Quality of care and monitoring in paediatric end stage renal disease
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CHAPTER 1

General introduction, aim and outline
INTRODUCTION

In the Netherlands, each year about 30 children (aged 0-19 years) develop end-stage renal disease (ESRD) and need to be treated with renal replacement therapy (RRT), haemodialysis, peritoneal dialysis or pre-emptive kidney transplantation [1, 2]. Although the incidence is low, paediatric ESRD has a high morbidity and mortality [2-7]. A recent study in the United States showed a one-year mortality rate in children on dialysis of 4.31 and 4.52 per 100 person years for haemodialysis and peritoneal dialysis, respectively [8]. Within Europe, Chesnaye et al. showed a 55-fold higher risk of mortality for children on RRT as compared to the general paediatric population in Europe. Children starting on haemodialysis had an increased risk of mortality as compared to children starting on peritoneal dialysis (HR 1.79, 95% CI 1.20-2.66) [9, 10]. The Late Effect of Renal Insufficiency in Childhood (LERIC) study showed that young adults with ESRD since childhood frequently suffer from cardiovascular disease (CVD) and the most important cause of death in these patients was CVD, reaching up to 41% [5]. Comparable results were seen in another late outcome study from Australia [11]. Furthermore, the LERIC study showed that almost forty percent of the patients suffered from Chronic Kidney Disease – Mineral and Bone Disorder (CKD-MBD) and a large number of patients experienced a decreased physical quality of life (QOL) [4, 12]. The above illustrates that ESRD is a rare, but life threatening disease with high morbidity in which possibly improvement of outcome can be achieved by improving the quality of care and prevention of CKD-MBD and cardiovascular disease.

In The Netherlands and Belgium, encompassing a relatively small geographical area, paediatric nephrology care is organized in 10 small centres, of which only 4 centres in the Netherlands. Up to 2007 there was no structural consultation or collaboration between these centres. Multiple studies have shown that central registration, collaboration and peer reviewing may lead to improvement of the quality of care [13-15]. In 2007, an initiative for such collaboration was undertaken by initiation of a project called RICH-Q (the Renal Insufficiency in Children – Quality assessment and improvement) project. In this project, all Dutch and Belgian centres for chronic RRT in children declared to collaborate with the primary objective to improve the quality of care for children on RRT. The sequential steps to obtain this goal were as followed: 1. Assessment of current quality of care for children on RRT in the Netherlands and Belgium, 2. Assessment of the effect of registration and peer reviewing, 3. Creating a platform for multi-centre studies, 4. Harmonization of guidelines for RRT in children and searching for best practices. For this, a comprehensive database was created in which anonymous data on treatment characteristics and physical and psychosocial health outcomes were registered prospectively concerning all children with ESRD treated in the 10 RICH-Q associated hospitals. In the RICH-Q registry data is included of all prevalent Dutch and Belgian patients aged < 19 years on chronic dialysis on October 1st 2007, and all Dutch and Belgian patients aged < 19 years who started RRT or were transplanted from October 1st, 2007 to date. In 2011
and 2012, respectively, two German centres, Cologne and Bonn, joined the consortium and included all their incident patients aged <19 years on RRT from that moment. Earlier studies within the RICH-Q framework by Schoenmaker and Tromp already showed that between the RICH-Q centres considerable variations exist on treatment and management policies [13-18]. Furthermore, Schoenmaker et al. showed that within the patients included in RICH-Q disparities exist between children from immigrant parents and children from non-immigrant parents with regards to dialysis treatment and outcome [17]. This has been described in other studies earlier as well [19, 20]. Differences on treatment and management policies are due to a lack of child-specific evidence based guidelines. Overall, children with ESRD suffer from a decreased quality of life [21-24]. On top of that, within RICH-Q, Schoenmaker et al. found that children from immigrant parents with ESRD suffer from a decreased quality of life as compared to the children with ESRD from non-immigrant origin [16]. Furthermore, earlier studies showed that conventional echocardiography is unreliable to monitor cardiovascular disease in paediatric ESRD [25].

