Services aimed at achieving desirable clinical outcomes in patients with chronic kidney disease and diabetes mellitus: A narrative review

Fergus William Gardiner¹,²,³, Ezekiel Uba Nwose¹, Phillip Taderera Bwititi³, Judith Crockett¹ and Lexin Wang³

Abstract
There is a large number of patients with chronic kidney disease (CKD), diabetes mellitus (DM), and hypertension (HT) but whether the targets on blood pressure (BP) control in patients with DM and/or CKD are met is not clear. This narrative review therefore investigated evidence on services aimed at achieving desirable clinical results in patients with CKD and DM, and HT in Australia. Literature pertaining to pathology diagnosis and management of these patients as well as the complexities in management were considered. This involved evidence from PubMed-listed articles published between 1993 and 2016 including original research studies, focusing on randomised controlled trials and prospective studies where possible, systematic and other review articles, meta-analyses, expert consensus documents and specialist society guidelines, such as those from the National Heart Foundation of Australia, American Diabetes Association, the Department of Health, The Royal College of Pathologists of Australasia, and The Australasian College of Emergency Medicine. Based on the literature reviewed, it is yet unknown as to how effective programs, such as diabetes inpatient services, endocrine out-patient services, and cardiac rehabilitation services, are at achieving guideline recommendations. It is also not clear how or whether clinicians are encumbered by complexities in their efforts of adhering to DM, HT, and glucose control recommendations, and the potential reasons for clinical inertia. Future studies are needed to ascertain the extent to which required BP and glucose control in patients is achieved, and whether clinical inertia is a barrier.

Keywords
Australian health services, blood glucose control, blood pressure control, complexity in management, pathology test

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Introduction: the need for blood glucose and blood pressure controls
A complication of diabetes mellitus (DM) is diabetic nephropathy since DM causes cirrhosis and thickening of nephrons impairing function that manifests as albuminuria, among others. High blood pressure (BP) or hypertension (HT) damages the blood vessels in the kidney, impairing function, and also patients with diabetic nephropathy often have HT. ¹ It is known that treatment outcomes in co-morbidities involving chronic kidney disease (CKD) patients with DM are variable. For instance, both progression and regression of kidney disease commonly occur in diabetes patients after the development of persistent albuminuria. ²,³ Therefore, it is thinkable that if albuminuria is identified early, it can be slowed with treatment, but the kidney function may progressively worsen in the absence of timely treatment or clinical inertia. The primary treatment strategies to slow progression

¹School of Community Health, Charles Sturt University, Canberra, ACT, Australia
²Calvary Hospital, Canberra, ACT, Australia
³School of Biomedical Sciences, Charles Sturt University, Canberra, ACT, Australia

Corresponding author:
Fergus William Gardiner, School of Community Health, Charles Sturt University, Canberra, 4 Mary Potter Circuit, Bruce ACT 2617, Australia.
Email: gus_gardiner@hotmail.com
of kidney damage, and progression to CKD, include controlling HT and blood glucose levels (BGLs), and this includes medications and lifestyle changes. CKD is a significant cause of mortality in patients with DM.4–7 As such, it is important to review key services aimed at addressing diseases related to progression and management of CKD, including hospital DM and CKD inpatient services, cardiac rehabilitation (CR) outpatient programmes, and endocrine outpatient services.

Treatment barriers in patients with HT, DM, CKD, and cardiovascular disease (CVD) have been explored and have often been associated with clinical inertia.8–10 Clinical inertia is when the clinician fails to escalate care in the presence of competing demands from multiple co-morbidities.11–13 It has been reported14 that clinical inertia is a major factor that contributes to inadequate chronic disease care in patients with DM, HT, and CKD. Despite evidence that intensified therapy is usually needed to achieve and maintain evidence-based chronic disease care goals, a number of studies document high levels of clinical inertia in patients with DM15 and demonstrate that more active clinical management improves HbA1c14 and systolic blood pressure (SBP) control.16

This narrative is focused on and organised in the following sequential three sections:

- Chronic disease services and benefits to BP and BGL control in diabetic CKD, including the following:
  - Hospital DM inpatient services;
  - Hospital management of CKD inpatients;
  - Endocrine outpatient services;
  - CR outpatient programmes.

