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Quality of life in children living with PKU – a single-center, cross-sectional, observational study from Hungary

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ABSTRACT

Background: Phenylketonuria (PKU) is an inherited error of metabolism, screened at 48–72 h of life since 1975 in Hungary. The patients have to keep a strict lifelong protein-restricted diet, resulting in PKU and its treatment can lead to social and financial burdens. The current study aimed to evaluate the health-related quality of life (HRQoL) of children living with PKU.

Patients and methods: A single-centre, cross-sectional, observational study was conducted at the Center of Newborn Screening and Inherited Metabolic Disorders of Budapest, Hungary, using the PKU-quality of life (PKU-QoL) questionnaire. Responses of 59 parents and 11 teenagers were collected. Numerous aspects regarding HRQoL were analysed according to clinical compliance and severity. The patients were classified into groups with good or suboptimal adherence based on regular phenylalanine (Phe) values. The online officially translated versions of the adolescent or parental PKU-QoL questionnaire were used and analysed anonymously. Differences in HRQoL were compared - PKU vs. Hyperphenylalaninaemia (HPA) and good vs. suboptimal adherence.

Results: Twenty-five of 32 examined parameters had no or little impact on HRQoL. The most frequently reported symptom was irritability. Food enjoyment was the most impacted domain, with a major severity score in the adolescent group (median 62,5, IQR: 25–75). The emotional impact was scored at moderate severity by both the adolescents and parents. Classical PKU patients with good metabolic control were more frequently tired than HPA patients (0,0027). The group with poor metabolic adherence showed more frequent tiredness ($p = 0,03$), slow thinking ($p = 0,018$) and anxiety ($p = 0,015$).

Conclusion: Overall, our patients showed an excellent HRQoL; most domains (29/36) were reported as little/no impacted. Worse QoL was found in patients with suboptimal metabolic control. Particular attention should be paid to the emotional health of PKU patients.

1. Background

1.1. Phenylketonuria

Phenylketonuria (PKU, OMIM 261600) is an autosomal recessive inborn error of metabolism, first described by Asbjorn Folling in 1934 [1]. Poorly treated patients often develop mental retardation, epilepsy, neuropsychological and psychiatric problems are presented [1–6]. Prevalence is around 1:8500 in Hungary [7].

Treatment is based on a lifelong protein-restricted diet complemented by phenylalanine-free medical formulas (protein substitutes) [8,9]. The patients are monitored with regular dried blood spot (DBS) self-sampling and clinical visits by a physician and dietitian following the recommendations of the current European guideline [10]. The latter recommends 120–360 μmol/l target Phe concentrations under 12 years and 120–600 μmol/l above this age. The guidelines define poor metabolic control in children under 12 when >50% of the Phe levels are out of target range for six months [10,11].

Abbreviations: DBS, dried blood spot; DPR, dietary protein restriction; GMP, glycomacropeptide; HPA, hyperphenylalaninaemia; HRQoL, health-related quality of life; IQ, intelligence quotient; IQR, interquartile range; PAH, phenylalanine hydroxylase; PKU, phenylketonuria; QoL, quality of life,; SD, standard deviation.

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1.2. Health-related quality of life among patients with PKU

The subjectively perceived impact of PKU on patients' everyday lives receives increasing attention. One strategy to measure quality of life (QoL) among PKU patients consists in using general health-related QoL (HRQoL) questionnaires. HRQoL can be described as a multidimensional, self-reported questionnaire, which is a subjective perception of the following domains: physical, psychological, social functioning, and overall well-being [12].

Several (QoL assessment data have been reported ~~i~~n adult PKU populations [13]. Analysis of the social state of adults with PKU revealed a delayed autonomy and a low rate of forming normal adult relationships [14]. While most of the studies found a normal QoL in adult PKU patients [14–17], Demirdas et al. reported a significantly lower HRQoL with regard to cognitive functioning [18].

