

REGULAR ARTICLE

## Adherence to diet and quality of life in patients with phenylketonuria

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### ABSTRACT

**Aim:** To investigate adherence to dietary treatment and quality of life (QoL) in patients with phenylketonuria (PKU).

**Methods:** In the setting of a tertiary paediatric hospital, 41 early-treated patients affected by PKU aged more than 3 years old were enrolled in a cross-sectional study. Three-days dietary assessment, QoL questionnaires for patients <18 years old (Child Health Questionnaire) and Short Form for adults were completed.

**Results:** Of 41 patients, 23 (56.1%) were considered adherent to the dietary prescriptions as their phenylalanine intake was less than prescribed. Phenylalanine intake was significantly in excess of prescribed if mothers had a lower level of education. Adherence was not correlated with age. Metabolic control was obtained in 41.5–51.2% of the patients depending on the target. QoL was reduced in children and adolescents. There was no significant correlation between adherence and QoL, except for the domains of Global Health and Family Activities ( $\rho = 0.42$  and  $0.46$ , respectively). The overall agreement between adherence and metabolic control varied according to different targets of metabolic control (51.2–65.9%).

**Conclusions:** It is necessary to improve the adherence to diet and the QoL in children and adolescents affected by PKU.

Phenylketonuria (PKU; OMIM 261600) is a rare, inherited metabolic disease requiring strict diet control after early diagnosis, presently obtained through neonatal screening. Mutations in the gene coding for phenylalanine hydroxylase cause a deficit in the conversion of phenylalanine (Phe), an essential amino acid, to tyrosine. The accumulation of Phe in the central nervous system leads to severe mental retardation. Presently, the cornerstone of treatment is a low Phe diet, which allows normal development.

Blood levels of Phe are reported to be a marker of compliance (1–5), or adherence (6,7), even though it actually represents only the biological outcome, and therefore, it can be considered only a surrogate. The term 'adherence' is presently preferred to 'compliance' as it underlines the partnership with healthcare workers and includes the wide range of interventions in chronic diseases; it has been defined as 'the extent to which a person's behaviour-taking

medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a healthcare provider' (8).

It must be taken into account that the biological outcome, namely the plasma level of Phe, depends on many factors (9), including the dietary prescription and actual Phe intake, the phenotype and intercurrent diseases. Finally, a definite level of Phe restriction is lacking (10), and targets of blood Phe vary from country to country but also within countries (11,12) so that a patient can be considered adherent in one centre and nonadherent in another. Targets for blood Phe levels are defined for different age bands, set at 10 years in France, at 10 and 15 years in Germany and at 5 and

### Abbreviations

IQR, inter-quartile range; Phe, phenylalanine; PKU, phenylketonuria; QoL, quality of Life; SD, standard deviation.

### Key notes

- About half of the patients affected by phenylketonuria adhere with dietary prescriptions.
- Adherence does not necessarily agree with suggested metabolic control.
- Quality of Life is significantly reduced in children and adolescents.

**Table 1** Recommended Phe levels by country

	$\mu\text{mol/L}$	mg/dL
France		
0–10 years	120–420	2–7
>10 years	<1200–1500	<20–25
Germany		
<10 years	40–240	0.7–4.0
10–15 years	40–900	0.7–15.0
>15 years	40–1200	0.7–20.0
United Kingdom		
0–5 years	120–360	2.0–6.0
6–16 years	120–480	2.0–8.0
>16 years	120–700	2.0–11.7

16 years in England, with lower levels in the latter country [Table 1 (11)].

Adherence has also been investigated using questionnaires (2,9,13,14) with questions differing from country to country; these questionnaires were self-completed and could be biased for the purpose of the patients to show their adherence to instructions of healthcare workers rather than to indicate clearly their problems with various aspects of the treatment.

Recently, another outcome, health-related Quality of Life (QoL), has widened the spectrum of biomedical outcomes to include many aspects of psychological functioning, particularly relevant in adolescent patients suffering from chronic conditions (15). The construct of QoL is a multidimensional measure of functioning, including domains addressing physical functioning, symptoms, emotional status and social relationships. It analyses the outcomes from the patient's point of view rather than the physician's one, considering the patients' subjective assessment of the impact of dysfunction associated with the illness, but with limitations because of medical treatment too.

