Title: Multimorbidity in people with CKD: implications for outcomes and treatment

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Abstract

Purpose of review:

With ageing populations the prevalence of multimorbidity is increasing. This review discusses recent developments in the understanding multimorbidity in the context of chronic kidney disease (CKD, co-occurring with a wide range of comorbidities). It explores the associated treatment burden and the implications for key outcomes and patient care.

Recent findings:

Comorbidity and polypharmacy are common in CKD, even at early stages, and are associated with significant treatment burden. Both 'concordant' and 'discordant' comorbidities have a negative impact on mortality, cardiovascular disease, hospitalisation and length of stay. In addition, quality of life is influenced by many factors beyond CKD, including comorbidities and certain medications. Several factors may reduce treatment burden for people with CKD, though research on this is at an early stage. While patient activation is desirable to support self-management among people with multimorbidity, there are significant challenges that impact patient capacity among elderly populations with complex needs.

Summary:

Comorbidities are common in CKD and have important implications for patients, clinicians and health services.

Keywords:

Multimorbidity, chronic kidney disease, polypharmacy, treatment burden

Introduction:

The prevalence of chronic kidney disease (CKD) rises with age and commonly occurs in the context of multiple comorbid conditions and polypharmacy for the large population of older people with the condition.[1-3] Multimorbidity is often defined as having two or more co-existing chronic morbidities (although this definition has been the subject of debate), and people with CKD who have one (or more) comorbidity therefore meet this definition. Comorbidities add to overall disease burden for patients and a greater degree of multimorbidity is often experienced (or experienced at younger age) by those least equipped to cope (such as those of lower socioeconomic status including lower education and lower income).[4] Comorbidities are sometimes conceptualised as 'concordant' and 'discordant' (i.e. sharing or not sharing a common pathophysiological pathway with CKD) and both have an adverse impact on prognosis.[2,3] Discordant comorbidities (such as depression and chronic pain) are surprisingly common in the CKD population though are perhaps less likely to be the primary concern for nephrologists than concordant conditions such as diabetes and cardiovascular disease.[3] Recently there has been greater recognition that comorbidities, as well as any given index condition, create a 'treatment burden' – the demands placed on patients as they undertake the actions required to manage their conditions.[5] Linked to this are the concepts of cumulative complexity (the accrual of complicating factors over time that impact care and outcomes) and patient capacity (the ability to handle the 'work' of being a patient). [6] Over-burdened patients may, through no fault of their own, fail to self-manage their conditions and may not engage successfully with health services, leading to poor outcomes. This engagement has been described as 'patient activation' and is defined as 'an individual's knowledge, skill, and confidence for managing their health and health care'.[7] In addition to symptoms directly attributable to CKD, the prognosis, in terms of both clinical outcomes and quality of life, may depend heavily on the nature and extent of comorbidities, the degree of treatment burden and their capacity and degree of activation. This review will discuss recent developments in the understanding of the nature and extent of comorbidities in CKD, the associated treatment burden and the implications for key outcomes and patient care.

Text of review:

Multimorbidity and CKD

There is an important two-way implication of the high prevalence of comorbidities in CKD. The presence of reduced renal function and its associated complications affects treatment decisions for other conditions, while at the same time other conditions represent an important component of the clinical burden experienced by people with CKD (See Figure 1). This has implications not only for specific, key components of kidney disease management (such as the decision to start dialysis), but also broader considerations around the need to integrate care, including resolving conflicts in individual disease-specific guidelines.[8]
A large Canadian database study by Tonelli et al has highlighted the importance of concordant and discordant comorbidities in CKD. Data from 530,771 adults with CKD were analysed by grouping 29 comorbidities into ‘concordant’, ‘discordant’ and ‘mental health/chronic pain’ categories. Results showed that greater degree of any comorbidity was associated with poorer outcomes, such as all-cause mortality, hospitalisation and length of stay (see Table 1).[3]

Figure 1. CKD and comorbidities and their implications for patients, clinicians and health systems

(**ORIGINAL**: This figure has not been published elsewhere)

Table 1. Adjusted ratios of outcomes by number of concordant, discordant and mental health / chronic pain comorbidities. Used with permission from Tonelli M, Wiebe N, Guthrie B, James MT, Quan H, Fortin M, Klarenbach SW, Sargious P, Straus S, Lewanczuk R, et al.: Comorbidity as a driver of adverse outcomes in people with chronic kidney disease. Kidney Int 2015, 88:859-866