During the last decade, studies assessing the QoL of children living with PKU have been also were published. Although quality of life scores did not differ between PKU patients and the age-matched control group in terms of total score ($p = 0.66$) [19,20] Landolt et al. nevertheless reported fewer positive emotions in children affected by PKU [20]. No difference was observed for age, type, and sex, but significantly lower scores were observed among adolescents for family cohesion and parental impact time [21]. Poor dietary adherence was highlighted and tended to worsen with older age. No significant differences were found in HRQoL scores of adherent and non-adherent children and adolescents [22]. There has been no systematic analysis of the QoL in the Hungarian PKU population using non-PKU-specific questionnaires.

1.3. PKU-specific QoL questionnaire

In 2015, Regnault et al. developed and validated the first set of PKU-specific HRQoL questionnaires for patients with PKU and their [23]. Disease-specific QoL questionnaires can describe specific disease-related problems that general questionnaires fail to fulfill [24,25]. Patients with PKU showed good HRQoL, although the negative impact of PKU on a patient's life, including the emotional impact of PKU and its management was underscored by the developers of PKU-QoL across all age groups (children [$n = 92$], adolescents [$n = 110$], adults [$n = 104$]). According to PKU severity, an increasing trend was observed in the overall impact of the diet and guilt if the diet was not followed. Patients with mild or moderate PKU enjoyed their food more compared to those with severe PKU. Suboptimal food enjoyment and adherence to diet were also reported by the parents of patients with severe PKU [26].

Barta et al. assessed the short- and long-term consequences of suboptimal diet adherence using the PKU-specific questionnaire in Hungarian adults. Short-term poor metabolic compliance has not had an effect, but patients showed significantly better scores after 10 years of good metabolic control [27].

Alptekin et al. conducted a study with 20 children (9–11 years), 22 adolescents (12–15 years), and 21 adults. The 9–11 age group was found to be most affected by the emotional effects of PKU. Slow thinking was the most frequent symptom, but almost all examined domains reached a moderate/major frequency in children. Adolescents reported problems with their general health, emotional effects of PKU, adherence to supplements, and dietary protein restriction. All age groups found the taste of supplements unsavory [28].

Eighteen mothers who participated in a study by Morawska at al reported the highest impact of PKU on their children's anxiety during blood tests on their own HRQoL and guilt related to poor adherence to dietary restrictions and supplementation regimens. Higher scores were shown in the emotional, social and overall impact of PKU [29].

The current study aimed to examine the QoL and the relationship between metabolic adherence, severity, and HRQoL among the Hungarian pediatric population living with PKU, with particular focus on the responses of adolescents and the parents.

2. Patients and methods

2.1. Study design

This observational, single-center, cross-sectional study was conducted between May 2020 and October 2020. HRQoL was examined using the adolescent and parenteral PKU-QoL questionnaire of MAPI Devel LTD [23]. Patients filled out the online version of tests at home. The analysis was completely anonymous. HPA and classical PKU adolescents aged between 12 and 18 years as well as the parents of the 0–18 years old children were included. Patients with BH4-treatment were ($n = 6$) excluded prior to the statistical analysis. The study followed the principles of the guidelines in the World Medical Association Declaration of Helsinki of 1975. The local ethics committee approved the study (registration number: 30912–4/2019/EKU). All the participants signed the informed consent form.

2.2. Good and poor adherence

Good and poor adherent groups were defined based on regularly sent Phe levels. For each patient, all Phe levels were considered from their birth and annual mean Phe levels were calculated. Adherence was deemed poor if more than 50% of the annual Phe levels were above the target range~~.~~, poor compliance was considered. The DBS Phe levels were determined by mass spectrometry (API2000; Perkin-Elmer Sciex, Toronto, ON, Canada) at the 1st Department of Pediatrics, Semmelweis University, Budapest.

2.3. Enrolled patients

After the exclusions, answers of 59 parents about their PKU/HPA children were analysed. Our study also included 11 self-reported answers of adolescents. The details of the included patients are shown in Table 1. Among the children where the parents responded, the Phe level differed between those of HPA and classical PKU, with good compliance ($p = 0.039$), the different was also significant in the classical PKU group if classified by good or poor adherence (0.002). The distribution of sexes was similar among the sexes in HPA and classical PKU with good compliance ($p = 0.287$), on the contrary, it differed between good and poor adherence, with significantly more boys in the non-adherent group ($p = 0.002$). The ages of the children were similar in both groups analysed ($p = 0.303$ and 0.91).