For this thesis the following topics of interest were chosen: a. Quality of care with respect to 3 important quality indicators, being transplantation policy, prevention of growth retardation and control of hypertension after transplantation, b. quality of monitoring of 2 of the most important comorbidities, Chronic Kidney Disease related mineral bone disease (CKD—MBD) and Cardiovascular Disease (CVD) and c. the effect of the RICH Q intervention on quality of care over time.

Schoenmaker and Tromp have already shown that management and treatment policies in dialysis differ [17, 18]. Kidney transplantation is regarded as the most optimal mode of RRT for children to an extent that starting RRT without prospects for transplantation is generally considered unethical for children with ESRD. An optimal transplantation policy that ensures the longest possible RRT time with a good functioning renal graft –in the most ideal situation without prior dialysis treatment- should therefore be one of the major quality aims with regard to RRT treatment in children. We therefore analysed to which extent policies regarding transplantation differed between centres in the Netherlands and Belgium, compared policies with the actual care and analysed the impact of policy and treatment differences on access to transplantation and transplantation outcomes.

CKD-MBD is known to impair longitudinal growth that consequently affects health related quality of life. As growth hormone deficiency plays an important role in the origin of decreased longitudinal growth, treatment with recombinant growth hormone (rGH) is indicated after treatment of other causes of growth retardation. rGH therapy has shown to be safe and effective [26-30]. Nevertheless, recent data of the ESPN/ERA-EDTA database show that over 40% of the European ESRD children still have a moderate and 19% a severe final height deficit (SD< 1.88 and SD < -3.0, respectively) [31]. American and British data suggest that there might be undertreatment of rGH in ESRD children, but to date
no data exists on the situation with respect to rGH in the whole European community [32]. We therefore investigated differences in policies on growth hormone treatment, actual prescription and height outcomes in 28 European countries using data from the ESPN/ERA-EDTA registry.

As the treatment of paediatric ESRD has improved over time, more patients with childhood onset ESRD reach adult life. With increasing age, long-term complications, such as motor disabilities as a result of CKD-MBD arise, as shown by earlier research [2, 4, 33-36]. Currently, evidence based guidelines on the diagnosis and monitoring of CKD-MBD are lacking. Assessment of CKD-MBD consists of imaging of the hand with an X-ray or bone mineral density (BMD) assessment with Dual Energy X-ray Absorptiometry (DXA). The assessment of CKD-MBD with the help of DXA in (paediatric) ESRD has been a topic of debate over time. Whilst in healthy, especially post-menopausal women, DXA has shown to be a good discriminator for future fractures [37], in (paediatric) ESRD results are conflicting. A study by Alem et al. [38] showed that in adult patients with ESRD, a low BMD was associated with fracture. Jamal et al.[39] found an increased fracture risk (OR 1.56) for BMD at the radius measured by DXA in adult patients (mean age 63.3 years) with CKD stage 3-5. In 2012 Limori et al. found that total hip BMD together with a low PTH can be used in the prediction of fracture risk in CKD stage 5D patients [40]. The same group also examined 13 studies that were reviewed by the KDIGO CKD-MBD guideline development group. They found highly variable results between the studies assessing the association between fractures and BMD in CKD [40]. A recent review by Babayev and Nickolas stated that the role of DXA in ESRD, especially CKD, is not yet obsolete and needs re-examination[41]. Current existing guidelines still recommend performing DXA scans in paediatric ESRD ranging from no recommendation, every 6-12 months to only on indication [35, 42-48]. In this thesis the ability of DXA to prospectively discriminate subjects at risk for fracture was analysed. Children do not frequently suffer from fractures and children with (moderate) CKD-MBD have low fracture rate.

Therefore, we assessed BMD by DXA in 2000 and signs of bone disease and fracture in the subsequent 10 years in adult patients with childhood onset ESRD. If low BMD by DXA is associated with fractures later in life, the use of DXA in childhood could be of additional value for assessing their fracture risk later in life.

