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Health Related Quality of Life assessment among early-treated Hungarian adult PKU patients using the PKU-QOL adult questionnaire

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ABSTRACT

Background: The implementation of neonatal screening and the early initiation of lifelong therapy have helped to prevent severe complications and enabled much more favorable outcomes for early-treated phenylketonuria (ETPKU) patients. However, PKU patients tend to develop subtle cognitive and psychosocial abnormalities and the strict dietary therapy can present financial and social burden. Thus, PKU is expected to affect the quality of life (QoL) of these patients. There is insufficient evidence regarding the relationship between metabolic control and Health-Related QoL (HRQoL). We aimed to assess the effect of short- and long-term therapy on QoL among Hungarian adult PKU patients using the standardized PKU-specific PKU-QoL questionnaire.

Methods: We conducted a single-centre, cross-sectional, observational study in Hungary. We included adult PKU patients treated with diet and amino acid supplements only. Patients reported HRQoL using the standardized adult PKU-QoL questionnaire and mean blood Phe concentrations were assessed for three different time periods: the previous 10 years, the previous year and concentration at the time of completing the questionnaire. The correlation between patients' QoL scores and their Phe levels was assessed. The classical PKU group was further divided into "good" and "suboptimal" adherence groups based on individual mean Phe levels in the examined time period. We evaluated differences in QoL among the two subgroups of classical PKU patients. QoL scores between classical and non-classical patients were also compared.

Results: Data from 88 adult patients were analysed (66 had classical PKU). No median PKU-QoL score reached major or severe impact/frequent symptoms in any domain. The highest scores (meaning larger burden) were mostly related to emotional impact of PKU and disease management. When performing correlation analysis between Phe levels and QoL scores by all patients we found weak to fair positive correlation in several domains either short or long term. Patients with classical PKU reported greater financial impact of PKU than patients with less severe PKU. Classical PKU patients with good therapy adherence tended to report better HRQoL scores than patients with suboptimal adherence.

Conclusion: We conclude that patients showed good HRQoL using the PKU-specific questionnaire. Our study demonstrates that suboptimal metabolic control is negatively associated with patients' HRQoL.

1. Introduction

1.1. Phenylketonuria

Phenylketonuria (PKU, OMIM 261600) is a rare, autosomal, recessively inherited disorder which is caused by alterations in the phenylalanine hydroxylase gene (PAH; EC 1.14.16.1). This leads to insufficient conversion of the essential amino acid phenylalanine to tyrosine [1]. The incidence of PKU in Europe is estimated to be 1:10,000 [2]. The resulting accumulation of phenylalanine (Phe) and its

Abbreviation: PKU, phenylketonuria; ETPKU, early-treated phenylketonuria; AAS, amino acid supplements; GMP, glycomacropeptide; HRQoL, health related quality of life; Phe, phenylalanine; Tyr, tyrosine; PKU-QoL, Phenylketonuria Quality of Life questionnaires; HPA, hyperphenylalaninaemia; IQR, interquartile range; SD, standard deviation

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metabolites in blood and tissue has toxic effects. Untreated PKU leads to severe intellectual disability, emotional disturbances, psychosocial disabilities, and irreversible neurological abnormalities [3] [4].

The implementation of neonatal screening in the 1960–1970s, and the early initiation of lifelong therapy helped to prevent severe complications, thus enabling a much more favorable outcome for early-treated PKU (ETPKU) patients [5]. The basis of PKU therapy includes a lifelong diet restricted in Phe (natural protein-restricted) with daily consumption of Phe-free amino acid supplements (AAS). Tetrahydrobiopterine (BH4) serves as a potential option to partially liberalize diet and improve metabolic control for responsive patients. Glycomacropeptide (GMP) can partially substitute AAS but does not allow discontinuation of traditional diet therapy. A novel therapy using phenylalanine ammonia lyase (PegPal) may become increasingly available to more patients with PKU [6].

The greatest challenge in PKU is the lifelong adherence to the natural protein-restricted diet, and the consumption of AAS. It is well known that the adherence to therapy decreases in adolescence and adulthood [7] [8]. Avoiding foods which are naturally high in protein (meat, eggs, etc) and regularly taking AAS, which is required for nutritional fullness of the diet, can be unpalatable for many patients and can also be associated with financial and social burden [9].

Long-lasting, good metabolic control with blood Phe levels in the target range is associated with better intellectual ability in adulthood [10]. However, PKU patients may develop subtle cognitive, executive and psychosocial abnormalities [11] [12]. Enns et al. concluded that PKU patients have reduced capacity for mental flexibility, organizational strategy, and working memory, and the authors also noted a negative impact on academic progress and emotional development [13]. Thus, PKU - particularly when diet adherence is suboptimal - is expected to affect the quality of life (QoL) of both patients and their families.

