Etiology and prognosis of chronic kidney disease in children: Roma ethnicity and other risk factors

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Chapter 1

Introduction

This study focuses on the epidemiology in children with kidney diseases and tries to add to the existing knowledge about its determinants, in particular Roma ethnicity, and its outcomes. The first chapter mainly introduces the existing knowledge about chronic kidney disease in children, describes its incidence and prevalence and underlines its importance from a perspective of public health with a focus on populations at risk. Furthermore etiologies, risk factors and finally outcomes of CKD are stressed in this chapter. This first chapter also presents the further structure of this thesis.

1.1 Chronic kidney disease and public health

For long time no clear definition or a uniform name for impaired renal function existed. It was only in 2002 when the Kidney Disease Outcomes Quality Initiative (KDOQI) organization for the first time defined and classified CKD (National Kidney Foundation 2002; Levey et al. 2005). The current guideline of Kidney Disease Improving Global Outcomes (KDIGO) defines CKD as "abnormalities of kidney structure or function, present for >3 months, with implications for health" (Kidney Disease: Improving Global Outcomes 2012; Levey et al. 2011). This report recommends classify CKD based on cause, glomerular filtration rate category, and albuminuria category.

Until relatively recently end-stage renal disease (ESRD), the most severe stage of chronic kidney disease (CKD), was uniformly fatal. Only after 1943, when Willem Kolff introduced his unique invention, the hemodialysis machine, enabling purification of blood of individuals with failed kidneys, life with ESRD became possible. The scientific and technologic improvements during the second half of the 20th century led to a wide establishment of renal replacement therapy (RRT) on a routine basis as a life-sustaining option for ESRD patients. Treating ESRD however imposes a large burden on patients, the health care system, and society, including high associated costs. From a public health perspective this is a phenomenon of a shift from premature death to years lived with disability what imposes new challenges on the health system (Murray et al. 2012; Foley and Collins 2007). For instance in India, where less than 1% of gross domestic product is spent on healthcare, ESRD care has a low priority resulting in many patients to quit their maintenance dialysis due to the lack of funds (Sakhuja and Sud 2003).

According to the 2010 Global Burden of Disease study CKD is among top 10 leading causes of death and ranks 29th with regard to disability-adjusted life-years (Go et al. 2004; Murray et al. 2012; Murray et al. 2013). Rising numbers of incident and prevalent CKD and ESRD patients are reported from large registries e.g. the United States Renal Data System (USRDS) or the Australia & New Zeeland Dialysis and Transplantation Registry (ANZDATA) (Coresh 2005; Glassock and Winearls 2008). From a perspective of global disease burden there is a trend of a shift in middle- and high-income countries from infectious to non-communicable diseases (Murray et al. 2012). Data from the registries also indicate that the occurrence of ESRD is disproportionately high among certain ethnic minorities, and among individuals with certain clinical conditions e.g. low nephron endowment (Lopes et al. 1995; Tarver-Carr et al. 2002; Crews et al. 2010; Patzer et and McClellan 2012).

The pediatric population suffering from ESRD is growing as well, mainly due to the significantly improved survival of formerly lethal diseases. This is particularly true for the high-income countries of Europe, Japan, North America and Australia, where children with ESRD have access to RRT (Harambat et al. 2012). While the occurrence of ESRD is relatively well described in certain countries e.g. the United States of America, the United Kingdom and the Netherlands, less information is available on the epidemiology of ESRD in other (European) countries e.g. Slovakia, even more when it comes to ethnic minorities. This is probably a consequence of the absence of official national or regional registries in most of these countries, including Slovakia (Warady and Chadha 2007).

The numbers of ESRD children are just a fraction of those of adults, on the other hand ESRD children are just a tip of an iceberg in the ocean of CKD children which may progress into symptomatic stages of the disease later in adulthood. This is particularly alarming in the context of epidemics of (childhood) obesity which was shown to have a strong influence on the occurrence of CKD (Adelman et al. 2001; Hedley et al. 2004). Action plans are called for, in particular regarding prevention, but this requires a clear understanding of the occurrence and outcomes of the disease, antecedent risk factors, and appropriate treatments for populations at risk. The impact of CKD on the individual and on public health is thus even more apparent in children.

1.2 Determinants of CKD occurrence in children and its progression into ESRD

The main causes of CKD in children include congenital and hereditary diseases. The most common ones are congenital anomalies of kidneys and the urinary tract; these explain almost half of the CKD causes in children. Cystic diseases followed by glomerulonephritis come after

(U.S. Renal Data System 2013; Australia and New Zeeland Dialysis and Transplantation Registry 2013; Pruthi et al. 2013). Shares varies worldwide with glomerulonephritides being significantly more common in developing countries (Hurtado and Johnson 2005).

