Review Article

Quality of Life in Patients with Phenylketonuria: A Systematic Review

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Abstract

The impact of phenylketonuria (PKU) on Quality of life (QoL) has been a topic of interest in recent research. This article reviews current researches on the impact of PKU on QoL. The review examines factors that may influence QoL, such as age, metabolic control, and treatment adherence. In this systematic review study, relevant articles were identified using a search strategy built with the keywords phenylketonuria, PKU, or hyperphenylalaninemia (or their synonyms) and QoL in Web of Science, Scopus, and PubMed databases. After identifying the articles, duplicates, reviews, scientific abstracts, articles published in languages other than English, and non relevant studies were excluded. The search strategy identified 951 records from databases, and after excluding duplicates, irrelevant studies, and those published in non English languages, 26 records were left that contained data on 1816 patients with PKU/hyperphenylalaninemia. The studies included both children/adolescents and adults. Overall, the studies found that the QoL of PKU patients was comparable to normative data, but some aspects such as emotional health and school functioning were lower. Metabolic control was found to significantly correlate with QoL. Younger patients and men had better QoL in several studies, while late treated patients and those with lower education had worse outcomes. It is concluded that QOL in patients with PKU is similar to the general population. However, given the chronic nature of the condition, it is important to pay special attention to their QoL. Poor QOL is associated with female gender, lower education, older age, and poor metabolic control.

Keywords: Phenylketonuria, quality of life, systematic review

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Introduction

Phenylketonuria (PKU) is an uncommon genetic disorder caused by a deficiency of phenylalanine hydroxylase, which impairs the body's ability to metabolize phenylalanine. If untreated, PKU can result in serious neurological problems, seizures, and intellectual disability. Nevertheless, timely diagnosis and treatment can enable many PKU patients to live healthy and fulfilling lives.[1] Newborn screening programs for this inherited metabolic condition were first introduced in Europe and the USA during the 1960s.[2]

Although protein restriction is the primary treatment for PKU, assessing treatment efficacy based solely on metabolic control may not be sufficient due to the chronic nature of the disease and the required treatment. Patients with PKU must adhere to a lifelong low-phenylalanine diet to maintain normal blood phenylalanine levels, but compliance with treatment often decreases after childhood. Even with adequate treatment, individuals with PKU still exhibit some degree of intellectual impairment compared to healthy individuals.[3-5]

Due to the chronic and demanding nature of PKU and the need for ongoing care to prevent complications, individuals with PKU may experience a reduced quality of life (QoL).[6] As a result, an essential aspect of living with PKU is the QoL that the patient experiences. In recent years, there has been growing interest in understanding the impact of PKU on patients' QoL. QoL is a multidimensional concept that

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encompasses physical, psychological, and social well-being. Assessing QoL in patients with PKU can provide valuable insights into the burden of the disease and help identify areas where interventions may need to improve patient outcomes.[7]

Several studies conducted to explore the QoL of patients with PKU; however, the findings are inconsistent. Some studies have reported that patients with PKU have lower QoL scores compared to healthy controls,[6-9] while others have found no significant differences in QoL between patients with PKU and controls.[10-13] These controversial results highlight the need for a systematic review of the literature to synthesize the available evidence and provide a more comprehensive understanding of the impact of PKU on QoL.

The purpose of this paper is to conduct a systematic review of the literature on the QoL in individuals with PKU. We will specifically examine the methods used to evaluate QoL and the various factors that can affect it, such as dietary restrictions, social support, and access to medical care. By providing a comprehensive analysis of the available evidence, this review will enable healthcare providers to offer support that is more effective to PKU patients and promote their optimal QoL and well-being. Moreover, this review could also guide future research on QoL in individuals with PKU.

Materials and Methods

The study was conducted as a systematic review following the 2020 guideline of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). This study was conducted between May and June 2023 to investigate whether health-related QoL is impacted in patients with PKU due to the disease and its complications. To achieve this, a search was conducted through international databases for all studies that reported aspects of QoL in patients with PKU or hyperphenylalaninemia.

Search strategy

A systematic search of electronic databases including Web of Science, Scopus, and PubMed was conducted. The search was limited to studies published in the English language from January 2000 to June 2023. A combination of keywords and medical subject headings (MeSH) terms related to PKU and QoL such as PKU, hyperphenylalaninemia, QoL, health-related QoL, and their synonyms were used. The search strategy was modified according to the guidelines in each database [Appendix 1]. The reference lists of eligible studies were also evaluated to identify additional relevant articles.

Eligibility criteria

English language studies that evaluate QoL in individuals with PKU using validated QoL instruments or self-reported measures were included. Studies that focus on other metabolic disorders or those that do not report QoL outcomes were not included. Studies must have been published in peer-reviewed journals. Studies published before the year 2000 were excluded, as were scientific abstracts, guidelines, reviews, editorials, case reports, retracted articles, and articles with full texts in other languages.

Study selection and data extraction

Two independent reviewers screened the titles and abstracts of all identified studies for eligibility. Full-text articles were obtained for all potentially eligible studies and reviewed for inclusion and data extraction. Non-relevant articles based on the full text were ignored. Articles not related to PKU or those in which the QoL was not reported were excluded. Qualitative studies, validity studies, and interventional studies in which the baseline QoL of the PKU patients was not reported were also excluded. The study selection process is shown in Figure 1. Finally, eligible studies underwent further review and data extraction.

Data were extracted using a standardized data extraction form, including study characteristics, participant demographics, QoL assessment tools, and results.

Quality assessment

The quality of the included studies was assessed using Newcastle-Ottawa Scale for observational studies. Any discrepancies between reviewers are resolved through discussion and consensus.

Results

Out of 951 records retrieved, 318 were duplicates. After removing the duplicates, 24 articles published before 2000 were ignored. Non-relevant articles, conference abstracts, and articles published in languages other than English were also excluded. After removing articles based on the abstract, 109 records remained and were sought for retrieval and review. However, 83 articles were excluded due to reasons listed in Figure 1, and only 26 remained [Table 1].

