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

Bonthuis, M.

Publication date
2014
Document Version
Final published version

9

GENERAL DISCUSSION

GENERAL DISCUSSION

Achieving normal growth and controlling nutritional abnormalities are key aspects in the management of paediatric ESRD. In this thesis, we provided reference methods for measuring childhood growth and nutritional status. Furthermore, the size of and items related to specific nutritional issues in the European paediatric RRT population have been shown. In this last chapter, we summarise our findings, elaborate and comment on them.

PEDIATRIC REFERENCE DATA

During childhood many physiological parameters (like BMI and calcium levels) change during growth and maturation. Furthermore, these measures could differ between sexes, especially during the pubertal period. In case of chronic diseases like ESRD it is important to know how these measures relate to measures in healthy children. To determine whether anthropometric or clinical data deviate from 'normal' is, however, a difficult issue. Data of the individual child can be compared to data from a reference population, which preferably provides clear cut-off levels for abnormal values. Ideally, these cut-off values should be based on clinical correlates, i.e. they should be associated with clinical manifestations or health outcomes. As clinical events do not generally occur until middle age, reference values for the paediatric population are, however, often rather arbitrary.
Because of the availability of many different reference data (as was the case for height-for-age charts described in **chapter 2**), the choice for the most appropriate reference method may be difficult. Some variables show substantial variation across populations, therefore, reference data based on a representative sample of the population of interest are preferable.
Different height-for-age charts based on national and international samples exist for studying height in children. In 2006, the WHO released growth standards for children from birth to 5 years age [1], which were constructed on data from children in six different countries around the globe living under ideal conditions in order to show 'optimal' growth. These standards consist of a longitudinal (from birth to 24 months) and a cross-sectional component (18-71 months of age). However, in the cross-sectional part infant feeding practices were less strict, and mothers did not receive any support in order to optimise their child's nutrition, making it questionable whether these children really lived under optimal conditions. For both the longitudinal and cross-sectional part, the researchers reported a very similar growth in children from these distinct geographical locations, therefore, these standards were intended to be used for worldwide growth monitoring of young children. For children above 5 years of age, the WHO released a revised version of the NCHS/WHO growth charts in order to create a smooth transition between the growth standards and NCHS/WHO charts at the age of 5 years [2]. However, the WHO growth charts for 5-18 year old children are based on growth data from US children, and do thus not represent an international sample. Defining

the most appropriate reference population for studying height in children thus remains a matter of debate. In order to find the most appropriate growth reference for studying longitudinal growth of European children on ESRD, we compared different height-for-age charts in **chapter 2**. We found considerable variation across the different charts, reflecting true population differences in height, as well as differences in the time periods in which growth data were collected. We did not find significant differences in height SDS between the WHO growth standards and national growth charts constructed from recent growth data for children below the age of 2 years. Therefore, we concluded that the WHO growth standards (longitudinal part) provide an appropriate reference for children below 2 years of age. For older children, considerable variation was found between recent national growth charts and WHO growth standards (cross-sectional part: 2-5 years) or WHO growth charts (5-18 years), and recent national data probably best reflect the current growth of a population. If such recent national growth charts are not available the newly constructed growth charts for Northern and Southern Europe could serve as up to date reference charts. It should be noted that if resources are available countries should be encouraged to develop their own national growth charts based on representative growth data.