- Pathology services and complexity in diabetic CKD management.

- Clinical inertia in minimising adherence to guideline recommendations associated with BP and BGL control in diabetic CKD.

**Methodology: narrative review**

This narrative article reviews the evidence regarding hospital DM and CKD inpatient services, CR outpatient programmes, and endocrine outpatient services, aimed at achieving clinical results, in patients with CKD, DM, and HT in Australia. Clinical results specifically focused on improvement measures, associated with BP, weight, random blood glucose, albumin excretion, estimated glomerular filtration rate (eGFR), creatinine, urea, calcium, C-reactive protein (CRP), cholesterol, and HbA1c. Furthermore, we conducted a search on information concerning CR measures including the Patient Health Questionnaire (PHQ-9) and on the participants’ 6-min walk test (6MWT). The literature pertaining to Australian services, pathology treatment methods, and complexity in management, patient benefits, and clinical inertia in treatment of BP and BGL was also considered. The searches included articles from PubMed-listed articles published between 1993 and 2016. The study included original research studies, focusing on high-quality randomised controlled trials and prospective studies where possible, systematic and other review articles, meta-analyses, expert consensus documents, and specialist society guidelines, such as those from the National Heart Foundation of Australia, American Diabetes Association, the Department of Health, The Royal College of Pathologists of Australasia, and the Australasian College of Emergency Medicine.

**Australian chronic disease services and benefits to patients**

*Hospital diabetes inpatient service education and gaps in the literature*

DM education is effective in helping patients with DM in controlling their illness and maximising their health.17–20 Outpatient DM education programmes have been found to bring sustained benefits in DM patient outcomes, including reduced hospital treatment, reduced mortality;21 adherence to therapeutic targets,22 and medical measures such as improved heart rate (HR), BP, and blood pathology.23 These benefits have not been widely studied in an inpatient hospital setting, and an Australian study24 to determine the prevalence of DM in inpatients within 11 hospitals in Melbourne recruited 2308 adult inpatients in all wards apart from intensive care, emergency, obstetrics, and psychiatry. The study concluded that DM prevalence ranged from 15.7% to 35.1% and determined that the high burden of DM inpatients had major implications for patient health and health care expenditure. Furthermore, the researchers suggest that optimising care has the potential to decrease inpatient morbidity and length of stay.

There are significant research gaps in DM inpatient education, and hospital admission provides an opportunity to fill this DM education gap.24 Appropriate management of DM early in admission may help shorten length of stay and decrease readmissions rates. Hospital DM education services aimed at educating patients about DM self-management have become a focus among health care professionals and are advocated for patients with type 2 diabetes mellitus (T2DM) to acquire the skills for active self-management.18,25,26 Self-management education is recognised as an important component in the management of T2DM.27,28 Even with these benefits, the literature has not included the benefits of a DM education service within the Australian hospital health care system. This includes a dearth, gained via a search of PubMed-listed articles, of data regarding the significance of DM education as it pertains to BP and blood glucose control. As such, a future article will investigate the following:

1. Whether diabetes education within hospital leads to reduced BGLs;
2. Whether diabetes education within hospital leads to reduced HbA1c level after discharge.
**Endocrine outpatient service and gaps in the literature**

Chronic diseases, such as DM, HT, and CKD require a high level of patient self-management. Patients who maintain a near to normal BGL are able to reduce the incidences of DM complications, such as eye and renal diseases, and neuropathy. Furthermore, patients receiving specialist care from hospital DM (or endocrine) clinics have a better prognosis in terms of glycaemic control, DM complications, survival, and risk of hospital readmission. It has been acknowledged that patients who do not attend specialist clinics often do not receive optimum management and are likely to be hospitalised later with advanced DM complications, such as increased BP and reduced kidney function.