Of the remaining articles, 20 were from European countries,[8,10-28] one from Australia,[9] one from Brazil,[6] one from Iran,[7] one from the USA,[29] one from New Zealand[30], and one from Egypt.[1]

The total number of patients included was 1804, with 932 females. Children and adolescents were reported in ten studies,[1,6,9,14,15,17,22,25,27,30] while ten studies only included adults.[7,10,11,13,16,18-20,26,28] Six studies included both adults and children.[8,12,21,23,24,29]

Table 1 displays the SF-36, pediatric quality of life inventory (PedsQL), TNO-AZL, and World Health Organization QoL questionnaire as commonly used questionnaires. In German studies, pediatric patients were often assessed using KINDL. The table also includes information on the degree of metabolic control and disease severity, if mentioned.

Some studies have found a significant relationship between the degree of metabolic control and QoL.[13,15,22-24,30] Younger patients generally had better outcomes compared to older patients,[1,10,17] while late-treated patients had worse outcomes.[7] A study in Turkey reported worse outcomes for children.[8]

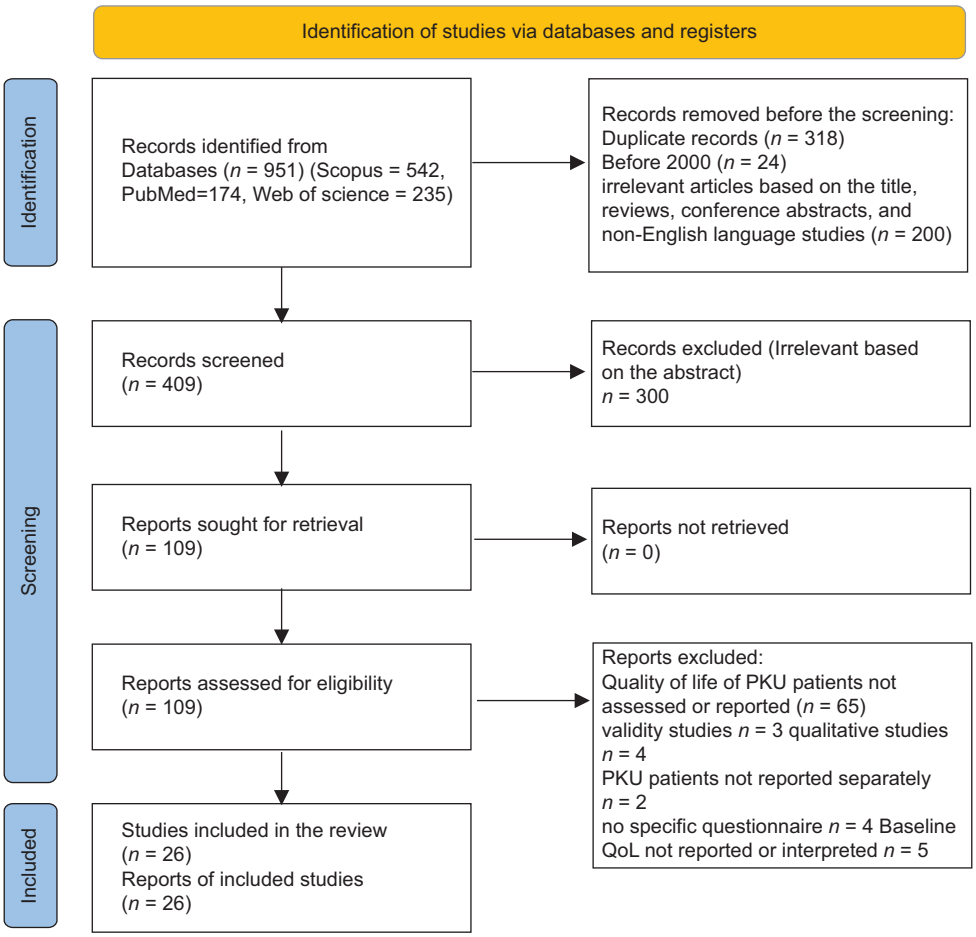

Figure 1: Study selection flowchart

Women tended to have poorer QoL.[10,23,28] In Brazil, a study using the PedsQL revealed that patients had significantly lower scores compared to controls.[6] Another study showed that PKU patients received more special education during primary school.[19]

An adult study found that PKU patients displayed more anxious relationship styles, and partial adherence was associated with lower mental and physical QoL scores.[16] In the Netherlands, a study showed that children had lower autonomy, cognition, and positive emotions scores, while adolescents had lower scores across all domains compared to controls.[23] Another study found that children aged 8–12 reported higher physical functioning scores, while those aged 13–17 had higher scores on total and psychosocial functioning in the PedsQL. Adult patients reported lower scores in the TAAQOL cognitive domain. Mothers of children aged 5–7 also reported a trend towards lower HRQoL scores on the "school and social functioning" scales.[21]

Discussion

This systematic review aimed to investigate the QoL in patients with PKU or hyperphenylalaninemia. The majority of the articles included in the data extraction were conducted in European countries, with only a few outside Europe. The results of the review showed that despite the negative impact of PKU on QoL particularly in terms of social functioning, psychological well-being, and physical health, the studies generally reported an acceptable QoL in patients with high blood phenylalanine levels, whether they had classical PKU requiring lifelong treatment and dietary restrictions or hyperphenylalaninemia.

Adolescents with poor treatment adherence were found to report more symptoms, while those with better adherence had lower enjoyment of food.[15] Some studies have reported lower health-related QoL scores in PKU patients.[6,23,30]

One study conducted in seven European countries found that, except for social functioning, the results for children were comparable to normative data.[12] Mental functioning according to SF-36 scores was slightly worse in adults with PKU, and tiredness was the highest symptom score reported by patients. The emotional impact of PKU and its management, anxiety about blood phenylalanine levels, and guilt related to poor adherence to dietary restrictions or Phe-free amino acid supplement intake had the highest PKU-QOL impact scores.

