingham offspring cohort	Nonsmoker Smoker (≥ 1 cig/d)	Mean 18.5 years	Incident CKD defined as GFR (mL/min/1.73m^2) Male < 64.25 Female < 59.25		OR (95% CI)
							Nonsmoker	Ref
							Smoker	1.42 (1.06–1.91)
							Adjusted for age, sex, DM, BMI, baseline GFR	

Note: GFR = glomerular filtration rate, cig = cigarette, d = day, sCr = serum creatinine, CI = confidence interval, OR = odds ratio, Ref = reference, DM = diabetes mellitus, HTN = hypertension, NHANES II = Second National Health and Nutrition Examination Survey, ESRD = end-stage renal disease, CKD = chronic kidney disease, RR = relative risk, MI = myocardial infarction, BMI = body mass index, CVD = cardiovascular disease, ETOH = ethanol, Cr Cl = creatinine clearance, HR = hazard ratio, BP = blood pressure, d/c = discontinuation.

Table 3: Characteristics and results of included studies of the association between obesity and development and/or progression of chronic kidney disease

Study	N	Study design	Participants	Exposure definition	Duration of follow-up	Outcome definition	Results
Hsu et al[8]	320 252	Cohort	Adult members of Kaiser Permanente with screening check-ups 1964 to 1985	BMI (kg/m^2): 1) Normal: 18.5–24.9 2) Overweight: 25.0–29.9 3) Class I obesity: 30.0–34.9 4) Class II obesity: 35.0–39.9 5) Extreme obesity: ≥ 40	8 347 955 person-years of follow-up	ESRD (from USRDS)	RR (95% CI) Normal Ref Overweight 1.87 (1.64–2.14) Class I 3.57 (3.05–4.18) Class II 6.12 (4.97–7.54) Extreme 7.07 (5.37–9.31) Adjusted for age, sex, race, education, smoking, prior MI, cholesterol, proteinuria, hematuria, creatinine
Stengel et al[2]	6341	Cohort	NHANES II participants	BMI (kg/ m^2): Thin: < 18.5 Normal: 18.5–24 Overweight: 25–29 Obese: 30–34 Morbidly obese > 35	Mean 13.2 years	ESRD- or CKD-related death	RR (95% CI) Normal Ref Thin 1.0 (0.2–3.8) Overweight 0.7 (0.4–1.3) Obese 0.7 (0.4–1.4) Morbid Obesity 1.7 (0.6–4.5) Adjusted for physical activity, smoking, age, gender, race, DM, CVD, HTN, SBP, baseline sCr
Fox et al[6]	2585	Cohort	Framingham offspring cohort	BMI	Mean 18.5 years	Incident CKD defined as GFR (mL/min/1.73m^2) Male < 64.25 Female < 59.25	OR (95% CI) of developing CKD associated with each SD unit increase in BMI: 1.23 (1.08–1.41). Adjusted for age, sex, baseline GFR, BMI, smoking, diabetes
Kramer et al[9]	5897	Cohort	Hypertension Detection and Follow-up Program	BMI (kg/m^2): Ideal: 18.5–24.9 Overweight: 25–29.9 Obese ≥ 30	5 years	GFR < 60 mL/min/1.73 m^2	OR (95% CI) Ideal Ref Overweight 1.21 (1.05–1.41) Obese 1.4 (1.20–1.63)

							Adjusted for BP, diabetes, age, sex race
Gelber et al[10]	11 104	Cohort	Physicians Health Study	BMI as a continuous measure	14 years	GFR <55 mL/min	Each unit increase in BMI associated with OR (95% CI): 1.03 (1.01–1.05) risk of developing CKD Adjusted for age, sex, diabetes, BP, cholesterol, CVD
Iseki et al[11]	100 753	Cohort	Screening exam in Japan		NA	ESRD	Each unit increase in BMI associated with OR (95% CI) 1.11 (1.0 –1.22) risk of ESRD. Adjusted for age, gender BP, proteinuria

Note: BMI = body mass index, ESRD = end-stage renal disease, USRDS = United States Renal Data System, RR = relative risk, CI = confidence interval, Ref = reference, MI = myocardial infarction, NHANES II = Second National Health and Nutrition Examination Survey, CKD = chronic kidney disease, DM = diabetes mellitus, CVD = cardiovascular disease, HTN = hypertension, SBP = systolic blood pressure, sCr = serum creatinine, OR = odds ratio, GFR = glomerular filtration rate, SD = standard deviation, NA = not applicable.

Table 4: Meta-analyses of dietary protein restriction in chronic kidney disease

Author	No. of RCTs (total number of subjects)	Outcome measures	Mean protein intake for "low protein diet"	Results
Pedrini et al[21]	5 (*n* = 1413)	Renal failure or death	0.4–0.6 g/kg/d	Low protein versus normal protein diet: RR 0.56 (95% CI 0.40–0.77)
Kasiske et al[16]	13 (*n* = 1919)	Decline in eGFR (mL/min/1.73 m^2)	0.68–0.73 g/kg/d	Protein restriction reduced eGFR by 0.53 mL/min/year (95% CI 0.08–0.98)
Fouque et al[22]	7 (*n* = 1494)	Requirement for renal replacement therapy or death	0.3–0.6 g/kg/d	Low protein versus standard protein: OR 0.61 (95% CI 0.46–0.83)
Fouque et al[15]	8 (*n* = 1524)	Requirement for renal replacement therapy or death	0.3–0.6 g/kg/d	Low protein versus standard protein: RR 0.69 (95% CI 0.56–0.86)

Note: RCT = randomized controlled trial, RR = relative risk, CI = confidence interval, eGFR = estimated glomerular filtration rate, OR = odds ratio.

Table 5: Characteristics and results of included studies of the association between alcohol and development and/or progression of chronic kidney disease

Study	N	Study design	Participants	Exposure definition	Duration of follow-up	Outcome definition	Results	
Shankar et al[5]	3392	Cohort	CKD free	None Former heavy drinker Current heavy drinker (> 4 drinks/d)	5 years	CKD (GFR < 60 mL/min/1.73m^2	<u>OR (95% CI)</u> Normal Former Current Adjusted for age, sex, education, BMI, DM, CVD, smoking	 Ref 1.31 (0.65–2.63) 1.84 (0.88–3.88)
Schaeffner et al[18]	11 023	Cohort	Physicians Health Study	Alcohol consumption (drinks/week) ≤ 1 2–4 5–6 > 7	14 years	GFR <55 mL/min	<u>OR (95% CI)</u> ≤ 1/wk 2–4/wk 5–6/wk > 7/wk Adjusted for age, BMI, smoking, exercise, DM, family history MI, HTN	 Ref 1.01 (0.83–1.23) 0.77 (0.60–0.99) 0.75 (0.62–0.91)

Note: CKD = chronic kidney disease, d = day, GFR = glomerular filtration rate, OR = odds ratio, CI = confidence interval, Ref = reference, BMI = body mass index, wk = week, DM =- diabetes mellitus, CVD = cardiovascular disease, MI = myocardial infarction, HTN = hypertension.

Table 6: Characteristics and results of included studies of the association between exercise and development and/or progression of chronic kidney disease

Study	N	Study design	Participants	Exposure definition	Duration of follow-up	Outcome definition	Results
Eidemak et al[20]	30	RCT	Nondiabetics with median GFR 25 mL/min	30 min of bicycling daily (or an equivalent physical activity)	18 months	Decline in GFR	No difference in decline in GFR between the groups

Note: RCT = randomized controlled trial, GFR = glomerular filtration rate, min= minutes.

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Proteinuria

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Guideline 2.1: Measuring proteinuria

2.1.1. Screening for proteinuria should be performed in all patients who are at high risk of kidney disease (patients with diabetes, hypertension, vascular disease, autoimmune disease, estimated glomerular filtration rate < 60 mL/min/1.73m^2, or edema) (grade D, opinion).

2.1.2. Screening for proteinuria should be performed by spot urine samples for protein-to-creatinine ratio or albumin-to-creatinine ratio. In diabetic patients, albumin-to-creatinine ratio testing should be performed to screen for kidney disease (grade B).

2.1.3. Protein-to-creatinine ratios > 100 mg/mmol or albumin-to-creatinine ratios > 60 mg/mmol should be considered as thresholds to indicate high risk of progression to end-stage renal disease (grade D).

Background

Proteinuria is a marker of kidney damage. The presence of proteinuria in a urine sample on 2 of 3 consecutive measurements is needed to determine persistent proteinuria, at any level of glomerular filtration rate. It is the earliest marker of kidney damage and should be measured in patients at high risk of kidney disease (e.g., in patients with diabetes, hypertension, vascular disease, autoimmune disease, estimated glomerular filtration rate < 60 mL/min/1.73m^2, and edema). Population screening for proteinuria at present is not recommended.