1.2. Health Related Quality of Life in PKU patients

A few decades ago the goal of PKU treatment was to prevent severe intellectual impairment. Goal progress can be monitored by many objective and measurable parameters in PKU, such as IQ, mean or actual blood Phe and Tyr values. These are repeatedly measured in the longitudinal therapy of PKU. Recently, an additional goal of PKU treatment has emerged: that QoL be as normal as possible [14] [15].

The subjectively perceived impact, that PKU has on patients' everyday lives, has received increasing attention. One strategy to measure QoL among PKU patients is to use general health-related QoL (HRQoL) questionnaires. HRQoL is a broad, multidimensional patient reported outcome which measures a patient's subjective perception of the impact that disease and treatment have on daily life within the following domains: physical, psychological, social functioning, and overall well-being [16]. A recent review assessing the neurological and psychological phenotype of adults with PKU retrieved 11 articles that reported on HRQoL in adults with ETPKU [17], and only one of these used the validated PKU specific QoL questionnaire [18]. The majority of studies suggest that the HRQoL of patients with PKU is similar to that of the general population [19] [20] [21] [22] [23] [24]. There are only a few studies where suboptimal outcomes were observed for adult patients with PKU [25] [26].

While generic questionnaires can make it possible to compare patient groups to the general population, Disease-specific QoL questionnaires can detect specific problems that general QoL questionnaires cannot [27]. In line with this, the population-specific “PKU-QoL” questionnaires by MAPI were developed to assess the impact of PKU and its treatment on all aspects of a patient's life, including symptoms, the practical, social and emotional impact of PKU, struggles with low-protein dietary restriction and with food supplements. There are 4 versions available: child, adolescent, adult, and parent. [28]. The most recent European guidelines advise that PKU-QoL questionnaires be completed by all patients at least once in childhood, adolescence and adulthood [6].

The only study so far to use both the PKU-QoL and generic questionnaires among a large population (including more than 100 adults) was conducted by Bosch et al. and showed good HRQoL with generic methods [18]. Evidence is insufficient and contradictory regarding the relationship between metabolic control and QoL [29] [30] [31] [26].There is no data available to explore the HRQoL differences between PKU patients who have suboptimal or good metabolic control using the PKU-QoL. We aimed to assess the HRQoL of the Hungarian adult ETPKU population and to examine the relation between HRQoL and metabolic control using the MAPI PKU-QoL questionnaire.

2. Material and methods

2.1. Study design

We conducted a single-centre, cross-sectional, observational study between January 2018 and September 2019 using the standardized adult PKU-QoL questionnaire of MAPI Devel LTD [28] to assess the short and long term effects of therapy adherence on HRQoL in PKU patients. We included ETPKU adult patients (hyperphenylalaninaemia, mild, moderate, or classic PKU) who had attended the metabolic centre care for at least 10 years. Patients filled out the adult version of the printed questionnaire during their annual visit.

2.2. Phenylalanine level measurement

To evaluate the metabolic control of patients we calculated mean Phe concentration from the last 10 years and mean Phe concentration from the previous year. In addition, actual blood Phe concentration was also measured when completing questionnaire. “Lifetime Phe level” was calculated by 47 patients from birth. We measured Phe levels using dried blood spot analysis with API2000 LC/mass spectrometry (MS/MS; Perkin-Elmer Sciex, Toronto, ON, Canada) at the 1st Department of Pediatrics, Semmelweis University, Budapest.

2.3. The PKU-QoL questionnaires

The PKU-QoL questionnaires are available freely for use in non-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, *access time: 2018.01.02.*) and translated into Hungarian. The license to use and permission to translate were given by the owner. For evaluation of the answers we used the official scorer application (PKU-QoL electronic scorer, Mapi Research Trust, PKU-QOL © Biomarin Pharmaceutical Inc. – 2015).

2.3.1. Linguistic validation and translation

The British adult questionnaire served as basis for developing the Hungarian adult version. The validation consisted of the following steps as advised by Jurecki et al. [32]: 1) peer-reviewed translation and adaptation of the British version into Hungarian by the Hungarian Office for Translation and Attestation Ltd. 2) clinician review 3) interview with caregivers to test the adequacy and understandability. The validation process did not reveal any major semantic or cultural issues.

2.3.2. Structure of the adult questionnaire

The adult questionnaire with 65 questions consists of 4 modules targeting the most important areas of disease management. All modules comprise several domains (Table 1).