The same QoL of healthy populations has been observed both in Dutch and in German PKU adults (16,17) as in children and adolescents (18) but only 55% of adults in a multicenter Polish study (4) reported a positive well-being.

We hypothesized that adherence to diet could be related to the QoL, especially in adolescents and young adults, an issue not yet explored.

The aims of the present study were to assess adherence to dietary prescriptions and QoL in patients with PKU. Another objective was to assess the achievement of Phe target levels.

**PATIENTS AND METHODS**

A cross-sectional design was adopted. Patients registered in the database of PKU patients of the Division of Metabolic Disease of the Bambino Gesù Children's Hospital were included if they were more than 3 years old, not mentally retarded, and in follow-up.

One patient was excluded for severe mental handicap (late diagnosis) and three foreign patients who returned to their countries of origin (one severely handicapped, two after single consultations) were also excluded.

Dietary assessment was made by reviewing the 3-day food record that patients or their families routinely keep before the hospital follow-up consultation; these records were analysed by a dietitian (RN), who calculated the intake of Phe and other nutrients following the Italian food composition (19). Phe intake was also compared with Blau's (20) recommendations, which take the patient's age into consideration.

Adherence to dietary prescriptions was measured by calculating the difference between Phe dietary intake and prescription: a negative value indicates how much Phe less than the prescribed amount has been assumed by the patient, and a positive value indicates how much more than the prescribed amount has been assumed. Deviations were also calculated from prescription as percentage, dividing the differences by the prescribed Phe and multiplying by 100.

Phe intake was established based on the age of the patient, type of PKU (classic or mild) and individual tolerance, defined as the maximum amount of Phe that can be assumed without exceeding the recommended Phe levels, as deduced from previous controls. Plasmatic Phe levels, namely the single values concurrent to QoL assessment, were compared to recommendations of three European countries (Table 1).

Patients received a prescription of a low Phe diet, Phe-free protein substitutes, long-chain polyunsaturated fatty acids (LC-PUFAs) and vitamins.

Phe was measured using reversed-phase high-performance liquid chromatography (HPLC); the method involves precolumn derivatization. The analytical system used is the Agilent 1100 HPLC including autosampler, binary pump and fluorescence detector (Agilent Technologies 1200 Series, Waldbronn, Germany).

The samples in EDTA were centrifuged and the supernatant filtered, with the internal standard (norvaline), then applied in the column and separated by gradient of two mobile phases. Fluorescence detection was used.

QoL was assessed using the Child Health Questionnaire (CHQ), translated into Italian (21), and the CHQ-PF 50 version for parents. Briefly, it is a self-administered questionnaire devised to describe the physical, emotional and social well-being of children and adolescents 5–18 years old, comprising 50 questions using 4-point or 5-point Likert scales: very limited, partially limited, slightly limited, not at all for physical functioning domains, and always, often, sometimes, seldom, never for psychosocial functioning domains. It includes 15 health concepts (higher scores indicate better QoL), and two summary measures: the Physical and the Psychosocial summary scores.

In patients >18 years old, QoL was assessed with the SF-36 questionnaire, a self-administered questionnaire containing 36 questions and eight domains, translated into Italian (22). Higher scores indicate better QoL. Our results were compared with those of an Italian reference population 18–24 years old (23).

Scores of both questionnaires were standardized to a 0–100 points scale (T values), to allow comparison of scores across the different domains. Standardized T values range from 0 to 100 [mean 50, standard deviation (SD) 10].