Due to the low patient number among adolescents, group analyses could not be performed.

2.4. The questionnaires

The PKU-QoL questionnaires are freely available for use in non-

Table 1
Demographic characteristics and means of the lifetime Phe levels of the participants.

Data of patients	Number	Age- mean (SD)	Lifetime Phe- mean (SD)	Boys (%)
a) adolescents, self-reported questionnaire				
HPA	1	15	294.18	100
PKU with good adherence	9	14.3 (2.7)	307.43 (102.5)	66.67
PKU with poor adherence	1	14	516.54	100
b) children, parental questionnaire				
HPA	20	8.1 (5.2)	203.2 (62.34)	45
PKU with good adherence	30	9.6 (5.3)	256.81 (98.2)	40
PKU with poor adherence	9	9.6 (5.7)	451.63 (251.5)	88.89

funded academic research. The MAPI developed questionnaire was downloaded from MAPI research trust, Lyon, France (https://eprovide.mapi-trust.org/instruments/phenylketonuria-impact-and-treatment-quality-of-life-questionnaire) and translated into Hungarian with permission of the owner. Adolescent and parental versions were used. For translation, the advised steps by Jurecki were followed [30]. The adolescent version is composed of 58 questions; while the parental version features 54 questions. Both of the versions contain four modules, detailed in Table 2.

The recall period focused on the last one week for all sections except for 'patient's general feeling' where the recall period was 'in general'. The following interpretation rules were applied for all domain scores in a range from 0 to 100:

- for symptom scores, a higher score is associated with more frequent symptoms,
- for adherence scores, a higher score is associated with lower adherence,
- for other scores, a higher score is associated with a more significant impact [23].

Once items were scored, a domain score was calculated for each domain, with more than 70% of the items completed using the formula below.

Domain score = Sum of item scores within the domain/Number of non − missing item scores within the domain*25

According to the developers, the severity of domain scores are to be interpreted as follows: a score between 0 and 25 indicates little/no impact or symptoms; between 26 and 50 indicates moderate impact or symptoms; between 51 and 75 indicates major impact or symptoms, and scores over 75 indicate very severe impact or severe/frequent symptoms [26].

2.5. Statistics

Data were summarised using Microsoft Excel 2016 and analysed using the IBM SPSS 23 statistical software. Normality of data was tested by the Kolmogorov-Smirnov and Shapiro–Wilk tests and $p > 0.05$ was accepted as a normal distribution. The Quality of life scores was expressed as median and interquartile ranges (IQR). The phenylalanine levels followed a normal distribution; mean and standard variation levels were calculated. Mann–Whitney U probes were performed to assess group differences: HPA vs. classical PKU and good vs. poor compliance; the level of significance was set at $p < 0.05$.

Table 2
Structure of the questionnaire.

Modules	Domains
Symptoms	self-health rated status, headaches, stomach aches, tiredness, lack of concentration, slow thinking, irritability, aggressiveness, moodiness, sadness, anxiety
PKU in General	emotional impact, practical impact, social impact, anxiety on Phe levels and blood test
Supplement administration	adherence to supplements, the practical impact of supplements, the social impact of supplements, taste, guilt if poor adherence to supplements
Dietary Protein Restriction module	guilt if the diet is not followed, management of dietary protein restriction (DPR), food temptation, adherence to DPR, practical impact of DPR, the social impact of DPR, the overall impact of DPR, overall difficulty following DPR, taste, food enjoyment

3. Results

3.1. Severity/ frequency of domains among the patients

Most of the domains (25/32) had little/no impact. Moderate severity was reached for irritability (adolescent median 50, IQR 25–75), emotional impact of PKU (adolescent median 35, IQR 30–45), parental median 31.3 (IQR 14.1–43.8), guilt if poor adherence to supplements (adolescent median 37.5, IQR 25–62.5), adherence to dietary protein restriction in adolescents (median 28.1, IQR 18.8–46.9) and practical impact of dietary protein restriction (adolescent median 32.1, IQR 14.3–42.9). Only adolescent's food enjoyment reached a major impact on QoL (median 62.5, IQR 25–75). The impact of all domains is detailed in Table 3.

