CHAPTER 7
Discussion and Summary
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GENERAL DISCUSSION and SUMMARY

The treatment of phenylketonuria (PKU) has been very successful since the introduction of newborn screening in the 1960’s, Newborn screening has enabled doctors to identify patients and start dietary natural protein restriction within the first weeks of life. Early and continuous treatment has led to prevention of severe cognitive impairment and near normalization of outcomes. Despite these great achievements the treatment of PKU has also led to some new challenges in patient care. Some of these newly encountered issues may be due to the dietary restrictions, while others may be caused by the disease itself as early treated patients reach adulthood providing new challenges. Optimizing care in patients with PKU needs fine-tuning of the treatment itself and evaluation and management of adverse outcomes of the treatment. It is therefore of importance to provide continuous and specific care for newly emerging issues as patients reach adulthood. This thesis presents several studies focussing on the optimisation of care in PKU, which will be summarised and discussed in this chapter: multidisciplinary consensus on optimal care; the time burden, out-of-pocket-costs (OOPC) and health related quality of life (HRQoL) of patients with PKU and their parents; bone health in PKU; dietary intake and blood levels of micronutrients and essential fatty acids (FA) (chapter 1).

Consensus on optimal care

Summary

To provide the best possible care for patients with PKU one of the challenges to overcome are the differences observed in treatment between the different metabolic centers (chapter 2). To harmonize care provided in the Netherlands, the Dutch patient society for inborn errors of metabolism (the VKS) initiated the development of clinical pathways for 20 different inborn errors of metabolism (IEM), including PKU, in cooperation with pediatricians, internists and dieticians specialized in metabolic disorders. The aim was to achieve national consensus about the best provided care for these diseases using clinical pathways. Clinical pathways are of use to accomplish such
national consensus as they are a tool for multidisciplinary decision making and organization of care processes for well-defined groups of patients [1]. It has been demonstrated that the use of pathways increases interdisciplinary communication, enhances patient knowledge and self-awareness and leads to significant better coordination of care [2,3]. When frequently updated, it also presents a reference to the latest advancements in care [4] and provides direction for further research. We believe that multidisciplinary cooperation using a clinical pathway will improve communication and provide a clear route to best care, based on national consensus. For each IEM clinical pathways (one version for professionals and one for patients) were made freely available online through the VKS website [5].

**Implications**

The development of national clinical pathways for IEM has been successfully executed and the present best available multidisciplinary approach to care in PKU has been established. National consensus is of great importance in optimizing care for the patient with PKU. The pathways help to clarify to both patient and caregivers what the route in the care of individual patients broadly will be, and they are known to decrease duration of inpatient care, increase interdisciplinary communication, enhance patient knowledge and self-awareness, lead to significant better coordination of care and reduce costs [3]. The patient’s perspective and involvement is very important in this context as patients wish, and need, to be more and more involved in their own treatment. Patients are asking for more unified and consistent care trajectories [6]. Increasing patient involvement and self-management may lead to better outcomes and clinician-patient relationships [6,7]. To guarantee up-to-date information about the care trajectories stated in clinical pathways it is necessary for clinicians to remain in dialogue about the content, and all clinical pathways need to be regularly updated.

In chapter 2 we discuss the implementation and need for clinical guidelines nationally. In the care for PKU international diversity in treatment also exists [8-10]. For example, there is much debate on which blood Phe ranges are safest to target [6,8-10]. Furthermore, there are differences between countries and/or medical centers when it
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comes to the prescribed total dietary protein intake and care providers also define the food produce which patients are allowed to eat without restriction differently [8,9,11]. Transition to adult care [12-15], acceptable Phe blood concentrations during pregnancy [9,12] and the use of breastfeeding in newly diagnosed neonates with PKU [8] are also a matter of attention as these subjects are approached unalike internationally. It is important to acknowledge such dissimilarities in care and to strive to overcome them using multidisciplinary consensus on the best available treatment options. Open communication between providers of care for PKU (and patients) leads to uniformity in care, a better understanding of lacunas in knowledge/evidence based medicine and provides insight in areas that need further research. A European guideline involving physicians, dietitians and a patient society is currently being developed [16].

Health related quality of life, out-of-pocket costs and time burden

The impact of the severe dietary restrictions on patients is thought to be considerable in PKU. For this reason we hypothesized that HRQoL may be impaired. Furthermore, we expected that disease management could cause a considerable time burden for the patient and that it could lead to additional OOPC. To objectify the impact of disease management we used online questionnaires to investigate HRQoL and to assess OOPC and time burden concerning disease management.