For studying height in childhood it is important to use recent reference charts derived on a national level, but for BMI the contrary seems to be true. Age- and sex-specific centile curves for BMI are highly dependent on the prevalence of obesity in a population. Therefore, with an increasing prevalence of childhood obesity, centile curves will simultaneously move upwards. Furthermore, most BMI reference data are not based on clinical outcomes. To account for these problems we used cut-offs from the International Obesity Task Force (IOTF) to calculate prevalence estimates for underweight, overweight and obesity (**chapter 6**). These cut-offs are constructed to match the adult health related cut-offs at the age of 18 years, and are therefore less arbitrary than other BMI reference curves. Moreover, these cut-offs are based on international data [3,4]. However, when studying BMI in children with ESRD another problem arises, namely that these children usually suffer from growth retardation. BMI in childhood is dependent on age, sex, and sexual maturation. When growth or sexual maturity is affected, this association may be different. In case of growth failure this could lead to an underestimation of the BMI. Therefore, in paediatric ESRD it has been suggested to express the BMI according to height-age (i.e. the age at which a child's height would be at the 50th percentile) [5], but this approach has not been validated. Our results in **chapter 5** showed that BMI differed according to stature, with shorter children showing lower median BMI values compared to children with a normal stature. Therefore, from late infancy up to adolescent age BMI-for-height-age appeared to be the preferred method.

Besides cut-off levels for anthropometric data, specific paediatric target levels have also been defined for several clinical parameters. For example for mineral levels which are often abnormal in ESRD. In children, controlling these levels is not only important to avoid cardiovascular complications, but also to ensure adequate linear growth [6]. Different target levels have been recommended by US (K/DOQI) and European (EPDWG) guidelines [7,8],

but they are mainly opinion-based. For example, for many years the PTH guidelines established for adult patients have been applied to children. Recent data from the IPPN and ESPN/ERA-EDTA registries suggest, however, that possibly much lower PTH targets than the ones currently used could result in better outcomes [9]. For optimal calcium and phosphorus levels in paediatric RRT patients the clinical evidence remains, however, scarce. We applied paediatric phosphorus cut-offs according to European guidelines to estimate the risk of graft failure and found a statistically significant higher risk of graft failure when phosphorus levels were above the specified target levels (**chapter 8**). However, whether this finding also applies to morbidity and mortality in both paediatric dialysis and renal graft recipients remains to be elucidated. Furthermore, long-term future studies in both healthy and ESRD children should try to define cut-offs for several anthropometric and clinical parameters based on evidence.

GROWTH

A short stature affects health outcome, such as quality of life and self-esteem [10]. Therefore, reaching a normal adult height is one of the main goals of paediatric ESRD care. Growth charts are essential clinical tools for assessing normal growth and final height [11]. In **chapter 2** we reported that there are large differences between existing growth charts, and choosing the most appropriate one can be challenging. This may have important clinical implications, for example for the indication of growth hormone therapy. We found that 80% of the European countries use height SDS values below a certain cut-off (whether or not in combination with height velocity) to determine a child's eligibility for receiving growth hormone (rGH) treatment (**chapter 3**). Especially for children with ESRD, in which growth retardation is such a major problem, applying the most appropriate growth chart is therefore of paramount importance. We found considerable variation in growth hormone policies for paediatric RRT in Europe, and these differences affected the height of children on RRT. A policy allowing the prescription of growth hormone seemed to increase the mean height SDS during childhood ESRD treatment. However, even though according to the policy rGH treatment was allowed and reimbursed in the majority of European countries, its actual use was low. Some of this difference might be explained by the high costs of rGH treatment, but this finding was not only restricted to countries with low economic status, suggesting that besides financial constraints other factors might also play a role in not regularly prescribing growth hormone. Although its use has been found safe, there may be concerns about potential adverse effects, like increased acute rejection in renal transplant recipients or intracranial hypertension [12]. Furthermore, children might experience difficulties adhering to the daily subcutaneous rGH injections. Besides differences in growth hormone policies, differences in height of children on RRT in Europe could also be affected by differential nutritional policies. When studying the prevalence of overweight and obesity among RRT patients in Europe (**chapter 6**), we indeed found country differences which might imply differences in nutritional management. Exact data on nutritional therapies were not

available in the registry, but it would be interesting to study to which extent nutritional therapies interfered with growth hormone policies in affecting height. In this way, strategies for optimizing growth outcomes could be developed.
Despite the low use of growth hormone, and the admission of more challenging patients to RRT programmes in Europe, we still found an improvement in final height in recent years (**chapter 4**). The greatest improvement in final height seemed to be related to better growth management in the pre-ESRD period. As expected, cumulative time on a functioning graft also improved final height. Therefore, in order to further improve final height it should be attempted to develop programmes stimulating pre-emptive transplantation in children. Because of the low use of rGH, it could be expected that more regular use of growth hormone could also lead to further improvement in growth during the ESRD period. However, because of the lack of detailed information on growth hormone in our registry more research is needed relating growth hormone use and reasons for non-prescription to outcome measures (e.g. final height). Furthermore, the long term effects of rGH treatment during childhood are not known and warrant further investigation.