3.1.1. Symptoms module

Ten out of 11 (90,9%) domains had no/little frequency (median score < 25).

Irritability was the most frequent symptom among adolescents (median 50, IQR 25–75), stomach aches, and anxiety reported as rarest (medians 0, IQRs 0–25). Among parental answers, the most frequent symptoms were lack of concentration and irritability (medians 25, IQRs 0–50), the rarest was the headache (median 0, IQR 0–0).

3.1.2. PKU in general module

Almost all of the domains (8/9, 88,9%) had no/little impact on QoL.

The emotional impact of PKU was the most affected domain with regard to answers from adolescents (median: 35, IQR 30–45) and parental questionnaires (median: 31.3, IQR 14.1–43.8). The least affected were practical and social impacts among parental data (medians 0, IQRs 0–10) and anxiety from blood tests among adolescents (median 12.5, IQR 0–25).

3.1.3. Supplement registration module

Four out of six domains (66.66%) had no/little effect on QoL.

The guilt if poor adherence to supplements domain reached a moderate impact on QoL in 12–17 years old children (median 37.5, IQR 25–62.5) and the highest impact in parental data (median 25, IQR 0–75). The less affected domain was impact of supplements on family among adolescents (medians 0, IQR 0–12.5 and 0–25) and adherence to supplements from parental data (0, IQR 0–0).

3.1.4. Dietary protein restriction module

Seven out of 10 domains (70%) reached no/little impact on QoL. Dietary protein restriction seems to have the most severe impact on QoL among Hungarian children.

Food enjoyment showed the highest impact in both adolescent (median 62.5, IQR 25–75) and parental (median 25, IQR 0–43.75) groups. The least impacted domain was adherence to dietary protein restriction in parental answers (median 0, IQR 0–0) and the social impact of dietary protein restriction in adolescents (median 10, IQR 3.75–25).

3.2. The severity of domains according to metabolic compliance

In adolescents with good compliance, emotional impact and taste of supplements reached a moderate impact, while food enjoyment showed

Table 3
PKU-QoL scores among the participants.