Summary

Health related quality of life

We hypothesized that HRQoL in patients with PKU is impaired. Patients frequently express psychosocial issues resulting from disease and dietary management, and this possibly affects treatment adherence, social relationships, and job performance [14,17]. Therefore, we evaluated HRQoL of patients with PKU (Chapter 3). First, we aimed to obtain knowledge of the patients’ HRQoL during the period that only dietary treatment was available. Second, we intended to gain insight into the effects of the newly
introduced treatment with tetrahydrobiopterin (BH4) on HRQoL. We used online questionnaires aimed at measuring generic HRQoL and questionnaires assessing HRQoL in patients with chronic disease. We asked both patients and parents (depending on the age of the patient) to fill out the questionnaires at two time-points. The first time patients and parents answered our questionnaire was well before BH4 was introduced in the Netherlands as a treatment option in PKU. The second time was at least one year after BH4 responsive patients had started treatment with the new medication. In this manner we were able to evaluate baseline HRQoL of our patients, and we were also able to compare differences between the first and second measurements in patients who had started using BH4. In contrast to our hypothesis, outcomes of our study demonstrated that patients with PKU overall have a HRQoL comparable to or better than the general population (baseline measurement). Results also did not show any changes in HRQoL scores measured before and after the start of BH4 treatment within the group of BH4 responsive patients, nor did we find any differences between the treated BH4 responsive and unresponsive patients at the measurement well after BH4 implementation. Comparable outcomes on HRQoL have been published [18,19] and it is yet unclear whether found results truly reflect the HRQoL of patients, or if this results from the use of generic questionnaires which are not disease specific and therefore do not detect the possible negative consequences experienced by our patients. Ideally a PKU specific HRQoL questionnaire would have been used, but the introduction of BH4 in 2009 necessitated the timing of our study because one of our aims was to measure HRQoL before and after implementation of BH4. Furthermore, the fact that we did not find differences in HRQoL at the first and second measurement may be explained by the fact that the reported HRQoL of patients at baseline was already excellent, leaving no room for further improvement (‘ceiling effect’) when patients were able to relax their diet as a result of BH4 use. Based on this study, it is not possible to conclude that the use of BH4 improves the HRQoL of patients.
Time burden and costs

We hypothesized that the disease management of PKU would impose a considerable time burden on patients and families with PKU (chapter 4). In our study we showed that the median time burden associated with managing PKU was 1 h and 24 min/day for caregivers and 30 min/day for adult patients. Time was mostly spent on cooking and preparing meals specifically for a Phe-restricted diet, followed by monitoring protein intake. The significantly higher time burden for caregivers versus adult patients suggests that less time is required for PKU management as patients enter adulthood and begin caring for themselves. This fits with the idea that many adult patients tend to somewhat relax their diet. The outcome of time burden placed on caregivers of pediatric patients with PKU is considerable, especially because we measured disease specific time burden which is therefore cumulative to time spent on daily household tasks. As such, the time spent on managing PKU could take away time from other daily activities.

The median OOPC per patient was around € 604 annually. As amino acid supplements are reimbursed by the health insurances in the Netherlands, this amount was mainly spent on low-protein food products. It needs to be discussed if these costs are a true burden, because an average Dutch adult on a normal diet has been demonstrated to spend a mean amount of € 1200 annually on meat, cheese, milk, yoghurt and bread [20], products not or little consumed by the patient with PKU. For patients with PKU this expenditure is replaced by the costs of the low protein products. Taking this into account, it is unlikely that there will be a large burden of extra OOPC for families of patients with PKU. However, it must be stressed that to guarantee proper dietary treatment of patients with PKU and to avoid a disproportionate financial burden for patients and families, it is essential that costs of the Phe free protein supplements remain reimbursed by the Dutch health insurances. Costs of these supplements are of such a scale (over €30.000 per year per patient [21]) that not reimbursing them could be harmful for patient care outcomes and treatment.
Implications

HRQoL is an important outcome of treatment and disease management using patient (and/or parent) reported outcomes [22]. Decreased HRQoL in both parents and patients with IEM have been reported [23-25] and it has been an area of great interest for researchers in the PKU field [14,18-20,26]. It seems that available questionnaires are too generic to pinpoint quality of life related problems in patients with PKU. In order to assess HRQoL adequately it is of importance that the used questionnaire is evaluative and discriminative for the researched group of patients [22]. Our results did not show a change in HRQoL in patients when dietary restrictions were relaxed in BH4 responsive patients, but since our study others have been able to show an improvement using a self-designed PKU specific HRQoL questionnaire before and after the introduction of BH4 [27]. This specific questionnaire however is yet not validated and as such not widely applicable. For this reason it is important to design an internationally validated HRQoL questionnaire specifically for patients with PKU to further study the impact of PKU and of treatment on HRQoL. Very recently the validation process of an internationally developed PKU specific HRQoL questionnaire for all ages was published[28]. This type of questionnaire may be used in patient follow up as a tool to monitor problems and changes in HRQoL on a frequent basis, to intercept psychosocial problems early and intervene when needed, as well as to evaluate effects of new treatment options [29,30].