**Table 2** Dietary adherence to prescription by age, sex, type and mother's educational level

	Adherent n (%)	Not adherent n (%)	Total n (%)	p
Sex				
M	14 (56.0)	11 (44.0)	25 (100)	1
F	9 (56.3)	7 (43.8)	16 (100)	
Age				
<10 years	13 (54.2)	11 (45.8)	24 (100)	0.8
>10 years	10 (58.8)	7 (41.2)	17 (100)	
Educational level (mother)				
Higher (>8 years)	18 (62.1)	11 (37.9)	29 (100)	0.2
Lower (≤8 years)	5 (41.7)	7 (58.3)	12 (100)	
Type				
I 'classic PKU'	15 (50.0)	15 (50.0)	30 (100)	0.3
II 'mild PKU'	8 (72.7)	3 (27.3)	11 (100)	
Total	23 (56.1)	18 (43.9)	41 (100)	

PKU, phenylketonuria.

Intelligence quotients were assessed with Wechsler scales, appropriate for ages (24,25).

### Statistical analysis

Data were first tested for normal distribution; comparisons between means were performed with Student's *t*-test and comparisons between medians with the Mann-Whitney nonparametric test. Correlation was calculated with Pearson's *r* or Spearman's  $\rho$  as required. Categorical data were compared with chi-square or Fisher's exact test. SPSS software (13.0, SPSS Italia srl, Bologna, Italy) was used and a  $p < 0.05$  considered statistically significant. Informed consent was requested from the adult patients or from the parents if the patient was <18 years old. The ethical board of the hospital approved the research.

### RESULTS

A total of 41 patients were consecutively enrolled, 25 males and 16 females, mean age was 10 years 7 months (median 8 years, SD 6 months, range 3–24 years), affected by 'classic' PKU (type I, 30 patients, 73.2%) or by 'mild' PKU (11 patients, 26.8%). They were diagnosed by neonatal

screening, and means of intelligence quotients scored higher than 90 in the full scale, verbal and performance scales.

Median prescribed Phe was 500 mg [Inter-quartile range (IQR) 370–850] and median intake 502 mg (IQR 372–955). As expected, both were significantly higher in adolescents and young adult patients than in children. The median of these differences (Phe intake minus prescribed) that represents our continuous measure of adherence was  $-23$  (IQR  $-101$  to  $115$  mg), a median deviation of  $-2.2\%$  from prescription (IQR  $-16.4$  to  $21.8$ ).

The majority of patients were adherent to the diet, i.e. showed a nutritional Phe intake lower than that prescribed, with a higher proportion among offspring of mothers with a higher level of education and among patients with 'mild' PKU, even if statistical significance was not reached (Table 2).

When we took into consideration the continuous measures of adherence, i.e. the quantity or the excess of Phe with respect to the prescription, the children who had mothers with a lower educational level showed a significant excess compared to those whose mothers had a higher level (median  $158$  mg vs.  $-36$  mg, respectively,  $p = 0.045$ ), while no difference was found between the two groups taking into consideration the fathers' education (median  $-35.5$  vs.  $-2.00$ ,  $p = 0.9$ ). There was no correlation with age ( $\rho = 0.03$ ,  $p = 0.8$ ).

Adherent patients showed a deficit of Phe intake over prescribed of  $-72$  mg (median, IQR  $-171$  to  $-36$ ,  $-11.3\%$ ) and nonadherent ones an excess of  $171$  mg (median, IQR  $45$ – $387$ ,  $p < 0.001$ ,  $23.0\%$ ).

When we evaluated the metabolic control, our results varied, as expected, across different international targets, showing a satisfactory metabolic control ranging from 36.6% of the English target to 48.8% of the French one. A significant association between adherence and achievement of the target could only be demonstrated for the English standards; age >10 years was the only variable significantly associated with an optimal control of the disease, independent of the level of the targeted blood Phe (Table 3).

