A public health perspective on CKD and obesity

William M. McClellan and Laura C. Plantinga

1Department of Epidemiology, Rollins School of Public Health, Atlanta, GA, USA,
2Division of Nephrology, Emory University School of Medicine, Atlanta, GA, USA and
3Laney Graduate School, Emory University, Atlanta, GA, USA

Correspondence and offprint requests to: William McClellan; E-mail: wmcclel@sph.emory.edu

Keywords: CKD, obesity, public health, translational research

Abstract

End-stage renal disease (ESRD) is a growing health burden for global populations, which has generated keen interest in interventions to prevent or delay the progression of its antecedent chronic kidney disease (CKD). There are biologically plausible mechanisms that link increased adiposity to pathways of kidney injury, animal models of obesity-related kidney disease and specific glomerular disease that is observed in extremely obese humans. Further, individuals with progressive kidney disease and incident ESRD are more obese than their counterparts in the general population. These observations raise the consideration that population-based policies targeted at delaying progressive CKD should recommend interventions for treatment of obesity in these individuals. We examine this proposition first by describing the public health infrastructure that exists to translate CKD public health policy, illustrating it by examples familiar to the practicing nephrologist. Next, we suggest that, despite the evidence supporting an association between increased body weight and progressive CKD, it is premature to contemplate public health recommendations for weight reduction in CKD patients. This prematurity reflects the lack of strong evidence that reduction in body weight delays or prevents the progression of CKD and persistent uncertainty about the direction of the association between obesity and mortality in individuals with advanced kidney failure. We conclude by noting that this position is not that of therapeutic nihilism but rather a caution to approach weight management in CKD on an individual, patient-to-patient basis, and an emphasis for further randomized clinical trials to resolve these uncertainties.

Chronic kidney disease (CKD) is a major international public health problem. Although there is substantial population-to-population variation in CKD prevalence, with estimates ranging from 0.6 to 42.6%, the within-population burden of kidney disease is generally comparable with that of diabetes [1]. CKD is ranked as the 12th most common cause of death in the world [2], and impaired kidney function increases the risk of death, cardiovascular disease and end-stage renal disease (ESRD) among diverse populations across the globe [3, 4]. Although the considerable health and economic burdens of CKD challenge all countries, the numbers of individuals dying from CKD and the costs of CKD and especially ESRD treatment are particularly a concern among the less developed economies of the world [5].

Obesity is a major risk factor associated with CKD. There is an ongoing epidemic of obesity throughout the world, particularly in less economically developed populations [6, 7]. As reviewed in this issue of Nephrology Dialysis Transplantation, obesity is linked to pathogenic mechanisms of kidney injury and associated with kidney disease in animal models. Obesity is a modifiable risk factor for diabetes and hypertension, the two most common causes of progressive CKD and ESRD in most populations. There is ample evidence that extreme obesity is associated with albuminuria, a biomarker of kidney injury, and a distinctive obesity-related glomerulopathy. There is also evidence that behavioral, pharmacological and surgical treatment of obesity-related CKD may be effective in modifying biomarkers of kidney injury (i.e. increased the renal blood flow and proteinuria). Finally, extensive evidence is presented that individuals with CKD and those who progress to ESRD have a higher prevalence of obesity than others within studied populations.

These observations serve as the context for a discussion of whether current evidence supports recommendations for public health action to reduce the burden of obesity-related CKD. This is not a trivial concern. The emergence of CKD and similar chronic diseases as major public health burdens has promoted the development of policies and programs to improve their prevention, detection, treatment and control [8–10]. Couser et al. [11] have made a strong case that
interventions targeted at CKD should be integrated into these national strategies. They recommended public health actions that would focus on improving the awareness, detection and treatment of CKD, especially in high-risk groups. They also note that extensive activities are already being conducted by the International Society of Nephrology to foster the development of cost-effective early detection and treatment programs in resource poor countries. Additionally, in 2010, Healthy People ([http://www.healthypeople.gov](http://www.healthypeople.gov)), a US program that provides sets of goals and objectives with 10-year targets designed to guide national health promotion and disease prevention efforts, intensified its focus on CKD (14 Healthy People 2020 objectives, 6 of which are specifically for pre-ESRD CKD) and obesity (4 Healthy People 2020 objectives toward healthier food access). However, none of the objectives addresses modification of obesity in the setting of kidney disease. This paper focuses on the question: to what extent should obesity among individuals with CKD be targeted for population-level interventions?