Despite the different etiologies, once chronic kidney disease develops, the subsequent response of the failing kidney is similar. An increasing body of evidence suggests that progression of CKD may be largely determined by pathophysiologic mechanisms that are unrelated to the activity of the initial disease. These include among others hyperfiltration with subsequent intraglomerular and systemic hypertension, impairment of calcium-phosphate metabolism as well as acidobase imbalance, secondary anemia, hyperlipidemia, and systemic inflammation (Wuhl and Schaefer 2008). The kidney initially adapts to this damage by increasing the filtration rate in the remaining normal nephrons, a process called adaptive hyperfiltration. As a result, patients with mild CKD often have a normal or near-normal serum creatinine concentration. Adaptive hyperfiltration, although initially beneficial, appears to result in long-term further damage to the glomeruli of the remaining nephrons, which is manifested by systemic hypertension and albuminuria/proteinuria. The irreversibility of this process appears to be one of the key players responsible for the progression of CKD and development of ESRD (Brenner and Mackenzie 1997). It is necessary to add that the occurrence of CKD and subsequent rate of loss of renal function are highly variable among individuals with the same underlying cause of renal injury or degree of functional impairment. The individual variability of risk reflects the multifactorial nature of the biological mechanisms that are involved in the underlying disease process (McClellan and Flanders 2003).

The Brenner theory of hyperfiltration has highlighted low nephron endowment as a significant risk factor for developing hypertension and consequent renal failure (Brenner and Mackenzie 1997). According to this hypothesis low nephron endowment leads to increased filtration rate per nephron with consequent premature damage to the remaining nephrons what generates systemic hypertension and puts patients on a higher risk for renal failure. Epidemiologic studies supported this hypothesis by showing a close association between the risk of CKD/ESRD and certain ethnic populations with low nephron endowment (Nelson et al. 1996; McDonald et al. 2010). For instance the incidence of ESRD in Australian Aborigines is significantly higher compared to non-indigenous inhabitants, the age-adjusted rate reaches 20-fold in some age categories (McDonald et al. 2010). Similarly Indo-Asian immigrants in the United Kingdom (UK) have approximately 3–5 times higher incidence rates of ESRD compared to the majority population in the UK (Lightstone 2003).

Ethnic differences regarding the occurrence of CKD/ESRD have been shown for many parts of the world, but evidence fully lacks for

Roma who represent a significant minority in Europe. The risk for kidney diseases in Roma could be hypothesized to be high, considering the high occurrence of ESRD in India where Roma may have come from (Sakhuja and Sud 2003; Modi and Jha 2006; Agarwal and Srivastava 2009) and among the Indian immigrants in Europe (Lightstone 2003).

1.3 Prognosis of CKD/ESRD in children

Pediatric end-stage renal disease (ESRD) patients nowadays frequently survive until adulthood and beyond, but their overall mortality remains high. If reaching adulthood, the mean life-expectancy of dialysis patients is still 40-50 years less, and of transplant patients 20-25 years less than an age- and race-matched population (U.S. Renal Data System 2011). According to these data from the United States 22-32% of all these premature deaths is explainable by cardiovascular disease. Infectious diseases may explain another about 20% (U.S. Renal Data System 2011; Mitsnefes 2012).

Although the long-term survival of children with ESRD has increased during the past decades, the quality of life (QoL) of these patients remains poor (Goldstein et al. 2006; Kaptein et al. 2010; Copelovitch et al. 2011). This influences not only the patient's current life but it may also influence the patient's functioning in the future in terms of decreased school attainment, disability and thus lower ability to find a job in the future. Published research has shown that many adults with childhood-onset kidney disease have significant impairments in educational, social, and physical functioning (Rosenkranz et al. 1992; Rosenkranz et al. 2005). Evidence-based clinical practice guidelines support early recognition and treatment of CKD–related complications to improve growth and development and, ultimately, the QoL in children with this chronic condition (National Kidney Foundation 2002; Kidney Disease: Improving Global Outcomes 2013).

A decreased GFR is associated with complications in virtually all organ systems. High blood pressure, anemia, malnutrition, mineral bone disease, neuropathy, and resultant decreased overall functioning and well-being are the main characteristics of CKD children (Wuhl and Schaefer 2008). In looking more closely at cardiovascular complications, which explain most of the premature deaths, it is important to stress that nearly 50% of all these patients suffer from left ventricular hypertrophy (LVH) and life-threatening vascular changes (Groothoff 2005). Cardiac arrest is the most common cause of death, followed by arrhythmia, cardiomyopathy and cerebrovascular disease (U.S. Renal Data System 2011). Certainly patients with CKD should be considered as the highest risk group for subsequent cardiovascular disease (CVD) events. The excess risk of CVD may be attributed to two big groups of risks factors, namely 'uremic' or 'CKD-related' and 'traditional' CVD risk factors which are significantly