Recall period is focused on the last one week for all questions (except self-rated health status). By all items a score from 0 to 4 was obtained. All domain scores range from 0 to 100 and are calculated using the following method: *The sum of all item scores in a domain is divided*

Table 1
Modules and domains of the adult questionnaire

PKU Symptoms module	PKU in General module	Administration of Phe-free Protein Supplements module	Dietary Protein Restriction module
Self-health rated status	Emotional impact of PKU	Adherence to supplements	Food temptations
Headaches	Practical impact of PKU	Practical impact of supplements	Adherence to dietary protein restriction
Stomach aches	Social impact of PKU	Guilt if poor adherence to supplements	Social impact of dietary protein restriction
Tiredness	Overall impact of PKU	Impact of supplements on family	Practical impact of dietary protein restriction
Lack of concentration	Anxiety-blood test	Taste - supplements	Overall impact of dietary protein restriction
Slow thinking	Anxiety-blood Phe levels		Taste of low protein food
Trembling hands	Anxiety-blood Phe levels during		Guilt if dietary protein restriction not followed
Irritability	pregnancy		Overall difficulty following dietary protein
Aggressiveness	Financial impact of PKU		restriction
Moodiness	Information on PKU		Food enjoyment
Sadness			
Anxiety			

with the number of non missing item scores in the same domain then this result is multiplied by 25. If less than 70% of items were completed in a domain then the domain score was set to be missing.

For symptom scores, the higher the score the frequenter are the symptoms. Higher adherence scores are associated with poorer adherence. For other domains a higher score means larger impact [28]. According to the developers of this standardized PKU-QoL, severity of domain scores should be interpreted as follows: a score between 0 and 25 indicates little/no; between 26 and 50 indicates moderate; between 51 and 75 indicates major, and scores over 75 indicate very severe impact or severe/frequent symptoms [18]. Self-rated health status is rated from 0 to 4: Poor (4), fair (3), good (2), very good (1) or excellent (0).

2.4. Data analysis

We examined the correlation in the total patient group between HRQoL scores and Phe concentration. Phe levels were assessed in three different time periods: last 10 years, last year and Phe level at the time of filling out the questionnaire. We performed subgroup analysis among the 47 patients ("lifetime Phe group") by whom lifetime Phe levels were available: we examined the correlation between HRQoL scores and lifetime Phe levels. Total patient group was then divided based on disease severity into either classical or non-classical (HPA, mild, moderate) PKU groups. We performed group comparison between QoL scores of Classical and Non-classical PKU patients. For classification we used a combination of methods: Patients with pretreatment Phe over 1200 μmol/l were classified as classic PKU. In cases where pretreatment Phe levels were not decisive (mostly because of early commencement of diet) phenylalanine tolerance and course of the disease were also assessed for classification [33].

In all three examined time frames classical PKU group was further divided into two subgroups based on the individual Phe levels: 1) classical PKU with good therapy adherence and 2) classical PKU with suboptimal therapy adherence. We evaluated differences in HRQoL among the two subgroups of classical PKU patients with the main objective of defining the relevance of good or suboptimal diet adherence on HRQoL outcome. In line with guideline recommendations the cut-off value was mean Phe concentration of 600 μmol/l in the examined periods [6]. We included no patients with Sapropterin dihydrochloride or large neutral amino acid treatment in the study.

2.5. Statistical analysis

Statistical analyses were performed with JASP Team (2019), JASP (Version 0.11.1) for windows 7 professional. We performed normality checks using Shapiro-Wilk test. We report normally distributed results as mean ± SD, whereas non-normally distributed data are reported as median and interquartile range (IQR).

For group comparison when the distribution of scores was non-normal, we performed one-tailed Mann-Whitney tests and we report the rank-biserial correlation for effect size. When the distribution of scores was normal (comparison based on diet adherence in the classical PKU subgroup: the practical and overall impact of diet, the emotional impact of PKU domains), we ran independent *t*-tests and we report Cohen's D for effect size. We performed correlation analyses using Pearson's correlation test for normally distributed variables (Qol scores and Phe levels comparison: the practical and overall impact of diet, te emotional impact of PKU domains) and Spearman's rank correlation test for all other, non-normally distributed variables. We considered *P*-values under 0.05 significant.

The study followed the principles of the guidelines in the World Medical Association Declaration of Helsinki of 1975. The University of Semmelweis ethics committee approved the study (registration numberIF-2983-2/2017 ÁNTSZ). Patients participating in the study gave written informed consent.

3. Results

3.1. Descriptive results

We included a total of 88 patients, all of their blood Phe levels were available for the previous 10 years (Table 2). Distribution between females and males was balanced (46 female, 42 male). Median age was 31

Table 2
Baseline demographics and blood Phe measurements of patients according to disease severity. Tests are two-tailed, using independent samples *t*-test. Significance: $^*p < .001$. SD = standard deviation, IQR = (25th–75th percentile).