Continuing medical care, including DM and HT self-management education, for example, provided by medical professionals with expertise in the endocrine system, is essential to minimise long-term complications. Furthermore, specialist DM, renal, and HT care has been shown to deliver better glycaemic and BP control outcomes than that of conventional care.

It appears that there is no Australian literature on benefits associated with patients attending a specialist hospital outpatient clinic, and specialist care is reported as beneficial. A study aimed to elucidate the effects of 1 year’s specialist care on the management of T2DM, looked at 745 Japanese patients within 11 outpatient clinics and concluded that DM patients under specialist care experienced substantial improvement in glycaemic and BP control.

A major limitation in Australia to the treatment of high BGLs and BP is a gap in knowledge on the effectiveness of endocrine specialist clinics in control and adherence to BP and glucose recommendations. Furthermore, there has been no Australian research that considers whether clinical inertia effects adherence to BP and glucose recommendations in an endocrine clinic. By understanding this information, resources will be allocated effectively. As such, a future study will aim at the following:

- To determine whether an endocrine outpatient clinic has positive effects on BP and glucose management;
- To determine how effective an endocrine clinic is at achieving BP and HbA1c guideline recommendations in patients with DM (type 1 diabetes mellitus (T1DM) and T2DM), HT, and CKD;
- To determine whether achieving the target BP and BGLs in patients with CKD and DM is affected by clinical inertia.

**CR outpatient programme and gaps in the literature**

CR is a recommended treatment protocol, for the treatment of CVD, and has evolved from a simple patient monitoring process to a multidisciplinary approach focusing on patient education, tailored exercise programmes, modification of patient risk factors, and overall well-being of the patient. The patient’s benefits associated with a CR programme include reduced mortality, symptom relief, smoking cessation, enhanced physical ability, and improved psychological well-being. CR programmes are underutilised by patients with CVDs, mainly due to referral problems, poor enrolment and support, and limited resources.

CR programmes are effective in reducing the risk of future cardiac events. Bright (1836) was the first to report the association between CKD and CVD abnormalities, and by taking the view that renal disease is the primary disorder and cardiovascular changes are secondary, he established the concept of renal origin of CVD. Many studies have reported that low eGFR and raised albuminuria are associated with CVD. These studies found that cardiovascular mortality was about twice as high in patients with stage 3 CKD and three times higher in stage 4 than that in patients with normal kidney function. Many CVDs have been associated with impaired kidney function, and the risk of heart failure is roughly doubled in patients with eGFR lower than 60mL/min/1.73 m², compared to patients with preserved eGFR. This risk is similarly increased for stroke, peripheral artery disease, coronary heart disease (CHD), and atrial fibrillation. CKD is frequently the result of HT and DM, and those with CKD should be viewed as high-risk groups for CVD. Even with this association, no Australian studies have directly considered the benefits of a CR programme to DM and CKD patients. As CVD is linked to DM, HT, and CKD, it may be logical that CR programmes also play a part in reducing risk factors such as high BP and glucose control in DM patients. This association has not been studied within Australia, and this limitation appears to be consistent in other countries, such as America, thus possibly contributing to underutilisation of CR programmes. As such, future studies will aim at the following:

1. To determine whether the CR programme benefited the patient medically, including reductions to pathological risk factors, improvements to functional capacity, and improvements in mental health;
2. To determine the extent to which the targets for BP control in patients with HT and DM are achieved;
3. To determine the patients’ perceived benefits in participating in the CR programme and the various reasons for declining the programme.

**Hospital CKD inpatient service and gaps in the literature**

The research examining various BP targets or comparing active treatment with placebo has been consistent in suggesting that lowering BP consistently to <140/90mmHg helps...
prevent major cardiovascular events and reduces the risk of progression to CKD. The generally accepted Australian BP target is <130/80 mm Hg if tolerated or <140/90 mm Hg. The Australian Renal Diseases Health Network: Chronic Kidney Disease Model of Care recommends the following for the treatment of early-stage CKD: reducing BP for uncomplicated HT to <140/90 mm Hg and for HT in DM to <130/80 mm Hg and use of angiotensin-converting enzyme (ACE) inhibitors as first-line therapy. Angiotensin 11 receptor blockers (ARBs) may provide similar kidney protection.