There was no clear association between the severity of PKU and symptoms, but a consistent pattern emerged regarding the

Table 1: Quality of life data in Patients with PKU

Name of author, country, year of study	Number of PKU patients	Age (mean, (SD)) and sex	Questionnaire	Metabolic control status/disease severity	QoL
Landolt *et al.*,[25] Switzerland, 2001 (publication year)	37	10.9 (4.3) years (3-18 years), 18 female, 19 male	TNO-AZL Questionnaire for Children's Health-Related QoL	Phenylalanine level: In the first year of life 264 (97) µmol/L (mean (SD)), 331 (169) µmol/L (mean (SD)) during the preceding 12 months	PKU patients had a reduction in positive emotions but similar to reference values in most other aspects of QoL. Phe during the preceding 12 months did not have any association with the QoL but higher Phe levels during the first year of life had a long-term negative impact on some dimensions and the average level of blood Phe during the first year of life was found to be a significant predictor of psychological adjustment and some dimensions of health-related QoL. Sex, socioeconomic condition, and family situation did not have any significant correlation with TACQOL. The age of the child also didn't correlate to measures of QoL.
Simon *et al.*,[10] Germany, July 2003	67	Median (range) 25 years (17-38)	Profile of QoL in the Chronically Ill (PLC) questionnaire		The self-assessed QoL was not significantly different from the control group. Patients over 25 years old reported more PKU-specific symptoms. Women reported lower levels of positive mood and psychological functioning, but higher scores in the "social well-being" category (p-values were above 0.001, Bonferroni corrected).
Channon *et al.*,[11] the UK, 2005 (publication year)	25	26.68 (4.92) years (18-33) 12 female, 13 male	SF-36	Phenylalanine level: Concurrent (n=24) mean (SD) 758.79 (261.27) range 221.00–1,233.00 Recent Phe level mean (SD) 797.62 (240.80) range 283.40–1,153.00 Disease severity: 24 classical, 1 atypical PKU	SF-36 Mental category 51.58 (6.97) (mean, SD) SF-36 Physical category 56.48 (4.17) (no significant difference with the healthy group).
Bosch *et al.*,[19] the Netherlands, 2007 (publication year)	32	24.6 (3.6) years (18 to 30 years) old, 22 female, 10 male	the Course of Life questionnaire, SF-36, and the cognitive scale of the TNO-AZL Adult QoL (TAAQoL)	Phenylalanine level: Mean 1801 µmol/L (range 480–3636 µmol/L) (at birth, n=19)	PKU patients had similar results to the control group although a higher number of PKU patients received special education in primary school. There were no significant differences between PKU patients and the control group in any of the QoL scales. There were no significant differences between PKU patients and their peers on the TAAQoL cognition scale.
Mütze *et al.*,[28] Germany, 2005 to 2008	48	Above 18 years of age, 26 female, 22 male	Questions on Life Satisfaction - module (general module)	Phenylalanine level: median (range) 690 (109-1325) µmol/L (adulthood), median (range) 853 (230-2136) (Childhood)	The average QoL score for the study group was 64.4±35.0, with men (n=20) having a score of 67.3±30.4 and women (n=26) having a score of 62.2±38.7. The QoL for the study group (n=46) was similar to the average QoL score for the German population. Men reported a better QoL.
Thimm *et al.*,[22] Germany, May 2008 to May 2009	50	median age 9.9 years, 32 female, 18 male	KINDL-R questionnaire, Strengths and Difficulties Questionnaire	In 7–9-year-old children, there is a trend towards worsening metabolic control as only 33% of phenylalanine concentrations are in the desired range. However, 62% of phenylalanine concentrations are within the recommended range.	QoL did not differ significantly between PKU patients and healthy peers in the total score, but parents of PKU patients rated school or nursery school functioning significantly lower. Adherence to target Phe concentrations improved significantly above 10 years old. A positive correlation between poor metabolic control and conduct problems was observed (patient's self-assessment). Metabolic control was correlated with QoL (KINDL-R), particularly in the field of everyday functioning. The behavior subscale of the Strengths and Difficulties Questionnaire (SDQ) also correlated with metabolic control (patient's self-assessment). The overall QoL score and emotional and physical well-being, self-esteem, and family and friends did not correlate with metabolic control (in both self-assessed and parent-answered questionnaires).

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Name of author, country, year of study	Number of PKU patients	Age (mean, (SD)) and sex	Questionnaire	Metabolic control status/disease severity	QoL
Douglas *et al.*,[29] USA, October 2008 to October 2009	37	19 participants 10-19 years, 18 adults 17 female, 20 male	PKU-specific questionnaire (QOLQ)		Total and sub-scores were high, with at least 74% of baseline sub-scores above the mid-score, and 94% having a total score above the mid-score. However, the total and all sub-scores except for the support sub-score were negatively correlated with age. The Worries sub-score was inversely associated with plasma tyrosine levels, while the general well-being sub-score had a positive correlation with self-reported physical activity level. Baseline QOL scores were not associated with marital status, income, metabolic control, diet, or education level.
Demirdas *et al.*,[21] The Netherlands, November 2009 to June 2010	69	18.4 (10.2) years (4 to 44 years), 36 female, 33 male	PedsQL, TNO-AZL (Adult QoL questionnaire), DISABKIDS chronic generic module		Mothers of children aged 5–7 reported a trend towards lower scores on the "school and social functioning" scales. The HRQoL of patients aged 5–12, was similar to that of the general population, while patients aged 13–17 reported significantly higher HRQoL scores than the general population. Patients aged 13–17 reported significantly higher HRQoL scores on both the "total" scale and "psychosocial functioning" compared to the general population. There was a trend towards higher scores on the "social functioning" and "school functioning" scales in patients aged 13–17. Children aged 8–12 years reported significantly higher scores on physical functioning, while children aged 13–17 years reported higher scores on total and psychosocial functioning, as measured by the PedsQL. Adult patients reported lower scores in the cognitive domain.
Ziesch *et al.*,[27] Germany, 2009	14	10.31±4.1 years, 6 female, 8 male	KINDL	Phenylalanine level mean (SD): 365 (169) µmol/L during the last year Disease severity: 2 HPA, 5 mild PKU, moderate PKU 4, 3 classical PKU	Upon entering the study, the total HRQoL of PKU patients was similar to that of a healthy reference population (n=19) in both self-assessment and parent proxy versions. However, PKU patients rated their physical well-being significantly higher than their healthy counterparts of the same age.
Cazorla *et al.*,[18] Italy, January 2008 to March 2010	15	21.1 (19–30) mean (range), gender not reported by the type of the disorder	multidimensional World Health Organization QoL questionnaire (WHOQOL-100)	Disease severity: 11 classical, 4 moderate forms	Among the groups on special dietary treatment, the PKU patients showed significant differences compared to the others.
Cotugno *et al.*,[17] Italy, 2011 (publication year)	41	Above 3 years of age, mean (SD) 10 years 7 months (6 months) (median 8, range 3–24 years) 16 female, 25 male	Child Health Questionnaire (CHQ), SF-36	Disease severity: 30 classical, 11 mild PKU	Pediatric PKU patients had a reduced QoL (compared to a published reference Italian population). Except for the domains of Global Health and Family Activities, there was no significant correlation between adherence and QoL. The study found lower scores in both Physical and Psychological summary scores and most of the single domains (related to the patients or their families). The study also found significant correlations between adherence and both Global Health and Family Activities, while only a marginal significance was found for Global Behavior. The study found that adolescents had significantly lower scores than younger patients in two family domains: family cohesion and parental impact-time.

