Improving outcomes in diabetes and chronic kidney disease: The basis for Canadian guidelines

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The prevalence of diabetes is on the rise in Canada, and there has been a corresponding increase in the rate of micro- and macrovascular complications. Among the worst of these is chronic kidney disease (CKD). It may be diagnosed either through the detection of persistent albuminuria or an estimated glomerular filtration rate that is persistently less than 60 mL/min/1.73 m². Patients with diabetes and CKD have a lower quality of life and higher health care costs, and face the prospect of end-stage renal disease requiring dialysis. More importantly, this group has an extremely elevated cardiovascular risk and correspondingly reduced survival. Research over several decades has led to two important conclusions. First, progressive worsening of kidney disease is not inevitable in people with diabetes; it can be slowed or even stopped. Second, the elevated cardiovascular risk in this population can be significantly reduced through an aggressive approach to cardiovascular risk factor reduction. These conclusions have prompted Canadian guideline groups, such as the Canadian Diabetes Association and the Canadian Hypertension Education Program, to release clinical practice guidelines that address the management of people with diabetes and CKD. In the present article, the studies that have influenced these Canadian guidelines are examined, and areas in which further research is still required are identified.

Key Words: *Cardiovascular disease; Chronic kidney disease; Clinical practice guidelines; Diabetes*

Diabetes is on the rise in Canada. Recent estimates in Ontario place the prevalence of diabetes at almost 9% and rising (1). One of the most common and devastating complications of diabetes is chronic kidney disease (CKD). Kidney damage due to diabetes is associated with a lower quality of life, higher cardiovascular event rates and shortened survival. One-half of all new dialysis cases in Canada are due to diabetes (2), and the average survival for a dialysis patient older than 65 years of age with diabetes is only approximately 2.5 years (2), with an average quality of life worse than that seen in patients with metastatic liver cancer (3,4). The costs associated with this condition are crippling. For example, in Canada, the cost of providing hemodialysis to a single patient for one year is approximately \$70,000 (5,6). It is incredible that more than one-half of all patients with diabetes have CKD (7-10). However, the cardiorenal risks associated with CKD in diabetic patients are potentially reducible. In the present article, we

Améliorer les issues du diabète et des maladies rénales chroniques : Le fondement des lignes directrices canadiennes

La prévalence du diabète est en hausse au Canada, et on remarque une augmentation correspondante du taux de complications microvasculaires et macrovasculaires. La maladie rénale chronique (MRC) fait partie des pires complications de ce type. On peut la diagnostiquer grâce au dépistage d'une albuminurie persistante ou d'un taux de filtration glomérulaire estimé toujours inférieur à 60 mL/min/1.73 m². Les patients diabétiques atteints d'une MRC ont une moins bonne qualité de vie et des soins de santé plus coûteux, et ils risquent une insuffisance rénale de phase terminale exigeant une dialyse. Par-dessus tout, ce groupe présente un risque cardiovasculaire extrêmement élevé et une survie réduite correspondante. Des recherches menées sur plusieurs décennies ont permis de tirer deux conclusions importantes. D'abord, l'aggravation évolutive de la maladie rénale n'est pas inévitable chez les diabétiques; on peut la ralentir ou même l'interrompre. Ensuite, le risque cardiovasculaire élevé au sein de cette population peut être considérablement réduit par une démarche dynamique de réduction des facteurs de risque cardiovasculaires. Ces conclusions ont incité des groupes de lignes directrices canadiennes comme l'Association canadienne du diabète et le Programme éducatif canadien sur l'hypertension à diffuser des guides de pratique clinique sur la prise en charge des diabétiques atteints d'une MRC. Dans le présent article, on examine les études qui ont eu une incidence sur ces lignes directrices canadiennes et on détermine les domaines qui nécessitent des recherches supplémentaires.

examine how to identify CKD in people with diabetes, and how aggressive therapeutic approaches can reduce cardiovascular risk and delay progression of kidney damage in this population. Because the authors of the present manuscript have been involved in the Canadian Hypertension Education Program (CHEP), the Canadian Diabetes Association (CDA) or the Canadian Society of Nephrology clinical practice guideline groups, they will provide some insight into how important clinical trials have impacted treatment recommendations for people with diabetes and CKD in Canada.