The gold standard for measuring proteinuria is 24-hour urine protein excretion, but it is cumbersome and subject to collection errors. Because of the excellent correlation between 24-hour urine protein excretion and urine protein-to-creatinine ratio, the preferred method of screening for proteinuria is a single urine sample.[1-3] First morning specimens are preferred, but random urine samples are also acceptable. Alternatively, urine protein excretion can be quantitated and monitored by urine albumin-to-creatinine ratio.[4] Urine albumin-to-creatinine ratio is unreliable in detecting proteinuria secondary to predominantly low molecular weight protein excretion (such as in multiple myeloma or tubulo-interstitial disease). Thus, if chronic kidney disease (CKD) is suspected secondary to paraproteinemia or predominantly tubulo-interstitial disease, proteinuria should be quantified by urine protein-to-creatinine ratio. In order to convert the ratio from mg/mmol into mg/d/1.73m^2, the ratio can be multiplied by 10.[2]

The standard urine dipstick method relies on estimating protein concentration in the urine. Thus, this measurement is influenced by the concentration of the urine. It is only a rough guide to presence or absence of proteinuria, does not quantify proteinuria, and lacks specificity.[5] In dilute urine, a 1+ on the dipstick may represent pathological proteinuria whereas in concentrated urine it may represent normal protein excretion. The urine dipstick detects predominantly albumin and not low molecular weight proteins. A

combination of dipstick proteinuria and specific gravity may be better in the detection of abnormal proteinuria than the dipstick alone.[6]

Proteinuria implies persistent excessive amounts of protein in the urine. Normally, the urine contains less than 150 mg/d of protein of which < 30 mg/d is albumin and the rest is low molecular weight proteins such as Tam Horsfall protein. Microalbuminuria is defined as urine albumin excretion of 30–299 mg/d. In CKD, the percentage of albumin in urine with respect to total protein varies and is usually between 50%–70%.[4] Besides kidney disease, transient increased excretion of protein in urine may occur secondary to upright posture, heart failure, urinary tract infection, sleep apnea, exercise, and fever.[7-9] Pathopysiologically, proteinuria occurs as a result of: a) increased filtration across damaged glomerular capillary walls, b) decreased reabsorption of normally filtered low molecular weight proteins because of tubulo-interstitial damage, and c) increased excretion of low molecular weight proteins because of overproduction in conditions such as multiple myeloma.

Proteinuria is one of the most important risk factors for progression to end-stage renal disease[10-14] and is a strong risk factor for cardiovascular mortality and morbidity.[15-17] Risk of end-stage renal disease increases with increasing proteinuria. The rate of decline in glomerular filtration rate with proteinuria > 1 g/d is substantially higher.[18-22] Proteinuria of 1 g/d corresponds to approximately a protein-to-creatinine ratio of 100 mg/mmol or an albumin-to-creatinine ration of 60 mg/mmol. Reduction in proteinuria correlates with a slower rate of decline in the glomerular filtration rate. In the Modification of Diet in Renal Disease (MDRD) study, a reduction in proteinuria, independent of blood pressure, was associated with a slower decline in glomerular filtration rate.[23] In the REIN study,[24] reduction of proteinuria with angiotensin converting enzyme inhibition correlated with slowing the decline in glomerular filtration rate. A meta-analysis performed by Jafar et al in nondiabetic kidney disease also supports the benefits of proteinuria reduction.[25] Therefore, reducing proteinuria is of paramount importance in retarding the progression of CKD. Although proteinuria is a strong risk factor for end-stage renal disease, there have been no randomized trials primarily addressing the issue of how much of a reduction in proteinuria is optimal.

Guideline 2.2: Treatment of proteinuria

2.2.1. Adults with diabetes and persistent albuminuria (albumin-to-creatinine ratio > 2.0 mg/mmol in males, > 2.8 mg/mmol in females) should receive an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker to delay progression of CKD (grade A).

2.2.2. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are the drugs of choice for reducing proteinuria (grade A).

2.2.3. In carefully selected patients, aldosterone receptor antagonists may decrease proteinuria (grade D).

2.2.4. Protein-controlled diet as well as weight reduction (for patients with an elevated BMI) may provide some benefit in decreasing proteinuria (grade D).

Clinical practice recommendation

In adults with persistent proteinuria (protein-to-creatinine ratio > 50 mg/mmol), in the absence of hypertension or diabetes, consideration should be given to starting an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker.

Pharmacologic therapy

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

It is now well recognized that angiotensin-converting enzyme inhibitors can reduce urinary protein excretion in both diabetics and nondiabetics. In the REIN study, nondiabetic patients with persistent proteinuria and impaired renal function received either ramipril or a placebo, with both arms having equal blood pressure control. In stratum 1 (baseline proteinuria 1–3 g/d), despite equivalent blood pressure control in both arms, there was a 13% decrease in urinary protein excretion in the ramipril arm, compared to a 15% increase in the placebo arm (but there was no change in glomerular filtration rate).[26] In stratum 2 (baseline proteinuria > 3 g/d), there was a 55% decrease in urinary protein excretion, compared to no change in the placebo arm, again despite equivalent blood pressure control.[24] Confirming these findings, a meta-analysis of 1124 patients in 41 trials showed that angiotensin-converting enzyme inhibitors were associated with a 40% decrease in urinary protein excretion, compared to 17% with non-angiotensin-converting enzyme inhibitor treatment.[27] In the same analysis, the mean change in blood pressure was -12% and -11% in the angiotensin-converting enzyme inhibitor and non-angiotensin-converting enzyme inhibitor arms, respectively.

In a meta-analysis of 10 trials involving 646 type 1 diabetic patients with microalbuminuria,[28] 2 years of treatment using angiotensin-converting enzyme inhibitors led to a reduction in mean urinary albumin excretion of 51% compared to non-angiotensin-converting enzyme inhibitor therapy. Moreover, the angiotensin-converting enzyme inhibitor treated patients had an odds ratio of 0.36 for progression to macroalbuminuria and an odds ratio of 3.07 for regression to normoalbuminuria, compared to non-angiotensin-converting enzyme inhibitor treatments.

In a trial of 1209 patients with type 2 diabetes and normoalbuminuria, 3 years of trandolapril therapy significantly delayed progression to microalbuminuria.[29] In the trandolapril-treated arms the rate of progression was 5.8%, while in the nontrandolapril arms the rate of progression was 10.9%. This effect was maintained after controlling for blood pressure differences. Angiotensin-converting enzyme inhibitors have also shown benefit in preventing progression to overt albuminuria. One hundred and eight patients were randomized to enalapril or placebo and followed for 5 years. In the enalpril arm, mean albmuniria stabilized (143 mg/24 h to 140 mg/24 h), while in the placebo group albuminuria increased (123 mg/24 h to 310 mg/24 h).[30] This was associated with a 2 mmHg difference in mean arterial pressure between the arms. The authors calculated that enalapril use was associated with a 30% reduction in absolute risk of progression to overt nephropathy (macroabluminuria). Furthermore, this effect was still apparent at 7 years of follow-up.[31]

Angiotensin receptor blockers have been shown to be effective in reducing proteinuria. Five hundred and ninety patients with type 2 diabetes and microalbuminuria were randomized to placebo or 1 of 2 doses of irbesartan. The investigators noticed a dose-response relationship for reduction of urinary albumin excretion rate by irbesartan. While the placebo arm had a 2% decrease in albumin excretion rate, the 150 mg irbesartan arm had a 24% decrease, and the 300 mg irbesartan arm had a 38% decrease in urinary albumin excretion.[32] Additionally, reversion to normoalbuminuria was observed in 34% of the 300 mg arm, 24% of the 150 mg arm, and 21% of the placebo arm. In a separate study, 1715 patients with type 2 diabetes, who had a median of 1.9 g/d of proteinuria, were randomized to irbesartan, amlodipine, or placebo in order to determine the effects of these medications on incidence of end-stage renal disease or death. After 52 months of follow-up, the urinary protein excretion decreased by 33% in the irbesartan arm, 6% in the amlodipine arm, and 10% in the placebo arm.[33] Another study compared the effects of lorsartan or placebo in 1513 patients with type 2 diabetes and overt nephropathy. Again, the primary outcomes were incidence of end-stage renal disease or death. In this study, use of losartan was associated with a 35% decrease in urinary albumin excretion.[34] In patients with type 2 diabetes and established nephropathy, a trial compared the effect of enalapril or telmisartan on the rate of change of glomerular filtration rate over 5 years. This study found no significant difference in the change of albumin excretion rate between the 2 arms.[35] The authors concluded that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers were equally effective in reducing proteinuria in type 2 diabetes mellitus.

High doses of angiotensin receptor blockers have also been explored for reducing proteinuria. One study of 58 patients with type 2 diabetes and microalbuminura randomized patients to 300, 600, or 900 mg of irbesartan. There was a 15% greater reduction in albuminuria in the high-dose arm compared to the standard-dose arm.[36] There were slightly more complaints of dizziness in the higher dose groups, but no significant difference in blood pressure or potassium in the groups. A separate study compared increasing the dose of candesartan from 16 mg to either 32 or 64 mg of candesartan in 32 patients with both diabetic and nondiabetic nephropathy. While the 32-mg arm did not show a significant improvement in proteinuria, the 64 mg arm's urinary protein excretion declined by 44% at 16 weeks.[37] There were no significant changes in blood pressure or creatinine clearance. No mention is made of serum potassium values.

Combination therapy of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

In nondiabetic CKD, the COOPERATE study compared the effects of losartan, trandolapril, or their combination in 263 patients. Both the only-angiotensin-converting enzyme inhibitor and only-angiotensin receptor blocker arms showed a significant reduction in urinary albumin excretion (41% and 44%, respectively)[38] compared to baseline. Moreover, the combination therapy arm recorded a decrement of 76% in urinary albumin excretion.[38] Thus, in proteinuric nondiabetic CKD, a combination of an

angiotensin-converting enzyme inhibitor and an angiotensin receptor blocker should be considered.

In diabetes, the effect of combination therapy seems less effective. A meta-analysis extracting data from 10 studies revealing a reduction in mean proteinuria of 210 mg/d, as compared to nondiabetics, who had a reduction of 582 mg/d.[39]

Aldosterone receptor antagonists

There has recently been increased interest in the use of specific aldosterone antagonists (spironolactone, eplerenone) for reducing urinary protein excretion. Short-term studies have shown that the addition of spironolactone or eplerenone can induce a reduction in urinary protein excretion.

