Quality of care and monitoring in paediatric end stage renal disease
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GENERAL DISCUSSION

This thesis describes aspects of quality of care for children with End Stage Renal Disease (ESRD) in The Netherlands, Belgium, part of Germany and part of Europe with particular focus on the quality of monitoring of the most important comorbidities of ESRD, being Chronic Kidney Disease Mineral Bone Disorder (CKD-MBD) and cardiovascular disease (CVD). It also evaluates the effect of the RICH Q intervention on the quality of care for these children.

The first part addresses the quality of care for children with ESRD with respect to important quality indicators in Paediatric ESRD: prevention of growth retardation, access to transplantation and prevention of hypertension. Differences in policies for children with a renal transplant and with regards to growth and growth hormone were assessed. Furthermore, local and (inter)national guidelines on the care for paediatric renal transplant recipients were reviewed, as well as policies and practices on donor characteristics. Quality indicators, prevalence of hypertension after renal transplantation and the differences in outcome parameters were assessed.

In the second part quality of monitoring of CKD-MBD and CVD in children with ESRD is assessed. The usefulness of Dual Energy X-ray Absorptiometry (DXA) to predict bone disease in adults with childhood onset ESRD has been studied and the reliability of the measurement of longitudinal myocardial deformation with Speckle Tracking Echocardiography (STE) was assessed.

In the last chapter of the first part the RICH-Q project is evaluated as a quality improvement collaborative trying to improve the quality of care for children with ESRD in the Netherlands and Belgium.

In this chapter we discuss the impact and implications of the most important findings. Possible consequences and recommendations for daily clinical practice are addressed and recommendations for future research are given.

First, a summary of the most important results of the studies presented in this thesis is displayed.

MAIN RESULTS

1. Management policies for children with a renal transplant in 11 paediatric nephrology centres in The Netherlands, Belgium and part of Germany show considerable variations. These variations may affect treatment and hence health outcome.
2. Evidence based guidelines for the management of renal transplantation in children are lacking.
3. Policies and practices with regard to the indication and use of Growth Hormone in children with ESRD in 38 European countries vary, hereby affecting health outcome, especially final height, which is associated with quality of life later in life.
4. High prevalence of (uncontrolled) hypertension is seen in both children and young adults with a functioning renal transplant. Longitudinal assessment of blood pressure showed an increase in blood pressure at a younger age as compared to healthy individuals.
5. RICH-Q as a quality improvement collaborative has shown to improve the quality of care by enhancing the proportion of (pre-emptive) living related kidney transplantations. 

6. Quality improvement initiatives in paediatric ESRD might encounter a ceiling effect in which further improvement of care does not lead to better attainment of the currently used clinical benchmarks, hampering the measurement of further improvement.

7. DXA is not able to predict bone disease in adults with childhood onset ESRD since DXA is not able to distinguish between low, high or mixed turnover bone disease.

8. Speckle tracking echocardiography is more sensitive to detect systolic dysfunction of the myocardium in children with ESRD than conventional ultrasound.

**IMPLICATIONS**

**Quality of care**

**Transplantation**

We found important differences in policies and practices with regard to renal transplantation in children with ESRD between all sites for paediatric renal replacement therapy in the Netherlands and Belgium. Both pre- and post-transplantation policies differ between centres. We found differences on minimum accepted weight of the renal transplant recipients, maximum accepted donor age and maximum accepted cold ischemia time. As evidence based guidelines on these topics are lacking and literature is limited or results conflicting, local practices and policies are expert opinion based. These differences imply that children or donors with the same characteristics may be treated differently in different centres. For example, a living related donor with the age of 65 years might be considered eligible to donate his kidney in centre A, whereas in centre B the donor is rejected based on his age. The same accounts for minimum accepted recipient weight and acceptance of a non-heart beating donor kidney. Children with a body weight of 8 kilograms could be accepted for transplantations in centre C, however in another centre the same child could spend another year on dialysis before being considered eligible for transplantation. One additional year dialysis could cause important complications and co-morbidities.