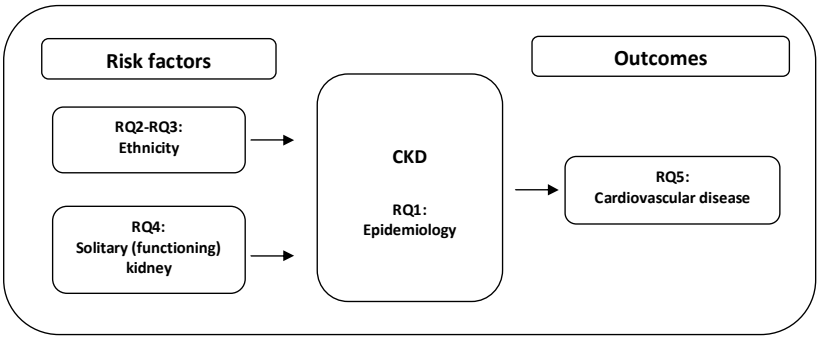
more prevalent in a population of CKD individuals. Further studies are needed to shed more light on the risk factors to improve survival and potentially QoL of these patients.

1.4 Primary aim of the thesis and research questions

The primary aim of this thesis is to explore the epidemiology of CKD and some of its determinants and outcomes in children with specific attention for ethnic issues. As a first step this study will focus on the incidence and prevalence of the most severe stage of CKD in Slovakia compared to the remainder of Europe, and its changes over the past decade. Furthermore it will analyze the etiology of ESRD among children. Then, we will deal with ethnic issues focusing on the relative risk (RR) of ESRD and on the share of ethnic minority within CKD patients overall. Additionally we will analyze the share of the Roma ethnic minority according to primary renal diseases. Next, we will study solitary kidney patients, a population with (congenital) reduction in renal mass, to clarify if having only one (functioning) kidney puts them at risk for CKD/ESRD and finally we will focus on outcome of CKD and ESRD patients focusing on cardiovascular complications, especially LVH (Figure 1.1).

The five research questions listed below are formulated based on the model as depicted in Figure 1.1.

Figure 1.1 Model describing relationship between risk factors and outcomes of CKD according to the research questions (RQ1-RQ5)



Research question 1:

1a. What are the actual incidence and prevalence rates of ESRD and RRT in Slovak children?

1b. What are the differences in these rates regarding 2003–2009 compared with those from earlier epidemiological surveys carried out in Slovakia?

1c. What are the incidence and prevalence rates of ESRD and RRT in Slovak children compared with those of children from other European countries?
1d. What is the etiology, i.e., primary renal diseases and treatment modes, compared with earlier studies on Slovak children and with children from other European countries?

Research question 2:
What is the difference in occurrence of ESRD between Roma and non-Roma and what is the relative risk (RR) of Roma for ESRD by age?

Research question 3:
What is the share of Roma and non-Roma in a tertiary nephrology clinic for children compared with that in the general population, and secondly what is the share of Roma and non-Roma regarding early signs of primary renal diseases (PRD) and specific PRD?

Research question 4:
What is the occurrence of renal injury as defined by presence of severely increased albuminuria, hypertension and/or decrease of glomerular filtration rate (GFR) <60ml/min/1.73m^2 in solitary functioning kidney (SFK) children?

Research question 5:
What is the change in left ventricular hypertrophy in ESRD children before and after transplantation?

1.5 The structure of the thesis

The thesis consists of 8 chapters. The Introduction **(Chapter 1)** provides information about public health aspects of CKD, CKD in children and its prognosis. Furthermore, a model and five research questions regarding the epidemiology of CKD, risk factors and outcomes are formulated. **Chapter 2** 'Data sources, measures and statistical analyses' deals with data sources, measures and statistical analyses. In **Chapter 3** 'End-stage renal disease in Slovak children: epidemiology from a European perspective' the epidemiology of ESRD in children is discussed from a European perspective. **Chapter 4** 'End-stage renal disease among Roma and non-Roma: Roma are at risk' deals with ethnic differences in the relative risk of ESRD of children and adults. In **Chapter 5** 'Kidney diseases in Roma and non-Roma children from eastern Slovakia: are Roma children at risk?' ethnic issues are studied in a population of CKD children of all stages visiting the outpatient department of the pediatric clinic. **Chapter 6** 'Solitary functioning kidney in children – a follow-up study' focuses on the outcome of patients with one functioning kidney from childhood.

Chapter 7 'Left ventricular hypertrophy in children and adolescents before and after renal transplantation' explores the outcome of CKD patients from a perspective of the cardiovascular consequences particularly left ventricular hypertrophy. Finally, the Discussion **(Chapter 8)** presents the condensed outcomes of this study, discusses them in the framework of the existing knowledge, argues their strengths and weaknesses, goes into their implications for practice and offers new possibilities for further research.

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