NUTRITIONAL ABNORMALITIES

During childhood ESRD nutritional abnormalities occur frequently, stressing the importance of the nutritional therapy in the management of paediatric ESRD [13]. These abnormalities include among others obesity, dyslipidaemia, and a disturbed mineral metabolism, which all have been related to cardiovascular morbidity and mortality in adults and data from the general childhood population point towards the same direction [14,15].

Historically, the prevention of malnutrition received major attention when treating childhood ESRD. However, nowadays modern lifestyle related diseases also affect paediatric RRT patients as we found a much higher proportion of patients being overweight (20.8%) or obese (12.5%) than being underweight (3.5%) (**chapter 6**). Furthermore, we found a very high prevalence of dyslipidaemia in our cohort, and both a low and a high BMI were associated with less favourable lipid profiles (**chapter 7**). In addition, malnutrition remains a problem in paediatric RRT, especially in very young children, and a substantial proportion of the infants was underweight (15.8%). As vomiting and poor caloric intake occur frequently in this subgroup of patients, they may benefit from supplemental feeding. It should however be discontinued timely, as supplemental feeding for prolonged periods of time might lead to overweight and obesity [16]. Moreover, increased (dietary) energy intake of PD patients has been associated with higher triglyceride and cholesterol levels [17], and we found the highest prevalence of dyslipidaemia in young children on PD.
(Early) renal transplantation is the most optimal treatment for paediatric ESRD, as it corrects the uremic environment, thereby leading to better growth and less nutritional problems. Indeed, we found a lower prevalence of dyslipidaemia and a more favourable lipid profile

in transplanted patients, suggesting that transplantation could be an important step towards a better cardiovascular risk profile in paediatric ESRD patients. On the other hand, the highest prevalence of overweight and obesity was found among transplanted children. Moreover, we found that a short stature among transplanted patients was associated with a higher risk of being overweight or obese. This could be due to the effect of corticosteroid therapy leading to both impaired growth and weight gain [18] or due to the effect of protein-energy wasting with an inappropriate response to caloric supplementation leading to growth retardation and obesity [19]. In order to improve both the prevalence of obesity and disturbances in the lipid profile after renal transplantation steroid withdrawal may be considered. Steroid use was associated with a higher risk for being overweight and with an adverse lipid profile, in keeping with data from a recent randomized controlled trial (RCT) studying the effect of early steroid withdrawal in paediatric renal allograft recipients [21]. Additionally, steroids have a deleterious effect on growth, and the investigators found a significant growth potential of pre-pubertal children (age 1-12 years) in the steroid withdrawal group. In younger children (1-6 years at time of transplantation) this effect was even stronger, and the authors concluded that steroid avoidance regimes might enable young children to realize their final adult height potential [21]. Of course, steroid withdrawal regimens should be implemented with caution and balanced against the risk of rejection and potential side effects. Furthermore, most studies focusing on steroid withdrawal in paediatric renal transplant patients include small numbers and have a short follow-up period. Therefore, more research is needed to study long-term effects in larger patient groups.
As both obesity and dyslipidaemia are risk factors for cardiovascular disease, preventing and treating these factors should become an integral part of paediatric renal care. Further research should focus on the effect of nutritional (and lifestyle) interventions to prevent and reduce overweight and abnormal lipid levels, as well as on the long-term effects of overweight and dyslipidaemia in this population.