To address this question, first we must define what is meant by ‘population-level interventions’, or, synonymously, ‘public health action’, when discussing policies and programs targeted at CKD in a population. Such public health activities are aimed at improving the extent to which individuals at risk for a chronic disease are aware of their risk or disease state, receive evidence-based care and are treated successfully. If levels of detection, treatment and control are less than satisfactory, then public health policies and programs are targeted toward redressing the deficiencies. Stated more formally, public health actions to improve the control of a chronic disease like CKD focus on the translation of evidence-based knowledge and innovations into effective care of at-risk populations [12]. These translational activities, in turn, are based on the ability to identify at-risk communities/populations with less than adequate care [13].

These essential elements of this definition are shown in a simple translation model (Figure 1). The model presented is adapted from a US Centers for Disease Control and Prevention (CDC) translational model that was published to summarize the application of public health action to diabetes control [14] and was also shown to be applicable to many other chronic diseases [12] such as CKD. The model depicts a repeating process wherein epidemiology is used to characterize disease burden and variations in both detection and evidence-based treatment of at-risk populations. Basic and clinical researchers develop new or modified interventions (pharmacological, behavioral, educational or environmental) and assess the risk modification associated with these interventions. This evidence-based information is translated to healthcare providers, often through clinical practice guidelines, and used to provide more effective care. Finally, the success of these translation efforts is assessed through surveillance programs that routinely collect, analyze and disseminate information about the detection, treatment and control of the disease targeted for public health action [15, 16], and this new epidemiologic evidence continues the bi-directional cycle of continuous translation (Figure 1) and, ideally, improvement in care and outcomes.

A successful application of this process for CKD can be illustrated for the treatment of Stage 5 CKD in the US population (Figure 1) [17]. This example will provide a familiar, empiric framework for the discussion of a public health perspective on obesity and CKD. A good starting point is the Morbidity, Mortality and Prescription of Dialysis Symposium held in 1989 in Dallas, TX [18]. This important conference reviewed and published admittedly sparse clinical and epidemiologic evidence that raised concerns that high mortality rates in the US ESRD population, compared with other ESRD populations, might reflect inadequate dialysis dose [18]. This information fostered a substantial clinical research program as

![Figure 1: Cycle of surveillance, epidemiological and basic research, clinical trials and translation leading to improved care and outcomes (inner diagram), with an example of dialysis dose improvement and subsequently reduced mortality among dialysis patients (outer diagram). Adapted from models presented by Narayan et al. [14] and Khoury et al. [12].](image-url)
well as the development of educational and environmental interventions to promote the adoption of the best ‘dialysis dose practice [19–22]’. Adoption and use of information on how to attain hemodialysis adequacy targets was promoted through a modified industrial statistical process control method called ‘continuous quality improvement [23]’. Guideline adoption at a population level was initially fostered by the US ESRD Network system, and later these guidelines were widely adopted throughout the US dialysis industry [24]. The facilitated guideline adoption was associated with increased adequate hemodialysis care [25], and the improved hemodialysis care was shown to be associated with reduced mortality among ESRD patients [26]. This process has been through multiple iterations (Figure 1), driven by new guidelines for hemodialysis adequacy [27] and has been applied to other aspects of hemodialysis care [28].