IDENTIFYING CKD IN DIABETES

CKD in diabetes can be due to classical diabetic nephropathy or other forms of kidney damage. Classical diabetic nephropathy is characterized clinically by a slowly progressive increase in urinary protein excretion over many years (8,11-15). Renal function typically does not decline significantly until late in

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TABLE 1
Clinical and laboratory factors favouring the diagnosis of classical diabetic nephropathy or an alternative renal diagnosis

Factors that favour diabetic nephropathy	Factors that favour alternate renal diagnosis
Persistent albuminuria	Extreme proteinuria (>6 g/day)
Bland urine sediment	Persistent hematuria (micro- or macroscopic) or active urine sediment (red or white blood cell casts)
Slow progression of disease	Rapidly falling eGFR
Low eGFR associated with overt proteinuria	Low eGFR with little or no proteinuria
Other complications of diabetes present	Other complications of diabetes absent or relatively less severe
Known duration of diabetes mellitus >5 years	Known duration of diabetes mellitus <5 years
	Family history of nondiabetic renal disease (eg, polycystic kidney disease)
	Signs or symptoms of systemic disease other than diabetes

Note: low estimated glomerular filtration rate (eGFR) implies ≤ 60 mL/min/1.73 m², and rapidly falling eGFR implies ≥ 5 mL/min/1.73 m² loss per year

the disease. Classical diabetic nephropathy is characterized by a distinctive pathological appearance on biopsy, with mesangial expansion, diffuse or nodular glomerulosclerosis with Kimmelstiel-Wilson lesions and arteriolar sclerohyalinosis. However, the diagnosis of diabetic nephropathy is usually made based on clinical characteristics, with biopsy reserved for patients with atypical presentations (Table 1) (16-19). What is increasingly apparent is that people with diabetes can have renal disease that does not follow the pattern of classical diabetic nephropathy. As many as one-half of patients with diabetes and reduced kidney function have normal urinary protein levels (9). While some of these cases may represent treated classical nephropathy, many represent alternative causes of renal damage. For example, kidney damage due to hypertension or diffuse microvascular atherosclerosis are common causes of CKD in diabetes. Such cases will typically present with reduced renal function and urinary protein levels in the normal or microalbumin range. Other less common causes of glomerulonephritis or glomerulosclerosis may also be seen in people with diabetes. This increases the complexity of identifying CKD in diabetes and presents the clinician with a larger differential diagnosis. However, this can be balanced by two important factors. First, the risk of progression to end-stage renal disease requiring dialysis in people with diabetes is usually not affected by the cause of renal damage (20). Second, the approach to treatment of CKD in diabetes is usually the same, regardless of the cause of kidney damage. The exception to these statements is the rare patient with CKD due to either a primary renal disease (eg, membranous nephropathy), or a systemic disease other than diabetes or hypertension (ex, lupus nephritis).

Previously, identification of CKD in diabetes focused on the identification of albuminuria. However, this is now insufficient, because such an approach misses those whose CKD is not due to classical diabetic nephropathy and who have reduced renal function with normal albumin excretion. A more inclusive screening approach would identify a person with diabetes as having CKD if they had either persistent albuminuria, regardless of the level of renal function, or persistently reduced renal function (estimated glomerular filtration rate less than 60 mL/min/1.73 m²), regardless of the level of albuminuria. Clinicians screening for CKD in people with diabetes should watch for clinical clues that would prompt a more aggressive workup of renal disease, including a renal biopsy (Table 1).

TREATING CKD IN DIABETES

Overview

The major cause of morbidity and mortality in diabetes relates to cardiovascular complications. A person with diabetes has an

annual mortality rate more than twice as high as a similar person without diabetes (21). The presence of early kidney disease roughly doubles the cardiovascular risk (22). Patients on dialysis have a mortality rate between 10 and 1000 times higher than age-matched controls (23). Patients attending a predialysis clinic are between two and 10 times more likely to die of a cardiovascular event than they are to require dialysis (24). It is important to recognize that people with diabetes and CKD are among those at highest risk for cardiovascular events. Their care should be oriented toward reducing cardiovascular risk. In 2003, the CDA recommended (25) that an aggressive, multifactorial approach to cardiovascular risk reduction be considered for all people with diabetes who are at high cardiovascular risk. This strategy targeted glycemic control (glycated hemoglobin less than 7%), lipid control (low-density lipoprotein cholesterol less than 2.5 mmol/L at that time and less than 2.0 mmol/L now), hypertension control (blood pressure [BP] lower than 130/80 mmHg), lifestyle interventions (eg, diet, exercise, weight reduction, smoking cessation), and consideration of the use of acetylsalicylic acid and angiotensin-converting enzyme (ACE) inhibitors. Such an approach has been found to reduce cardiovascular events by 50% in people with diabetic nephropathy (26), and now forms the foundation of any care plan for a person with diabetes and CKD.