**Growth Hormone**

In a European study on the policies and practices on the use of growth hormone in children with ESRD, we found remarkable differences with regard to the indications and use of growth hormone. National rules regarding prescription of growth hormone in a particular country was associated with the final height of children with ESRD. Also, despite being eligible to receive growth hormone, both children on dialysis and those with a functioning graft were prescribed growth hormone far less often than expected based on the stated indications for growth hormone. Although many data exist on the beneficial effect of growth hormone and the negative effect of growth retardation on quality of life [1-10], physicians reported to feel hesitation to prescribe growth hormone. Additionally, fear for non-adherence in combination with high costs of the medication and fear of triggering an episode
of rejection when prescribing growth hormone after renal transplantation could be factors involved in the low prescription rate [11]. This suggests that both patient and doctor related factors influence growth hormone prescription and hence final height. More education on the beneficial effect of growth hormone and positive effect of final height on quality of life might improve growth hormone prescription, eventually affecting health outcome.

**Hypertension**

We found a high prevalence of hypertension after transplantation in all age groups but most pronounced in young adult patients up to 30 years of age. We also found that the increase in blood pressure with age is far more progressive at young adult age than in healthy peers. This might partly explain the undertreatment in this group of patients. Nephrologists involved in the care for young adults with a renal transplant need to be aware of this as high blood pressure or hypertension is significantly associated with adverse outcome. We did not find an increase of prevalence of hypertension after transition to adult care. When young adolescents transfer from the paediatric care to the adult care they might experience a less strict guidance and follow up [12, 13]. However, as these patients tend to express higher blood pressure than in the years proceeding, nephrologists might consider increasing the frequency of the outpatient clinic visits in the young adult kidney recipient in order to monitor blood pressure more accurately and being able to act on rising blood pressure at an earlier stage.

In the last chapter we analysed the extent to which RICH-Q as a quality improvement collaborative actually improved the quality of care based on information from the RICH-Q registry. Although there were no statistically significant differences on health outcome measurements based on hard quality indicators such as proportion of patients with anaemia or hyperphosphatemia, we found a trend towards improvement. An increase was found in the proportion of children with a living and pre-emptive kidney transplantation of 12% and 7%. Although this was not statistically relevant, this increase is clinically relevant as living donor (pre-emptive) kidney transplantations are preferred over deceased donor kidney transplantations and have superior outcome with regards to e.g. rejection and survival [14-16]. When comparing RICH-Q data with information from other European countries with a comparable or higher Gross Domestic Product (i.e. other high income countries) from the ESPN/ERA-EDTA registry, we found similar results, apart from a lower proportion of children with growth retardation after transplantation in the RICH-Q population. This might indicate that the quality of care in Western Europe has reached a ceiling, at least with regard to currently used quality indicators [17]. Outcome measurements as indicators of quality of care as selected by doctors might differ from those that are considered to be important by patients and/or their caregivers. Whereas doctors are focused on long-term outcome measurements and parameters associated with complications and mortality, patients, especially young adolescents, may consider other, non-medical factors more important. Therefore, improving quality of care in paediatric ERSD should include patient involvement and focus more on patient reported outcome measurements and quality of
Furthermore, possibly no evidence of effect could be found as the follow up of the patients registered in the RICH-Q database is too short. With passing time, possibly an increase of quality of care could be measured. However, as patients’ compliance is essential for the success of a treatment, all efforts of increasing the quality of care may fail when patients do not adhere to the treatment and prescribed medication. Nevertheless, as all participating doctors stated to be willing to proceed with the project and slowly current policies and practices are being harmonised, RICH-Q have shown to be of additional value.

QUALITY OF MONITORING

DXA
The first chapter of part 2 describes an analysis of the ability of detecting and monitoring CKD-MBD by DXA in middle-aged patients with paediatric ESRD. This study showed that bone mineral density assessed by DXA did not predict which of these individuals would suffer from a fracture in the subsequent ten years, even if corrected for short stature and hence correction for the underestimation of bone mineral density in small bones. This can be explained by the fact that CKD-MBD can be caused by either high or low turnover bone disease, each of which affects bone mineral density in a different way [21-25]. High turnover bone disease results in thickening of the trabecular bone and consequently an increase of the volume of the bone. However, when the disease progresses, trabecular bone degrades and bone volume decreases. Eventually, there will be a degradation and loss of volume of trabecular bone and a decreased thickness of the cortical bone. In low turnover bone disease, bone volume is decreased at all stages and leads to all kinds of alterations in trabecular bone [26, 27]. DXA cannot discriminate between cortical and trabecular bone and does not give information on bone microarchitecture. Therefore, it cannot discriminate between high and low turnover bone disease. The results imply that DXA might not be suitable for detecting individuals at risk for fractures. Nevertheless, in the absence of imaging tools with a better predictive value, many nephrologists still use DXA as instrument of monitoring CKD-MBD. However, in interpreting DXA results and their implications, nephrologists should consider other factors influencing fracture risk such as corticosteroid use, physical activity or strain, co-morbidity and history of renal replacement therapy. Furthermore, these results warrant further research to develop more reliable tools to predict fracture risk in ESRD patients.