In a randomized controlled trial of 20 patients with type 1 diabetes with macroalbuminuria and preserved glomerular filtration rate, 25 mg of spironolactone in addition to conventional angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy reduced proteinuria by 30%, compared to conventional therapy alone.[40] In a crossover trial of 21 patients with type 2 diabetes and macroalbuminuria and preserved glomerular filtration rate, the addition of 25 mg of spironolactone to conventional angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy also reduced proteinuria by 30%.[41] In a third randomized controlled study of 20 patients with diabetese (both type 1 and 2) with nephrotic range proteinuria and mildly decreased glomerular filtration rate (~60 mL/min/1.73m^2), the addition of 25 mg of spironolactone to conventional angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy reduced proteinuria by 32%.[42] In all of these studies (performed at the same centre in Denmark), significant hyperkalemia (potassium level > 5.5 mmol/L) was observed in 1, 0, and 2 patients respectively. Of note, the authors excluded patients with glomerular filtration rate < 30 mL/min or baseline potassium level > 4.5 mmol/L in these studies.

In a study of 40 Australian patients with both diabetic and nondiabetic nephropathy, Chrysostomou and colleagues compared the effect of angiotensin-converting enzyme inhibitor alone, angiotensin-converting enzyme inhibitor + angiotensin receptor blocker, angiotensin-converting enzyme inhibitor + spironolactone, or all 3 medications on renal function and proteinuria. These patients had a serum creatinine < 200 µmol/L and a urinary protein excretion of > 1.5 g/24 h, as well as a potassium level < 5.0 mmol/L and HCO_3 > 20 mmol/L. The authors found that the addition of spironolactone was equally effective in reducing proteinuria as the addition of an angiotensin receptor blocker and that triple therapy did not confer any additional benefit.[43] A total of 3 patients experienced potassium levels > 6.0 mmol/L, which responded to diuretic therapy.

Eplerenone is a selective aldosterone antagonist. In a study of hypertensives with intact renal function, patients were randomized to eplerenone or enalapril. In the 20% of patients with an albumin-to-creatinine ratio > 30 mg/g, eplerenone reduced proteinuria by 61%, compared to 26% in the enalapril group, despite equal reductions in blood pressure.[44] All of the studies evaluating aldosterone receptor antagonists have been of

short duration and conducted in carefully monitored settings. It appears that in carefully selected patients, aldosterone receptor antagonists are effective in decreasing proteinuria.

Nonpharmacological therapies

Dietary protein restriction

Low protein diets have been advocated for preventing progression of CKD. The evidence has been controversial, with several studies providing conflicting or inconclusive results.[23,45-49] The effects on protein excretion rates are less well studied. Dussol and colleagues randomized 63 diabetics with a glomerular filtration rate > 80 mL/min and < 1g/d of proteinuria to either a normal (1.2 g/kg/d) or low (0.8g/kg.d) protein diet.[50] All patients were on renin angiotensin system blocking agents. There was no significant decrement in protein excretion. In 2 separate randomized controlled trial in diabetics, a less severe protein restriction (0.8 g/kg/d) failed to alter rate of albuminuria.[50,51] In the largest study to date, the MDRD study, 585 patients with nondiabetic moderately deceased glomerular filtration rate (glomerular filtration rate 25–55 mL/min/1.73m^2) and a reduced protein intake (0.58 g/kg/d) achieved a greater reduction in urine protein excretion compared to the usual protein diet group (17.1% versus 3.9%).[49] There was no significant relationship between baseline proteinuria and the effect of treatment. While there is insufficient evidence that protein restriction to 0.6 g/kg/d delays progression of CKD, it may have a beneficial impact on urinary protein excretion. It should be noted that implementation of a low protein diet is difficult and if attempted should be in conjunction with a well-trained dietitian.

Salt restriction

In short-term studies, acute reduction of sodium intake uniformly has a favorable impact on urinary protein excretion.[52-55] The long-term impact of sodium restriction on proteinuria has not been well documented. In a retrospective review over 3 years, patients ingesting < 200 mEq/d of sodium had a lower rate of glomerular filtration rate decline and a stabilization of urinary protein excretion, while patients who ingested > 200mEq/d had an increase in urinary protein excretion.[56] No prospective trials have been conducted evaluating the effect of salt restriction in patients with CKD and abnormal urine protein excretion.

Weight loss

In patients with established CKD, there are few prospective studies with regard to obesity and/or weight loss. Praga et al demonstrated that, in obese patients with biopsy proven glomerulonephritis and a mean of 2.9 g/d of proteinuria, a hypocaloric diet resulted in a body mass index (BMI) decrement of 5 kg/m^2 and a reduction in proteinuria to 0.4 g/d.[57] A separate study randomized 30 patients with > 1g/d of proteinuria and a creatinine < 177 µmol/L to a hypocaloric diet or control arm.[58] At 5 months, BMI decreased from 33.0 to 31.6 kg/m^2, while proteinuria decreased from 2.8 to 1.9 g/d. Both of these changes were statistically significant. There were no changes in blood pressure or creatinine clearance. In neither of these studies were there any reports of adverse events related to the hypocaloric diet. Both of these studies enrolled small numbers of patients

and were short term. In the short term, limited data suggests that modest weight reduction (< 10% total body weight) in obese patients appears safe and effective in reducing urine protein excretion in patients with CKD.

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Anemia

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Guideline 2.3: Assessment of anemia in stage 3–5 chronic kidney disease patients

2.3.1. Anemia is diagnosed in patients with chronic kidney disease (CKD) and a hemoglobin level (grade D, opinion):

- < 135 g/L in all adult males
- < 120 g/L in all nonpregnant iron-replete adult females.

Background

Anemia may develop early in the course of patients with CKD and is nearly universal in patients with stage 5 CKD.[1] Anemia, associated with CKD, may begin to develop at glomerular filtration rate levels < 60 mL/min/1.73m^2 as estimated by the Modification of Diet in Renal Disease (MDRD) formula, and becomes more common at more severe levels of kidney failure (i.e., stage 4 and 5 CKD.[2] Anemia may develop earlier and be more severe in patients with CKD who have diabetes.[3] Current evidence would suggest that patients with CKD should have their hemoglobin levels checked at least annually.[4]

The importance of identifying patients with anemia in the presence of CKD is 2-fold. First, significant anemia in the general population may represent nutritional deficits, systemic illness, or other significant disorders that warrant attention. Second, anemia in patients with CKD, with or without diabetes, is strongly associated with adverse clinical outcomes,[5-7] including hospitalizations, cardiovascular disease, and mortality.[2,7,8] This does not imply that all CKD patients with anemia warrant immediate treatment with erythropoietic stimulating agents as significant adverse events can occur with this therapy (see below). However, assessment of patients with anemia and CKD may reveal a treatable cause for anemia (e.g., iron deficiency), and given that anemia is a risk factor for adverse events including cardiovascular disease, it may identify patients who may benefit from more aggressive cardiovascular risk factor modification.

Guideline 2.4: Initial evaluation of anemia in stage 3–5 chronic kidney disease patients

2.4.1. Consider testing patients with CKD and a hemoglobin level < 120 g/L for the following (grade D, opinion):

- hemoglobin
- white blood count and differential
- platelet count
- red blood cell indices
- absolute reticulocyte count
- serum / plasma ferritin
- transferrin saturation.

Background

Although erythropoietin deficiency is common among patients with anemia and CKD, other potential causes and contributing disorders should be assessed. Clinicians should consider investigating for other causes of anemia (as above) when the severity of the anemia is disproportionate to the degree of renal dysfunction, when there is evidence of iron deficiency, or when there is evidence of abnormalities in any other blood cell line, since this may indicate a bone marrow problem requiring hematology assessment. In the absence of these findings and when the anemia is not severe (i.e., > 120 g/L), further workup for other causes of anemia may not be required in all nonreferred CKD patients.

For several technical reasons, measurement of hemoglobin, rather than hematocrit, is preferred during the assessment of anemia.[2] In general, the anemia of CKD is normochromic (assessed using the MCV) and normocytic (assessed using the MCH), similar to patients with anemia of chronic disease. Patients with anemia of CKD also have a low absolute reticulocyte count, a marker of insufficient erythrocyte proliferation, due most commonly to insufficient erythropoietic stimulation, or lack of available iron. Erythropoietin levels are not routinely useful in distinguishing erythropoietin deficiency as the cause of anemia from other causes of anemia in the CKD patient and should not be ordered.[9,10]

Serum ferritin levels are surrogate markers for the adequacy of tissue stores of iron, whereas the transferrin saturation is more commonly thought of as indicating the iron that is effectively available for erythropoiesis. Checking iron status with these tests before treating anemia in patients with CKD assesses the contribution of iron deficiency to the anemia, which, if present, would require appropriate workup.[2]

Workup of CKD patients with classic iron deficiency (ferritin levels below the lower limit of normal for males and females as identified using local laboratory ranges) should incorporate the same approach as for the non-CKD patient with iron deficiency.

Unfortunately, current iron status tests do not accurately predict an individual's likelihood to respond to iron supplementation with an increase in hemoglobin. However, patients may respond with an increase in hemoglobin following iron therapy even when the iron status results do not indicate classic iron deficiency as defined above.

Guideline 2.5: Use of erythropoietin-stimulating agents in stage 3–5 chronic kidney disease patients

2.5.1. For CKD patients with anemia and adequate iron stores (see below), erythropoiesis-stimulating agents should be initiated when the hemoglobin level falls below 100 g/L (grade D, opinion).

2.5.2. For CKD patients receiving erythropoiesis-stimulating agents, the target hemoglobin level is 110 g/L (grade A). An acceptable hemoglobin range is 100–120 g/L.

2.5.3. Erythropoiesis-stimulating agents should be prescribed in conjunction with a specialist with experience in prescribing these agents (grade D,

opinion).