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Name of author, country, year of study	Number of PKU patients	Age (mean, (SD)) and sex	Questionnaire	Metabolic control status/disease severity	QoL
					Specifically, the scores for family cohesion were 64.9 for adolescents and 86.5 s. for younger patients, while the scores for parental impact-time were 52.5 for adolescents and 75.6 for younger patients. No other differences were observed based on age, type, or sex. However, when examining the QoL of adult patients, no significant differences were found compared to the reference population. Except for body pain, global behavior, self-esteem, general health perception, and family cohesion, there were no significant differences between PKU patients and healthy individual
Bosch *et al.*,[12] France, Germany, Italy, The Netherlands, Spain, Turkey, and the United Kingdom, December 2011 to November 2012	358 (92 children, 110 adolescents, 104 adults, and 52 young children)	4.4 (2.5) years (young children), 9.8 (0.8) (children), 14.5 (1.6) (adolescents), 25.8 (6.6) adults, 191 female, 165 male	Pediatric Quality-of-Life Inventory, SF-36, Child Health Questionnaire 28 item Parent Form	Disease severity: 32 young children, 66 children, 75 adolescents, and 67 adults had classical PKU	Results were comparable to the normal population. The emotional impact of PKU and its management, anxiety about blood Phe levels, and guilt related to poor adherence to dietary restrictions or Phe-free amino acid supplement intake had the highest scores (PKU-QOL). Patients with PKU experience anxiety about Phe levels during pregnancy. Those with milder PKU and treated with BH4 have lower practical and emotional impacts related to diet and supplement intake. The highest symptom score reported was for tiredness. Pediatric patients had results similar to those of US children 8 to 16 years (except for social functioning, which was higher in the PKU population). Adolescents and adults rated their health as good or very good. Physical health scores were higher than the US general population in adult PKU patients while scores on mental domains were slightly lower (physical functioning was less affected). No association was found between the severity of PKU and its symptoms but a consistent pattern was found regarding the impact of Phe-free amino acid supplement according to PKU severity. In adolescents, there was an association between the impact of dietary restriction and PKU severity. Children with classical PKU had poorer dietary adherence and experienced a greater impact from the diet. The practical impact of Phe-free amino-acid supplement was lower in patients treated with BH4 than those on diet only, and there was a better adherence to supplements in the first group than in the later one. The impact of dietary restriction was lower in adolescents and adults treated with BH4, including overall impact, and social and practical impact.
Cazzorla *et al.*,[24] Italy, March to July 2012	43	17.1±9.0 years, 20 female, 23 male	WHOQOL questionnaire-100 (WHOQOL-100) (adults), Pediatric QoL inventory (PedsQL (pediatrics)	Phenylalanine level: In children: 357±150 µmol/L concurrent, 359±131 µmol/L during the last year In adults: 826±261 µmol/L concurrent, 777±240 µmol/L during the last year Disease severity: 22 with mild PKU, 21 with classical form	In both groups, Phe level during the last year and concurrent level were significantly associated with QoL. The global scores for QoL (QoL) appeared to be normal for classical and mild PKU patients. In patients with mild PKU under BH4, significantly higher scores were observed. Additionally, QoL increased significantly in individuals with long-standing PKU. Among adults, males and those with lower education or employment status showed lower QoL scores compared to students. However, parents' perception of patients' QoL did not show any significant differences when compared with normative data for children. Similarly, patient's perceptions of their own QoL did not significantly differ from normative data.