The need for prompt follow-up and referral, combined with appropriate medications to achieve a BP control (<140/90 mm Hg), is important and emphasised in Australian guidelines. Even with guidelines, previous studies have highlighted that treatment is often inadequate. Most guidelines for HT management and studies concerning control have mainly concentrated on the outpatient setting. Studies indicating recognition and control of HT in the inpatient hospital setting are limited, especially in patients with high-risk conditions, such as DM and CKD.

In 2009, the Australian Diabetes Society published a position statement recommending individualisation of glycaemic targets. The general HbA1c target is <7.0% (<53 mmol/mol), although it recommends the following:

- For people without known CVD, a long duration of DM, severe hypoglycaemia, or another contraindication, the target should be <6.5% (<48 mmol/mol);
- For people with reduced hypoglycaemia awareness or major co-morbidities (such as CKD), the target may be increased to <8.0% (<64 mmol/mol);
- People with limited life expectancy (<1 year of expected life) aim for symptom control;
- Women planning a pregnancy aim for the tightest achievable control without severe hypoglycaemia, preferably <6.0% (<42 mmol/mol).

These recommendations reflect The Royal College of Pathologists of Australasia (RCPA) recommendations and other studies that a HbA1c result <8.0% (64 mmol/mol) indicates good control in DM and CKD patients. There is concern that the benefits of intensive HbA1c management targeting an HbA1c <7% is unclear and may be potentially harmful, though. Tight glycaemic control early in the DM is desirable and possibly leads to the greatest benefit for the prevention of micro- and macrovascular complications, as well as mortality. Importantly, tight glycaemic control in advanced disease is effective in retarding the development and progression of microvascular disease, which in the case of CKD is important.

It is not known how well Australian clinicians control BP and BGL in hospital inpatients, especially in patients with chronic conditions, such as CKD. Furthermore, it is unknown whether clinical inertia impacts adherence. As such, a future research project will aim to determine to what extent the targets for BP and blood glucose control in patients with CKD are achieved and to what extent is clinical inertia affecting BP and glucose control in patients with CKD and DM.

Given the concern over predictive analytics of pathology tests including HbA1c, it behoves that review of pathology services and complexity in diabetic CKD management is necessary.

### Australian pathology services and complexity in management

#### Medical testing

The investigation and management of patients with CKD, DM, and HT include measurement of the patients’ BGLs, eGFR, and BP. High BP is a risk factor for CVD and CKD (Figure 1), and BP cut-off values are used to aid diagnosis and management decisions. The BP categories and grades of HT are shown in Table 1. Diagnosis of HT is based on multiple BP measurements taken on separate occasions, at least twice, 1 or more weeks apart, or sooner if BP is suspected to be severe.

Diagnosis of DM (non-pregnant patients) includes testing of patient glucose levels and HbA1c levels, and the accepted reference level for fasting venous plasma or serum glucose level in Australia is 3.0–5.4 mmol/L, and the recommended RCPA random venous plasma or serum glucose level is 3.0–7.7 mmol/L. In a patient with symptoms suggestive of DM, a fasting plasma glucose >7.0 mmol/L, or a plasma glucose of >11.1 mmol/L at least 2 h after a meal, or in the case of an oral glucose tolerance test (OGTT), is diagnostic of DM. An HbA1c value of >6.5% (>48 mmol/mol) suggests DM and is an alternative to traditional glucose-based methods, although it should not replace glucose testing. The HbA1c result reflects the average blood glucose concentration over the life of the red cells and should be measured every 3 months. Ideally, HbA1c targets should aim to maintain levels as close as possible to non-diabetic levels (<6.5% (48 mmol/mol), but goals must be individualised by age and by the presence of chronic diabetic complication. The eGFR is a good indicator of kidney function and is calculated using the patient’s age, sex, and serum level and expressed relative to a ‘standard’ body surface area of 1.73 m². Table 2 shows various stages of CKD.

