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OVERSEAS PEDIATRIC RESEARCH

Growth assessment in children with phenylketonuria

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Abstract: Objective To investigate the growth parameters of children with phenylketonuria and assess the impact of a phenylalanine-restricted diet on their physical development. **Methods** The study involved 39 children diagnosed with phenylketonuria through newborn screening at the Central Child Teaching Hospital, Baghdad, Iraq. Data were collected during scheduled monthly check-ups, including phenylalanine levels, diet compliance, and anthropometric measurements. The children were divided into two groups based on their phenylalanine levels during the 3-year follow-up period: well-controlled group (average phenylalanine level of less than 360 μmol/L, with no single reading exceeding 600 μmol/L; n=14) and poorly-controlled group (one or more phenylalanine readings above 600 μmol/L during the follow-up period; n=25). **Results** The mean height readings for all time points (at birth and 3, 6, 9, 12, 15, 18, 21, 24 and 36 months of age) were higher in the well-controlled group than the poorly-controlled group, however, only at 3 months of age the difference was statistically significant. Height Z-scores revealed a clearer pattern: although the poorly-controlled group had higher height Z-scores at birth (P=0.001), the well-controlled group showed significantly higher height Z-scores at 3, 6, 12, 15, 18, 24, and 36 months (P<0.05). The well-controlled group exhibited significantly higher mean weight measurements compared to the poorly-controlled group at 3, 6, 9, 15, 18 months and 21 months (P<0.05). From 6 to 36 months, the well-controlled group consistently had significantly higher weight Z-scores than the poorly-controlled group (P<0.05). The well-controlled group showed more favorable height and weight Z-score distributions at 36 months of age compared to the poorly-controlled group, but the differences were not statistically significant (P>0.05). Both groups had height and weight Z-scores within the normal range at 36 months of age. **Conclusions** The children with phenylketonuria who receive good dietary control show better improvements in growth parameters compared to those with poor dietary control, however, both groups maintain height and weight Z-scores within the normal range, indicating generally adequate physical development across the cohort.

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Key words: Phenylketonuria; Phenylalanine; Growth; Diet; Child

苯丙酮尿症儿童的生长评估

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［**摘要**］**目的** 探讨苯丙酮尿症（phenylketonuria, PKU）患儿的生长参数，并评估苯丙氨酸限制饮食对其体格发育的影响。**方法** 研究对象为伊拉克巴格达中央儿童教学医院通过新生儿筛查确诊的39例PKU患儿。在定期月度随访中收集数据，包括苯丙氨酸水平、饮食依从性及人体测量学指标。根据3年随访期间患儿的苯丙氨酸水平将患儿分为两组：饮食控制良好组（平均苯丙氨酸水平<360 μmol/L，且单次检测值均未超过600 μmol/L；n=14）和饮食控制不良组（随访期间一次或多次苯丙氨酸测定值高于600 μmol/L；n=25）。比较两组患儿3~36月龄期间生长指标的差异。**结果** 在出生时及3、6、9、12、15、18、21、24、36月龄各时间点，饮食控制良好组的平均身高均高于饮食控制不良组，但仅在3月龄时差异有统计学意义。身高Z评分呈现更清晰的模式：尽管饮食控制不良组出生时身高Z评分较高（P=0.001），但饮食控制良好组在3、6、12、15、18、24和36月龄时的身高Z评分均显著高于饮食控制不良组（P<0.05）。在3、6、9、15、18和21月龄时，饮食控制良好组的平均体重显著高于饮食控制不良组（P<0.05）。在6~36月龄期间，饮食控制良好组的体重Z评分持续显著高于饮食控制不

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良组（P<0.05）。36月龄时，饮食控制良好组展现出优于饮食控制不良组的身高和体重Z评分分布，但差异无统计学意义（P>0.05）；两组患儿的身高和体重Z评分均处于正常范围内。**结论**　接受良好饮食控制的PKU患儿，其生长参数优于饮食控制不良者；两组患儿的身高和体重Z评分均维持在正常范围，表明该队列患儿的总体体格发育基本正常。
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［关键词］苯丙酮尿症；苯丙氨酸；生长；饮食；儿童