Background

In patients with CKD, anemia is associated with left ventricular hypertrophy and adverse cardiovascular and clinical outcomes. Moreover, anemia is associated with a reduction in quality of life, though in the only clinical trial that has compared a low hemoglobin target with an intermediate target, quality of life did not differ between these 2 strategies.[2,11] As such, the goal of treating anemia in iron-replete patients with erythropoietic stimulating agents is to reduce the likelihood of cardiovascular events, improve patients' survival, and/or improve patient's quality of life while minimizing any deleterious effects of the drug. Given that erythropoietic stimulating agents increase blood pressure and have other potential side-effects, it is also important to assess whether the use and quantity of the erythropoietic stimulating agent used might contribute to adverse events such as more rapid deterioration of kidney function and earlier requirement for dialysis. In addition to achieving these therapeutic goals without significant adverse events, it is acknowledged that, if left untreated, patients with severe anemia may require blood transfusions, which have associated risks and costs and potential negative implications for patients awaiting a kidney transplant. As such, when considering the use of erythropoietic stimulating agents in most developed countries, the question has often not been whether to use erythropoietic stimulating agents or not, but when to use and what target hemoglobin to aim for in CKD patients with significant anemia.[12]

The earliest anemia correction studies in CKD patients compared the use of erythropoietin alfa with placebo.[11,13,14] Most early studies were not designed and powered to examine clinical outcomes other than quality of life and no differences in non-quality-of-life outcomes were apparent. Several of the studies showed improvements in quality of life compared with placebo.[11,13,14]

Subsequent randomized controlled trials have tended to examine the impact of using erythropoietic stimulating agents to achieve different target hemoglobin ranges on surrogate endpoints such as left ventricular mass, where patients in the lower hemoglobin target would be less likely to require the use of an erythropoietic stimulating agent or would require lower doses to maintain the prespecified lower target hemoglobin. In the 4 randomized controlled trials involving nondialysis-dependent CKD patients that compared intermediate (90–105 g/L) and high hemoglobin targets (120–140 g/L)[4,15-17] and measured left ventricular mass, no differences in left ventricular mass were observed. However, variable effects in quality of life were seen in 3 out of 4[15-17] of these studies and in the much larger CHOIR trial.[18] (Quality of life outcomes have not been reported from the trial by Levin et al.[4]) In the study by Roger and colleagues, there was no significant difference noted in quality of life scores though the prescribed difference in achieved hemoglobin levels in the intermediate and high arms was not achieved (108 versus 121 g/L).[15] In the ACORD study, which randomized patients with diabetes and stage 1–3 nondialysis-dependent CKD, there was a clinically small, but statistically significant difference reported in 1 of the 8 measured domains of the Short Form 36 Health Survey (SF-36).[16] Although quality of life in the CREATE trial[17] improved in the higher hemoglobin target group across all 6 measured domains, the effect size diminished

with time. Finally, no quality of life benefits were observed for the high hemoglobin target group in the CHOIR trial.[18]

Two studies specifically designed to test the effect of different target hemoglobin levels or ranges on hard clinical outcomes have been completed in nondialysis-dependent CKD patients.[17,18] In the CHOIR study, 1432 patients with nondialysis-dependent CKD were assigned to receive either an erythropoietic stimulating agent dose targeted to achieve a hemoglobin level of 135 g/L or a dose targeted to achieve a level of 113 g/L. The primary endpoint, a composite of death, myocardial infarction, hospitalization for congestive heart failure (without renal replacement therapy), and stroke, occurred in 125 patients in the high-hemoglobin group, as compared with 97 patients in the intermediate-hemoglobin group (hazard ratio [HR] 1.34; 95% confidence interval [CI] 1.03–1.74; $p = 0.03$).[18] The HR for death comparing high versus intermediate hemoglobin target was 1.48 ($p = 0.07$). As discussed above, using the Kidney Disease Questionnaire and the SF-36, the investigators found no difference in health-related quality of life for patients in the intermediate and high groups. Patients randomized to the high hemoglobin group had more serious adverse events.

In the CREATE study, 603 patients with nondialysis-dependent CKD and mild-to-moderate anemia were randomly assigned to a target hemoglobin value of 130 to 150 g/L, or 105 to 115 g/L.[17] The primary endpoint, a composite of 8 cardiovascular events, occurred in 58 patients in the high hemoglobin group and 47 patients in the intermediate hemoglobin group (HR 0.78 for intermediate versus high groups; $p = 0.20$). Dialysis was required in more patients in the high hemoglobin group than in the intermediate hemoglobin group (127 versus 111; $p = 0.03$) even though rates of change in glomerular filtration rate were similar. While higher hemoglobin targets led to improvements in quality of life, the magnitude of these effects diminished over time. In addition, it is unknown whether the nonblinded nature of the trial influenced these quality of life findings. There was no significant difference in the combined incidence of adverse events between the 2 groups.

Subsequent to the completion of these studies, a meta-analysis was completed to determine whether targeting different hemoglobin concentrations with erythropoietic stimulating agents was associated with altered all-cause mortality and cardiovascular events in CKD patients with anemia.[19] This meta-analysis included studies that assessed the effects of targeting different hemoglobin concentrations in CKD patients with anemia who were randomly assigned to treatment with erythropoietic stimulating agents, recruited at least 100 patients, and had a minimum follow-up of 12 weeks. The results of 9 randomized controlled trials enrolling 5143 patients were included. There was a significantly higher risk of all-cause mortality (risk ratio 1.17; 95% CI 1.01–1.35; $p = 0.031$) in the higher hemoglobin target group compared with the lower hemoglobin target group.

Summary

Targeting a hemoglobin above 130 g/L using higher doses of erythropoietic stimulating agents does not provide clinically significant benefits and is associated with an increased

incidence of death and/or the need for dialysis in patients with nondialysis-dependent CKD. The target hemoglobin in the intermediate hemoglobin groups in the largest randomized controlled trials generally ranged from 90–120 g/L, and it is unknown at what "target hemoglobin" level above this range the incidence of adverse events increases. Given this, and noting that the quality of life improvements associated with high hemoglobin targets were inconsistently noted and/or were clinically small, for all CKD patients receiving erythropoietic stimulating agent therapy, we recommend a target hemoglobin of 110 g/L. Given that it is not practical to achieve a hemoglobin of exactly 110 g/L, a hemoglobin range between 100 and 120 g/L (aiming for 110 g/L) is acceptable for monitoring compliance with this clinical practice guideline. Practical aspects of achieving this target hemoglobin and avoiding hemoglobin levels above 120 g/L, as recommended by the recent Health Care Professional Letter released jointly by Health Canada and the makers of Eprex and Aranesp, have been discussed in the recently released Canadian Nephrology Society Anemia Guidelines.

Given that there has been no demonstrated benefit to starting erythropoietic stimulating agents early, and that an increased risk of adverse events has not been ruled out, asymptomatic nondialysis-dependent CKD patients should not receive erythropoietic stimulating agent therapy *until the hemoglobin falls below 100 g/L* and only then once iron supplementation has been considered and other reversible causes of anemia have been treated.

Of Note:
This guideline engendered significant discussion and debate both among the Canadian Nephrology Society Anemia Guideline members and at the Canadian Nephrology Society Annual Meeting, particularly given the recent Health Care Professional Letter released jointly by Health Canada and the makers of Eprex and Aranesp stating that the hemoglobin during erythropoietic stimulating agent therapy should not be higher than 120 g/L. It should be noted that other hemoglobin targets (i.e., target hemoglobin 105 g/L, or target hemoglobin range 100–110 g/L) were considered by the CKD work group. All work group members agreed that targeting hemoglobin above 120 g/L should not be undertaken. There was less agreement as to the extent of the safety concern for patients in whom the hemoglobin rises incidentally above 120 g/L, despite targeting at 110 g/L, and whether they were at increased risk of cardiovascular events. It was generally agreed that hemoglobin levels above 120 g/L should be avoided.

Guideline 2.6: Use of iron therapy in stage 3–5 chronic kidney disease patients

2.6.1 For CKD patients *not* receiving erythropoiesis-stimulating agents and with a hemoglobin level < 110 g/L, iron should be administered to maintain the following iron indices (grade D):
- ferritin > 100 ng/mL
- transferrin saturation > 20%.

2.6.2. For CKD patients receiving erythropoiesis-stimulating agents, iron should be administered to maintain the following iron indices (grade D):
- ferritin > 100 ng/mL

- transferrin saturation > 20%.

2.6.3. For CKD patients, oral iron is the preferred first-line therapy (grade D, opinion).

2.6.4. Chronic kidney disease patients who do not meet serum ferritin and/or transferrin saturation targets on oral iron or who do not tolerate oral iron should receive intravenous iron (grade D, opinion).

Background

Chronic kidney disease patients with anemia may increase their hemoglobin level following any form of iron therapy, even when iron status results do not indicate classic iron deficiency. For instance, in 2 randomized controlled trials that enrolled nondialysis CKD patients with a mean hemoglobin of ~ 100 g/L and ferritin levels of ~ 100 ng/mL, the average hemoglobin level increased by 4–7 g/L and 7–10 g/L over 6–8 weeks in patients randomized to receive oral and intravenous iron, respectively.[20,21]

It is unknown if treating CKD patients with a hemoglobin > 110 g/L, and a ferritin of < 100 ng/mL or transferrin saturation below 20% with oral iron is either effective at increasing hemoglobin levels or associated with improvement in any clinical outcome of interest. In the absence of this data, and given the potential side effects of oral and intravenous iron, treatment of CKD patients without evidence of classic iron deficiency cannot be justified in patients whose hemoglobin is > 110 g/L.