Lowering BP

There appears to be a linear relationship between the level of BP and the rate of loss of kidney function in people with CKD and diabetes (27). Many treatment trials have demonstrated that people with diabetes should have their BP lowered to lower than 130/80 mmHg when possible. The target systolic BP (SBP) of lower than 130 mmHg is supported by the normotensive Appropriate Blood pressure Control in Diabetes (ABCD) trial (27), which studied people with diabetes and a BP lower than 140/90 mmHg, and targeted a diastolic BP (DBP) of lower than 80 mmHg in the intensive arm. The achieved mean BP in the ABCD trial was 128/75 mmHg in the intensive arm versus 137/81 mmHg in the control arm. The ABCD trial demonstrated that aggressive strategy reduced strokes, and delayed the progression of nephropathy and retinopathy (29). The DBP target of lower than 80 mmHg is derived from both the ABCD and the Hypertension Optimal Treatment (HOT) trials (30), which studied hypertensive individuals (1501 of whom had diabetes) who were randomly assigned to one of three DBP targets: 90 mmHg or lower, 85 mmHg or lower, or 80 mmHg or lower. The HOT trial demonstrated a reduction in cardiovascular events and mortality in people with diabetes who were randomly assigned to the

80 mmHg or lower group. The currently recommended target and threshold BP for people with diabetes, regardless of the presence of CKD, is 130/80 mmHg. In the past, guidelines have suggested a lower target BP (lower than 125/75 mmHg) in people with diabetic nephropathy; however, this was primarily based on the Modification of Diet in Renal Disease (MDRD) study (31), which studied people with CKD, most of whom did not have diabetes. Canadian guideline groups have decided that the MDRD study had insufficient evidence for a lower BP target in people with diabetes. The recent REnoprotection In patients with Non-diabetic chronic renal disease (REIN-2) study (32), which also studied patients with nondiabetic CKD, failed to show any additional renal benefit to lowering BP below 130/80 mmHg, although this result may have been due to the antihypertensive class studied. Trials such as the yet uncompleted Action to Control Cardiovascular Risk in Diabetes (ACCORD) study are currently underway, and are examining BP targets lower than 130/80 mmHg. Until further convincing evidence for both the safety and efficacy of lower BP targets exists, 130/80 mmHg is the target BP for diabetes in patients with or without CKD.

Blockade of the renin-angiotensin-aldosterone system

In addition to raising BP, activation of the renin-angiotensin-aldosterone system (RAAS) can contribute to the development and progression of CKD through a number of mechanisms. Angiotensin II causes efferent arteriolar constriction, leading to intraglomerular hypertension. RAAS activation is a driver of mesangial expansion and glomerulosclerosis, and has been implicated as a contributor to vascular inflammation and endothelial dysfunction. All these factors can contribute to progressive loss of renal function independent of systemic BP. With this background, it is no surprise that ACE inhibitors and angiotensin II receptor blockers (ARBs) have been demonstrated to have powerful renal protective effects. ACE inhibitors and ARBs have been demonstrated to reduce the progression of kidney damage in both type 1 and type 2 diabetes (33-37). 'Renal death' (ie, patient death, or the necessity for dialysis or renal transplantation) has been shown to be reduced by ACE inhibitors in type 1 diabetes (33) and by ARBs in type 2 diabetes (37). ACE inhibitors have been shown to reduce the development of new nephropathy in type 2 diabetes (38). In addition, ACE inhibitors have been shown to slow the progression of renal disease and delay the need for dialysis in nondiabetic CKD (39-42). Consistently, these benefits appear to be independent of the BP-lowering effects of these agents and are seen in people with diabetic nephropathy who have normal or near normal BP. ACE inhibitors reduce progression of nephropathy in normotensive individuals with type 1 (43-46) or type 2 diabetes (47).