Phenylketonuria (PKU) is an inborn error of phenylalanine (Phe) metabolism, inherited in an autosomal recessive pattern. It affects approximately 450 000 individuals worldwide. PKU impairs the conversion of Phe into tyrosine, which subsequently affects the production and transport of tryptophan and tyrosine across the blood-brain barrier. In healthy individuals, blood Phe concentrations typically range from 50 to 110 μmol/L. However, levels exceeding 1 200 μmol/L are classified as classic PKU. If left untreated, PKU can lead to irreversible cognitive impairment and neurological damage. Therefore, early diagnosis through newborn screening (NBS) and prompt intervention are essential[1-4]. A protein-restricted diet is recommended, with the exclusion of high-protein foods such as meat, eggs, and nuts, while the intake of cereals, potatoes, and milk must be strictly regulated. In contrast, fruits and vegetables can be consumed without restriction[3,5-6]. Dietary control aims to maintain blood Phe levels within a safe range, particularly in young children, where levels should remain below 360 μmol/L for those younger than 6 years[7-8]. Pharmacological treatment for PKU has been limited. Until 2018, tetrahydrobiopterin was the only approved drug. However, only a small proportion of patients exhibit a positive response to this treatment[9-10]. Some early studies have reported growth retardation in children with PKU compared to healthy controls, other studies indicate normal growth patterns. Nonetheless, reports of suboptimal final height in adolescence persist. The long-term effects of PKU and its treatment on growth remain a topic of ongoing debate[6-8,11].

This study aims to evaluate growth parameters in children with PKU and explore the effects of Phe-restricted diet control on the physical development and growth of those children.

1　Materials and methods

1.1　Research subjects

A retrospective study was conducted on 39 children diagnosed with PKU from June 2022 to June 2024, using the medical records of children diagnosed with PKU by NBS in the Metabolic Clinic of Central Child Teaching Hospital, Baghdad, Iraq. The data were documented at scheduled monthly check-up visits as part of the follow-up protocol used in the clinic.

1.2　Inclusion and exclusion criteria

Patients had to meet the following requirements in order to be considered for the study: (1) early diagnosis of PKU through NBS; (2) exclusive and ongoing management with a Phe-restricted diet, starting within a few weeks or days of the patient's birth; and (3) consistent attendance at their planned clinical check-ups.

The following patients were excluded: patients with a delayed diagnosis, those whose follow-up check-up attendance lasted fewer than three years, premature infants, and patients with any other illness that is known to impact their growth and development.

1.3　Data collection

Detailed information included: date of birth, age at diagnosis, initial Phe concentrations, Phe/tyrosine ratio, age of starting treatment, compliance to diet, and serum Phe readings monthly.

Anthropometric measurements were made during prearranged check-up appointments. Up until the age of 15 months, the length and weight of the patients were measured with a measuring board and a manual baby scale, respectively. After that, body weight was calculated using digital scales to the closest 100 g and standing height was measured using a wall-mounted stadiometer. The same qualified staff members conducted these measurements. In the present study, weight and height were collected at

birth and every month thereafter. The weight and height measurements are plotted on the Centers for Disease Control and Prevention (CDC) growth charts (for either girls or boys) to obtain a percentile ranking and a Z-score. These values are calculated using the anthropometric calculator from PediTools, which is based on the CDC charts[12-13]. For statistical purposes, 10 readings were included in the study (first reading at birth and 3-month interval readings thereafter until the first 24 months of age and at 36 months of age).

1.4 Grouping

The study population was divided into two groups based on their Phe levels during the 3-year follow-up period. One group, labeled the "well-controlled group", had an average Phe level of less than 360 μmol/L, with no single reading exceeding 600 μmol/L. The other group, labeled the "poorly-controlled group", had one or more Phe readings above 600 μmol/L during the follow-up period.