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Name of author, country, year of study	Number of PKU patients	Age (mean, (SD)) and sex	Questionnaire	Metabolic control status/disease severity	QoL
Das *et al.*,[20] Germany, 2013 (publication year)	51	26.6±6.6 years, 32 female, 19 male	Alltagsleben (AL)	Phenylalanine levels were acceptable (higher with a normal diet).	There were no notable shortcomings observed regarding the overall perception of health, social, emotional, and physical role functioning, medical follow-up, and energy as compared to the general populace. There was a correlation between mood and the average Phe during the first 10 years of life. Patients under a strict diet with amino acid supplements did not feel worse than those on a normal diet.
Randell *et al.* ,[30] New Zealand, between 2007 and 2014	12	10.80 (4.31) years (HPA), 10.53 (3.82) years (PKU)	the Phenylketonuria QoL, PedsQL questionnaire	Phenylalanine levels: 281.50 µmol/L (83.38 µmol/L) at birth (means, SD) (HPA), 1,248.00 µmol/L (541.83 µmol/L) at birth (means, SD) (PKU) 167.50 (69.91) concurrent (means, SD) (HPA), 450.00 (136.75) concurrent (means, SD) (PKU); Disease severity: 6 with PKU, 6 with HPA	Individuals with PKU had lower scores compared to healthy controls and patients with HPA, especially in school functioning. Tiredness, lack of concentration, headaches, anxiety related to blood testing, slow thinking, irritability, low food enjoyment, moodiness, and stomach aches were symptoms reported by PKU patients and their parents and they experienced the emotional impact of the disease and adherence difficulties, especially for supplements. School functioning (self- and parent-assessed) was significantly and negatively correlated to metabolic control (birth and concurrent Phe). In PKU patients, birth Phe was significantly positively correlated with self-reported tiredness, concentration difficulties, and overall health. Current Phe showed a significant positive correlation with conduct disorder, aggression, and compulsive behavior as answered by the parents, adherence difficulties, and social impact.
Neto *et al.*,[6] Brazil, March 2012 to July 2014	51	6 to 18 years, 22 female, 29 male	PedsQL	Disease severity: 33 classical, 17 mild or moderate, one unknown	PedsQL scores (self- and proxy-reports) were significantly lower than the controls (in terms of Phe levels, no significant differences were found).
Hatami H *et al.*,[7] Iran, 2014	82	Adults with late diagnosed PKU, 57.3% were female, 42.7% male	World Health Organization QoL questionnaire (WHOQOL-BREF)	late diagnosed patients (more than 7 months at diagnosis)	The overall QoL was lower than the average. Education level had a significant impact on the QoL while gender did not. Patients above 40 years had significantly lower QoL and mental health. Patients with higher education levels had better QoL. The psychological and physical health showed better results compared to social and environmental connections which were significantly lower.
Mütze *et al.*,[26] Germany, January 2013 to September 2015	96	32 years (18–62) (median, range), 56 female, 40 male	QoL (FLZm)	Phenylalanine level: during the study: 673.0 (213.0–1381.1) µmol/l (median (range)) current: 658.7 (109.1-1458.5) (median (range)) (*n*=96)	27 (16 females and 11 males) answered life satisfaction: 66.7±31.7 (adult German population 62.7±37.1). 70.2±36.5 vs. 61.6±23.7 (female vs. male, not statistically significant). patients on diet had higher scores compared to those off diet (72.9±33.9 vs. 52.0±20.5).
Alptekin *et al.*,[8] Turkey, January 2016 to May 2017	63	15.7 (6.4) years, 41 female, 22 male	PKU-QoL		Except for tiredness, all domains were different by age. Adults were more adherent to supplements (children showed worse results). The most frequent symptom: tiredness and lack of concentration. In children, slow thinking anxiety-blood Phe levels were the highest score in the PKU in the general module (higher scores in children).

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Name of author, country, year of study	Number of PKU patients	Age (mean, (SD)) and sex	Questionnaire	Metabolic control status/disease severity	QoL
Huijbregts *et al*,[23] the Netherlands, 2018 (publication year)	90	21 (10.1) years, 53 female, 37 male	TNO-AZL	Phenylalanine levels: Concurrent: 366±207 µmol/L, lifetime: 307±73 µmol/L (in 7-12 years old patients) Concurrent: 337±216, lifetime: 299±56 (in 12-15 years old patients) Lifetime: 439±148, childhood: 344±128 (in patients≥16 years)	In children, autonomy, cognition, and positive emotions showed lower scores than the control group. In adolescents, all scores were lower than the controls and had lower cognitive functioning compared to healthy controls. In adults, all scores were lower than the controls except for daily activities and sleep. In this group, lifetime metabolic control showed a significant negative correlation with pain, anger, sexuality, and sleep. Concurrent Phe levels were negatively associated with sexuality. Social functioning, happiness, and anger were different between adult patients who used BH4 and didn't use it. Gender differences in QoL were not significant in children and adolescents but adult women showed lower QoL.
Barta *et al*.,[13] Hungary, January 2018 to September 2019	88	Median IQR age 31, 25–40 years, 46 female, 42 male	PKU-QoL	Phenylalanine level: current 600±236, last year 584±212, last 10 years 588±197 µmol/L Disease severity: 66 (75%) classical PKU, 12 (14%) moderate, 6 (7%) mild, and 4 (5%) HPA	No domains showed a major impact. Greater impact: Anxiety—Phe levels during pregnancy, Tiredness, Taste–supplements, Emotional impact of PKU, Guilt if poor adherence to supplements, Guilt if dietary protein restriction not followed. Last 10 years blood Phe showed significant correlations with some aspects such as the practical impact of PKU and adherence to treatment. Last year correlated with the overall impact of PKU and domains such as the practical impact of PKU, the social impact of dietary protein restriction, and treatment adherence. The overall impact of PKU was also affected by concurrent Phe levels. A greater impact was observed in the group with poorer adherence. Lifetime Phe level showed a correlation with the emotional impact of PKU. Except for financial impact, classical patients didn't differ significantly from the other patients.
Bösch *et al*.,[14] Germany, Italy, 2020 (publication year)	90 PKU patients	11.2 (3.64) years, 39 female, 51 male	generic PedsQL 4.0		School functioning and emotional health were impaired compared to the normative data. In PKU patients, mothers reported lower school functioning and psychological and emotional health. Physical functioning as reported by the patients themselves didn't differ significantly but the score reported by mothers was significantly lower than the controls. For psychological score and emotional functioning, both mothers and the patients reported a lower score compared to healthy children.
Morawska *et al*.,[9] Australia, 2020 (publication year)	18	6.89 (3.68) years, 12 female, 6 male	PKU-QoL	Phenylalanine levels: Mean (SD) 289.11 (59.89) µmol/L (lifetime) Disease severity: Classical *n*=8 (44.4%), mild *n*=5 (27.8), HPA *n*=5 (27.8)	The most significant impacts: the child's anxiety during blood tests and guilt related to poor adherence Scores didn't differ between groups (according to the disease severity). However, the impact of guilt related to poor adherence was more severe in classical patients. Parenting stress and emotional and behavioral difficulties of the child: higher PKU symptoms and impact of dietary restriction, in addition to the higher overall, emotional, and social impact of PKU. The study found significant correlations between PKU symptoms and emotional maladjustment, behavioral difficulties, intensity (child adjustment and parent