		Non-classical PKU (n = 22)	Classical PKU (n = 66)	All patients (N = 88)
Age	median, IQR (years)	30, 24–38	33, 26–41	31, 25–40
Gender	male (n)	7	35	42
	female (n)	15	31	46
Blood Phe last measurement	mean ± SD (μmol/l)	421 ± 175*	660 ± 236*	600 ± 236
Blood Phe last year	mean ± SD (μmol/l)	427 ± 176*	637 ± 198*	584 ± 212
Blood Phe last 10 years	mean ± SD (μmol/l)	441 ± 185*	636 ± 176*	588 ± 197

Table 3
Most severely affected domains among all patients. Median (25th–75th percentile).

Affected domains	Median (IQR)
Tiredness	50 (25–50)
Anxiety - Phe levels during pregnancy	50 (25–100)
Emotional impact of PKU	35 (15–50)
Taste - supplements	50 (25–50)
Guilt if poor adherence to supplements	25 (25–75)
Guilt if dietary protein restriction not followed	50 (25–75)

(25–40) years. Mean Phe over the last 10 years was 588 ± 197 μmol/l ranging from 122 to 1174. 66 of our patients (75%) had classical PKU, 12 (14%) had moderate, 6 (7%) had mild and 4 (5%) had HPA. In terms of their overall health status, 77% of the patients rated this as "good" or better. Median score for this domain was 50 (25–50). In the lifetime Phe group of 47 patients median age was 30 (25–37) years, 23 of the patients were male and 24 female, mean lifetime Phe was 543 ± 200 μmol/l.

In the total patient group, we found no domain with a median score reaching major or severe impact/frequent symptoms (median score bigger than 50). All domains with medians indicating moderate impact/symptom (median score: 26–50) are listed in Table 3. "Guilt if poor adherence to supplements" is also included because of the substantial number of patients with mayor impact. Median scores of all domains can be found in *additional file 1*.

In the symptom-associated modules, stomach aches (median, IQR [0, 0–25]), slow thinking (0, 0–25), trembling hands (0, 0–25), aggressiveness (0, 0–25) and sadness (0, 0–50) were the least often present. In the other modules, food enjoyment (0, 0–25), impact of supplements (0, 0–0), practical impact of supplements (0, 0–19), anxiety – blood tests (0, 0–25) and financial impact of PKU (0, 0–25) were the most spared domains.

3.2. QoL scores and Phe levels

When performing correlation analyses between blood Phe levels (1, 10-year mean, and actual levels) and HRQoL scores from 88 patients, we found that there is a weak to fair positive correlation in several domains, some of which were significant, correlations are detailed in Table 4.

3.3. "Good" vs. "Suboptimal" adherent groups

Mean Phe among the classical PKU patients was 636 ± 176 μmol/l ranging from 270 to 1174 and 30 (45%) patients were able to maintain a good diet adherence (mean Phe under 600 μmol/l) during the previous 10 years. In this time frame mean Phe level for "good adherence" group was 495 ± 98 μmol/l, whereas "suboptimal adherence" group's mean Phe level was 753 ± 137 μmol/l.

The number of good and suboptimal diet adherent patients did not fluctuate immensely based on examined time frames: of the 66 classical PKU patients: 27 kept a good diet right before the yearly clinician visit, 34 in the last year whereas 30 of them had mean Phe levels under 600 μmol/l during the examined 10 years.

When performing a subgroup analysis among the 66 patients with classical PKU, significant differences were found: the patient group with suboptimal diet adherence tended to have higher scores (meaning larger impact/symptom severity) than the group with good diet adherence.

The following domain impact scores were positively associated with phenylalanine levels both in the short (last measurement) and long term (last 10 years). Adherence to supplements (short term $p = .050$ and U = 421; long term $p = .021$ and U = 447), adherence to dietary protein restriction (short term $p = .003$ and U = 547; long term $p = .011$ and U = 529), anxiety about phenylalanine levels (short term $p = .006$ and U = 687; long term: p = .01 and U = 689).

Several differences were only significant when analyzing HRQoL differences based on actual therapy adherence (based on last phe measurement). Patients with good diet adherence at the time of filling out the questionnaire had lower (better) scores in: slow thinking ($p = .038$; U = 616, Rank-Biserial = 0.23), taste of low protein food ($p = .017$; U = 353; Rank-Biserial = 0.30), food temptation ($p = .045$; U = 570, Rank-Biserial = 0.25), practical impact of supplements ($p = .047$; U = 524, Rank-Biserial = 0.22), overall impact of dietary protein restriction ($p = .021$; $t = 2{,}08$; Cohen's D = 0.55), practical impact of dietary protein restriction ($p = .041$; $t = 1{,}77$; Cohen's D = 0.47).

Patients with long term good metabolic control achieved lower (better) HRQoL scores in the following domains: trembling hands (p = .021; U = 669; Rank-Biserial = 0.239), stomach aches ($p = .023$; U = 612; Rank-Biserial = 0.237), food enjoyment ($p = .019$; U = 541; Rank-Biserial = 0.293).