Besides a high prevalence of the traditional cardiovascular risk factors, obesity and dyslipidaemia, ESRD patients also suffer from several uraemia-related cardiovascular risk factors, of which a disturbed mineral metabolism is an important one. Abnormalities in mineral metabolism were highly prevalent in paediatric renal graft recipients (**chapter 8**). Although our data suggest that mineral levels improve over time, serum phosphorus, calcium x phosphorus product and PTH levels were inversely associated with graft function, and serum phosphorus levels were independently (even after adjustment for eGFR) associated with a higher risk of graft failure. As our data are observational, it remains unclear whether high phosphorus levels are the cause or the consequence of the failing transplant. However, evidence from in vitro, clinical, and epidemiological studies suggests that increased phosphorus levels are independently associated with vascular calcification and mortality [22].

METHODOLOGICAL ISSUES

The studies presented in this thesis are performed within the framework of the ESPN/ERA-EDTA registry. An important strength of the registry is the inclusion of data from multiple countries throughout Europe. Currently, 37 different European countries are participating, which enabled us to study country differences. Moreover, data are collected on an annual basis providing the opportunity to perform longitudinal analyses. Some "essential" data are collected for every single patient. However, the data collection for many clinical parameters is on a voluntary basis, resulting in missing values in our database. To deal with potential bias associated with these missing values we applied several novel statistical techniques. First, we used longitudinal data models. These models do not only correct for the correlation of repeated measurements within the same patient, they can also deal with missing data. Second, in several studies we used a multiple imputation method to substitute missing data as recommended by the STROBE guidelines [23,24].

A difficulty occurring with most registry studies is the absence of a central laboratory for measuring clinical parameters. The different participating centres determined values according to local practice by using different analytical tools. For most variables different methods yield similar results, but for some parameters (e.g. PTH and lipids) a high inter-method variability has been reported [25,26]. Although this might have caused variability in the measurements, it is likely that this mainly resulted in an underestimation of the reported effects. This concept is called non-differential misclassification: the potential error in the measurements is likely to occur to the same degree in all subgroups of the outcome variable, for example in patients with and without elevated lipid levels.

Moreover, because of the observational nature of the registry the studies reported in this thesis are hypothesis driven and cannot prove causality. To study causal effects of therapies on outcome measures RCTs are needed. Although this study design is considered the gold standard, RCTs are highly time-consuming and expensive, and in some cases they are not possible. In such situations observational studies provide a very good alternative, as long as their limitations are taken into account [27]. In paediatric RRT, the small and heterogeneous population hampers the conduction of sufficiently powered clinical trials, whereas large registries provide the opportunity to analyse potential risk factors in relation to patient outcomes.

CONCLUSIONS

Although growth remains sub-optimal in European paediatric RRT, we found recent improvements in final height. In order to further optimize growth, growth monitoring should occur by using appropriate reference data (recent national growth charts). In this way, the right children would be considered eligible for growth hormone therapy. We found, however, that the majority of children with a short stature never used growth hormone and more research is needed to find out reasons for this low prescription. Early transplantation, preferably in combination with steroid withdrawal, could improve growth and the nutritional status of this patient population. Because of the high prevalence, the prevention and treatment of obesity should become an integral part of the management of paediatric ESRD. The effect of these prevention strategies, as well as the long-term health effects of dyslipidaemia and obesity would be interesting topics for future studies.