With respect to the effectiveness of intravenous versus oral iron in increasing hemoglobin levels in anemic patients with nondialysis CKD,[20-23] 2 randomized controlled trials have shown that intravenous iron is more effective than oral iron.[20,21] However, the absolute difference in hemoglobin was small, and in the only study that measured quality of life, no difference was noted between patients receiving oral or intravenous iron.[21] Finally, there are safety concerns with the use of intravenous iron as infusion-related adverse events occurred in 5 of 117 (4.3%) patients receiving intravenous iron.[21,23]

Reflecting concern that frequent intravenous iron infusion may jeopardize future options for vascular access, and the fact that intravenous iron is considerably more expensive than oral iron, we recommend that oral iron be considered first. The use of intravenous iron can be considered in those patients whose hemoglobin has fallen below 110 g/L who either do not tolerate oral iron or who do not meet iron status targets despite the maximally tolerated dose of oral iron. The results of iron status tests, hemoglobin, erythropoietic stimulating agent dose, and the overall condition of the patient should be interpreted together to guide iron therapy. For complex patients, the involvement of a physician with expertise in CKD anemia management is recommended.

With regard to the safety and efficacy of ongoing iron administration in patients with elevated ferritin levels, limited data exist to determine whether a serum ferritin upper limit of 500 ng/mL, or even a higher limit of 800 ng/mL, should be used to guide the clinician's decision regarding the risk and benefit of intravenous iron at or above those levels. Only 1 randomized controlled trial has been published which addresses this issue and it was performed in hemodialysis patients.[24] While this study showed that

administration of intravenous iron in patients with transferrin saturation < 25% and elevated ferritin levels (> 500 ng/mL and even 800 ng/mL) resulted in a greater increase in hemoglobin compared with patients who were not given additional iron, it is unknown if this data is generalizable to nondialysis CKD patients. Safety of iron at various serum ferritin levels will remain a major concern as long as it remains untested in adequate trials. Thus, every clinician should balance the probability of achieving an increase in hemoglobin or reduction in erythropoietic stimulating agent dose in light of their specific patient's perceived risk, when considering ongoing iron administration in patients with serum ferritin levels above commonly seen levels.

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Mineral Metabolism

Martina Reslerova

Disclaimer: Currently there is limited evidence regarding the impact of mineral metabolism abnormalities (or treatment thereof) on outcomes in patients with chronic kidney disease (CKD) who are not on dialysis. The following recommendations are primarily extrapolated from data obtained from the dialysis patient population, and thus statements are limited in scope due to the need for an evidentiary base.

Guideline 2.7: Assessment of mineral metabolism abnormalities in chronic kidney disease, and therapeutic targets

2.7.1. Serum calcium, phosphate, and parathyroid hormone levels should be measured in adults with stage 4 and 5 CKD and in adults with stage 3 CKD and progressive decline in renal function (grade D, opinion).

2.7.2. Serum phosphate levels should be maintained within normal range (grade C).

2.7.3. Serum calcium levels should be maintained within normal range (grade D).

2.7.4. Intact parathyroid hormone level may be elevated above normal value; the target level of serum intact parathyroid hormone is unknown (grade D, opinion).

Background

The term ***chronic kidney disease – mineral and bone disorder*** (CKD-MBD) was proposed by a panel of experts of the Kidney Disease: Improving Global Outcomes (KDIGO) group and represents a useful conceptual framework for clinical management of mineral metabolism abnormalities.[1] Furthermore, the terminology allows a framework in which to study and understand this complex condition. CKD-MBD is defined as a clinical syndrome manifested by an abnormality in one or more of the following:

1. Laboratory abnormalities (calcium, phosphorus, parathyroid hormone, vitamin D metabolism)
2. Bone abnormalities (the term "renal osteodystrophy" is to be used exclusively to describe altered bone morphology)
3. Extraosseous calcifications (vascular or other).

When managing patients with CKD-MBD, all 3 aspects of the disorder should be considered.

1. Laboratory abnormalities

Renal excretory function plays an important role in the maintenance of calcium and phosphate balance. In addition, the kidney is a site of 1α-hydroxylation of 25-hydroxyvitamin D (calcidiol, $25(OH)D_3$) to its active form, 1,25-dihydroxyvitamin D (calcitriol, $1,25\text{-}(OH)_2D_3$). As renal function declines in CKD, calcitriol deficiency promotes parathyroid gland hyperplasia and increased parathyroid hormone synthesis, ultimately leading to secondary hyperparathyroidism.

In earlier stages of CKD, high parathyroid hormone increases fractional phosphate excretion and maintains serum calcium levels within normal limits. With progressive loss of renal function, and despite "compensatory" parathyroid hormone elevation, hyperphosphatemia and hypocalcemia develop relatively late in the course of secondary hyperparathyroidism.[2] In a recent study of predominantly stage 3 CKD patients, increases in parathyroid hormone were observed at estimated glomerular filtration rate levels of approximately 45 mL/min/1.73 m^2, while hyperphosphatemia and hypocalcemia did not develop until estimated glomerular filtration rate decreased to < 20 mL/min/1.73 m^2.[3]

The potential deleterious effects of hyperphosphatemia are 2-fold: classical role in pathophysiology of secondary hyperparathyroidism and emerging role in pathophysiology of vascular calcification. Hyperphosphatemia impairs calcitriol synthesis, promotes parathyroid hormone synthesis, and increases skeletal resistance to parathyroid hormone, resulting in secondary hyperparathyroidism and its known effects on bone. Observational studies in the general population, CKD and hemodialysis patients suggest an association between phosphate level and mortality risk.[4-6] To date, there have been no prospective trials demonstrating that improved phosphorus control improves survival.

Given the metabolic abnormalities that develop with CKD, measurement of calcium, phosphate, and parathyroid hormone is recommended. Although the optimal frequency of monitoring is unknown, consideration should be given to yearly monitoring in progressive stage 3 CKD, with more frequent monitoring in stage 4 and 5 or if dietary interventions or pharmacotherapy are initiated.

2. Bone abnormalities

Traditionally, the main focus of CKD-MBD was bone abnormalities, namely high turnover bone disease (osteitis fibrosa cystica). However, a number of factors including treatment with calcium containing phosphate binders and vitamin D analogs, as well as changes in patient demographics (older age, increased prevalence of diabetes, and increased ethnic minority groups) have altered the spectrum of bone disease in CKD.[7]

The rationale for treating elevated parathyroid hormone is to normalize bone turnover and histology. It is unknown what target levels of parathyroid hormone are appropriate at CKD stages 3 to 5 to maintain normal bone histology. In stage 5, immunoreactive parathyroid hormone < 13.2 pmol/L was associated with adynamic bone disease and > 450 pg/mL with renal osteodystrophy.[8] Larger prospective studies are needed to determine appropriate immunoreactive parathyroid hormone targets.

Both undertreatment (uncontrolled hyperparathyroidism) as well as overtreatment (adynamic bone disease) are potentially deleterious. Adynamic bone disease predisposes patients to fractures, at least in dialysis patients.[9,10] Increased risk of fracture is also observed in dialysis patients with poorly controlled hyperparathyroidism.[11] In dialysis patients, immunoreactive parathyroid hormone around 33 pmol/L is associated with the lowest risk of fractures.[12] Similar data are not available for earlier stages of CKD.

Furthermore, prospective studies are needed to confirm that maintenance of parathyroid hormone within target range results in fewer complications in dialysis or CKD patients.

3. Extraosseous calcification

Excessive cardiovascular calcification has been reported in dialysis patients,[13] including pediatric patients.[14] Population-based studies report increased incidence of coronary calcification in patients with stage 3–5 CKD (not on dialysis).[15] In vitro studies have implicated high extracellular phosphate concentrations in pathophysiology of uremic vascular calcification. Rather than passive precipitation, "uremic" vascular calcification is a highly regulated active process involving endogenous promoters as well as inhibitors of mineralization.[16] Of relevance to CKD patients, extracellular calcium potentiates phosphate-induced mineralization in vitro.[17] In the clinical setting both hyperphosphatemia as well as therapy for hyperphosphatemia (calcium containing phosphate binders) could exacerbate uremic vascular calcification and contribute to morbidity and mortality in CKD patients.

Guideline 2.8: Treatment options

2.8.1. Dietary phosphate restriction should be used continuously to treat hyperphosphatemia (grade D).

2.8.2. Therapy with calcium containing phosphate binders (calcium carbonate or calcium acetate) should be initiated if dietary restriction fails to control hyperphosphatemia and if hypercalcemia is not present (grade D).

2.8.3. If hypercalcemia develops, reduce dose of calcium containing phosphate binders or vitamin D analogues (grade D, opinion).

2.8.4. Correct hypocalcemia if symptomatic or associated with increasing parathyroid hormone levels (grade D, opinion).

2.8.5. Consider using vitamin D analogues if serum intact parathyroid hormone levels > 53 pmol/L; discontinue therapy if hypercalcemia or hyperphosphatemia develops or if parathyroid hormone falls below 10.6 pmol/L. Vitamin D analogues should be used in conjunction with a specialist with experience in prescribing these agents (grade D, opinion).

2.8.6. There is insufficient evidence to recommend use of non-calcium-containing phosphate binders, novel vitamin D analogs, or calcimimetics (grade D, opinion).

Rationale

Given that hyperparathyroidism in end-stage renal disease is associated with worse outcomes and is difficult to treat once parathyroid gland hyperplasia develops, the CKD working group and experts have recommended that preventing hyperparathyroidism in earlier CKD would be of benefit. In the absence of hard outcome data supporting this practice, the following is considered "best practice": maintenance of normal calcium and phosphate levels to attenuate the rise in parathyroid hormone, and supplementation with active vitamin D if parathyroid hormone is elevated**.**

Background

Management of hyperphosphatemia

Dietary phosphate restriction (800–1000 mg/d) is an initial step in control of hyperphosphatemia and hyperparathyroidism.[2] With progression of CKD, the majority of patients eventually require administration of phosphate binders. Dietary education is crucial, and patients should learn to adjust their phosphate binder dose according to the phosphate content of each meal.