In the self rated health status domain ($p = .043$; U = 616; Rank-Biserial = 0.245) patients with a history of at least 10 years of good diet adherence reported better subjective health status compared to "suboptimal" adherent classical PKU patients whereas in short term there was no significant difference (Fig. 1).

All results in all examined time frames can be found in the additional files (See additional file 2).

Table 4
Correlation analysis of QoL scores and metabolic control. Tests are one-tailed, for positive correlation using Spearman test (except three domains). Alternative hypothesis states that there is a positive correlation between domain score (impact/ symptom severity) and Phe level in the examined time frames. Pearson's test was used in 3 cases because the pairs of variables follow a bivariate normal distribution in the population. Rs = Spearman's Rho, Rp = Pearson's Correlation. In bold p-value < .05. Significance: *$p < .05$; **$p < .01$

Domain name		Blood Phe last measurement	Blood Phe last year	Blood Phe last 10 years
Trembling hands	Rs	0.145	0.114	**0.213***
Taste - Low-protein food	Rs	**0.284****	**0.258***	0.172
Food temptation	Rs	0.173	**0.248***	0.161
Social impact of dietary protein restriction	Rs	**0.263***	**0.231***	**0.203***
Adherence to supplements	Rs	**0.235***	**0.290****	**0.344****
Adherence to dietary protein restriction	Rs	**0.264***	**0.350****	**0.268***
Practical impact of dietary protein restriction	Rp	**0.198***	**0.202***	0.17
Overall impact of dietary protein restriction	Rp	**0.265***	**0.252***	**0.228***
Anxiety - Phe levels	Rs	**0.186***	**0.209***	0.163
Practical impact of PKU	Rs	**0.253***	**0.210***	**0.219***
Overall impact of PKU	Rs	**0.203***	**0.206***	0.165
Emotional impact of PKU	Rp	**0.306****	**0.251***	0.172

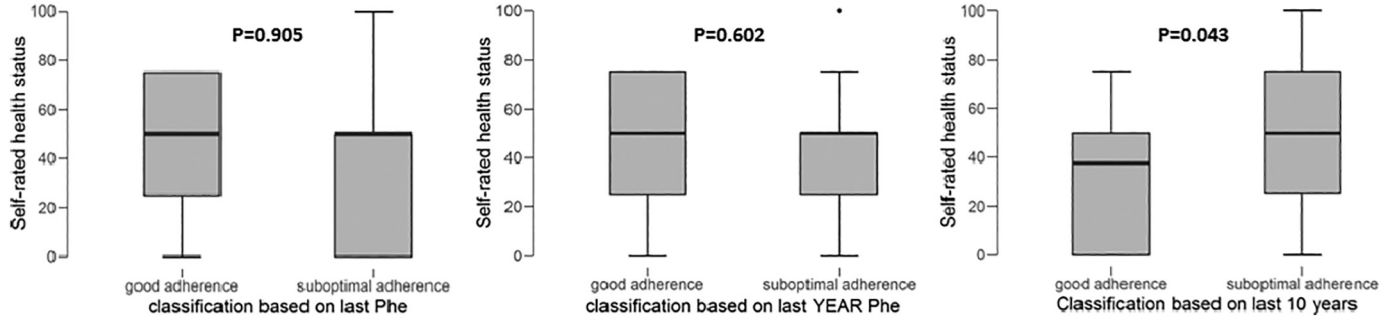

Fig. 1. Comparison of self-rated health status PKU-QoL scores related to diet adherence among classical PKU patients in different time frames. Higher scores mean worse self-rated health status. Boxplot presents the following: Interquartile range (Q1-Q3); −: Median; bottom and top bars: Observed minimum and maximum values; ○: Outliers. Tests are one-tailed Mann-Whitney tests. Significance: $p < .05$

3.4. QoL scores and lifetime Phe levels

Upon assessing the correlation between lifetime Phe levels and QoL scores in the "lifetime Phe" group we found a fair positive correlation in the trembling hands domain (Rs = 0.468, $p < .001$) and weak positive correlation (Rs = 0.291, $p = .025$) in the emotional impact of PKU domain.

3.5. Classical vs. Non-classical PKU group

We assessed the differences in QoL between the classical PKU (66 patients) and the non-classical PKU group. Except for the financial impact domain ($p = .039$; U = 840; Rank-Biserial = 0.231) no significant difference has been found between the two groups. Patients with classical PKU reported a larger impact of financial burden in conjunction with PKU.

4. Discussion

There are limited results available in the literature about the QoL of PKU patients using the validated PKU-QoL MAPI questionnaire. This may be for a number of reasons, including the rarity of the disease, the limited number of languages in which the questionnaires are available, and the novelty of the questionnaires. Although the European guideline (publicated in 2017) recommends using the PKU-QoL at least once in adult care by all patients [6], we found only one article using the PKU-QoL since then which targets the differences of QoL in the different age groups [34]. To the best of our knowledge, ours is the only study on this topic which has a similar patient number to the original study. We also assessed the consequences of inappropriate diet adherence as measured by blood Phe levels.