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They also demonstrated a significant association between both concordant and discordant conditions and the population attributable risk of these adverse outcomes. This confirmed the expected adverse influence of concordant conditions such as hypertension, heart failure and diabetes on hospitalization, length of hospital stay, myocardial infarction and death. Importantly, they also demonstrated that discordant conditions such as dementia and pain or mental health conditions had significant population-attributable risks for hospitalisation and all-cause mortality. [3] By far the largest study of its kind to date in CKD, the authors admit that the study was inevitably limited by the use of administrative data, the potential for residual confounding from other factors such as smoking, the potential for disease status misclassification, and having been conducted in one locality in Canada. In addition, their distinction between ‘discordant’ and ‘mental health’ conditions could be considered somewhat arbitrary and patients frequently have co-existing comorbidities falling into more than one of these categories. Nevertheless, the study has highlighted the need to adopt a holistic approach and consider discordant conditions as well as the ‘usual suspects’ if a true understanding of the relationship between CKD, comorbidities and outcomes is to be achieved.[3]

There is growing evidence that comorbidities may be of more immediate concern than kidney function for people with CKD, particularly at earlier, asymptomatic stages.[9,10] In the

Kidney Early Evaluation Program (KEEP) study (a large US community-based health-screening program targeting adults at high risk of kidney disease) comorbidities were common. Among 27,000 people aged 65 or over with CKD, over 40% had two comorbid conditions and over 30% had three or more. A similarly high prevalence of comorbidity was identified among people with CKD in the National Health and Nutrition Examination Survey (NHANES) and a large Medicare population.[1] An important issue raised by this study is how to define the distinction between ‘comorbidities’ and ‘complications’ in CKD. The authors considered hypocalcaemia, hyperphosphataemia, hyperparathyroidism and high cholesterol as CKD complications and hypertension as a comorbidity. However, hypertension is arguably a risk factor, comorbidity and a complication of CKD. Future consensus on this issue would aid consistency of reporting.

A recent UK study has further emphasized the importance of comorbid conditions in early or mild CKD. The distribution and prognostic implications of eleven comorbidities were examined among 1741 people with CKD stage 3 in primary care. The analysis found that isolated CKD was rare and the prevalence of comorbidity as well as polypharmacy was high. Only 78/1741 of participants (4%) had no comorbidities, 453 (26%) had only one comorbidity (most commonly hypertension), 508 (29%) had two comorbidities and 702 (40%) had more than two comorbidities (see Figure 2).[11] Similarly, 1033/1741 (59%) were taking five or more medications and 198 (11%) were taking ten or more. Greater degree of multimorbidity was associated with lower education status and poorer survival. In keeping with the data from Tonelli et al., having three or more comorbidities was associated with an independent hazard ratio of 2.81 (95%CI 1.72-4.58) for all-cause mortality compared with having none or one. This represented the single highest independent contributory factor (greater than smoking for example).[2] Although limited by geographical location and ability to only consider a smaller range of conditions, this study had the advantage of being conducted as part of a formal cohort study and was therefore not reliant on routine or administrative data to determine the presence or absence of comorbidities. It was also able to consider the high medication burden experienced by people with moderate CKD and its association with lower education status. The odds ratio of taking more than five mediations per day was 1.44 (95%CI 1.10-1.90) among people with no formal qualifications compared with people with degree-level qualifications. These are important components of treatment burden and patient capacity respectively. [2]

Figure 2. The distribution of 11 comorbidities in a cohort of 1741 people with CKD stage 3 in the UK. The figure represents the proportion of people with different degrees of comorbidity who had each of the 11 conditions.

(**PREVIOUSLY PUBLISHED AS ABSTRACT**: This figure has been previously included in a poster presentation at the European Dialysis and Transplant Association-European Renal Association conference 2015. See:

http://ndt.oxfordjournals.org/content/30/suppl_3/iii185.3.short

It has not been published elsewhere)

Treatment burden

Many papers have highlighted the challenge of achieving optimal management of all aspects required to achieve maximum renal and cardiovascular risk reduction in people with CKD, but few have focussed on the problem of treatment burden. Treatment burden comprises objective treatment-related tasks (e.g. attending appointments, taking multiple medications, dose-adjustment, tests, interventions, including attending dialysis) and perceived treatment burden (patients' experience of the demands placed on them by clinicians and the health system). In the context of CKD, as with many chronic conditions, treatment goals have dual aim – symptom control or future risk reduction. Both incur treatment burden.