Can this model be extended to less severe stages of CKD? It is beyond the scope of this discussion to review the extensive basic, observational and clinical research into the mechanisms and interventions to modify progressive CKD. The translational step of the model can be illustrated by evidence-based clinical practice guidelines addressing the detection, treatment and control of early-stage CKD [29–32]. An early and widely disseminated example of these guidelines was developed for the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) project [33, 34]. The dissemination, assimilation and adoption of the KDOQI CKD guidelines have been recently described for regions throughout the world, including Europe [35], Egypt [36], Brazil [37], Mexico [38], south Asia [39, 40], Japan [41], China [42], Australia and Canada [43, 44]. These and other CKD guidelines serve to foster population-based efforts to improve CKD care within the respective populations.

Surveillance systems are integral to these translational efforts [14, 45]. The US CDC initiated a population-based surveillance system of pre-ESRD CKD in October 2006, and inaugurated a web-based, publicly available system in October 2012 (www.cdc.gov/ckd/surveillance) [46]. The system includes nearly 200 indicators addressing many aspects of CKD, such as disease burden (prevalence and incidence), awareness, risk factors (including obesity) and health consequences, along with process of care and healthcare system capacity for CKD.

There are international examples of CKD surveillance as well. The Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps) (http://www.arborresearch.org) is an effort to develop nationally representative samples of nephrology clinics within participating countries that will gather detailed information about the practice patterns for the treatment of advanced CKD patients that will be used to improve care and outcomes for patients. The program is modeled after the successful Dialysis Outcomes and Practice Patterns Study (DOPPS) conducted since 1996. CKDopps is launching programs in France, Germany and Brazil in 2013 [47].

Further, preliminary results about German nephrology practice have recently been published for a cohort of CKD patients and [47, 48] similar efforts have been described for, among others, Spain [49], Canada [50], Japan [51] and Italy [52]. A program in the UK is particularly instructive [53]. Following a review and adoption of the KDOQI guidelines, a national effort was conducted to disseminate and apply them to the primary care of CKD within the UK National Health Service. Subsequent surveillance found progressive adoption of the guidelines and substantial improvement in the detection and care of CKD, including detection and control of high blood pressure and use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

These examples serve to illustrate the evolving global public health infrastructure with which public health initiatives to improve CKD care can be contemplated. Based on this model, what can we say about its relevance to obesity and CKD? As reviewed in this supplement and alluded to above, there are biologically plausible mechanisms that link adiposity to mediators of progressive kidney injury, including the following: obese animal models for proteinuria; observational studies establishing obesity as a risk factor for prevalent CKD; specific glomerulopathies (FSGS) in massively obese subjects, which respond to weight reduction interventions and causal associations of an increased body mass with risk factors for CKD/ESRD, including diabetes, HBP, the metabolic syndrome and CVD. Also, as discussed above, there are effective mechanisms in place to generate and disseminate clinical practice guidelines for CKD care.

Why, then, is there a lack of kidney-related obesity goals? The most evident missing element from the translational model related to obesity is the paucity of high-level evidence supporting interventions to modify obesity in patients with progressive CKD. There have been a number of recent systematic reviews of this evidence based on multiple databases (Medline, Cochrane and SCOPUS), reference lists of pertinent articles, meeting abstracts and Web of Knowledge that have found few randomized trials of weight reduction in patients with CKD [54–56]. The available observational and clinical trial studies were uniformly small and of short duration. The aggregate results of these studies, which show reductions in proteinuria, glomerular hyperfiltration and blood pressure, support a proof of concept for the utility of weight reduction interventions in the management of CKD. However, there is at present, very little evidence to suggest that weight reduction is effective in achieving hard CKD endpoints [57], and some observational results that suggest no effect [58–60].