	adol. Median (IQR)	parental median (IQR)	ado vs. parental (p)	PKU median (IQR)	PKU-good adherence median (IQR)	PKU- poor adherence median (IQR)	PKU good vs. poor adherence (p)	HPA	HPA vs. good adherence of PKU (p)
Symptoms module									
General health	25 (0–50)	12.5 (0–25)	0.295	25 (0–25)	0 (0–25)	25 (0–25)	0.715	25 (0–25)	0.927
Headache	25 (0–25)	0 (0–0)	0.063	0 (0–0)	0 (0–0)	0 (0–25)	0.2	0 (0–0)	0.986
Stomach-aches	0 (0–25)	0 (0–25)	0.513	0 (0–25)	0 (0–25)	25 (0–25)	0.176	0 (0–25)	0.87
Tiredness	25 (25–25)	25 (0–25)	0.285	25 (0–25)	25 (0–25)	25 (25–50)	0.03	25 (0–50)	0.053*
Lack of concentration	25 (0–50)	25 (0–50)	0.769	25 (0–25)	25 (0–25)	50 (25–50)	0.125	25 (0–50)	0.859
Slow thinking	25 (0–25)	0 (0–25)	0.127	0 (0-25)	0 (0–0)	0 (0–25)	0.018	0 (0–25)	0.205
Irritability	50 (25–75)	25 (0–50)	0.059	25 (0–50)	25 (0–31.25)	50 (25–75)	0.226	25 (0–50)	0.235
Aggressiveness	0 (0–25)	0 (0–25)	0.689	0 (0–0)	0 (0–0)	0 (0–25)	0.355	0 (0–18.75)	0.08
Moodiness	25 (0–25)	25 (0–25)	0.964	25 (0–25)	25 (0–25)	25 (25–50)	0.125	25 (0–50)	0.399
Sadness	25 (0–25)	0 (0–25)	0.176	0 (0–25)	0 (0–25)	25 (0–25)	0.109	0 (0–25)	0.798
Anxiety	0 (0–25)	0 (0–25)	0.631	0 (0–25)	0 (0–0)	25 (0–50)	0.015	0 (0–25)	0.181
PKU in general module									
Emotional impact of PKU	35 (30–45)	31.3 (141-43.8)	0.401	28.2 (18.8-37.5)	28.13 (18.8-39)	25 (12.5-31.3)	0.14	25 (6.3–53.1)	0.325
Practical impact of PKU	16.7 (0–33.3)	0 (0−10)	0.081	4.2 (0-12.5)	4.2 (0–15.6)	4.2 (3.1–8.8)	0.89	0 (0–5)	0.202
Social impact of PKU	16.6 (10.4–33.3)	0 (0–10)	0.049	10 (5-20)	10 (5–19.1)	10 (5–20)	0.5	10 (0–15)	0.838
Financial impact of PKU	NA.	10 (3.75-20)		25 (0–25)	25 (0–25)	0 (0–25)	0.286	0 (0–0)	0.02
Overall impact of PKU	20.5 (15.9–31.8)	11.7 (7.2-22.4)	0.101	12.5 (8.9–21.7)	13.8 (10.7–21.7)	8.6 (7.9–13.8)	0.164	16.7 (8.3–27.7)	0.88
Child anxiety – Blood test	12.5 (0–25)	25 (6.25-50)	0.124	12.5 (0-37.5)	12.5 (0–37.5)	37.5 (12.5-50)	0.165	43.8 (25–75)	0.02
Impact of blood test	NA	25 (12.5-50)		25 (9.4-37.5)	12.5 (0–37.5)	25 (18.8–62.5)	0.207	43.8 (12.5–82)	0.068
Child anxiety on Phe levels	25 (25–50)	25 (25-68.8)	0.730	25 (25-75)	25 (25–56.3)	25 (0–75)	0.715	25 (18.8–50)	0.303
Information about PKU	NA	25 (25-50)		25 (25-50)	25 (25–50)	25 (0–50)	0.613	50 (31.5–50)	0.045
Supplement administration module									
Guilt if poor adherence to supplements	37.5 (25–62.5)	25 (0-75)	0.335	25 (0-75)	25 (0–75)	25 (0–56.3)	0.853	n.r.	1
Adherence to supplements	12.5 (0–18.75)	0 (0–0)	0.052	0 (0–0)	0 (0–0)	0 (0–0)	0.684	n.r.	
Impact of supplements on family	0 (0–12.5)	0 (0–25)	0.58	0 (0–25)	0 (0–25)	25 (18.8-56.3)	0.047	n.r.	
Management of supplements	NA	0 (0–25)		0 (0–25)	0 (0–0)	25 (0–75)	0.073	n.r.	
The practical impact of supplements	15.6 (6.3-23.4)	0 (0–8.3)	0.025	0 (0–8.3)	0 (0–8.3)	0 (0–8.3)	0.641	n.r.	
Taste-supplements	37.5 (12.5–50)	NA		NA	NA	NA		n.r.	
DPR module									
	25 (25–25)	25 (0–68.8)	0.805	25 (0–50)		12.5 (0–25)	0.176	62.5 (25–100)	0.314

(*continued on next page*)