4.1. Results of the questionnaire

We found skewed distribution for responses for most PKU-QOL items; this finding is not surprising given the good general health of most patients. No median score reached major or severe impact/frequent symptoms (> 50). Most of our patients rated their health status as good or better (77%). This is slightly better than what Bosch et al. [18] reported (71%), however in most domains we found similar results.

The highest observed symptom score was tiredness whereas the highest impact scores were mostly related to the emotional impact and disease management (guilt if poor adherence to diet and supplements, emotional impact of PKU, anxiety – pregnancy). The most affected domain was anxiety regarding blood Phe levels during pregnancy. This reveals that our patients are aware of the risks to the fetus by non-controlled pregnancies. The taste of Phe-free AAS turned out to be a problematic domain for our patients too, which supports the well-known poor palatability of these products.

4.2. QoL scores and Phe levels

We found no strong correlation between metabolic control and PKU-QoL scores. In several domains weak to fair correlation was found. Patients who had greater Phe values either in the last 10 years or had increased lifetime Phe levels suffered from trembling hands more often. This symptom is a well-known neurological consequence of long-term elevated Phe levels [35,36].

In the module of dietary protein restriction: food temptation, taste of low protein food, adherence to diet, and impact scores of dietary protein restriction (social, emotional, practical) had weak to fair positive correlations with Phe levels either short or long-term. These findings may have several explanations, among others a major determinant for the burden of disease is tolerance to dietary phenylalanine [37]. Patients with lower Phe tolerance logically need more rigorous protein restriction to keep good metabolic control. Also, social environment and living conditions of the patient may be an influencing factor.

In terms of the PKU in general module, patients with higher short-term Phe levels were more anxious about their Phe levels, which further verifies that patients are aware of their diet non-adherence and this presents frustration. Overall and emotional impact of PKU (unfairness having PKU, worries about current and future children, disease acceptance, self-esteem) domains also showed a weak positive correlation in short term among all patients and had also greater impact on patients with higher lifetime Phe levels. It is possible that emotional difficulties may be related to the stress of living with a chronic disease rather than to high

levels of Phe [38].

Comparing classical and "non-classical" PKU patients significant difference in QoL was only shown in the financial impact of PKU domain. This finding is in line with the results of Bosch et al. [18].

4.3. "Optimal" vs. "Suboptimal" adherent groups

We aimed to examine how diet adherence affects HRQoL among patients with classical PKU. In these patients Phe tolerance is greatly impaired; a strict diet is needed to maintain good general condition. This is the first study to investigate the QoL differences between good and suboptimal diet adherent populations. Patients with suboptimal diet adherence had higher impact and symptom scores than patients with good diet adherence.

Among our patients, even those who were not able to maintain their blood Phe in the optimal range kept their diet at least partially (all of them attended metabolic care regularly, "suboptimal adherence" group's mean Phe level was 753 ± 137 μmol/l in the last 10 years). It is likely that QoL score differences in the modules of symptoms and disease impact would have been more unambiguous when compared to a population totally off-diet.

Classical PKU patients with suboptimal diet adherence both short- and long-term reported higher anxiety about their phenylalanine levels.

Patients who had therapy fallout proven immediately before the questionnaire reported higher food temptation, overall and practical impact of supplements (embarrassment taking supplements, lack of spontaneity, etc.) and practical impact of dietary protein restriction (difficulty eating out, burden of estimating quantity of protein, etc.). These findings are in line with earlier results from Bik-Multanowski et al., who concluded that some adult patients on relaxed diet suffer from severe emotional distress and returning to diet can increase quality of life by them [26].

Moreover, patients with suboptimal short-term diet adherence suffered from increased frequency of slow thinking. Interestingly, this finding was not significant based on the previous 10 years metabolic control. It is possible that patients with long-term suboptimal therapy are less aware of the minor changes regarding their cognitive function.

In the short term no significant difference was found between the two groups regarding self-reported health status, but after 10 years of good metabolic control patients had significantly better scores than those with long term suboptimal diet adherence. This outcome is in line with the results of Mutze et al. [30], who found that patients on diet had better scores in general life satisfaction than patients off diet.

Our findings suggest that good diet adherence by classical PKU patients is associated with better HRQoL. There are two ways to interpret these results: either we assume that good adherence leads to positive changes in life satisfaction or good subjective health status facilitates therapy adherence. Future research is needed to clarify the cause-effect relationship.

4.4. Limitations

We need to add that ceiling effect is detectable in HRQoL-results. Since it is a common problem in QoL questionaires, comparison of these results with alternative assesment methods are needed. In our study it is a limitation, that such an alternative method was not performed. As alternative methods one may use: reporting close family members, using structured interview by experts or patient generated indexes of QoL [39] [40]. Furthermore, organizing focus group meetings can provide a good forum to discuss individual or general needs while giving access to more patients [41].