Speckle Tracking Echocardiography
Speckle Tracking Echocardiography (STE) was shown to be able to detect systolic dysfunction in paediatric ESRD at an earlier stage than conventional echocardiography. Furthermore, STE, which is in part an automated measurement and thus less dependent on the observer, is more reliable. STE might be able to show systolic dysfunction independently of left ventricular mass (LVM) since more than LVM alone influences myocardial dysfunction. Uremic toxins, FGF23 and phosphate are considered to cause myocardial fibrosis and thereby influence left ventricular function as well [28-30]. Assessment of uremic toxins, FGF23 and phosphate...
might be part of the assessment of cardiovascular risk in patients with ESRD. Prospective studies are needed to assess to what extent these parameters are associated with long-term outcome.

RECOMMENDATIONS FOR FURTHER RESEARCH AND PRACTICE

Harmonising care and generating evidence based guidelines
The RICH-Q project was initiated to improve the quality of care for children with ESRD in the Netherlands and Belgium. Due to small numbers and a lack of good and reliable quality indicators in paediatric ESRD, large scale prospective studies to evaluate quality of care and health outcome are scarce. Evidence based guidelines are lacking due to small numbers and insurmountable hurdles to perform randomized clinical trials in this population. Furthermore, the assessment of quality of care is hampered by a possible ceiling effect on currently used quality indicators. This shows the need to consider a shift of the quality paradigm in which patient relevant outcomes may become more important than the traditional medical and physiological parameters. Especially since patients consider improvement of health-related quality of life more important. Therefore, in future studies of quality of care, patients and their caregivers/parents need to be involved.

Quality of care
Long-term follow-up studies assessing differences in policies and consequently health outcome in children with ESRD are needed to evaluate to what extent differences in policies actually influence health outcome. An important topic is the use of growth hormone. We need more insight in the current barriers and hurdles for prescribing growth hormone in order to enhance the current prescription rate and improve outcome in growth retarded children with ESRD. Growth retardation has shown to affect quality of life, as it is associated with both physical and social functioning and, maybe even more important, self-esteem. When patients reach a normal final height, self-esteem may be higher, enabling those patients to achieve their maximum potential. The prevalence of (uncontrolled) hypertension in young kidney transplantation recipients needs to be assessed, as children become more frequently transplanted at a younger age and little is known about blood pressure and blood pressure course in these patients. Especially since hypertension at a younger age is associated with adverse outcome later in life. Patient involvement in study design and in the selection of outcome measures are needed to assess (improvement of) quality of care.

Quality of monitoring
With respect to the diagnosis and monitoring of CKD-MBD, current and new imaging tools should be correlated with histomorphological findings in bone biopsies in order to assess their reliability and validity. In the paediatric population techniques without radiation, such as microMRI or (quantitative) ultrasound are preferred over for example peripheral quantitative CT (pQCT). In recent studies, microMRI and (quantitative) ultrasound showed
promising results and might be able to discriminate between subjects who are and aren’t at risk for fractures in the CKD population [31, 32] Furthermore, as currently used imaging techniques detect CKD-MBD at a relatively late stage, more research is needed to assess which parameters (such as FGF23, Klotho, sclerostin) are able to predict individuals at risk for developing CKD-MBD and when they should optimally be applied. In children bones are still developing and a disturbed bone mineral accrual could influence bone quality and longitudinal growth. Furthermore, as it has been shown that CKD-MBD and CVD in adult patients with ESRD are clearly related and share mutual pathophysiological mechanisms and biomarkers, more long-term follow-up studies on the so-called bone-heart axis in children with ESRD are needed [33]. Finally, prospective follow-up studies are needed to assess the (consequences of) impaired myocardial function measured with STE in children with ESRD.
REFERENCES