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Name of author, country, year of study	Number of PKU patients	Age (mean, (SD)) and sex	Questionnaire	Metabolic control status/disease severity	QoL
					efficacy scale), parental stress, parent-child (P-C) dysfunctional interaction, and difficult child (parenting stress index). Significant correlations reported for the emotional impact were: intensity, behavioral difficulties, parental stress, difficult child, and P-C dysfunctional interaction. Significant correlations reported for the social impact were: behavioral difficulties, emotional maladjustment, parental stress, intensity, difficult child, and P-C dysfunctional interaction. The overall impact of PKU: over-reactivity, behavioral difficulties, intensity, P-C dysfunctional interaction, and difficult child. Administration of Phe-free protein supplements: over-reactivity. Dietary protein restriction: difficult child, lifetime Phe levels, intensity, parental stress, behavioral difficulties, and P-C dysfunctional interaction
Becsei *et al.*,[15] Hungary, May to October 2020	70 (11 teenagers and 59 parents of children with PKU)	Adolescents: HPA (n=1, 15 years, male), PKU with good adherence (n=9, 14.3 (2.7) years, male: 66.67%), PKU with poor adherence (n=1, 14 years, male), children: HPA (n=20, 8.1 (5.2) years, 45% male), PKU with good adherence (n=30, 9.6 (5.3) years, 40% male), PKU with poor adherence (n=9, 9.6 (5.7) years, 88.89% male)	PKU-QoL	Phenylalanine levels: Adolescent patient with HPA: Lifetime Phe 294.18 µmol/L (mean (SD)) PKU with good adherence (adolescents) 307.43 (102.5) µmol/L (mean (SD)) PKU with poor adherence (adolescents) 516.54 µmol/L (mean (SD)) Children with HPA 203.2 (62.34) µmol/L (mean (SD)) PKU with good adherence (children) 256.81 (98.2) µmol/L (mean (SD)) PKU with poor adherence (children) 451.63 (251.5) µmol/L (mean (SD))	Of the 32 domains assessed, 25 showed little or no impact, the food enjoyment domain being the most impacted, especially in the adolescents with good adherence. Adherence to dietary protein restriction in adolescents, the guilt of poor adherence to supplements, and the practical impact of dietary protein restriction domains showed a moderate impact. Irritability was the most common symptom in the poor adherence group. The emotional impact of PKU on adolescent patients was considerable (in the adherent group). Poor metabolic control was associated with more symptoms including anxiety, slow thinking, and tiredness, and good adherence to treatment was associated with lower food enjoyment.
Afifi *et al.*,[1] Egypt, July to October 2020	120	1-12 years, 63 female, 57 male	PedsQL questionnaire		QoL was found to be very high in children under 5 years of age but children five years or older had low scores on all scales. Receiving a special diet and supplements in children less than 5 was associated with higher median physical, emotional, and total scores. Disease severity significantly correlated to scores on social and physical functioning.

Contd...

Table 1: Contd...

Name of author, country, year of study	Number of PKU patients	Age (mean, (SD)) and sex	Questionnaire	Metabolic control status/disease severity	QoL
Aitkenhead *et al*.,[16] London, 2021 (publication year)	149	33.93 (8.90) years, 90 female, 59 male	SF-36	Index of dietary control (IDC) (mean, range, µmol/L): 425 (159, 208-1051) (0-6 years), 569 (210, 230-1185) 6-12 years, 731 (257, 201-1387) 12-18 years, 837 (327, 185-1770) above 18 years of age low Phe (according to the index of dietary control) *n*=27 IDC<600 (childhood) and above or equal 1000 (adulthood) *n*=38 IDC above equal 600 (childhood) and equal 1000 (adulthood) *n*=9 (*n*=74 available data in terms of metabolic control)	Mental health: 42.36 (13.67) (mean, SD) PKU group (*n*=149), 45.60 (13.45) control group (*n*=74), physical health; 50.67 (8.70) (mean, SD) PKU group (*n*=149), control group 50.73 (8.06) (*n*=74) (didn't differ significantly between the two groups). PKU patients showed more anxious relationship styles. Partially adherence led to significantly lower QoL scores

impact of Phe-free amino acid supplement intake based on the severity of PKU. In adolescents, there was an association between the impact of dietary restriction and the severity of PKU. The parent version showed that children with classical PKU had poorer dietary adherence and experienced a greater impact from the diet than those with mild or moderate PKU.

Correlations with metabolic control

Some studies have investigated the correlation between QoL and metabolic control in patients with PKU.

In a study, it was found that blood phenylalanine (Phe) levels over the last 10 years were significantly correlated with certain aspects of PKU such as practical impact and treatment adherence. Phe levels over the last year were significantly correlated with the social impact of dietary protein restriction, adherence to treatment, practical impact, and overall impact of PKU. Concurrent Phe levels were correlated with an overall impact of PKU and some other aspects of QoL, with a greater impact observed in the group with poorer adherence. Lifetime Phe levels were correlated with the emotional impact of PKU. Classical patients did not differ significantly from other patients except for financial impact.[13]

Another study found that lifetime metabolic control was negatively correlated with pain, anger, sexuality, and sleep in adults, while concurrent Phe levels were negatively associated with sexuality.[23] A study in Germany also found that metabolic control was correlated with mood.[20] Patients' self-assessments revealed a positive correlation between poor metabolic control and conduct problems. Parents of PKU patients rated everyday functioning significantly lower than parents of healthy children. Metabolic control in PKU patients was correlated with QoL measured with the KINDL-R, particularly in the field of everyday functioning as answered by parents.[22] Phe levels during the last year and concurrent levels were significantly associated with QoL regardless of severity in one study,[24] while the Worries score was inversely associated with plasma tyrosine levels and the General well-being score in another study.[29]

It is suggested that there appears to be a positive correlation between QoL and metabolic control in patients with PKU. Good metabolic control is associated with higher levels of QoL and better overall well-being. However, other factors such as social support including educational courses[7,24] for both patients and parents, and psychological interventions may also play a significant role in improving QoL for PKU patients, regardless of their metabolic control. Further research is needed to better understand these complex relationships and to develop interventions to improve the QoL of PKU patients.

Differences by gender

In the reviewed studies, some have investigated gender differences in the QoL of patients with PKU. While some studies have found significant gender differences, others have not.