Our study on time burden and OOPC in patients with PKU shows that patients do not have a high burden of costs as a result of their disease management. This is partly because patients do not use food sources rich in protein. However, the most important reason is that patients in the Netherlands are reimbursed by the healthcare insurances for the expensive amino acid substitutes that they depend on for their dietary intake [21]. In contrast, we showed that time burden is considerable especially for caregivers of pediatric patients and imposes a significant burden on patients and families. It is of importance for clinicians to realize this impact of imposed dietary treatment on patients in order to improve the physician-patient relationship and to perhaps better understand problems in adherence.
Bone health

Many studies have postulated that bone mineral density (BMD) is affected in patients with PKU. Hypotheses have been stated that the cause of such an impairment in BMD may either be caused by high or fluctuating blood phenylalanine (Phe) values, or by nutritional deficiencies as a result of the natural protein restricted diet of patients. In order to assess the BMD of patients and the clinical implications of a possibly impaired BMD, we systematically reviewed the literature on this subject and performed a meta-analysis on pooled patient data from available studies. Furthermore, to objectify the bone health of our Dutch early and continuously treated patients, we conducted a clinical multi-center study in which we researched BMD measured with dual-energy X-ray absorptiometry scans (DXA) and we looked at bone turnover markers (BTM) in blood.

Summary

Meta-analysis

The systematic review and meta-analysis (chapter 5) that we conducted showed that BMD Z-scores in early and continuously treated patients with PKU were lower in some patients when compared to the general population, but within the normal range in most patients. We found that the overall effect sizes of BMD Z-scores calculated from pooled data of 247 patients, retracted from 11 studies, were: total body BMD −0.45 (95% CI −0.61, −0.28); lumbar spine BMD −0.70 (95% CI −0.82, −0.57); femoral BMD −0.96 (95% CI −1.42, −0.49). These outcomes of Z-scores for BMD are categorized as normal by recommendations of the Society for Clinical Densitometry (ISCD), stating that BMD is low if the Z-score is below −2. Based on the assumptions that our data are normally distributed and the overall effect sizes for BMD Z-score are as stated, approximately 10% of early treated patients with PKU may have a lumbar spine BMD Z-score below −2. These patients with low BMD may benefit from care aimed at preventing osteoporosis. However, 90% of early treated patients with PKU seem not to be at risk for low BMD, which is a much better outcome than expected from earlier literature. It was not possible to assess fracture risk of patients with PKU, or effect of BTM, dietary outcomes...
and Phe blood values based on the systematic review because evidence from the included studies was limited and heterogeneous.

Clinical study

The results on bone health from the clinical multi-center study (chapter 6), which we performed in collaboration with three metabolic centers in the Netherlands, are in accordance with findings from our review. We showed that BMD in our population is overall normal, although Z-scores below -2 were found in 4.9% of our patients for lumbar BMD and 7.4% for femoral BMD. None of our individual patients had osteoporosis as defined by the ISCD and the lifetime fracture prevalence of patients with PKU seemed comparable to the age-standardized lifetime fracture prevalence of the general population in England.

Both the measured bone formation and resorption marker, the first more than the latter, were elevated. With these abnormalities in BTM, we hypothesize that bone turnover in our population may be affected. Even though most patients have a BMD within the normal range, this could possibly lead to adverse outcomes after the age of fifty years.

Implications

Over the last few decades an impaired BMD has been often suggested to occur in patients with PKU. For this reason we performed a systematic review to determine the extent and significance of low BMD in early treated patients with PKU. To objectify BMD results in patients with PKU as reported in literature we used ISCD recommendations which state that the diagnosis of osteoporosis (and thus an increased fracture risk) can be made when the patient has a BMD Z-score below -2 and a significant fracture history (two or more long bone fractures by age ten years and/or three or more long bone fractures at any age up to nineteen years, or at least one vertebral compression fractures in the absence of trauma) [33]. Our meta-analysis showed that BMD Z-scores were within the normal range in most patients. However,
based on the assumption that the pooled data was normally distributed, 10% of early and continuously treated patients with PKU have a BMD Z-score below -2. Fracture risk could unfortunately not be assessed because data was not available about fracture history from the included studies. We found consistent results on BMD Z-scores in our clinical multi-center study, which showed that around 7% of Dutch patients with PKU had a Z-score below -2. This is a slightly higher prevalence of low BMD than the 2.3% found in the general population. Furthermore, in our study we saw that BTM were elevated indicating that there is an imbalance in bone formation and resorption. The combination of these findings may have effect on bone health when patients become older. To objectify these possible effects, further research is indicated. The oldest patient in our study was 39 years old as a result of newborn screening only being implemented in the Netherlands in 1974. Female patients turning fifty years old will be a particular important group to be studied in the future. Especially because women of that age in the general population already have a higher prevalence of osteoporosis related fractures, and early and continuously treated women with PKU might have an even greater risk based on our findings.