Reference List

1. de Onis M, Garza C, Victora CG, et al. (2004). The WHO Multicentre Growth Reference Study: planning, study design, and methodology. *Food Nutr Bull* 25: S15-S26.
2. de Onis M, Onyango AW, Borghi E, et al. (2007). Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ* 85: 660-667.
3. Cole TJ, Bellizzi MC, Flegal KM, et al. (2000). Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 320: 1240-1243.
4. Cole TJ, Flegal KM, Nicholls D, et al. (2007). Body mass index cut offs to define thinness in children and adolescents: international survey. *BMJ* 335: 194.
5. Schaefer F, Wuhl E, Feneberg R, et al. (2000). Assessment of body composition in children with chronic renal failure. *Pediatr Nephrol* 14: 673-678.
6. Schmitt CP, Mehls O (2011.) Mineral and bone disorders in children with chronic kidney disease. *Nat Rev Nephrol* 7: 624-634.
7. Klaus G, Watson A, Edefonti A, et al. (2006). Prevention and treatment of renal osteodystrophy in children on chronic renal failure: European guidelines. *Pediatr Nephrol* 21: 151-159.
8. National Kidney Foundation (2005). K/DOQI clinical practice guidelines for bone metabolism and disease in children with chronic kidney disease. *Am J Kidney Dis* 46: 1-122.
9. Haffner D, Schaefer F (2013). Searching the optimal PTH target range in children undergoing peritoneal dialysis: new insights from international cohort studies. *Pediatr Nephrol* 28: 537-545.
10. Rosenkranz J, Reichwald-Klugger E, Oh J, et al. (2005). Psychosocial rehabilitation and satisfaction with life in adults with childhood-onset of end-stage renal disease. *Pediatr Nephrol* 20: 1288-1294.
11. de Onis M, Wijnhoven TM, Onyango AW (2004). Worldwide practices in child growth monitoring. *J Pediatr* 144: 461-465.
12. Hodson EM, Willis NS, Craig JC (2012). Growth hormone for children with chronic kidney disease. *Cochrane Database Syst Rev* 2: CD003264.
13. National Kidney Foundation (2009). KDOQI clincal practice guideline for nutrition in children with CKD: 2008 Update. *American Journal of Kidney Diseases* 53: S1-S124.
14. Juonala M, Magnussen CG, Berenson GS, et al. (2011). Childhood adiposity, adult adiposity, and cardiovascular risk factors. *N Engl J Med* 365: 1876-1885.
15. Nicklas TA, von Duvillard SP, Berenson GS (2002). Tracking of serum lipids and lipoproteins from childhood to dyslipidemia in adults: the Bogalusa Heart Study. *Int J Sports Med* 23: S39-S43.
16. Rees L, Jones H (2013). Nutritional management and growth in children with chronic kidney disease. *Pediatr Nephrol* 28(4): 527-536.
17. Tanaka Y, Hataya H, Araki Y, et al. (2002). Hyperlipidemia in children on peritoneal dialysis: effect of energy intake on serum triglyceride. *Perit Dial Int* 22: 426-428.
18. Rashid R, Neill E, Smith W, et al. (2006). Body composition and nutritional intake in children with chronic kidney disease. *Pediatr Nephrol* 21: 1730-1738.
19. Mak RH, Cheung WW, Zhan JY, et al. (2012). Cachexia and protein-energy wasting in children with chronic kidney disease. *Pediatr Nephrol* 27: 173-181.
20. van der Sluis IM, Boot AM, Nauta J, et al. (2000). Bone density and body composition in chronic renal failure: effects of growth hormone treatment. *Pediatr Nephrol* 15: 221-228.
21. Mericq V, Salas P, Pinto V, et al. (2013). Steroid withdrawal in pediatric kidney transplant allows better growth, lipids and body composition: a randomized controlled trial. *Horm Res Paediatr* 79: 88-96.
22. Shroff R (2013). Phosphate is a vascular toxin. *Pediatr Nephrol* 28: 583-593.
23. Sterne JA, White IR, Carlin JB, et al. (2009). Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 338: b2393.
24. Von EE, Altman DG, Egger M, et al. (2007). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 370: 1453-1457.
25. Souberbielle JC, Boutten A, Carlier MC, et al. (2006). Inter-method variability in PTH measurement: implication for the care of CKD patients. *Kidney Int* 70: 345-350.

26. Stein EA, Myers GL (1995). National Cholesterol Education Program recommendations for triglyceride measurement: executive summary. The National Cholesterol Education Program Working Group on Lipoprotein Measurement. *Clin Chem* 41: 1421-1426.
27. Jager KJ, Stel VS, Wanner C, et al. (2007). The valuable contribution of observational studies to nephrology. *Kidney Int* 72: 671-675.