Another long-term complication of ESRD and possible lethal condition is cardiovascular disease. Left ventricular hypertrophy may be due to (chronic) hypertension, ischemia, inflammation and uremic toxins [49-56]. However, Schoenmaker et al showed that the assessment of LVH in children with ESRD by paediatric cardiologists differ and is not reproducible [57]. New, highly reproducible methods of assessment of cardiac dysfunction exist, such as Speckle Tracking Echocardiography (STE) [58-66]. In this thesis the assessment of myocardial mechanics with STE in children on dialysis and children with a functioning graft is presented. STE findings in children with ESRD are compared with results in healthy, age-matched controls.
Hypertension in ESRD is an important risk factor for cardiovascular disease and is known to be highly undiagnosed and under treated [67-73]. In children and young adults with a renal transplant, little is known about the prevalence of (uncontrolled) hypertension. Earlier papers reported prevalence of hypertension in these patients varying from 66% in children up to 85% in elderly adults [69, 74-78]. However, to date, no study has been performed to assess prevalence of hypertension in both paediatric and young adult renal transplant recipients and over time. In this thesis a study is presented in which the prevalence of (uncontrolled) hypertension in paediatric (0-19 years) and young adult (19-30 years) patients with a renal transplant has been analysed. Transition, the process of transferring care from the paediatrician to adult care is known to be a risk for treatment adherence. Especially in renal transplant recipients, transition is believed to increase the risk for graft failure [79-82]. Therefore, the influence of transition of care from paediatric to adult nephrology care on the prevalence of hypertension in these patients was assessed. Finally, after 8 years of RICH-Q, the effect of RICH-Q on quality of care with regards to quality indicators, harmonizing care and add on studies was assessed.
AIM OF THIS THESIS

Aim of this thesis is to study the current quality of care in children and young adults with ESRD, regarding transplantation, post-transplant hypertension and growth hormone use. Furthermore, this thesis aims to address the current and new methods of diagnosing CKD-MBD and cardiac dysfunction. Finally, RICH-Q as a quality improvement collaborative is evaluated. The following questions had to be answered:

1. Which guidelines currently exist on the care for paediatric renal transplant recipients?
2. Do Dutch, Belgian and German centres providing renal transplantation have child-specific transplantation policies, on what are these policies based and do the clinicians adhere to the policies?
3. Are there policies on the use of rGH in paediatric ESRD across Europe and to which extent do differences in policies affect health outcome, more specific (final) height?
4. What is the prevalence of (uncontrolled) hypertension after renal transplantation in children and young adults in the Netherlands?
5. Is the prevalence of (uncontrolled) hypertension influenced by transition (the transfer of care from the paediatric to adult nephrologist)?
6. What are current policies in paediatric and adult nephrology centres with regards to post-transplant hypertension?
7. Is DXA a reliable method to assess future fracture risk in young adults with childhood onset ESRD?
8. Does Speckle Tracking Echocardiography enable the paediatric cardiologist to diagnose myocardial dysfunction in paediatric patients with ESRD?
9. Does a collaborative initiative aiming to improve the quality of care for paediatric ESRD in the Netherlands, Belgium and part of German actually improve care?
Chapter 1

OUTLINE

Chapter 1 provides a short general introduction and aim of this thesis. Part 1 provides an overview on quality of care by the assessment of current practices regarding paediatric renal transplantation in the RICH-Q centres (chapter 2), growth hormone use and (final) height outcome in 28 European countries (chapter 3) and hypertension prevalence and management in paediatric and young adult renal transplant recipients (chapter 4). Part 2 describes the monitoring of care regarding CKD-MBD and cardiac dysfunction. Chapter 5 present the results of a prospective study on the role of DXA in predicting fracture risk in young adults with paediatric onset ESRD. In the last chapter (chapter 6) of part 2 the results are presented of the assessment of myocardial dysfunction with the help of Speckle Tracking Echocardiography in paediatric ESRD. In part 3 an overview is presented with regards to RICH-Q, its achievements, barriers and future perspectives. Part 4 consists of a discussion of all findings as presented in this thesis. Also, implications for clinical practice are given, as well as recommendations and suggestions for future research.
REFERENCES

Chapter 1


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