It should be emphasized that agreement between adherence and an optimal metabolic control was suboptimal because the two categories were concordant (i.e. Phe target

**Table 3** Metabolic control by Phe target, age, sex and phenylketonuria type: number (%)

Phe target	Adherence		p	Age (years)		p	Sex		p	Type		p
	Yes	No		<10	>10		M	F		I	II	
French												
Achieved	13 (56.5)	7 (38.9)	0.4	4 (16.7)	16 (94.1)	0.001	12 (48.0)	8 (50.0)	1	15 (50.0)	5 (45.5)	1
Not achieved	10 (43.5)	11 (61.1)		20 (83.3)	1 (5.9)		13 (52.0)	8 (50.0)		15 (50.0)	6 (54.5)	
English												
Achieved	12 (80.0)	3 (20.0)	0.04	5 (20.8)	10 (58.8)	0.03	10 (40.0)	5 (31.2)	0.8	8 (26.7)	7 (63.6)	0.06
Not achieved	11 (42.3)	15 (57.7)		19 (79.2)	7 (41.2)		15 (60.0)	11 (68.8)		22 (73.3)	4 (36.4)	
German												
Achieved	10 (43.5)	7 (38.9)	1	1 (4.2)	16 (94.1)	0.001	10 (40.0)	7 (43.8)	1	14 (46.7)	3 (27.3)	0.3
Not achieved	13 (56.5)	11 (61.1)		23 (95.8)	1 (5.9)		15 (60.0)	9 (56.2)		16 (66.7)	8 (72.7)	
Total	23 (100)	18 (100)		24 (100)	17 (100)		25 (100)	16 (100)		30 (100)	11 (100)	

**Table 4** Quality of Life scores (mean and standard deviation) in phenylketonuria patients compared with a reference population (Child Health Questionnaire)

	Reference (n = 788)	Patients (n = 32)	p
Physical functioning summary score	54.5 (4.3)	45.5 (9.7)	<0.001
Psychological summary score	51.2 (7.7)	47.1 (7.2)	0.002
Global health	85.4 (16.1)	76.7 (23.6)	0.003
Physical functioning	96.7 (11.9)	90.8 (18.1)	0.006
Role social limitation-emotional	95.8 (15.0)	90.5 (22.2)	0.049
Role social limitation – physical	95.3 (15.5)	87.7 (24.4)	0.007
body pain	88.3 (17.0)	86.5 (16.3)	0.6
Behavior	81.2 (14.3)	75.1 (15.1)	0.02
Global behavior	80.1 (18.6)	76.8 (19.3)	0.2
Mental health	74.9 (15.8)	65.9 (14.6)	<0.001
Self-esteem	78.0 (16.4)	79.8 (13.3)	0.8
General health perception	78.5 (18.3)	74.3 (15.8)	0.1
Parental impact-emotional	76.5 (24.2)	64.7 (23.9)	0.006
Parental impact–time	92.1 (17.9)	82.1 (25.4)	0.002
Family activities	91.8 (13.1)	82.3 (20.0)	<0.001
Family cohesion	73.2 (22.2)	70.7 (20.0)	0.4

– Achieved with Adherence – Yes, and, conversely, Phe target – Not achieved with Adherence – No) only in 51.2–65.9% of the patients, depending on the different standards adopted. No association of achievement of an optimal Phe level was found with sex and PKU type (Table 3).

Nonadherent patients showed a significant excess of ingested over recommended Phe in comparison with adherent patients (median 18.5, IQR –283.0 to 128.0 mg vs. –64 mg, IQR –27.0 to 792.8,  $p = 0.008$ ).

As regards the QoL of patients, we found lower scores in comparison with a published reference Italian population (20) in both the summary measures (Physical and Psychological summary scores) and in most of the single domains, referring either to the patient or to the family (Table 4).

Significant correlations were found between adherence and both Global Health ( $\rho = 0.42$ ,  $p = 0.02$ ) and Family Activities ( $\rho = 0.46$ ,  $p = 0.008$ ), while only marginally significance was found for Global Behavior ( $\rho = 0.32$ ,  $p = 0.07$ ). It should be noted that the positive correlation means that, as the Phe intake increases in excess of prescription, so the QoL increases (and vice versa). No correlation was found between adherence and the two summary measures (Physical Functioning and Psychological score) or between adherence and the single domains.

Significantly lower scores were observed among adolescents compared to younger patients for two family domains: Family Cohesion (64.9 vs. 86.5,  $p = 0.04$ ) and Parental Impact–time (52.5 vs. 75.6,  $p = 0.03$ ); no other difference was observed for age and for type and sex (data not shown). Conversely, when exploring the QoL of adult patients, we found no significant difference in comparison with the reference population (data not shown).