Whether ACE inhibitors and ARBs provide equal renal protection remains controversial. The Diabetics Exposed to Telmisartan and enalapril (DETAIL) study (48) concluded that ACE inhibitors and ARBs provided equal renal protection in diabetes; however, methodological issues, such as a generous noninferiority margin and imputation of missing end point data, made this study unlikely to find differences between the classes. A small study from Japan (49) suggested that ACE inhibitors were superior to ARBs in preventing progressive renal damage in nondiabetic nephropathy; however, the ARB group was disadvantaged by worse baseline characteristics, and had higher BPs and potentially suboptimal ARB-dosing. In a

meta-analysis (34), both ACE inhibitors and ARBs were found to reduce the progression from microalbuminuria to overt nephropathy to a similar extent. The magnitude of risk reduction for the prevention of the loss of renal function and the requirement for dialysis appears to favour ACE inhibitors; however, these studies examined heterogeneous populations and were not direct comparisons of these two classes of drugs (34). At this point, it appears that both ACE inhibitors and ARBs are superior to other classes of antihypertensives at preventing renal outcomes, and further direct comparisons of these classes are needed to clarify their relative potencies as renal protective agents.

Some authorities have suggested that the typical maximum dose of an ACE inhibitor or an ARB may maximally lower BP, but may not provide the maximum renal protective effect of that drug. Renal protection strategies have been developed to provide even greater blockade of the RAAS, including ACE inhibitor plus ARB combination therapy, or supramaximal dosing of monotherapy with either an ACE inhibitor or an ARB. In nondiabetic nephropathy, the combination of an ACE inhibitor and an ARB was more effective than either agent alone at preventing a combined end point of doubling of serum creatinine or dialysis (50). Although trials examining ACE inhibitor plus ARB combination therapy in diabetes have demonstrated beneficial effects on proteinuria (51), many of these trials have been confounded by lower BPs in the combination group and submaximal dosing in the monotherapy arms. Supramaximal doses of ARBs have also been shown to reduce proteinuria independent of BP (52,53). Hard renal end point trials for ACE inhibitor plus ARB combination therapy or supramaximal dosing of monotherapy in patients with diabetes have yet to report. Alternatively, blocking the RAAS at other sites has been examined. Aldosterone blockade through the use of spironolactone has been shown to reduce proteinuria (53), but again, hard renal end point trials have not been completed, and the safety of spironolactone in combination with other RAAS agents outside the clinical trial setting has been questioned (55). Clinical trials of direct renin inhibitors are also now underway. The optimal strategy for RAAS blockade in people with diabetes and CKD has yet to be established.

Based on these studies, Canadian guideline groups recommend that patients with CKD and diabetes should receive either an ACE inhibitor or an ARB for control of BP and for non-BP-mediated renal protection. Combinations or supramaximal doses of RAAS agents are not currently recommended for the routine management of CKD in diabetes.

Other antihypertensive agents

Individuals with diabetes typically require multiple antihypertensive agents in combination to achieve good BP control (30,56,57). An angiotensin system medication is usually the first antihypertensive agent prescribed to a patient with diabetes, CKD and hypertension, but what should be the second (or third, or fourth...)? Many clinicians prefer the combination of an angiotensin system medication and a thiazide diuretic. This combination is effective in reducing BP, has the added benefit of controlling edema, and may reduce the mild hyperkalemia that can be seen when ACE inhibitors or ARBs are used in this population. Thiazide diuretics have been shown to be effective in reducing cardiovascular risk in hypertensive patients with diabetes (58); however, thiazides can have adverse metabolic effects even in low doses and when combined with angiotensin system medications (which are generally

thought to be metabolically advantageous) (59), and may be insufficient for controlling the salt and water balance when kidney function is low. Calcium channel blockers (CCBs) are also frequently prescribed for the control of BP. Nondihydropyridine (NDHP) CCBs have consistently demonstrated their ability to reduce proteinuria to an extent greater than predicted by the reduction in BP, either alone (60) or in combination with angiotensin system medications (60,61). In one study (62), the use of NDHP CCBs was associated with a slower loss of renal function than was the use of beta-blockers, and the rate of loss was similar to that seen with ACE inhibitors. However, there are no hard renal end point trials for NDHP CCBs in diabetes, and these agents failed to prevent the development of new nephropathy in diabetes (36). Dihydropyridine CCBs do not have a BP-independent renoprotective effect on CKD (36,63,64); however, in the Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure-Lowering Arm (ASCOT-BPLA), a dihydropyridine CCB (in combination with an ACE inhibitor in over 50%) was superior to a beta-blocker (in combination with a thiazide diuretic in over 50%) at preventing cardiovascular events and death. The ASCOT-BPLA included 5145 people with diabetes. Other antihypertensive classes lack large, randomized controlled trials studying people with diabetes and CKD.