Table 3 (*continued*)

	adol. Median (IQR)	parental median (IQR)	ado vs. parental (p)	PKU median (IQR)	PKU-good adherence median (IQR)	PKU- poor adherence median (IQR)	PKU good vs. poor adherence (p)	HPA	HPA vs. good adherence of PKU (p)
Guilt if dietary protein restriction (DPR) was not followed					25 (25-50)				
Management of DPR	NA.	12.5 (8.3-25)		12.5 (6.3-22. 9)	12.5 (5.2-20.6)	16.7 (12.5-25)	0.362	12 (0–20.8)	0.856
Food temptation	25 (12.5-56.2)	NA		NA	NA	NA		NA	
Adherence to DPR	28.1 (18.8–46.9)	0 (0–0)	<0.001	0 (0–0)	0 (0–0)	0 (0–25)	0.59	0 (−0)	0.576
Practical impact of DPR	32.1 (14.3–42.9)	25 (20.5-39.3)	0.921	25 (21.4-39.3)	25 (21.4-39.3)	21.4 (21.4-32.1)	0.282	42.8 (42.8–51.8)	0.056*
Social impact of DPR	10 (3.75–25)	12.5 (0–18.75)	0.468	12.5 (0–21.88)	0 (0–12.5)	12.5 (0–37.5)	0.412	6.25 (0–12.5)	0.942
Overall impact of DPR	21.88 (11.98–31.25)	NA		NA	NA	NA		NA	
Overall difficulty following DPR	25 (0–25)	NA		NA	NA	NA		NA	
Taste- low protein food	25 (18.75–50)	NA		NA	NA	NA		NA	
Child food enjoyment	62.5 (25–75)	25 (0-43.75)	0.016	25 (0–25)	25 (25-43.8)	0 (0–6.3)	0.023	50 (37.5–50)	0.328

DPR: dietary protein restriction, NA: not asked, n.r.: not relevant

Table 4
Most severe/frequent impacted domains of the patients according to clinical compliance
DPR = dietary protein restriction.

	Adolescents with good adherence (*n* = 11)	Adolescents with poor adherence (n = 1)	Parents of children with good adherence (*n* = 55)	Parents of children with poor adherence (n = 9)
Severe/ frequent impact (score > 75)	1: food enjoyment (75)	6: lack of concentration, irritability, sadness, moodiness, impact of supplements on family, guilt if poor adherence to supplements	–	–
Major impact (score 51–74)	–	7: social imp. of DPR, practical imp. of DPR, the overall impact of DRP, practical imp. of PKU, adherence to diet, pract. Imp. of supplements, the emotional impact of PKU	–	–
Moderate impact (score 26–50)	2: the emotional impact of PKU, the taste of supplements		1: the emotional impact of PKU	3: anxiety of blood test, lack of concentration, irritability

a severe impact. Only one patient filled out the questionnaire in the adolescent group with poor compliance; more domains were marked as moderate/major impacted. According to the parents' answers, the emotional impact was moderate in children with good compliance. In families with poor adherence based on parental answers, there were three moderate marked domains: the anxiety of blood test, lack of concentration, and irritability (Table 4).

3.3. "Good" vs. "poor" adherent groups

When performing a subgroup analysis among 30 parents of classical PKU children with good adherence and nine parents of children with poor adherence, significant differences were found in the following domains: tiredness, slow thinking, anxiety, food enjoyment, management of supplements, and impact on family supplements (Table 3).

Tiredness (median 25, IRQ 0–25 vs. median 25, IQR 25–50, $p = 0.03$), slow thinking (median 0, IQR 0–0 vs. median 0, IQR 0–25, $p = 0.018$) and anxiety (median 0, IQR 0–0 vs. median 25, IQR 0–50, $p = 0.015$) are less frequent symptoms with good adherence.

Children with good adherence enjoyed their food less (median 25 vs. 0, $p = 0.025$). The supplements generated more arguments in the children's families with poorer adherence (median 25 vs. 0, $p = 0.047$).

A noteworthy result is that the two groups do not differ in general health ($p = 0.72$) and have similar information on PKU ($p = 0.61$).

3.4. HPA vs. classical PKU

The two groups did not differ in the frequencies of the symptoms When solely analysing the data of children with good adherence and the HPA group, only tiredness showed a near significant difference ($p = 0.053$) and interestingly had a higher impact on the latter group.

The financial effect of PKU had a higher impact on patients with good compliance versus the HPA group (p = 0,002).

The patients with HPA had higher anxiety before the blood test than children with good compliance the ($p = 0.002$).

Typically, HPA patients - as in the current study, do not need to take protein supplements. In the HPA group, seven patients needed a protein-restricted diet, but not so strict as in the classical PKU.