**DISCUSSION**

We found an adherence to dietary prescriptions slightly in excess of 50%, similar to that commonly reported for

adherence to drugs (8). A lower than normal QoL was found in patients <18 years old, while in the group of young adults, with a different instrument, QoL was normal.

As expected, a better adherence was observed with a high level of education of the mother (26), which could suggest the possibility of specific intervention directed towards less educated families, but the observation could also be related to the overall social condition, which is a rather difficult factor to change at the level of the single family.

The higher adherence among patients with mild PKU was also to be expected, as prescription obviously takes into account the severity of the metabolic deficiency; however, it was not possible to demonstrate a significant association, probably due to the limited size of our group. Adherence of adolescents has been explored in previous studies: 23% of them reported that preparation of food was too time-consuming, and two-thirds needed to make a considerable effort to comply with the diet (13). Our results did not show any correlation between adherence and age, and adolescents seem not to be at particular risk of nonadherence.

Different targets for Phe blood level to be considered appropriate mean different conclusions about their effective achievement, but in our series, the proportion of Phe targets reached was <50%, whatever the target. Achievement of appropriate Phe levels has been reported to decrease with increasing age in a study performed in one Australian and three English centres: concentrations above the upper recommended limits were measured in 28% of infants, in 50% of patients in early adolescence and 79% of late adolescents (15–19 years old) (27). We found an opposite result when we split our group of patients into two age categories, i.e. children and adolescents and young adults, whatever the target. As adherence is very similar in these two age groups, alternative explanations could include different dietary approaches, possibly connected with different school meals.

When we tested the association between adherence and metabolic control, expressed by plasmatic Phe levels, we found a significant association only for the English standards. The two categories showed disagreement, casting some doubt about the use of Phe levels to express adherence; to our knowledge, this issue has not been investigated, possibly because of overconfidence concerning laboratory examinations and/or difficulties in gathering and analysing food records.

We found that adherence decreases as Global Health, Family Activities and Global Behavior increase, but, due to the cross-sectional design of our study, we cannot be sure about cause–effect relationship, in other words whether a better perception of these domains of QoL decreases adherence or, conversely, a relaxed adherence to diet ameliorates these aspects.

To our knowledge, our findings about QoL of our children and adolescents are comparable only with those of a Swiss survey (18) [mean age 10.9 years, range 3.1–18.0 years), which found a normal QoL, except for the domain of global-positive emotional functioning; however, this study used a different instrument to measure QoL.

Furthermore, the Swiss results were obtained in a central European country, as opposed to a Mediterranean country like Italy.

A comparison of QoL with another chronic condition in the same culture using the same instrument can be performed taking in consideration the findings in children and adolescents affected by juvenile idiopathic arthritis: in an Italian survey, the Physical Functioning and Psychological summary scores were better only in the group with persistent oligoarthritis (49.6 and 49.8, respectively). Physical Functioning, Role/Social Limitation-emotional, Body pain and General Health Perception scored worse in all groups, including those with systemic or polyarticular onset and extended oligoarthritis (21); similar findings were observed about Body pain and General Health Perception when patients with the same disease were studied from 32 European countries (28). Our results showed lower scores for Parental Impact and Family Cohesion and confirm the findings of an American study (29).

Two studies reported a better QoL among adults on diet than off diet (4,30) but these results cannot be extrapolated to children and adolescents on diet, whether adherent or not.

In conclusion, there is room for improvement of adherence to diet, particularly if the patient's parents have a lower level of education. QoL in children and adolescents is reduced, but few domains (Global Health, Family Activities and Global Behavior) seem to be related to adherence, and improvement can be looked for without fear of compromising QoL.

The relationship between adherence and a satisfactory plasmatic Phe level is inconsistent across standards of different countries and its use as an indicator of adherence should be questioned. Whatever the target, metabolic control is only achieved by <50% of patients.

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