According to a study conducted on adults in Germany, men had better QoL scores, but overall, patients had acceptable

results.[28] Conversely, in another study, adult women reported lower QoL scores.[23]

In yet another study, women reported lower levels of positive mood and psychological functioning, but higher scores in the "social well-being" category although not significant according to the defined *P*-value.[10]

In another study conducted on adults, males and those with lower education or employment status had lower QoL scores compared to students.[24]

The reasons for these gender differences are not entirely clear. One possible explanation is that females may be more susceptible to the emotional and social impacts of PKU due to societal expectations and gender roles. Females may also face additional challenges related to pregnancy and childbirth, which can affect their metabolic control and QoL.[12] Another possible explanation is that males may be more likely to engage in physical activities, which can improve their physical functioning and overall QoL.

Overall, while some studies have found gender differences in the QoL of PKU patients,[10,28] the evidence is not entirely consistent. Further research is needed to better understand the factors that contribute to these differences and to develop interventions to improve the QoL of both male and female PKU patients.

Differences by age

The impact of age on the QoL of PKU patients has been reported in some studies.

In a study, adolescents had lower scores than younger patients in family cohesion and parental impact-time, indicating reduced QoL.[17] Another study found that older patients with late-treated PKU may have worse mental health, while higher education was associated with better results.[7] Patients over 25 years old reported more PKU-specific symptoms.[10] In a study in the USA, the total QoL score was negatively correlated with age.[29] A study showed that the QoL in most dimensions of children with PKU was similar to reference values, except for a reduction in positive emotions. Higher phenylalanine levels during the first year of life had a long-term negative impact on some dimensions of QoL.[25] In Egypt, QoL tended to decrease as the patient got older, but under-five children who received a special diet and supplements had higher median physical, emotional, and total scores compared to those who did not.[1]

In contrast, in one study in Turkey, children showed worse results, with the most frequent symptom being slow thinking. The most frequent problem, in general, was lack of concentration and tiredness.[8]

However, not all studies have found significant age-related differences in QoL among PKU patients.[25] The reasons for these age-related differences are not entirely clear. One possible explanation is that as patients age, they may become more aware of the challenges associated with PKU, which can lead to a decline in QoL. Older patients may also face additional challenges related to aging, such as comorbidities and social isolation. On the other hand, younger patients may be more resilient and adaptable to the challenges of PKU.

However, it is suggested that age appears to be an important factor in determining the QoL of patients with PKU. Further research is needed to better understand the factors that contribute to these age-related differences and to develop interventions to improve the QoL of patients across all age groups.

Differences in disease severity

The severity of PKU can vary widely, depending on factors such as the degree of residual enzyme activity and adherence to dietary restrictions. Several studies have investigated the impact of disease severity on the QoL of PKU patients.

One study found that disease severity was significantly related to physical and social functioning scores,[1] while another study found no significant difference between groups in terms of disease severity. However, classical patients may experience a more severe impact of guilt related to poor adherence.[9] In a study from New Zealand, patients with PKU had worse scores on the PedQL compared to those with HPA.[30]

In a study by Bosch *et al*.[12] in seven European countries, no association between the severity of PKU and its symptoms was found. However, they did report a consistent pattern regarding the impact of Phe-free amino acid supplement intake according to the severity of PKU. In adolescents, there was an association between the impact of dietary restriction and PKU severity, with children with classical PKU having poorer adherence to diet and a greater impact from the diet.

Patients with milder forms of PKU may have fewer dietary restrictions and may be less likely to experience cognitive impairment, which could contribute to better QoL outcomes.[1,30]

However, other studies have found that even patients with mild or moderate PKU can experience significant impairments in QoL.[17]

The reasons for these differences in QoL outcomes are not completely clear. One possible explanation is that even patients with mild or moderate PKU may experience some degree of cognitive impairment or other symptoms related to the condition, which could contribute to lower QoL scores.[17] Additionally, the burden of adhering to a strict diet may be challenging for patients with any form of PKU, which could also contribute to lower QoL outcomes.

It seems that disease severity appears to be an important factor in determining the QoL of patients with PKU.[1] Patients with milder forms of PKU may have better QoL outcomes than those with classic PKU,[9,30] but even patients with mild or moderate PKU can experience impairments in QoL. Further research is needed to better understand the factors that contribute to these differences in QoL outcomes and to develop interventions to improve the QoL of all patients with PKU.

Impact of tetrahydrobiopterin (BH4)

Tetrahydrobiopterin (BH4) is a cofactor that is essential for the proper function of enzymes involved in phenylalanine metabolism. BH4 supplementation has been shown to improve the activity of these enzymes and reduce the levels of phenylalanine in the blood of PKU patients.[12]

Some studies have investigated the impact of BH4 on the QoL of PKU patients. One study found that BH4 supplementation led to significant improvements in the QoL in adult PKU patients.[23] Another study reported similar improvements in children with PKU.[24] Overall, BH4 appears to be a promising treatment option for PKU patients, with the potential to improve both metabolic control and QoL.

Pregnancy and QOL

Pregnancy in women with PKU requires careful management of blood phenylalanine levels to prevent fetal complications. Elevated maternal phenylalanine levels during pregnancy can lead to intellectual disability, microcephaly, and other developmental abnormalities in the fetus. However, strict dietary control can be challenging for pregnant women with PKU and may impact their QoL.[12,13]

In some studies, the impact of PKU on the QoL of pregnant women has been investigated. One study found that pregnant women with PKU had lower scores on measures of social support and QoL compared to healthy controls.[12]

Despite the challenges associated with managing PKU during pregnancy, it is important to emphasize that strict dietary control can lead to positive outcomes for both the mother and the fetus.

However, pregnancy in women with PKU requires careful management of blood phenylalanine levels to prevent fetal complications. Although strict dietary control can be challenging, it is important to emphasize the potential benefits for both the mother and the fetus. Further research is needed to better understand the impact of PKU on the QoL of pregnant women and to develop interventions to support their mental health and well-being.

Limitations

Our review was limited to a small number of databases and only included articles written in English, with no assessment of articles written in other languages. Conference papers were not included in our review. Furthermore, different studies used different questionnaires to evaluate QoL, which made it difficult to conduct further quantitative analysis.

Conclusion

While the overall quality of life (QoL) in patients with PKU is generally acceptable, research has shown that it could harm the QoL of patients, particularly in terms of social functioning, psychological well-being, and physical health. Therefore, it is important to consider QoL as a measure of health in patients undergoing treatment for PKU. Female patients, older patients, and those who are diagnosed later tend to have worse outcomes. Improvements in metabolic control have been associated with better QoL.