1.5 Ethical approval

The study was carried out in accordance with the Declaration of Helsinki's ethical guidelines. Before the sample was taken, the patients gave their consent. A local ethics committee evaluated and approved the consent form, the study protocol, and the subject information (the document number: 4/2022 in 17/04/2022).

1.6 Statistical analysis

SPSS software version 25.0 was used for all statistical analyses (SPSS, Chicago). The Shapiro-Wilk test, a normality test, was applied to continuous data. Student *t*-test was used to evaluate data having a normal distribution, which were displayed as mean and standard deviation ($x\pm s$). The Fisher's exact test was used to assess categorical variables, which were represented as numbers and percentages. $P<0.05$ indicates a statistically significant difference.

2 Results

2.1 Demographic characteristics of the patients

Of the 39 children with PKU, males represented 51% (20 children); the median age at diagnosis and treatment was 30 days (range: 13-130 days) and 60 days (range: 20-315 days), respectively; the median Phe concentration was 1 188 μmol/L (range: 180-2 556 μmol/L).

Fourteen children (36%) had good diet control (well-controlled group), while 25 (64%) had poor diet control (poorly-controlled group). In the well-controlled group, 6 (43%) were male and 8 (57%) were female. In the poorly-controlled group, 14 (56%) were male and 11 (44%) were female.

2.2 Association between height and diet control

Both the poorly-controlled and well-controlled groups showed a steady height increase over time, following a typical growth curve (Figure 1).

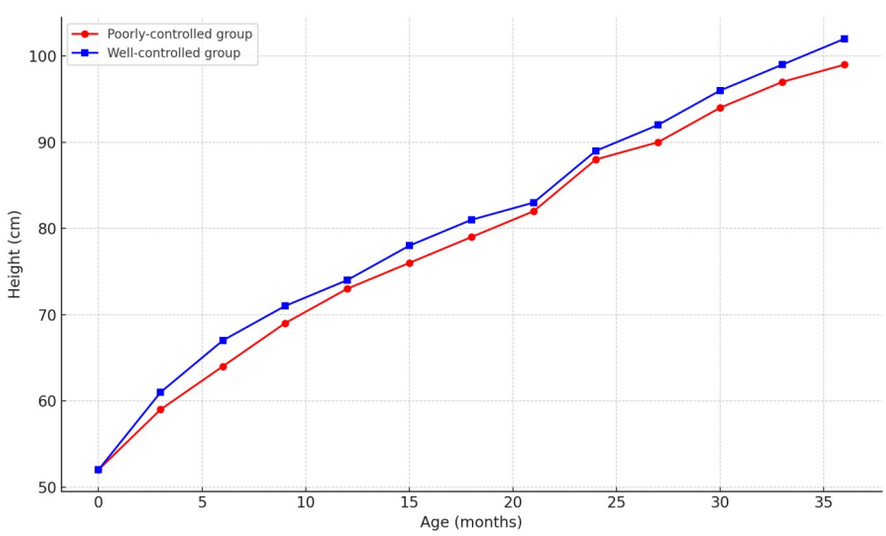


Figure 1 Mean heights from birth to 36 months in the well-controlled and poorly-controlled groups

The mean height readings for all time points were higher in the well-controlled group than the poorly-controlled group, but except at 3 months of age there were no significant differences were observed (P>0.05). See Table 1.

The poorly-controlled group had a higher mean height Z-score at birth, however by 3 months of age, the well-controlled group demonstrated significantly better height outcomes. This trend continued across most subsequent time points, with statistically significant differences observed at 3, 6, 12, 15, 18, 24, and 36 months (P<0.05). See Table 2.