HT and DM are primary risk factors for atherosclerosis and its related complications such as heart attack, stroke, and CKD. DM, HT, and CKD have substantial overlap in their aetiology and disease mechanism (Figure 1). In clinical practice, DM and HT, which contribute to CKD, are found in the same patients often than can be explained by chance alone, with the overlap between dysglycemia and elevated BP is more common. A study conducted in Hong Kong found that only 42% of people with DM had normal BP (<120/80) and only 56% of patients with HT had normal glucose tolerance. Similar findings and conclusions have been found in other populations.
These studies suggest that there are shared genetic and/or environmental factors in the HT, DM, and CKD aetiology.

**Complexity of treatment and management**

One of the initial steps in controlling hyperglycaemia in T2DM is lifestyle changes including appropriate diet and exercise.\(^1\)\(^,\)\(^7\) Drugs are commonly used but on the condition that there are no contraindications. The complexity of treatment lies in the fact that several drugs have contraindications. For instance, metformin and other common antidiabetic drugs have contraindications for patients who have severe renal disease,\(^79\) and there is therapeutic inertia for prescribers.\(^80\) Insulin is an option considered, especially if the HbA1c is $>9.0\%$ ($>75$ mmol/mol) after administering an oral agent.\(^57,81\)\(^,\)\(^85\)

The research examining various BP targets or comparing active treatment with placebo is consistent in suggesting that lowering BP consistently to $<140/90$ mm Hg helps prevent major cardiovascular events and reduces the risk of progression to CKD.\(^47\)\(^,\)\(^54\) There is, however, debate on whether BP targets should be lowered further in patients with DM and CKD,\(^47\)\(^,\)\(^54\) and the literature is inconclusive. The evidence suggesting benefits for lowering BP target to $<140/90$ mm Hg are mixed with modest benefits for patients with DM and inconsistency in observational study results.

As such, Kidney Health Australia\(^5\) guidelines recommend that all patients requiring antihypertensive medication are treated to a target of $<140/90$ mm Hg. Furthermore, the guidelines recommend that those at high risk, whom it is safe based on clinical grounds, to aim for a systolic BP of $<120$ mm Hg. In saying this, much of the literature supporting treatment to ‘optimal’ BP of $120$ mm Hg is derived from patients with existing co-morbidities who are already on antihypertensive.\(^5\) This is also pertinent when aiming for BP

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**Figure 1.** Pathophysiologic mechanisms in the development of HT in DM patients and its subsequent link to CKD.
of 120 mm Hg in inherently difficult patients (such as those who are uncooperative and those not responding to BP control treatments) with a high baseline BP and where attaining 140 mm Hg is challenging.5

The choice of antihypertensive medication is important, and many classes of antihypertensive drugs used in monotherapy decrease BP by similar amounts, such as ACE or ARB inhibitors are equally effective in BP reduction, noting difference in effective and not being interchangeable in some clinical conditions. However, response can be unpredictable, with an estimated 50%–70% of patients not achieving BP targets with a single drug. As such, in this circumstance, at least two antihypertensives from different classes are required.86 The initial drug choice should be based on the patient’s age, presence of associated conditions (renal/organ damage), interaction with other drugs, and potential for patient adherence. Based on the guidelines,5 it is recommended that thiazide diuretics, calcium channel blockers, ACE inhibitors, or ARBs are suitable for first-line treatment of HT. These can be used as monotherapy, or in some combinations, noting potential contraindications and co-morbidities. In combination therapy, ACE inhibitors and calcium channel blockers are superior to diuretics combined with either an ACE inhibitor or a beta-blocker. Based on guidelines, Table 3 shows effective drug combinations, and Table 4 highlights the combinational therapies to be used with caution, for in HT and/or DM patients and/or CVD patients.