Choice of phosphate binders: Use of aluminum hydroxide should be limited because of side effects related to aluminum accumulation with long-term administration (anemia, encephalopathy, bone abnormalities). Calcium-containing phosphate binders may lead to positive calcium balance due to calcium absorption and can lead to hypercalcemia, especially in patients treated with active vitamin D.[18] Calcium carbonate effectively controls hyperphosphatemia and lowers parathyroid hormone in patients with CKD[19]. Calcium acetate contains less elemental calcium (25% versus 40%) and binds more phosphorus per amount of calcium absorbed. In a meta-analysis performed by the Kidney Disease Outcomes Quality Initiative (KDOQI), it was suggested that calcium carbonate leads to more hypercalcemia that calcium acetate.[20]

Daily calcium intake in the form of phosphate binders (calcium load) has been associated with cardiovascular calcification in dialysis patients, especially in the presence of low turnover bone disease.[14,21,22] Non-calcium-containing phosphate binders (sevelamer and lanthanum) were recently developed which avoid excessive calcium loading; however, the evidence to support their use in CKD is limited.

Studies of sevelamer use have been conducted in the dialysis population, with varying results. Sevelamer has been shown to attenuate progression of cardiovascular calcification and cause less hypercalcemia.[23] In the Renagel in New Dialysis (RIND) trial of 129 patients starting hemodialysis, patients were randomized to either sevelamer or a calcium-containing phosphate binder.[24] The secondary endpoint of the original study, mortality, was decreased in the group originally treated with sevelamer compared with the calcium binder group. In addition, baseline calcification scores were predictive of mortality.[25] Despite limitations (secondary analysis, small sample size), this is the first study directly linking baseline coronary calcification with risk of mortality in hemodialysis patients. Further studies are needed to confirm this finding.

In the absence of data proving survival benefit to sevelamer-treated patients (presumably by decreasing cardiovascular calcification), replacement of calcium-containing phosphate binders by sevelamer cannot be recommended. In fact, the potential economic impact in Canada may be prohibitive.[26]

Lanthanum is a rare earth element with mainly biliary excretion. Like sevelamer, lanthanum binds dietary phosphate and lowers serum phosphate levels in dialysis patients with fewer episodes of hypercalcemia compared with calcium carbonate. Its use has also been associated with improvement in bone histomorphometry.[27] However, given the lack of studies with hard outcomes, particularly in the CKD population, and possible long-

term effects of such accumulation in bone,[28] lanthanum use cannot be recommended for the management of hyperphosphatemia.

Vitamin D analogues

Active vitamin D_3, calcitriol, inhibits parathyroid hormone synthesis in the parathyroid gland. It also increases bone formation and increases intestinal absorption of calcium and phosphate (with resulting hypercalcemia and hyperphosphatemia). The role of calcitriol supplementation in CKD remains controversial. Calcitriol improves bone abnormalities associated with secondary hyperparathyroidism in stage 3 and 4 CKD as evidenced by decreasing parathyroid hormone[29] and improving bone histomorphometry.[30,31] Similar effects are observed with alphacalcidiol (direct synthetic precursor converted to calcitriol by the liver) in early CKD.[32] Most studies performed to date have been short in duration, with no long-term data available on skeletal effects (including fractures), treatment failures, or histological correlates. Active vitamin D_3 supplementation increases incidence of hypercalcemia and hyperphosphatemia with possible deleterious consequences on extraosseal calcification. Adynamic bone (due to oversuppression of parathyroid hormone) may lack the buffering capacity to handle hypercalcemia.

Calcimimetics may represent an alternative to vitamin D analogs. These compounds, acting as allosteric modulators of the calcium-sensing receptor,[33] suppress parathyroid hormone directly. Unlike active vitamin D, their use is associated with hypocalcemia. Clinical studies of cinacalcet were reviewed by the Cochrane Collaboration: despite efficacy of cinacalcet in improving biochemical parameters (lowering parathyroid hormone) in dialysis patients, no morbidity or mortality benefits were demonstrated.[34] When results of 4 randomized trials with cinacalcet were pooled, an effect on fracture rate, parathyroidectomy, and cardiovascular mortality was observed.[35] Until these preliminary observations of effects of calcimimetics on bone histomorphometry, fracture rates, and parathyroidectomy are confirmed, widespread use of calcimimetics for treatment of secondary hyperparathyroidism cannot be recommended. In addition, the impact on extraosseous calcification and morbidity and mortality needs to be determined.

Emerging evidence suggests a potential role of calcidiol (in cases of calcitriol substrate deficiency) in development of secondary hyperparathyroidism.[36-38] It remains to be determined whether screening for and supplementation of calcidiol deficiency in CKD is warranted.

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Preparation for end-stage renal disease

Gihad E. Nesrallah, David C. Mendelssohn

Guideline 3.1: Components of care prior to initiation of renal replacement therapy

3.1.1. Where feasible, patients with an estimated glomerular filtration rate < 30 mL/min/m^2 should be managed in a multidisciplinary care setting including physicians, nurses, dietitians, and social workers (grade C).

3.1.2. A predialysis education program should include lifestyle modification, medication management, modality selection, and vascular access, as well as renal transplantation options (grade D, opinion).

Background

Multidisciplinary care

The Canadian Society of Nephrology has been advocating for multidisciplinary care since publication of its "Principles of End-Stage Renal Disease Care" in 1997.[1] Canadian nephrologists remain strongly supportive of this model of care.[2] In Canada, the composition of the multidisciplinary predialysis team typically includes dietitians, pharmacists, social workers, nurse clinicians and/or nurse practitioners, and nephrologists.[2] The impact of the multidisciplinary team on patient outcomes has been the focus of many studies, evaluating both the individual components and the impact of the team as a whole. Dietary counseling in the chronic kidney disease (CKD) clinic is associated with improved blood pressure control,[3] preservation of visceral protein stores and lean body mass,[4,5] and improvements in serum phosphate, potassium, and bicarbonate. Assessment by a clinical pharmacist offers an opportunity to identify drug interactions, over-the-counter medication use, and incorrect drug administration practices, and has also been shown to improve adherence.[6] This is particularly valuable in the CKD patient population, where polypharmacy is common and adherence is difficult to maintain.

Retrospective studies of multidisciplinary care have suggested that it is associated with greater use of angiotensin-converting enzyme inhibitors, iron, and bicarbonate therapy, as well as a greater likelihood of having a functioning vascular access and initiation dialysis.[7,8] Multidisciplinary predialysis care has been associated with improved patient-perceived health-related quality of life.[9] Results with respect to hospitalization rates and survival have been mixed, but in general most retrospective studies suggest improvements in both when multidisciplinary care is compared to standard care.[8,10,11] Given that most patients with stage 4 CKD are more likely to die than progress to end-stage renal disease,[12] survival bias may have limited the validity of these retrospective studies. A more recent prospective observational study of CKD patients over the age of 66 did, however, demonstrate a statistically significant 50% reduction in mortality with multidisciplinary care after matching multidisciplinary care–managed and nonmultidisciplinary care–managed patients by propensity score.[13] While most observational studies of multidisciplinary care have been positive, at least 1 study failed to show any improvement in metabolic parameters and anemia management in the

multidisciplinary care setting, and it therefore seems reasonable to subject multidisciplinary care to the rigors of a clinical trial.[14] Currently, a prospective randomized clinical trial evaluating the impact of multidisciplinary care at a number of Canadian centers is underway.[15]

Patient education

Patient education results in optimal renal replacement modality selection, increases pre-emptive transplant rates, and increases arteriovenous fistula use. Canadian studies have shown that patient education increases the length of time to end-stage renal disease, increases patients' survival on dialysis, and increases the likelihood of choosing self-care hemodialysis.[16-18] Educational media include videotaped presentations, written materials, classroom-based seminars, one-on-one instruction, and home-based multimedia programs. Materials distributed by the National Kidney Foundation and the Kidney Foundation of Canada are available in various languages and are widely used in the United States and Canada, respectively. Patients presented with unbiased modality-related education are more likely to select peritoneal dialysis or home hemodialysis, and, conversely, patients who do not receive adequate information about these modalities are more likely to end up on in-centre hemodialysis.[19,20]

Management of comorbidities

Chronic kidney disease is a well-established independent risk factor for cardiovascular events.[21] CKD and cardiovascular disease share many risk factors in common, including hypertension, dyslipidemia, diabetes, and sleep apnea. It is therefore mandatory that all of these factors be addressed in the predialysis clinical setting.