**Nutrient status**

We evaluated dietary intake and deficiencies of micronutrients, amino acids and fatty acids (FA) in one of the largest studied cohorts of patients with PKU (chapter 6), because the natural protein restricted diet has been reported to lead to nutrient deficiencies [34,35].

**Summary**

Micronutrients

Our results showed that the dietary intakes of micronutrients of patients with PKU were overall normal. However, the intake of vitamin D was inadequate in 20% of patients and serum 25-OH vitamin D2+3 levels were below reference range in 14% of patients. Despite near normal bone health outcomes (BMD, fracture risk and BTM), it seems advisable to yearly evaluate intake and determine blood levels of vitamin D, and to supplement patients when serum levels are <50 nmol/L. Furthermore, in our cohort
dietary intake of selenium was also below the advised range in 41% of patients and serum levels were below reference range in 46% of patients. Clinical symptoms linked to selenium deficiency such as cardiomyopathy and depression have been reported in the general population. Because the dietary intake of selenium in many of our patients is below the advised range, it seems advisable to annually evaluate intake and blood levels and consider supplementation of selenium. Especially if levels are also below the advised reference ranges.

Additionally, zinc serum levels were below reference range in 14% of patients, despite an intake above the safe advised range in 52% of patients. Zinc deficiency has been reported to cause several symptoms, one of which is impaired wound healing. The clinical relevance of our findings is debatable and further studies need to be done on how to effectively increase zinc uptake in PKU patients. Especially considering the fact that a large proportion of our patients already have intakes exceeding the safe advised range.

In contrast, folic acid was found to be high both in the dietary intake as in the serum levels of patients. As there is discussion on the safety of high levels [36,37] it deserves due consideration to lower folic acid amounts in amino acid mixtures.

Because serum levels below reference range of 25-OH vitamin D2+D3, zinc and selenium might also have clinical implications, it may be advisable to annually check-up on intake and blood levels of these micronutrients.

Amino acids

Protein intake in our patients was well above the minimally required daily intake. Investigating plasma amino acids we found that arginine, amongst others, was below the reference range. Further research is indicated to determine whether it is warranted to increase supplementation of arginine as it plays a main role in nitric oxide formation and in removing ammonia from the body. Other amino acids that were below the reference range were asparagine, 2-aminobutyric acid and tyrosine. Clinical implications of these findings is however unclear.
Essential fatty acids
Dietary fat intakes and erythrocyte bound essential FA were overall normal in our patients. We did, however, find that the level of eicosapentaenoic acid (EPA, C20:5ω3) in erythrocytes was lowered. Because EPA is a precursor of prostaglandins and has a positive effect on cardiovascular disease it may be considered to increase EPA supplements in amino acid mixtures.

Implications
The dietary treatment of PKU limits the intake of Phe by restricting the amount of protein ingested from natural food sources. To reach recommended intakes of total protein, a large part of the diet consists of (vitamin, mineral and sometimes FA fortified) amino acid mixtures, not containing Phe. In some amino acid mixtures calculation of the amount of micronutrients added is based on the required amount of calories, while in others the amount added is based on advised intakes of protein per kilogram bodyweight [38]. This leads to very different intakes of these nutrients per patient. Furthermore, some mixtures are fortified with FA and others are not. Such a diet might easily lead to altered intakes of micronutrients and FA when compared to the general population and deficiencies have indeed been reported [34,35,38]. Remarkably, intake and plasma levels of most micronutrients and FA were normal in the studied patients, however, some abnormalities were detected. To prevent clinically relevant deficiencies we advise that patients are annually checked for dietary intake and deficiencies of 25-OH vitamin D2+3 and selenium. Lowering folic acid amounts in amino acid mixtures should be considered as both dietary intake and serum levels of the micronutrient are high. Further research on altered outcomes of zinc, several amino acids and EPA is indicated. We found abnormal levels of these nutrients, but little is known about the clinical implications of our findings.
REFERENCES