Table 1 Comparisons of heights between the poorly-controlled and well-controlled groups ($\bar{x} \pm s$, cm)

Measurement time	Poorly-controlled group (n=25)	Well-controlled group (n=14)	t value	P value
At birth	51.2±2.0	52.0±2.5	-1.03	0.323
3 months	59.2±1.8	61.2±2.9	-2.37	0.034
6 months	64.5±2.5	66.4±3.6	-1.76	0.102
9 months	69.5±2.8	71.1±2.9	-1.61	0.132
12 months	73.4±2.4	74.4±3.3	-1.01	0.331
15 months	76.2±3.2	78.4±3.5	-1.99	0.068
18 months	79.6±3.2	81.3±3.9	-1.39	0.187
21 months	82.8±3.3	83.0±2.5	-0.24	0.816
24 months	87.4±3.6	88.8±2.5	-1.39	0.189
36 months	98.7±5.0	101.8±3.8	-2.13	0.053

Table 2 Comparisons of height Z-scores between the poorly-controlled and well-controlled groups ($\bar{x} \pm s$)

Measurement time	Poorly-controlled group (n=25)	Well-controlled group (n=14)	t value	P value
At birth	0.67±0.12	0.52±0.10	4.18	0.001
3 months	-0.34±0.20	0.45±0.18	-12.63	<0.001
6 months	-0.87±0.21	0.19±0.15	-18.26	<0.001
9 months	-0.24±0.25	-0.32±0.19	1.12	0.282
12 months	-0.53±0.23	-0.10±0.22	-5.76	<0.001
15 months	-0.70±0.24	-0.03±0.17	-10.14	<0.001
18 months	-0.71±0.25	-0.04±0.21	-8.91	<0.001
21 months	-0.50±0.28	-0.50±0.20	0.00	1.000
24 months	0.87±0.22	1.02±0.19	-2.23	0.044
36 months	-0.09±0.30	0.96±0.27	-11.19	<0.001

2.3 Association between weight and diet control

The well-controlled group exhibited significantly higher mean weight measurements compared to the poorly-controlled group at 3, 6, 9, 15, 18 and 21 months (P<0.05). However, beyond 24 months, the mean weight differences between the two groups were no longer significant (P>0.05). See Figure 2 and Table 3.

Weight Z-scores were analyzed at multiple time points to examine age-adjusted growth patterns. There was no statistically significant difference in the weight Z-scores between the poorly-controlled and well-controlled groups at birth (P>0.05). From 6 months to 36 months, the well-controlled group consistently showed significantly higher weight Z-scores compared to the poorly-controlled group (P<0.05). See Table 4.

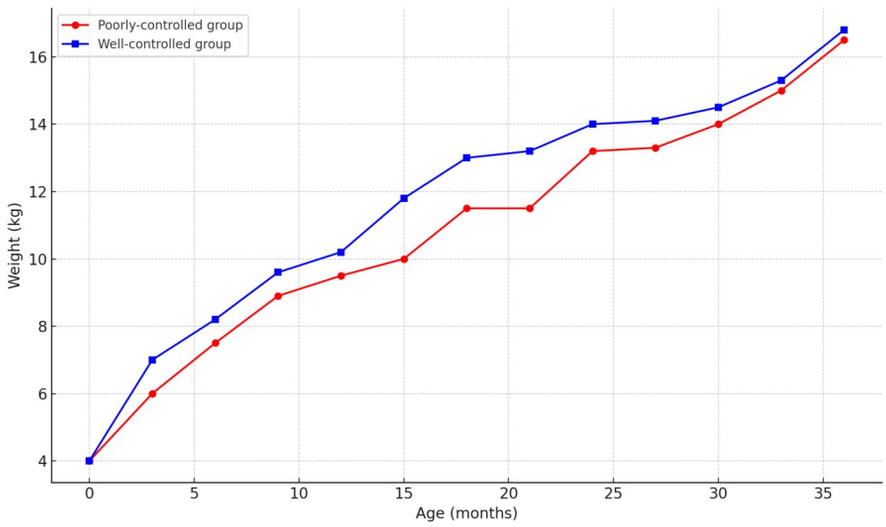


Figure 2　Mean weights from birth to 36 months in the well-controlled and poorly-controlled groups

Table 3　Comparisons of weight between the poorly-controlled and well-controlled groups　($\bar{x} \pm s$, kg)