Although the number of enrolled patients is relatively large compared to other QoL assessments in Phenylketonuria, a more robust patient population could enable us to detect even smaller differences among the subgroups and could prove or reject the minor correlations found between phenylalanine levels and QoL. As the developers of the PKU-QOL stressed, it is not possible to compare scores to a control group from the general population hence the questionnaire addresses issues which are relevant to PKU patients only [18].

5. Conclusion

This is the first study to assess the short- and long-term consequences of suboptimal diet adherence using the newly developed PKU-QoL questionnaire in adults. We conclude that the PKU-QoL questionnaire is a useful tool in evaluating the well-being of adult PKU patients. It is able to detect changes and therefore has the potential to improve patient care, although ceiling effect makes results harder to precisely assess. Our study demonstrates that suboptimal metabolic control is negatively associated with patients' HRQoL.

Classical PKU patients with good therapy adherence performed better in most domains, this indicates that monitoring HRQoL and maintaining good diet adherence are both key to improve outcome.

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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 governmental ethics committee approved the study (registration number: IF-2983-2/2017 ÁNTSZ). Patients participating in the study gave written informed consent.

Author statement

Contributors: AGB, CsSu and PR reviewed the literature and conceived the study. PR was in charge of overall direction and planning. CsSe, ZsT, EK and ES were involved in patient selection, sample and data collection. AGB interpreted the results and drafted the manuscript AGB, CsSe were involved in the statistical analysis. PR reviewed and edited the manuscript All authors discussed the results and contributed to the final manuscript.

Declaration of Competing Interest

The authors have no conflict of interest to report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2020.100589.

References

[1] M.I. Flydal, A. Martinez, Phenylalanine hydroxylase: function, structure, and regulation, IUBMB Life 65 (4) (2013) 341–349.
[2] J.G. Loeber, Neonatal screening in Europe; the situation in 2004, J. Inherit. Metab. Dis. 30 (4) (2007) 430–438.
[3] N. Blau, F.J. van Spronsen, H.L. Levy, Phenylketonuria, Lancet 376 (9750) (2010) 1417–1427.
[4] S.E. Waisbren, et al., Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis, Mol. Genet. Metab. 92 (1–2) (2007) 63–70.
[5] J. Vockley, et al., Phenylalanine hydroxylase deficiency: diagnosis and management guideline, Genet Med 16 (2) (2014) 188–200.
[6] A.M.J. van Wegberg, et al., The complete European guidelines on phenylketonuria: diagnosis and treatment, Orphanet J Rare Dis 12 (1) (2017) 162.
[7] E.L. Macleod, D.M. Ney, Nutritional Management of Phenylketonuria, Ann Nestle Eng 68 (2) (2010) 58–69.
[8] K. Ahring, et al., Blood phenylalanine control in phenylketonuria: a survey of 10 European centres, Eur. J. Clin. Nutr. 65 (2) (2011) 275–278.
[9] C. Bilginsoy, et al., Living with phenylketonuria: perspectives of patients and their families, J. Inherit. Metab. Dis. 28 (5) (2005) 639–649.
[10] R. Koch, et al., Phenylketonuria in adulthood: a collaborative study, J. Inherit. Metab. Dis. 25 (5) (2002) 333–346.
[11] J.J. Moyle, et al., Meta-analysis of neuropsychological symptoms of adolescents and adults with PKU, Neuropsychol. Rev. 17 (2) (2007) 91–101.
[12] A.E. ten Hoedt, et al., High phenylalanine levels directly affect mood and sustained attention in adults with phenylketonuria: a randomised, double-blind, placebo-controlled, crossover trial, J. Inherit. Metab. Dis. 34 (1) (2011) 165–171.
[13] G.M. Enns, et al., Suboptimal outcomes in patients with PKU treated early with diet alone: revisiting the evidence, Mol. Genet. Metab. 101 (2–3) (2010) 99–109.
[14] F.J. van Spronsen, P. Burgard, The truth of treating patients with phenylketonuria after childhood: the need for a new guideline, J. Inherit. Metab. Dis. 31 (6) (2008) 673–679.
[15] F.J. van Spronsen, A. Bélanger-Quintana, Outcomes of phenylketonuria with relevance to follow-up, J. Inherit. Metab. Dis. 1 (2011) 49–55.
[16] European Medicines Agency, Reflection paper on the regulatory guidance for the use of healthrelated quality of life (HRQL) measures in the evaluation of medicinal products, EMEA/CHMP/EWP/139391/2004. . 2005 [cited 2019 10.19.]; Available from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003637.pdf.
[17] A.P. Burlina, et al., The neurological and psychological phenotype of adult patients with early-treated phenylketonuria: a systematic review, J. Inherit. Metab. Dis. 42 (2) (2019) 209–219.
[18] A.M. Bosch, et al., Assessment of the impact of phenylketonuria and its treatment on quality of life of patients and parents from seven European countries, Orphanet Journal of Rare Dis 10 (2015).
[19] A.M. Bosch, et al., The course of life and quality of life of early and continuously treated Dutch patients with phenylketonuria, J. Inherit. Metab. Dis. 30 (1) (2007)