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.

The role of proteinuria reduction

Proteinuria is a common finding in kidney disease and represents an increase in macromolecule permeability of the glomerular basement membrane. The degree of proteinuria correlates with the rate of loss of kidney function and the likelihood of requiring dialysis, making proteinuria an attractive biomarker for predicting the extent of renal damage. More recently, proteinuria has been suggested to be one of the causes of progressive renal damage. The 'proteinuria hypothesis' postulates that protein filtered at the glomerulus is subsequently reabsorbed by the proximal convoluted tubule cell. This process can lead to direct injury of these cells, as well as the subsequent release of vasoconstrictors, growth factors and pro-inflammatory substances (65-67), which results in interstitial fibrosis and loss of renal function. This information is primarily derived from animal models, but if proven to be true in humans, it would make proteinuria a target for treatment independent of other strategies such as hypertension control.

In clinical trials of CKD with or without diabetes, the change in proteinuria in response to therapy strongly predicts the rate of progression of kidney damage (23,68-70). For example, in the Reduction in Endpoints with the Angiotensin Antagonist Losartan (RENAAL) study (70), which examined patients with diabetes, hypertension and advanced kidney damage, a reduction of proteinuria in response to an ARB was associated with a very slow rate of decline in kidney function, while the lack of an antiproteinuric response to an ARB was associated with a rapid decline in kidney function. Nearly the entire renal protective effect of the ARB was predicted by the change in urinary protein levels. This supports the hypothesis of a causative role for proteinuria in the progression of kidney

damage; however, a favourable antiproteinuric response may simply be a marker for earlier or more treatable disease. Randomized controlled trials targeting reduction of proteinuria as the primary intervention are required to help to establish the role of proteinuria as a cause of progressive kidney damage. Trials of agents such as sulodexide, which reduce proteinuria but do not affect the RAAS or BP, would be particularly informative. If proteinuria indeed causes kidney damage, further research is required to help to define which level of proteinuria is dangerous, which populations should be targeted for proteinuria reduction, the degree to which proteinuria should be reduced and the optimal antiproteinuric strategy. Although the reduction of proteinuria remains an attractive clinical strategy, guideline groups have not been able to generate clear recommendations regarding proteinuria reduction due to these issues.

Looking forward

Interest in the treatment of CKD in diabetes is increasing, and studies of renal protection are extending to agents traditionally used for other purposes. For example, post hoc analyses of large lipid reduction trials have suggested that statin use is associated with a slower loss of kidney function in patients with CKD (71). Thiazolidinediones have been shown to reduce albuminuria (72,73). There are studies underway that examine the renal protective properties of diverse agents such as erythropoietics, angiotensin, thromboxane receptor antagonists, adenosine 2A receptor antagonists, dopamine D3 receptor antagonists and immunosuppressants such as rapamycin. Results to date are too preliminary to recommend any of these agents for their renal protective properties; however, it is encouraging to see the increasing degree of interest in renal protection in people with diabetes.

CONCLUSIONS

CKD in diabetes can be identified through routine laboratory testing, and this helps clinicians to identify people who are not only at risk of loss of kidney function, but those who are also at significantly elevated cardiovascular risk. Several decades of trials support the conclusion that cardiorenal risk in this population is modifiable and have contributed to the development of Canadian clinical practice guidelines in this area. Groups such as the CDA and the CHEP encourage clinicians to identify CKD in people with diabetes, as well as to follow an aggressive, multifactorial approach aimed at reducing cardiorenal risk through lifestyle interventions, control of glycemia, lipids and BP, and the use of acetylsalicylic acid. ACE inhibitors or ARBs are strongly recommended in this population, for both the control of hypertension and the renal protective effects not mediated by BP. Despite this aggressive approach, this population continues to be at high risk for cardiovascular and renal events, and we await with great interest the future developments in this area.

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