Modality selection

With respect to renal replacement therapy, live donor kidney transplantation should be promoted as the first choice for eligible patients; outcomes with deceased donor kidneys are also significantly better than with dialysis.[22-24] For patients with progressive CKD with plans for hemodialysis, vascular access planning is an important component of their care in preparation for end-stage renal disease and may include detailed assessment (including venous mapping and avoidance of venipuncture or blood pressure measurements on the nondominant arm in order to protect it for access creation).[25] A comprehensive discussion of vascular access monitoring, infection prevention, and management of complications is included in the Canadian Society of Nephrology Hemodialysis Clinical Practice Guidelines.[26] More frequent and/or sustained dialysis such as nocturnal hemodialysis or peritoneal dialysis is an alternative to conventional thrice-weekly hemodialysis and should be offered to suitable patients on the basis of need and availability.[27]

Background

The number of renal replacement modality options continues to grow. The recent emergence and acceptance of more frequent and or sustained dialysis regimens such as

short-daily dialysis and nocturnal dialysis has led, to some extent, to resurgence in the use of home hemodialysis in Canada. This is particularly true in British Columbia, where more frequent hemodialysis is fully funded. The use of peritoneal dialysis began its decline in the mid-1990s and has stabilized to its current prevalence rate of around 20% across Canada, though most surveyed Canadian nephrologists believe that it could make up to 30%–40% of the modality mix.[28] Newer forms of renal replacement therapy such as daily hemofiltration and hemodiafiltration have not yet been adopted for widespread use in Canada, though published European data appear promising.[29]

Despite the apparent large number of renal replacement therapeutic options available, it is clear that all existing forms of renal replacement therapy are imperfect. Traditionally, the various renal replacement options have been viewed in a competitive light. It is the CKD working group's stated bias that the various options should rather be viewed as complementary, and that the role of the predialysis team, with respect to modality selection, is to match each patient with the most suitable form of renal replacement therapy. The various forms of renal replacement therapy currently available for the management of end-stage renal disease are discussed below, along with their respective benefits and recognized limitations. Dialysis-related aspects of the management of acute renal failure are omitted from this discussion.

Renal transplantation

Renal transplantation is generally regarded as the superior form of renal replacement therapy both with respect to cost and outcomes. From a system point of view, live kidney donor transplantation is more cost-effective than long-term dialysis and deceased donor transplantation, while having the added benefit of increasing the kidney donor pool.[22,30] If sufficient preparation time is available prior to the onset of end-stage renal disease, transplantation can be done pre-emptively (with living or deceased donors), thus averting the need for dialysis. Numerous studies have evaluated the clinical benefits of avoiding dialysis by pre-emptive transplantation, and the consensus is that, overall, patient and graft survival are improved significantly.[23,31-33] In Canada, pre-emptive transplantation is more commonly performed in patients with a living donor. In some provinces, pre-emptive transplantation with a deceased donor is possible as well, and patients can begin to accrue waiting time when the estimated glomerular filtration rate falls below 15 mL/min.

Outcomes with deceased donor kidneys are also significantly better than with dialysis.[24] Waiting times for deceased donor organs vary regionally in Canada, and range between 1 and 12 years. Unfortunately for many elderly patients, wait times can exceed their projected life expectancies at the initiation or renal replacement therapy. Expanded-criteria donor organ donation has been used to broaden the donor pool, by using kidneys from patients with lower estimated glomerular filtration rate, including older patients.[34] Patients with a shorter life expectancy, such as patients > 60 years or younger patients with multiple comorbidities, can be consented for expanded-criteria donor organs.[35] Dual kidney transplantation can provide better graft survival when expanded-criteria donor organs are used.[36] Organs from donors without a heartbeat provide long-term outcomes

that are comparable to those from donors with a heartbeat, though delayed graft function is more common.[37]

Peritoneal dialysis

Peritoneal dialysis is a relatively simple procedure as compared with hemodialysis and offers the additional advantage that it is portable and does not require blood access. A peritoneal dialysis catheter can be inserted percutaneously or surgically in patients with suspected intra-abdominal adhesions due to previous surgery. Contraindications to peritoneal dialysis are few. Patients or their caregivers can usually be trained within a matter of 1 to 2 weeks. A number of regimens involving manual daytime exchanges or automated nighttime exchanges, or both, constitute the majority of peritoneal dialysis prescriptions. Complications of peritoneal dialysis include peritonitis, catheter malfunction, abdominal wall herniae, and metabolic problems such as dyslipidemia, weight gain, hyperglycemia, and accelerated atherosclerosis due to the long-term effects of glucose exposure. Peritoneal dialysis outcomes appear to be best while residual renal function is present, and a timely switch to another form of renal replacement therapy is typically required when volume control, metabolic complications, suboptimal clearance, or other evidence of peritoneal membrane failure become manifest. In 2002, the average annual cost for peritoneal dialysis was $39,000 CAD per patient, as compared with $74,000 for in-centre hemodialysis.[38] Numerous observational studies have compared hemo- and peritoneal dialysis outcomes.[39,40] In general, outcomes are equivalent for the first 2 to 3 years, and typically favor hemodialysis after that point. This is likely do to a combination of loss of residual renal function, peritoneal membrane failure, and longer-term toxicity of glucose-based solutions (including atherosclerosis). Newer, more biocompatible peritoneal dialysis solutions may extend the durability of peritoneal dialysis,[41] but larger studies will be needed to confirm this.

Peritoneal dialysis catheters can be inserted via laparotomy, lapraoscopy, peritonioscopy, and fluoroscopy with comparable results, and practices vary across centres. Two to 4 weeks should be allowed for the catheter tract to heal, prior to beginning peritoneal dialysis.[42] Catheters can also be buried in a subcutaneous tract and exteriorized immediately prior to use, though the benefits of this approach have not yet been clearly established. A more detailed discussion of peritoneal dialysis catheter management is provided elsewhere.[43]

Hemodialysis

Hemodialysis remains the most widely used form of renal replacement therapy in the developed world. Most hemodialysis is performed in a fully-assisted care setting, though many patients participate in assisted care in self-care units, while even fewer administer their own therapy at home. Home hemodialysis utilization patterns vary worldwide, ranging from < 1% in the United States to > 15% in Australia and New Zealand. Complications of hemodialysis include hypotension, thirst, cramping, restless legs, headache, and vascular access complications such as infections and catheter dysfunction. The primary advantage of hemodialysis over peritoneal dialysis is that a relatively large

amount of uremic waste and fluid can be removed in a relatively short period of time. While on the one hand this might appear to offer greater convenience than daily therapy, excessively short hemodialysis treatment times, coupled with the intermittent nature of the therapy, are commonly associated with intradialytic symptoms, hypotension, and increased mortality, making thrice-weekly conventional hemodialysis an imperfect therapy.

More frequent or sustained hemodialysis

Since their advent in the early 1970s, short daily dialysis (2–3 hours per session, 6 days per week) and nocturnal hemodialysis (6–10 hours per session, 3–7 sessions per week) have been thought to offer a number of physiological advantages over conventional thrice-weekly hemodialysis. Over the last decade there has been growing interest in providing these therapies both at home and in centre. A growing body of observational data points to improvements in a number of intermediate outcomes including blood pressure control, nutritional indices, erythropoiesis, hyperphosphatemia, hyperparathyroidism, sleep physiology, endothelial function, and quality of life, as well as treatment-related costs. Recent systematic reviews in this area have identified inconsistencies across studies of both short daily and nocturnal dialysis, inconsistencies which are likely due to small sample sizes, dropout bias, selection bias, and informative censoring.[44,45] Despite this, the existing evidence has been viewed as sufficiently compelling to prompt payors to make these therapies available in certain jurisdictions, including British Columbia, the Netherlands, Finland, and Australia/New Zealand. Currently, 2 randomized controlled trials funded by the National Institutes of Health are underway that will evaluate a number of intermediate outcomes in patients treated with short daily and nocturnal hemodialysis.[46] Additionally, an international registry of more frequent and sustained dialysis is being used to assemble a large cohort for the purposes of conducting a survival study.[47] As experience with these therapies grows, their role in the current modality mix will become clearer. For now, it is recommended that they be used wherever available, and if limited in availability, they should be provided to patients most in need. Patients with fluid overload, suboptimal clearance, hyperphosphatemia, and failure to thrive may obtain the most benefit from these more intensive therapies.

Home hemodialysis

Home hemodialysis has seen a gradual decline in most developed countries over the last 2 decades, with some recent resurgence in some jurisdictions. Observational studies have suggested that home hemodialysis is associated with improved survival,[48] though unmeasured confounders and confounding by indication may have been factors in these studies. Regardless, there are many benefits to home-based renal replacement therapy that are intuitively obvious, including cost savings related to nursing costs, increased patient autonomy, and in many cases, the flexibility to schedule dialysis around one's work schedule.

Guideline 3.2: Timing the initiation of renal replacement therapy

3.2.1. No evidence currently exists upon which to recommend a level of glomerular filtration rate at which renal replacement therapy should be initiated in the absence of complications of CKD (grade D, opinion).

3.2.2. Patients with an estimated glomerular filtration rate < 20 mL/min/m^2 may require initiation of renal replacement therapy if any of the following are present: symptoms of uremia (after excluding other etiologies), refractory metabolic complications (hyperkalemia, acidosis), volume overload (manifesting as resistant edema or hypertension), or a decline in nutritional status (as measured by serum albumin, lean body mass, or Subjective Global Assessment) that is refractory to dietary intervention (grade D, opinion).

3.2.3. Living-donor preemptive renal transplantation should not be performed until the estimated glomerular filtration rate is < 20 mL/min/m^2 and there is evidence of progressive and irreversible renal damage over the preceding 6–12 months (grade D, opinion).

