Epidemiology of chronic kidney disease in Europe

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CHAPTER 1:

Introduction

INTRODUCTION

End stage renal disease (ESRD) requiring renal replacement therapy (RRT) has a substantial impact on both an individual patient's life as well as on national health care budgets (1, 2). At the global level the incidence of RRT varies greatly (3, 4), but even within the more homogeneous Europe there are huge differences in the incidence of RRT across countries (5). Apart from the access to RRT and the take on rate (4), the main factor determining RRT incidence is the number of patients reaching ESRD who require RRT. This number is influenced by two factors: 1) the number of chronic kidney disease (CKD) patients at risk for progression to ESRD, i.e. the CKD prevalence and 2) the outcomes of patients with CKD, i.e. rate of progression to ESRD and competing events such as (cardiovascular) mortality. If we can determine which factors cause the differences in the numbers of patients reaching ESRD across Europe, this may lead to the identification of health care measures effective in reducing the incidence of ESRD on a regional level. This information can then be used by policy makers to target health care planning aimed at reducing the incidence of RRT.

CKD prevalence

Several studies have reported the prevalence of CKD on a regional or national level (6-8). However, comparison of these studies is complicated by the use of different definitions of CKD and the influence of regional age distributions and differences in CKD risk factors.

In 2012, Kidney Disease Improving Global Outcomes (KDIGO) defined CKD as abnormal kidney structure or function for at least three months with implications for health (9). In practice, CKD patients are diagnosed based on the presence of albuminuria, representing kidney damage, and/or decreased renal function based on the estimated glomerular filtration rate (eGFR). eGFR can be calculated from serum creatinine using different formulas, such as the MDRD (10), CKD-EPI (11) and BIS equations (12). Studies reporting the prevalence of CKD have mostly used the definition as proposed by KDIGO, but they have used different eGFR formulas (13).

In Europe, some countries have a relatively old general population with the percentage of people aged 65 years or over as high as 21% in Italy. On the other hand some countries have a relatively young population such as Ireland, where only 13% of the total population is aged 65 years or older (14). CKD is strongly associated with age (15), with up to 30% of people aged 70 years and older affected by CKD (16). Due to this strong association with age, and the variation in general population age distributions across regions, it is essential to correct for these distributions when comparing CKD prevalence.

Another important factor contributing to the prevalence of CKD is the presence of co-morbidities. The most important comorbidities associated with CKD are hypertension, diabetes and obesity (17). The prevalence of these risk factors varies across countries (18,

19) and should therefore be taken into account when comparing CKD prevalence internationally. Apart from these diseases, lifestyle factors such as physical inactivity (20), high dietary salt intake (21) and smoking (22) may induce the development and progression of CKD. These comorbidities and lifestyle factors are not only associated with CKD but also with other important non-communicable diseases such as cardiovascular disease, which is the most important cause of death in most European countries (23). Hence it is likely that these factors are targeted in public health initiatives and it is of interest to investigate if currently implemented measures may explain the variation in the prevalence of CKD. If so, this can be used by policy makers to implement effective public health measures in countries were the prevalence of CKD is high.

CKD progression and outcomes

Apart from the disparity in the prevalence of CKD, different progression rates across European countries could lead to a variation in the number of patients with ESRD requiring RRT. As yet, a clear definition of CKD progression is lacking and it is unclear what rate of decline in eGFR can be considered as 'normal' progression of CKD (9). In light of this, KDIGO recommends that studies confirm what rate of decline in eGFR can be classified as slow, moderate or rapid progression of CKD (9). Importantly, only a minority of patients with CKD actually progress to ESRD, with most patients dying before ever reaching ESRD (17). For this reason mortality needs to be included in the analysis when investigating the progression of CKD. This is especially important when investigating the variation in ESRD across countries, as mortality will significantly influence the number of patients reaching ESRD.

Many studies have reported CKD progression and outcomes based on single centre or regional observations (24). Yet comparisons of these studies are hampered by differences in age, sex, baseline eGFR and proteinuria (9), primary renal disease (PRD) (25), the presence of comorbidities and treatment (9, 24, 26) all of which influence progression. If these factors are taken into account in an international comparison of CKD progression, this may lead to the identification of countries with slow progression of CKD independent of patient specific factors. This could be a first step in identifying health care systems which are effective in reducing the incidence of ESRD on a regional level.

Comparability/methodology

When investigating differences in CKD prevalence, progression and outcomes across studies, it is of utmost importance that these studies are comparable in their methodology. Both the method used to identify and select the study population (27) as well as the method of renal function assessment (28) can influence the result. Therefore, it is essential that studies have reported their methods and outcomes adequately to assess comparability.

European CKD Burden Consortium

In 2012, the European CKD Burden Consortium was established to enable cross study and country comparison of both the prevalence of CKD and outcomes of patients with CKD. Studies were invited to join the consortium and provide data on the prevalence of CKD, and/or the progression and outcomes of CKD. Currently, the consortium consists of a large group of nephrologists and epidemiologists from all over Europe. The main strength of the consortium is the use of standardization and adjustments which improve comparability of European study populations. The studies in Chapter 2, 3 and 6 are written on behalf of the European CKD Burden Consortium.

OBJECTIVES

The aim of this thesis is to investigate if differences in the prevalence of CKD and in outcomes of patients with CKD exist across European regions. In order to help answer this question, we investigated both differences in methodological aspects of studies and risk factors for CKD.

Part 1: CKD prevalence

Chapter 2 of this thesis is a systematic review to identify studies which collected data on the prevalence of CKD in the general population. As the methodology of studies can strongly influence their results we compared the methods used to recruit study participants and to determine the prevalence of CKD. In Chapter 3 we invited the principal investigators of the general population studies from chapter 2 to provide data to enable a cross country comparison of the prevalence of CKD. We used the received information to re-analyse the CKD prevalence using the same definition and standardized the results towards the European population. In addition we stratified the data by the presence of diabetes mellitus, hypertension and obesity in study subjects. In Chapter 4 we discuss the implementation and impact of public health measures aimed at important CKD risk factors, including life style factors.

Part 2: CKD progression and outcomes

In Chapter 5 we present a systematic review to evaluate the impact of the use of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement on the reporting of CKD cohort studies which investigated mortality in elderly patients with CKD. In Chapter 6, we compare the outcomes of CKD in patients attending nephrology outpatient clinics from five European countries. We use a sophisticated analysis tool to simultaneously investigate the progression and mortality risk of patients with CKD. In Chapter 7, we focus on a specific CKD cohort with hypertensive patients. In this cohort we investigated the longitudinal association between obesity and left ventricular hypertrophy, which are both risk factors for cardiovascular mortality.

This thesis ends with a general discussion of all chapters and recommendations for future research in Chapter 8. All findings are briefly summarized in English in Chapter 9 and in Dutch in Chapter 10.

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