In addition, interventions such as BH4 supplementation and good metabolic control during pregnancy have been shown to improve QoL in PKU patients. Further research is needed to develop and evaluate interventions to improve the QoL of PKU patients.

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Ethical approval

The protocol of the study was approved by the ethics committee of Isfahan University of Medical Sciences with the ethics code of IR.MUI.MED.REC.1402.063.

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Conflicts of interest

There are no conflicts of interest.

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Appendix 1: Search strategy

Database	Search strategy
Web of Science	#1 TI=(Classic Phenylketonuria OR Non- Classic Phenylketonuria OR BH4 Deficiency OR DHPR Deficiency OR Dihydropteridine Reductase OR Phenylalanine Hydroxylase OR Dihydropteridine Reductase Deficiency OR Dihydropteridine Reductase Deficiency Disease OR Folling Disease OR Folling's Disease OR Hyperphenylalaninemia OR Biopterin Metabolism defect OR BH4-Deficiency OR Non-Phenylketonuric Hyperphenylalaninemia OR Tetrahydrobiopterin Deficiency OR Hyperphenylalaninemia, Non-Phenylketonuric OR Oligophrenia Phenylpyruvica OR PAH Deficiency OR Atypical PKU OR Phenylalanine Hydroxylase Deficiency OR Phenylalanine Hydroxylase Deficiency Disease OR Phenylketonuria OR QDPR Deficiency OR Quinoid Dihydropteridine Reductase Deficiency OR Tetrahydrobiopterin Deficiency OR phenylketonuria I OR phenylketonuria II OR phenylketonuria type 2 OR phenylketonuria) #2 AB=(Classic Phenylketonuria OR Non- Classic Phenylketonuria OR BH4 Deficiency OR DHPR Deficiency OR Dihydropteridine Reductase OR Phenylalanine Hydroxylase OR Dihydropteridine Reductase Deficiency OR Dihydropteridine Reductase Deficiency Disease OR Folling Disease OR Folling's Disease OR Hyperphenylalaninemia OR Biopterin Metabolism defect OR BH4-Deficiency OR Non-Phenylketonuric Hyperphenylalaninemia OR Tetrahydrobiopterin Deficiency OR Hyperphenylalaninemia, Non-Phenylketonuric OR Oligophrenia Phenylpyruvica OR PAH Deficiency OR Atypical PKU OR Phenylalanine Hydroxylase Deficiency OR Phenylalanine Hydroxylase Deficiency Disease OR Phenylketonuria OR QDPR Deficiency OR Quinoid Dihydropteridine Reductase Deficiency OR Tetrahydrobiopterin Deficiency OR phenylketonuria I OR phenylketonuria II OR phenylketonuria type 2 OR phenylketonuria) #3 #1 OR #2 #4 ALL=(Quality of life OR HRQOL OR Health-Related Quality Of Life OR Life Quality) #5 #3 AND #4
Scopus	Modified: TITLE-ABS-KEY ("classic phenylketonuria" OR "non-classic phenylketonuria" OR "BH4 deficiency" OR "DHPR deficiency" OR "dihydropteridine reductase" OR "phenylalanine hydroxylase" OR "dihydropteridine reductase deficiency" OR "dihydropteridine reductase deficiency disease" OR "folling disease" OR "folling' s disease" OR "hyperphenylalaninemia" OR "biopterin metabolism defect" OR "BH4-deficiency" OR "non-phenylketonuric hyperphenylalaninemia" OR "tetrahydrobiopterin deficiency" OR "hyperphenylalaninemia, non-phenylketonuric" OR "oligophrenia phenylpyruvica" OR "PAH deficiency" OR "atypical PKU" OR "phenylalanine hydroxylase deficiency" OR "phenylalanine hydroxylase deficiency disease" OR "phenylketonuria" OR "QDPR deficiency" OR "quinoid dihydropteridine reductase deficiency" OR "tetrahydrobiopterin deficiency" OR "phenylketonuria I" OR "phenylketonuria II" OR "phenylketonuria type 2" OR "phenylketonuria") AND ALL ("quality of life" OR "health-related quality of life" OR "life quality")
PubMed	1# Classic Phenylketonuria[Title/Abstract] OR Non- Classic Phenylketonuria[Title/Abstract] OR BH4 Deficiency[Title/Abstract] OR DHPR Deficiency[Title/Abstract] OR Dihydropteridine Reductase[Title/Abstract] OR Phenylalanine Hydroxylase[Title/Abstract] OR Dihydropteridine Reductase Deficiency[Title/Abstract] OR Dihydropteridine Reductase Deficiency Disease[Title/Abstract] OR Folling Disease[Title/Abstract] OR Folling's Disease[Title/Abstract] OR Hyperphenylalaninemia[Title/Abstract] OR Biopterin Metabolism defect[Title/Abstract] OR BH4-Deficiency[Title/Abstract] OR Non-Phenylketonuric Hyperphenylalaninemia[Title/Abstract] OR Tetrahydrobiopterin Deficiency[Title/Abstract] OR Hyperphenylalaninemia, Non-Phenylketonuric[Title/Abstract] OR Oligophrenia Phenylpyruvica[Title/Abstract] OR PAH Deficiency[Title/Abstract] OR Atypical PKU[Title/Abstract] OR Phenylalanine Hydroxylase Deficiency[Title/Abstract] OR Phenylalanine Hydroxylase Deficiency Disease[Title/Abstract] OR Phenylketonuria[Title/Abstract] OR QDPR Deficiency[Title/Abstract] OR Quinoid Dihydropteridine Reductase Deficiency[Title/Abstract] OR Tetrahydrobiopterin Deficiency[Title/Abstract] OR phenylketonuria I[Title/Abstract] OR phenylketonuria II[Title/Abstract] OR phenylketonuria type 2[Title/Abstract] OR phenylketonuria[Title/Abstract] OR phenylketonuria[MeSH Terms] 2# Quality of life OR HRQOL OR Health-Related Quality Of Life OR Life Quality OR Quality of life[MeSH Terms] #1 AND #2