Treatment burden may be particularly important for people who have CKD as part of their multimorbidity. For example, stark changes in treatment may be needed as the condition progresses (from non-dialysis to dialysis and / or renal transplant) and this treatment burden transition in the context of other morbidities is not well understood.[12,13] A systematic review of the main attributes of treatment burden identified in 30 (non CKD) studies concluded that it changes over time with disease severity and development of comorbidities, that it is multidimensional (including physical, financial, temporal and psychosocial demands), and that it includes both objectively measurable and subjective elements.[14]

A qualitative study of treatment burden in 34 people with CKD-associated multimorbidity in the US identified four themes:

1) coherence (learning about CKD and understanding its implications)
2) cognitive participation (enlisting support from family and friends and organising personal resources to arrange medical activities)
3) ‘collective action’ (the work of self-management and following medical advice)
4) reflexive monitoring (reviewing self-care and making refinements).[15]

A generalised multimorbidity treatment burden measure has been developed in France and validated in English (in both UK and US) in the form of a seven-item (and several sub-items) questionnaire including aspects such as medication frequency, the need for laboratory tests, frequency of doctors’ visits and self-monitoring tasks.[16-18] A further measure in development is based on similar themes of the work patients must do to care for their health and factors that exacerbate the felt burden.[16,19] Such measures of treatment burden are valuable and have not yet been adopted in routine clinical settings, though their inclusion in clinical practice may be limited by the time they take to administer.

In early CKD, treatment goals are often directed predominantly at risk reduction, such as control of hypertension; in later stages CKD-related symptom control may become as (or more) important. There is therefore a change in treatment burden as CKD progresses. However, most patients with mild to moderate CKD do not progress to end stage disease and their overall treatment burden may be predominantly non-CKD or related to risk reduction activities. Factors that reduce treatment burden have been explored in a qualitative study of people with multimorbidity (that included some participants with CKD).[20] These factors included problem-focused strategies (such as routinising self-care, enlisting support, making plans for the future, and embracing technology), emotion-focused coping strategies (maintaining a positive attitude, focusing on other life priorities, and spirituality/faith), questioning the notion of treatment burden and comparing oneself (favourably) to others, social support and positive aspects of health care, including coordination of care and positive relationships with providers.[20] For those caring for people with CKD it is therefore important to recognise the role of comorbidities and their associated treatment burden as well as that imposed by CKD itself. Each will have implications for quality of life, an important outcome in CKD.

Quality of life and patient reported outcome measures (PROMs)

Many factors are known to negatively influence quality of life among people with CKD (though most research to date has been in later stage CKD). [13,21-25] Factors associated with reduced quality of life in CKD have included severity of CKD, age, gender, anaemia, diabetes, cardiovascular disease, certain medications (beta-blockers), the intrusiveness of renal replacement therapy and number of comorbidities.[21,22,24] Quality of life in dialysis is often poor compared with renal transplant, some of which may relate to the treatment burden associated with dialysis.[13] Patients with advanced CKD have been shown to report very poor quality of life determined by multiple factors, including family issues, general health, work / school, finances and leisure.[26]

Mujais et al explored quality of life in 1186 patients with CKD stage 3-5 using the Kidney Disease Quality of Life (KDQOL) questionnaire (which combines the generic SF-36 with 43 kidney disease-specific items). They showed that quality of life was adversely affected by age (particularly the physical functioning component of KDQOL), although emotional wellbeing tended to be higher in older people. Women had poorer quality of life in several domains including physical functioning, pain, energy/fatigue and general health.

Comorbidities were found to negatively impact quality of life, though this was predominantly due to their impact on physical rather than mental factors. Beta blockers were found to negatively impact physical functioning and emotional domains.[22]

There is considerable potential for reduced treatment burden to positively influence quality of life in earlier CKD. In the context of mild to moderate CKD with comorbidities, treatment decisions are commonly driven by condition-specific guidelines and relate to reducing future risk. These are often applied in primary care practice in the context of a holistic approach that needs to accommodate the wider context in which patients are operating.[27] Treatment decisions are therefore determined by discussion between clinician and patient on the balance of treatment burden vs. treatment benefit (either in reducing risk or symptoms or both). The Tonelli study identified the challenge of potentially conflicting therapeutic objectives (such as the use of non-steroidal anti-inflammatory agents in people with CKD in combination with arthritic disorder).[3] Tools for integrating guidelines have been proposed such as the ADAPTE process and the knowledge-to-action cycle.[8,28] The ADAPTE manual and toolkit follow a logical progression through a series of steps including identifying relevant guidelines, assessing those guidelines, deciding and selecting and then customizing guidelines for a particular scenario. This can be a complex process and has been found to be challenging in practice. It has been suggested that the knowledge-to-action cycle may be more valuable in the CKD context.[8,29]