29–34.
[20] S. Channon, et al., Effects of dietary management of phenylketonuria on long-term cognitive outcome, Arch. Dis. Child. 92 (3) (2007) 213–218.
[21] C. Cazzorla, et al., Quality of Life (QoL) assessment in a cohort of patients with phenylketonuria, BMC Public Health 14 (2014).
[22] S. Channon, C. Mockler, P. Lee, Executive functioning and speed of processing in phenylketonuria, Neuropsychology 19 (5) (2005) 679–686.
[23] U. Mutze, et al., Transition of young adults with phenylketonuria from pediatric to adult care, J. Inherit. Metab. Dis. 34 (3) (2011) 701–709.
[24] E. Simon, et al., Evaluation of quality of life and description of the socio-demographic state in adolescent and young adult patients with phenylketonuria (PKU), Health Qual. Life Outcomes 6 (2008) 25.
[25] S. Demirdas, et al., Evaluation of quality of life in PKU before and after introducing tetrahydrobiopterin (BH4); a prospective multi-center cohort study, Mol. Genet. Metab. 110 (Suppl) (2013) S49–S56.
[26] M. Bik-Multanowski, et al., Quality of life in noncompliant adults with phenylketonuria after resumption of the diet, J. Inherit. Metab. Dis. 31 (Suppl. 2) (2008) S415–S418.
[27] D.L. Patrick, R.A. Deyo, Generic and disease-specific measures in assessing health status and quality of life, Med. Care 27 (3 Suppl) (1989) S217–S232.
[28] A. Regnault, et al., Development and psychometric validation of measures to assess the impact of phenylketonuria and its dietary treatment on patients' and parents' quality of life: the phenylketonuria - quality of life (PKU-QOL) questionnaires, Orphanet J Rare Dis 10 (2015).
[29] A.M. Das, et al., Dietary habits and metabolic control in adolescents and young adults with phenylketonuria: Self-imposed protein restriction may be harmful, JIMD Reports, 2014, pp. 149–158.
[30] U. Mütze, et al., Ten years of specialized adult care for phenylketonuria - A single-centre experience, Orphanet J. Rare Dis. 11 (1) (2016).
[31] R. Gassio, et al., Do adult patients with phenylketonuria improve their quality of life after introduction/resumption of a phenylalanine-restricted diet? Acta Paediatr. 92 (12) (2003) 1474–1478.
[32] E. Jurecki, et al., Development of the US English version of the phenylketonuria - quality of life (PKU-QOL) questionnaire, Health Qual. Life Outcomes 15 (1) (2017) 46.
[33] N. Blau, et al., Diagnosis, classification, and genetics of phenylketonuria and tetrahydrobiopterin (BH4) deficiencies, Mol. Genet. Metab. 104 (Suppl) (2011) S2–S9.
[34] I.M. Alptekin, et al., The impact of phenylketonuria on PKU patients' quality of life: using of the phenylketonuria-quality of life (PKU-QOL) questionnaires, Clin. Nutr. Espen 27 (2018) 79–85.
[35] B. Perez-Duenas, et al., Characterization of tremor in phenylketonuric patients, J. Neurol. 252 (11) (2005) 1328–1334.
[36] J. Pietz, et al., Neurological outcome in adult patients with early-treated phenylketonuria, Eur. J. Pediatr. 157 (10) (1998) 824–830.
[37] E.L. MacLeod, et al., Reassessment of phenylalanine tolerance in adults with phenylketonuria is needed as body mass changes, Mol. Genet. Metab. 98 (4) (2009) 331–337.
[38] F. Manti, et al., Psychiatric disorders in adolescent and young adult patients with phenylketonuria, Mol. Genet. Metab. 117 (1) (2016) 12–18.
[39] D.A. Ruta, et al., A new approach to the measurement of quality of life. The Patient-Generated Index, Med Care 32 (11) (1994) 1109–1126.
[40] C.R. Spiroch, et al., Ask the patient: A semi-structured interview study of quality of life in advanced cancer, Am. J. Hospice Palliative Med. 17 (4) (2000) 235–240.
[41] L. Borghi, et al., The PKU & ME study: a qualitative exploration, through co-creative sessions, of attitudes and experience of the disease among adults with phenylketonuria in Italy, Mol Genet Metab Rep 23 (2020) 100585.