4. Discussion

Although the European guideline (2017) recommends using the PKU-QoL at least once in childhood and adolescence, we found only a limited number of publications using this questionnaire in patients under 18 years of age [26,28,29]. The low incidence of the disease, the limited availability of translated questionnaires, and the length and complexity of the query might account for this underutilisation.

Given the latter, our study focused on the HRQoL of 59 PKU/HPA children based on their parents' answers and of 11 adolescents, based on their responses. We assessed the consequences of the suboptimal diet adherence and examined the differences in HRQoL of children with HPA vs. classical PKU.

4.1. Patients and descriptive results

According to our study, PKU has a significant impact on the life of adolescents; with the median score of food enjoyment reached major severity, (median score: 62,5, IQR: 25–75). The only adolescent patient with poor adherence reported six severe/frequent and seven significant domains. However, further data are ultimately necessary for drawing accurate conclusions.

Based on the parental answers, no median score reached significant or severe impact/frequent symptoms (>50). The emotional impact of PKU reached a moderate impact on the group with good adherence. In the low adherence group, anxiety from the blood test, lack of concentration, and irritability reached a moderate impact.

A moderate emotional impact was observed in both adolescent and parental questionnaires, in concordance with previous studies describing related to emotional impact in the children [29]adulthood [27] and in all age groups [26]. Alptekin et al. found the 9–11-year age group to be most affected by emotional impact [28]. Emotional effects appear to be a typical, moderate/severe impacted PKU symptom, in which further support should be considered.

We compared our Our data were additionally compared with the results findings of a study carried out on patients from seven European countries [26]. Bosch et al. reported tiredness as the highest observed median symptom score for all self-reported age groups (median score 50, IQR 25–50 by the adolescents), which in the parents' perceptions presented just below the score indicating moderate symptoms (median 25, IQR 0.0–50.0). Patients in the present study, on the other hand, indicated tiredness as having no/little impact on QoL,.reaching the highest score in the group with poor compliance although failed to reach moderate severity (median 25, IQR 25–50). The emotional impact of PKU (adolescent median 30,0.0 IQR 20.0–40.0, parental 37.5 (25.0–62.5), and the acceptance of supplements' taste (adolescent median 50.0 IQR 25.0–50.0) were similarly highly impacted as in both the Bosch's cohort and current study. Adolescents in the study of Bosch et al. appreciated their protein-poor foods to a greater extent than our participants.

The low Phe-diet and the supplements respresent a huge challenge to living with PKU, with special attention needed maintain the lifelong adherence, as mentioned before by other authors [31–34]. Glycomacropeptide (GMP) containing low Phe, provides new management options for PKU, with better support in terms of psychological well-being and organic function [35]. The subjects claimed that GMP-supplemented regimens were superior in sensory qualities to their usual amino acid formulas [36,37].

Good vs. poor adherence.

The European guidelines recommend an increased frequency of blood phenylalanine monitoring and outpatient visits, and re-education when more than 50% of the phenylalanine concentrations are out of the target range during a period of 6 months, and it is considered as poor metabolic compliance [11]. Barta et al. defined "good" and "suboptimal" adherence groups based on individual mean Phe levels in the examined period (the last 10 years) [25]. In the current study, poor metabolic compliance refers to the children's lifetime Phe levels.

It is very important to clarify; our study does not contain children with no adherence (i.e. off the diet). Although the Phe levels of the children in the poor metabolic compliance group are out of the target range, they nonetheless maintained the diet at least partially and attend metabolic care regularly.

Better HRQoL was found in Hungarian adults if having good compliance [27] The present study was conversely focused on investigating the differences in QoL between good and suboptimal dietary adherence in a pediatric population.

According to our findings, children were more frequently tired, anxious and presented slow thinking with poor adherence. The only adolescent with poor adherence in our study group reported more frequent symptoms than the adolescent group with good adherence; however, these domains differed.

Due to the relaxed diet, children with poor compliance might enjoy their food more.

Correlations between PKU severity and tiredness [29], and the financial impact of PKU [26,29] were also reported in children in earlier studies.