There may be benefits to patients associated with moving from an implicit to an explicit recognition of the importance of treatment burden in such discussions. It has been argued that treatment burden may represent an important component of quality of care, linked to waste if over-burdened patients are unable to comply with healthcare processes.[30] The term ‘minimally disruptive medicine’ has been used to call for better ways of reducing treatment burden and improve quality of life for patients with multimorbidity.[31] Recent work involving the implementation of a ‘tele-patient-reported-outcome’ (telePRO) model in Danish clinics (including renal failure clinics) has demonstrated that incorporating several measures of patient status in a responsive IT-based system can result in reduction of the need for outpatient visits, thereby potentially reducing costs for providers while also reducing treatment burden and improving satisfaction for patients.[32]

Patient activation and capacity

Patient activation includes the patient-held belief that an active role is important, having the confidence and knowledge to take action, actually taking action and maintaining changes in the face of stress.[33] Measures of patient activation have been available for some time, though it is a relatively recent concept in the context of CKD. Patient activation measures (PAMs) are now being used in several countries along with PROMs in assessing compliance with risk reduction efforts and quality of life.[33, 34]

There is a need for patient activation and participation in self-management in people with multimorbidity that includes CKD, including lifestyle changes to reduce renal and cardiovascular risk. There are, however, significant challenges associated with patient activation among elderly populations with complex needs, including the important role of factors such as limited health literacy and hearing impairment.[35] One study identified unexpectedly lower patient activation in later stage CKD compared with stage 3. [34] Limited health literacy has been shown to be common among people with CKD. A 2012 systematic review identified a pooled prevalence of limited health literacy of about 23% (although there were a limited number of studies with a high degree of heterogeneity). There is a need to explore this further, particularly in pre-dialysis CKD.[36]

In the oncology setting there is evidence that use of PROMs may improve health literacy through better communication between the patient and the health care provider, patient satisfaction, ability to monitor treatment response and ability to detect otherwise unrecognised problems. [37]

Such aspects are part of patient ‘capacity’ defined as ‘the resources and limitations affecting patients’ ability or readiness to do work’.[6] This incorporates mental and physical functioning, socio-economic and psychological resources, literacy, language, and social support. It is adversely affected by unpleasant symptoms (such as pain and nausea), stress, depression and fatigue.[6]

The ability of patients to participate in their own care (their activation) is therefore influenced not just by disease burden, but also by treatment burden and capacity.

Implications for future research

In order to standardise reporting, it would be useful to reach consensus on what represents comorbidity versus complication in the context of CKD. Future observational and intervention studies should include more detailed assessment of comorbidities and more research is needed to clarify the interaction between CKD and concordant as well as discordant comorbidities. Research is also needed on the key determinants of treatment burden in people with CKD-related multimorbidity at different stages of CKD progression. Developing practicable methods of measuring treatment burden could empower patients, inform clinical decision-making and guide health services. Further exploration is needed of the best ways of delivering ‘integrated care’ and ‘minimally disruptive medicine’ for people with CKD and comorbidities.

Conclusion:

Comorbidity and polypharmacy are common in CKD, even at early stages of the disease. Both ‘concordant’ and ‘discordant’ comorbidities have a negative impact on outcomes such as mortality, cardiovascular disease, hospitalisation and length of stay. Treatment burden is an important aspect of life for people with CKD and may relate as much to comorbidities as to CKD itself. Similarly, quality of life for people with CKD is influenced by many factors beyond their CKD, including comorbidities and certain medications. While patient activation is desirable to support self-management, there are significant challenges that impact patient capacity among elderly populations with complex needs, and patient activation needs to accommodate capacity. With the growing prevalence of many chronic diseases due to an ageing population, there is a need for clinicians to find the optimum balance between treatment benefit and treatment burden for people with CKD and comorbidities.

Key points

1. Comorbidity and polypharmacy are common in CKD, even at early stages
2. Both ‘concordant’ and ‘discordant’ comorbidities have a negative impact on outcomes such as mortality, cardiovascular disease, hospitalisation and length of stay.
3. Treatment burden (the demands placed on patients as they undertake the actions required to manage their conditions) is an important consideration in CKD and is related to comorbidities as well as to CKD itself.
4. For CKD patients, quality of life is influenced by many factors beyond their CKD, including comorbidities and medications and the use of patient-related outcome measures may improve health literacy through better communication between the patient and the health care provider.
5. While patient activation is desirable to support self-management, there are significant challenges that impact patient capacity among elderly populations with complex needs.

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3. Conflicts of interest.

None

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