Further, in addition to the lack of strong evidence to support weight reduction as a treatment for progressive kidney disease, there is ambiguity on the association between increased body weight and risk of death among patients with advanced CKD [61, 62]. The unexpected survival benefit of an increased body mass in ESRD patients is poorly understood yet consistent with observations in other chronic diseases [63] and also in the general population [64]. Possible explanations for this persistent observation include the effects of residual confounding [65, 66]; mis specification of the exposure by using body mass rather than more direct measures of adiposity [67]; survivor bias, wherein those who have survived the ill effects of obesity may have greater resilience against the poor outcomes of ESRD than those who died prior to developing ESRD; false associations created by conditioning (via...
restriction of the study population) on a diseased group associated with obesity [68] and a possible true protective benefit of an increased body mass for individuals with a progressive chronic illness. Until further clinical trials resolve this issue, it is imprudent to make strong recommendations about the safety of weight reduction among individuals with advanced CKD.

What do we do as scientists and clinicians while we wait for further guidance? Lifestyle recommendations to reduce obesity in the early-stage CKD population are likely warranted, if only to control extant diabetes and hypertension, which are likely to contribute to faster progression of CKD if left uncontrolled. However, such efforts, if successful, are likely to reduce any direct effects of obesity on CKD progression and also to help prevent other poor outcomes that may be related to CKD, diabetes, hypertension and/or obesity, such as cardiovascular events and mortality. Thus, the independent effect of obesity reduction will likely be difficult to tease apart from the effects of other, related health improvements. With a lack of evidence suggesting a benefit and some evidence suggesting that harm could result from population-level recommendations regarding obesity reduction in late-stage CKD, it is likely advisable that providers recommend only the usual diet restriction recommendations for preventing hyperkalemia, hyperphosphatemia and other complications of late-stage CKD. This sparse evidence should serve as an impetus for further clinical and translational research examining obesity reduction in later-stage CKD, including testing of interventions, which can then serve as the substrate for public health decisions.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

29. MacGregor MS, Taal MW. Renal Association Clinical Practice Guideline on detection, monitoring and management of patients with CKD. Nephron Clin Pract 2011; 118(Suppl. 1): c71–c100
34. Vassalotti JA. The cycle of development, publication, and implementation of clinical practice guidelines for CKD. Kidney Int 2012; 81: 1159–1161
41. Garcia MG, Mujica MPV, Ocana JCM et al. Results of a coordination programme and shared clinical information between primary care and nephrology. Nefrologia 2011; 31: 84–90
49. Garcia MG, Mujica MPV, Ocana JCM et al. Results of a coordination programme and shared clinical information between primary care and nephrology. Nefrologia 2011; 31: 84–90
Body mass index and body fat distribution as renal risk factors: a focus on the role of renal haemodynamics

Arjan J. Kwakernaak*, Tsjitske J. Toering* and Gerjan Navis

Correspondence and offprint requests to: Arjan J. Kwakernaak; E-mail: a.kwakernaak@umcg.nl
*Both authors contributed equally.

ABSTRACT

Weight excess and/or central body fat distribution are associated with increased long-term renal risk, not only in subjects with renal disease or renal transplant recipients, but also in the general population. As the prevalence of weight excess is rising worldwide, this may become a main renal risk factor on a population basis, even more so because the risk extends to the overweight range. Understanding the mechanisms of this detrimental effect of weight excess on the kidneys is needed in order to design preventive treatment strategies. The increased risk associated with weight excess is partly attributed to associated comorbid conditions, such as hypertension, dyslipidaemia, insulin resistance and diabetes; however, current evidence supports a direct pathogenetic role for renal haemodynamics as well. Weight excess is associated with an altered renal haemodynamic profile, i.e. an increased glomerular filtration rate relative to effective renal plasma flow, resulting in an increased filtration fraction (FF). This renal haemodynamic profile is considered to reflect glomerular hyperfiltration and glomerular hypertension, resulting from a dysbalance between afferent and efferent arterial vasomotor balance. This unfavorable renal haemodynamic profile was found to be associated with renal outcome in experimental models and in human renal transplant recipients, and is associated with a blunted sodium excretion, and reversible by weight loss, renin-angiotensin-aldosterone system blockade or by dietary sodium restriction. More recent evidence showed that a central body fat distribution is also associated with an increased FF, even independent of overall weight excess. In this review, we provide an overview...