4.2. HPA vs. classical PKU

Bosch et al. compared mild-moderate PKU vs. classical PKU [26]. The parental scores were higher in the classical PKU group in general health status, emotional, financial, overall, and practical impact of PKU, practical impact of supplements, and child food enjoyment [26]. From these domains, we found a difference only in economic effects. It should to be noted that our HPA patients did not require taking a strict special diet and did not consume any supplements. In our cohort, HPA patients had higher anxiety prior blood tests, which may be due to their lower occurrence and thus were not as accustomed to the sample collecting procedure. The classical PKU patients had a greater information regarding PKU. This finding might be explained by the regular clinical and dietary visits and the involvement in the social life of the PKU community. Our HPA patients were more tired with a relative significance, although none of them correlated the latter with their illness.

4.3. Limitations and strengths

The strength of the study is that, to the best of our knowledge, this is the first study to compare subjective HRQoL in adherent and poorly adherent children using the MAPI PKU-specific QoL questionnaire battery.

However, the study has certain significant limitations. No alternative method such as reporting of close family members or teachers, structured interviews by experts, or patient-generated indexes of QoL [38] was used to further explore QoL in this patient group.

The patients filled out the questionnaires anonymously, thus correlations with Phe levels could not be assessed, although good vs. poor/suboptimal compliance analyses were examined.

Patients, who were off the diet completely and regularly missed their outpatients visits, could not be investigated.

Our study did not contain healthy control patients. As the developers of the PKU-QOL stressed, the questionnaire addresses issues relevant to PKU patients only, so the comparison to a control group from the general population is not possible [26].

Finally, the number of enrolled adolescents is relatively low, although we were able to recruit one third of our adolescents with PKU. Corresponding subgroup analyses could not be performed due to this low enrolment number, despite the fact that our centre provides care for children and adolescents with inborn errors of metabolism in the northern half of Hungary. According to the literature [33,34] adolescents have lower adherence and are more difficult to include in studies. The literature is also limited with regard to assessing the subjective perception of patients with poor adherence, particularly in children who

regularly miss their outpatient visits.

5. Conclusion

This study analysed the HRQoL of children living with HPA/PKU using the adolescent and parental forms of the newly developed PKU-QoL questionnaire. Overall, our patients showed a good HRQoL; most of the investigated domains (29/36) were marked with little/no impact. Moderately impacted domains were the emotional impact of PKU and food enjoyment. HPA patients have better QoL than classical PKU patients, which. Was also the case when we only compared PKU children with good metabolic control. Increased (worse) Poorer HRQoL were was found in patients with suboptimal metabolic control, indicating that regular clinical visits, dietary consultations, and regular monitoring of Phe levels are essential. Special attention should also be paid to the improvement of the emotional health of PKU patients. The finding that parents of children with poor adherence did not report difficulties with dietary protein restriction rules, may suggest that they have no or a sub-realistic view of the severity of PKU and the need for a lifelong Phe-restricted diet.

Based on these facts, we believe that our studies can provide impetus for further multicentre studies and meta-analyses exploring in detail the physical, psychological, and social functioning and overall QoL in this pediatric patient population, thereby enhancing attending physician awareness as well as improve patient adherence.

Author statement

DB, EK, ISz, JB, and PZs participated in the design of the project, providing clinical and scientific expertise regarding PKU. JB and PZs were in charge of overall direction and planning. DB, EK, ISz, JB and PZs contributed to the project administration, translation and adaptation of the questionnaire. DB and RH were involved in patient selection and data collection. DB interpreted the results and drafted the manuscript. EK, ISz, AA, GyR, AJSz, BJ and PZs critically reviewed and edited the manuscript. All authors discussed the results, read and approved to the final manuscript.

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Ethics approval

The study followed the principles of the guidelines in the World Medical Association Declaration of Helsinki of 1975. The local ethics committee approved the study (registration number: 30912–4/2019/EKU). All patients or their legally authorized representatives provided written informed consent before participation in the study.

Declaration of Competing Interest

The authors have no conflict of interest to report.

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