Background

Hemodialysis and peritoneal dialysis

The ideal glomerular filtration rate at which to initiate dialysis is not known. Excessively early initiation of dialysis can impact quality of life and treatment costs and result in unnecessary exposure to the complications of dialysis. Conversely, a late start may have a negative impact on nutritional status, morbidity, and mortality. To date, no randomized controlled trials that address the optimal level of renal function at which to initiate dialysis have been completed. The identification of such a threshold is complicated by the lack of a perfect measure of renal function as well as the great variability in patient characteristics (such as age and comorbidities) that might interact with the effect of the timing of dialysis. The Cockroft-Gault formula was previously recommended by the Canadian Society of Nephrology, largely for its ease of use.[49] Given the more widespread availability of MDRD[50] glomerular filtration rate calculators, most guidelines recommend the use of this formula for following patients with CKD, and it therefore seems reasonable that it be used throughout the CKD spectrum, up to the initiation of dialysis. The 2000 National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines on initiation of renal replacement therapy were partly based on the calculation of weekly renal Kt/V for urea, targeting a value of at least 2.0.[51] This recommendation, which was largely based on the notion that CKD patients should have at least the same clearance as patients already on dialysis (target Kt/V for peritoneal dialysis was > 2.0). This method, which required a 24-hour urine collection and a number of calculations, has largely been abandoned given its cumbersome nature and the lack of evidence that it significantly improves outcomes.[52]

Proponents of earlier initiation of renal replacement therapy have argued that, since renal function is inversely related to protein intake[53] and low protein stores at initiation of renal replacement therapy predict death,[54] an earlier start will improve nutritional status, and

hence survival.[49,55] Earlier studies showing a benefit to early initiation of dialysis may have been confounded by case-mix differences.[45,56] Subsequently, a study from the Netherlands suggested that longer survival was related to lead-time bias for patients who started earlier.[52] Lastly, a more recent and more methodologically rigorous observational study compared measured creatinine clearance with calculated MDRD-glomerular filtration rate, and their relative associations with mortality. In that study, a lower measured creatinine clearance at the onset of dialysis was not associated with increased mortality.[57] In addition, many "early starters" (with higher MDRD-glomerular filtration rate) had very low creatinine clearances, and many "late starters" (with low MDRD-glomerular filtration rate) had higher creatinine clearances, suggesting misclassification bias that favored early initiation.[57] Based on the existing literature, therefore, no clear thresholds can be recommended to serve as a sole criterion for the initiation of dialysis. A prospective clinical trial in Australia will have randomized over 800 patients to start either hemodialysis or peritoneal dialysis between either 5–6 or 10–14 mL/min/m^2, with results expected by 2008.[58] Until more compelling data are available, recommendations will remain largely opinion-based.

The Canadian Society of Nephrology Working Group on Preparation for Dialysis recommends that patients with a glomerular filtration rate < 20 mL/min/m^2 with evidence of malnutrition (decline in lean body mass, serum albumin or SGA score) should be started on renal replacement therapy, as should patients with symptoms of uremia, metabolic complications (refractory hyperkalemia or acidosis), or diuretic-resistant volume overload.

Transplantation

As discussed in the preceding section, pre-emptive renal transplantation is preferred over transplantation after the initiation of dialysis. The Canadian Society of Transplantation recommends that pre-emptive renal transplantation with a living donor be deferred until the glomerular filtration rate is < 20 mL/min/m^2 body surface area with concomitant evidence of irreversible decline in the preceding 6–12 months.[59] For patients ineligible for pre-emptive transplantation, the sooner after the initiation of dialysis, the better the outcome.[22] Patients should be referred for transplant assessment 12 months prior to the expected onset of end-stage renal disease, and patients requiring an urgent start of dialysis should be referred as soon as medically stable.[59]

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Comprehensive conservative management

Joanne Kappel

Guideline 3.3: Structure and process of comprehensive conservative management

3.3.1. Renal programs/care providers for patients with progressive chronic kidney disease (CKD) who choose not to pursue renal replacement therapies should ensure patients have access to an interdisciplinary team that provides comprehensive conservative management (grade D, opinion).

Background

Comprehensive conservative management for CKD begins when the patient and family have chosen to be managed without dialysis. The decision to forgo dialysis treatment has been made after the patient, family, and caregivers have been fully informed about their diagnosis and prognosis and the treatment options available to them. A time-limited trial of dialysis may also be considered as a treatment option. Various prognostic tools are available to assist the CKD team in predicting survival on dialysis.[1-7] Comprehensive conservative management for this group of patients is complex as these individuals often have significant comorbid conditions and require more supportive care.

Comprehensive conservative management requires that an interdisciplinary team be identified to provide services to the patient and family. This interdisciplinary team would include: nephrologists, CKD nurses, dietitians, social workers, psychologists, spiritual care workers, palliative care physicians/nurses, and appropriately trained and supervised volunteers. The patient's primary care physician is an integral part of the team.[8] The interdisciplinary team is available 24 hours per day, 7 days per week. The team can function in the outpatient department, in-hospital, in the palliative care unit, in the patient's home, or in a hospice. Hospice care treats the patient and not the disease. Hospice care can be provided in a special residential facility or within the patient's home. The role of the hospice is to provide good symptom control, respite care, and outreach and support to the entire family. Hospice care also provides bereavement support.

Appropriate training in comprehensive conservative management needs to be included in nephrology fellowship programs, as well as in the curricula for nephrology nurses, social workers, dietitians, and technicians.[9-12] Educational resources and continuing professional education on renal palliative care should be regularly provided and documented.

The interdisciplinary team, in conjunction with the patient and family, develop a care plan that addresses the physical, psychological, and spiritual needs of the patient/family and caregivers. Shared decision making is an integral component of this process. Care plan revisions are based on the changing needs and preferences of the patient and family and recognize the multifaceted, challenging, and shifting priorities in goals of care. A peer mentorship program may be more effective in some cultural groups in assisting with the care plan.[13-15]

The interdisciplinary team is committed to the highest quality of care and support for all patients and their families. To this end, quality improvement activities would include safety of care, timeliness of care, patient-centred care, and effective and equitable care.[16-19] A grief and bereavement program should be available to patients/families/caregivers as well as to health professionals.[6,10,19]

Guideline 3.4: Advance care planning

3.4.1. All CKD programs/care providers should have a mechanism by which to develop documents and processes for Advance Care Planning (grade D, opinion).

Background

Advance Care Planning is a process of communication between patients, families/friends, and the interdisciplinary team for the purpose of identifying a patient's preferred decision maker, clarifying treatment preferences, and establishing goals of care for end-of-life. Traditionally, the purpose of Advance Care Planning was to prepare for the patient's incapacity by focusing on the completion of a written advance directive. An advance directive is a document that is intended to instruct or inform others concerning the type of life-sustaining treatments the patient would want should he or she lose decision-making capacity or be unable to make his or her wishes known. There are 2 types of advance directives:

1. Instruction Directives – Also known as living wills. These are written documents that focus on life-sustaining treatment the patient would want in various medical situations.
2. Proxy Directives – Also known as durable power of attorney for health care. The patient appoints someone who will make health care decisions on his or her behalf should he or she be unable to do so.

Several provinces have passed laws recognizing advance directives. Some of these laws recognize proxy directives only, while others recognize both proxy and instruction directives. Patients, families, and health care professionals are encouraged to inquire about the requirements in their province to ensure that the advance directive is legally valid.[20-23]

Although a written advance directive may be the goal of Advance Care Planning with dialysis patients, the purpose of Advance Care Planning in patients with CKD is more complex. Advance Care Planning in this group of patients prepares for death, strengthens relationships with loved ones, achieves a sense of control over present and future care needs, and relieves burdens placed on caregivers and families. The Advance Care Planning process is an important part of supportive therapy that ideally should occur throughout the course of CKD well before decisions have been made to forgo renal replacement therapy. Health providers should not be reluctant to engage in Advance Care Planning. The interdisciplinary team can take the lead in the discussion but the team must be sensitive to the patient's readiness to participate. Advance Care Planning has been shown to improve patient quality of life by providing honest discussions about their

illness and providing hope for the future. The Advance Care Planning process must be sensitive to patient age and gender, to disease stage, and to social and cultural background.[10,20-26]

There are several tools available to assist the interdisciplinary team with Advance Care Planning.[10,20,22,24,25] A patient workbook for Advance Care Planning can be found at www.fraserhealth.ca/healthinfo.[27] Sample documents for Advance Care Directives and do-not-resuscitate orders can be found online at www.promotingexcellence.org/esrd and www.kidneyeol.org.[10,25]

Guideline 3.5: Components of comprehensive conservative management

3.5.1. Comprehensive conservative management protocols will include (grade D, opinion):

- symptom management
- psychological care
- spiritual care.

Background

Pain and other symptoms of end-stage renal disease should be managed based upon the best available evidence. Regular and ongoing assessment of pain and other symptoms (including but not limited to anorexia, pruritus, constipation, insomnia, restless legs, nausea, and vomiting) together with treatment side effects should be documented. Barriers to effective pain and symptom control should be recognized and addressed in a timely manner. Treatment may include pharmacological, nonpharmacological, and complementary therapies, all of which should be available. Education for patients/families and caregivers about symptom management is undertaken to ensure the best possible outcome for the patient. Where possible, treatment protocols are established to assist in care delivery by all members of the team.[6,8,18,28,29]

Regular assessment of psychological, social and spiritual reactions, including but not limited to stress, anticipatory grieving, and coping strategies, should be available and documented. Pharmacological, nonpharmacological, and complementary therapies should be employed as appropriate. A spiritual assessment should be utilized to identify religious or spiritual/existential background, preferences, and related beliefs of the patient/family/caregiver that will impact care. Assessment tools such as the Spiritual Well-Being Scale or the End-Stage Renal Disease Spirituality Questionnaire can be useful to guide discussion.[6,8,10,18,28,29]

A grief and bereavement program should be available to patients/families/caregivers as well as health professionals.[6,8,18,28,29]

Guideline 3.6: Care of the imminently dying patient

3.6.1. Coordinated end-of-life care should be available to patients and families (grade D, opinion).

Background

The signs and symptoms of imminent death are recognized and communicated appropriately to patient, family, and staff. End-of-life concerns and fears are addressed openly, honestly, and with empathy, in the context of the social and cultural beliefs of the patient and family. Where appropriate, the palliative care team is involved in assisting with provision of care.[6,15,17,19,28]

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