# Nutrition and growth in European children with end-stage renal disease

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# 1

# GENERAL INTRODUCTION

## END-STAGE RENAL DISEASE

The kidneys are essential for filtering the blood and removing excess fluid and waste products through producing urine. They are also involved in maintaining the acid-base balance of the blood, regulating bone metabolism, and regulating growth hormone [1]. In case of kidney damage or a decreased kidney function end-stage renal disease (ESRD) might develop, which is the terminal stage of renal failure. Usually ESRD develops at adult age; however, a small group of children develops ESRD, mainly due to inherited and congenital disorders [2]. At this terminal stage of renal failure patients need renal replacement therapy (RRT) in order to survive. There are two major types of RRT: dialysis (haemodialysis and peritoneal dialysis) and kidney transplantation. Kidney transplantation is the preferred therapy, as the life expectancy is much higher than on dialysis [3]. Furthermore, in children early transplantation is of particular importance, as longitudinal growth and quality of life improve after transplantation [4].

## ESPN/ERA-EDTA REGISTRY

As paediatric ESRD is such a rare condition, a multi-national framework is needed in order to facilitate a better understanding of the epidemiology of paediatric ESRD with the ultimate goal to improve outcome. Therefore, in 2007, the European Society of Paediatric Nephrology (ESPN) together with the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) established a pan-European registry collecting data on European children on RRT [5]. Currently, 37 countries report individual patient data on date of birth, gender, date and treatment modality at the start of RRT, cause of renal failure, and changes in treatment modalities on an annual basis. Furthermore, a variable set of clinical and medication related parameters is collected [6]. The studies described in this thesis have been performed within the framework of the European Society for Paediatric Nephrology/ European Renal Association and European Dialysis and Transplant Association (ESPN/ERA-EDTA) Registry.

## GROWTH

One of the major problems in childhood ESRD is growth failure with short adult height as a consequence. Multiple factors contribute to this growth failure, including nutritional, hormonal, and metabolic factors [7]. Growth reference charts are essential clinical tools for evaluating linear growth in children. In this way, the growth of an individual child can be compared to the growth of a healthy reference population, and the standard deviation score (SDS) from the normal height can be determined. Many different growth reference charts exist, based on different reference populations and periods. For an international study, finding the most appropriate reference chart can be challenging [8], especially when

comparing growth of children coming from different countries. Therefore, in **chapter 2** we compare the appropriateness of different growth charts.
Growth failure has been related to increased morbidity and mortality [9,10]. Furthermore, adult patients who started RRT during childhood had a lower quality of life and an impaired self-esteem [11]. Therefore, maintaining normal growth and attaining an adult height within the normal range is of major importance in this population. Several measures can be taken to preserve growth such as supplying adequate nutrition, treating metabolic acidosis, and early transplantation. When growth failure remains despite these measures, growth hormone (rGH) therapy can be indicated [12]. Despite its effectiveness, previous studies showed a very low use of rGH in paediatric ESRD [13]. In **chapter 3** we aim to quantify the variation among growth hormone use in Europe. Furthermore, we link the variation in policies to different height measures.
Due to improvement in the management of children with chronic kidney diseases final adult height might be improved during the last decades, but large Europe wide studies are lacking. Therefore, in **chapter 4** we present recent data on final height of European patients who started RRT during childhood.

**NUTRITIONAL ABNORMALITIES IN PAEDIATRIC ESRD**

Nutritional abnormalities are common in paediatric ESRD, emphasising the need for good nutrition [12]. Malnutrition and a poor appetite are frequent and many patients, therefore, require oral supplementation or tube feeding for an adequate supply of calories and nutrients [14]. However, now that the global prevalence of childhood obesity is rising, a parallel trend might occur in the paediatric RRT population [7]. Due to the existence of different measures and definitions for childhood obesity, the overall size of the problem in paediatric ESRD is not well documented. The body mass index (BMI), calculated as weight/height$^2$, is a straightforward measure and is easy to obtain during routine clinical visits. In childhood, BMI is age- and sex dependent and is therefore expressed as the number of standard deviations from the mean of age- and sex related peers. However, BMI seems to differ across heights, with taller children generally showing higher BMI values than shorter children [15], and expressing BMI according to chronological age might not be an appropriate measure in children with abnormal statures. In children with renal failure, it has therefore been suggested to express BMI relative to height-age (e.g. the age at which a child is growing at the 50$^{th}$ percentile) [12], but its validity was not formerly tested. Therefore, in **chapter 5** we compare the appropriateness of the use of BMI-for-age and BMI-for-height-age in children with abnormal statures. In **chapter 6** we report on the prevalence of and factors associated with underweight, overweight and obesity in the European paediatric RRT population.
Besides balancing the caloric intake to prevent malnutrition and overweight/obesity as well as to ensure adequate growth, dietary therapy in paediatric ESRD should also focus on

macro-nutrients. For example, dietary fat and cholesterol intake should be controlled as dyslipidaemia is common in paediatric ESRD due to a decreased catabolism of lipoproteins and inappropriate synthesis of very low density lipoprotein [16]. Although high prevalence rates of dyslipidaemia were reported in paediatric ESRD patients, most data originate from small cross-sectional single-centre studies. In **chapter 7** we focus on dyslipidaemia in European paediatric ESRD patients.

Moreover, protein intake is essential for the maintenance of normal growth and an adequate nutritional status in children. In renal patients it is import to control the protein intake in order to decrease the phosphorus load. As the kidneys regulate the calcium and phosphorus homeostasis, abnormalities in mineral metabolism, subsequently leading to growth failure, are frequent in paediatric ESRD [17]. In paediatric dialysis patients the mineral metabolism has been studied extensively [18]. Although mineral levels seem to improve after successful renal transplantation, data in paediatric patients are scarce. Therefore, in **chapter 8** we describe the mineral metabolism in paediatric renal transplantation patients in Europe.

Finally, in **chapter 9**, we summarise and elaborate on our major findings, discuss their implications, and give directions for further research.

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