Despite the increasing range of therapies available, the complexity of treatment is hallmarked by the fact that achieving glycaemic and BP targets can be difficult. Literature 88–92 indicates that blood glucose and the measurement of BP appear not to achieve the goals. However, there is dearth of data from Australian studies regarding adherence to BP and BGL control in diabetic CKD patients’ making. This is a major limitation in preventing DM and renal disease progression. Given the complexities in management, it will benefit to determine the extent to which (1) the targets of BGL and BP control in diabetic CKD are being achieved according to guidelines and (2) clinical inertia impacting achievement of targeted controls.

Clinical inertia

Treatment barriers in patients with DM, CKD, and CVD have been explored and have often been associated with clinical inertia (CI).8–10 To be defined as demonstrating CI, there was evidence that there was a failure to achieve guideline recommended BP and a failure to receive appropriate change or intensification of treatment. It has been reported14 that clinical inertia is a major factor that contributes to inadequate chronic disease care in patients with DM, HT, dyslipidaemia, depression, CHD, and other conditions such as CKD. Despite evidence that intensified therapy is usually needed to achieve and maintain evidence-based

<table>
<thead>
<tr>
<th>Stage</th>
<th>eGFRa</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>90+</td>
<td>Normal kidney function, but urine findings or structural abnormalities or genetic trait point to kidney disease</td>
</tr>
<tr>
<td>2</td>
<td>60–89</td>
<td>Mildly reduced kidney function and other findings (as for stage 1) point to kidney disease</td>
</tr>
<tr>
<td>3</td>
<td>30–59</td>
<td>Moderately reduced kidney function</td>
</tr>
<tr>
<td>4</td>
<td>15–29</td>
<td>Severely reduced kidney function</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 or on dialysis</td>
<td>Very severe or end-stage kidney failure (sometimes called established renal failure)</td>
</tr>
</tbody>
</table>

BP: blood pressure.
Source: National Heart Foundation of Australia.71

Table 2. Stages of chronic kidney disease.

<table>
<thead>
<tr>
<th>Category (general public)</th>
<th>Systolic (mm Hg)</th>
<th>Diastolic (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desirable</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Normal</td>
<td>120–129</td>
<td>80–84</td>
</tr>
<tr>
<td>High–normal</td>
<td>130–139</td>
<td>85–89</td>
</tr>
<tr>
<td>Mild hypertension</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Moderate hypertension</td>
<td>160–179</td>
<td>100–109</td>
</tr>
<tr>
<td>Severe hypertension</td>
<td>&gt;180</td>
<td>&gt;110</td>
</tr>
<tr>
<td>Isolated systolic hyperten</td>
<td>&gt;140</td>
<td>&lt;90</td>
</tr>
</tbody>
</table>

BP: blood pressure.
Source: National Heart Foundation of Australia.71

Table 1. BP diagnostic category for adults.
chronic disease care goals, a number of studies document high levels of clinical inertia in patients with diabetes or lipid disorders and demonstrate that more active clinical management improves HbA1c and SBP control. Even with these reported benefits, there have been no Australian studies that have considered whether clinical inertia impacts diabetic CKD patient care.

**Conclusion and future directions**

From this review of the literature, the effectiveness of programmes, such as the diabetes inpatient services, endocrine outpatient services, and CR services, at achieving guidelines recommendations is not clear and as such future studies need to examine the following:

- To what extent are the targets for BP and/or blood glucose control in patients with CKD and DM achieved?
- To what extent is clinical inertia affecting BP and glucose control in patients with CKD and DM?
- To what extent does hospital chronic disease services contribute to controlling DM patient BP and glucose?

It is not clear whether Australia clinicians adhere to DM, HT, and glucose recommendations and the potential reasons for clinical inertia. By understanding whether BP and glucose-level recommendations are not being achieved due to clinical inertia acting as a barrier to adherence is important since failure to control BGLs and BP leads to renal damage, which in turn worsened the burden on hospital. By understanding the barriers to control, targeted interventions, with the aim of improving patient outcomes, can be developed.

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**Declaration of conflicting interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethical approval**

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**Informed consent**

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