Measurement time	Poorly-controlled group (n=25)	Well-controlled group (n=14)	t value	P value
At birth	3.9±0.5	3.9±0.4	0.00	1.000
3 months	6.1±0.9	6.9±0.8	-2.86	0.013
6 months	7.5±0.8	8.1±0.7	-2.44	0.030
9 months	8.8±1.1	9.6±0.4	-3.27	0.006
12 months	9.5±1.1	10.1±1.2	-1.54	0.147
15 months	10.0±0.9	11.8±0.8	-6.44	<0.001
18 months	11.5±1.4	13.2±1.3	-3.81	0.002
21 months	11.5±1.4	13.4±1.2	-4.46	0.001
24 months	13.3±2.4	14.1±2.2	-1.05	0.311
36 months	16.5±4.4	16.8±3.1	-0.25	0.808

Table 4　Comparisons of weight Z-scores between the poorly-controlled and well-controlled groups　($\bar{x} \pm s$)

Measurement time	Poorly-controlled group (n=25)	Well-controlled group (n=14)	t value	P value
At birth	-0.19±0.12	-0.18±0.10	-0.28	0.785
3 months	-0.12±0.15	-0.51±0.18	6.88	<0.001
6 months	-0.28±0.20	0.40±0.15	-12.01	<0.001
9 months	-0.46±0.25	0.30±0.12	-12.79	<0.001
12 months	-0.57±0.23	-0.02±0.20	-7.80	<0.001
15 months	-0.47±0.24	0.03±0.17	-7.57	<0.001
18 months	-0.79±0.27	0.26±0.19	-14.17	<0.001
21 months	-0.27±0.26	0.22±0.40	-4.12	<0.001
24 months	0.12±0.28	0.34±0.21	-2.77	0.016
36 months	0.12±0.30	0.69±0.27	-6.07	<0.001

2.4 Association between height Z-score distribution and diet control

The height Z-score distribution between the poorly-controlled and well-controlled groups was similar at birth, with no significant difference (P=0.108). At 36 months, a trend shifted toward lower Z-scores in the poorly-controlled group, while the well-controlled group remained more stable, but this difference in the height Z-score distribution between the two groups was not statistically significant (P=0.144). However, all height Z-score readings in both groups were between -1 and 2 (normal range). See Table 5.

Table 5 Comparisons of height Z-score distribution between the poorly-controlled and accepted control groups [n(%)]

Z-score	At birth		At 36 months	
	Poorly-controlled group (n=25)	Well-controlled group (n=14)	Poorly-controlled group (n=25)	Well-controlled group (n=14)
< -2	0(0)	0(0)	0(0)	0(0)
-2 to < -1	0(0)	0(0)	0(0)	0(0)
-1 to < 0	7(28)	3(21)	14(56)	4(29)
0 to < 1	17(68)	10(71)	9(36)	10(71)
1 to < 2	1(4)	1(7)	2(8)	0(0)
⩾ 2	0(0)	0(0)	0(0)	0(0)
P value	0.108		0.144	

2.5 Association between weight Z-score distribution and diet control

At birth, there was no statistically significant difference in weight Z-score distribution between the two groups (P=0.741). By 36 months, although the weight Z-scores in the well-controlled group remained statistically indistinguishable from the poorly-controlled group (P=0.180), the well-controlled group exhibited a shift toward higher Z-score ranges, indicating improved weight outcomes. Specifically, the well-controlled group had a higher proportion of children in the 0 to <1 and 1 to <2 Z-score ranges. In contrast, the poorly-controlled group had a higher proportion of children in the negative Z-score ranges (−2 to <−1 and −1 to <0). Nevertheless, all children in both groups maintained weight Z-scores within normal limits. See Table 6.

Table 6 Comparisons of weight Z-score distribution between the poorly-controlled and well-controlled groups [n(%)]

Z-score	At birth		At 36 months	
	Poorly-controlled group (n=25)	Well-controlled group (n=14)	Poorly-controlled group (n=25)	Well-controlled group (n=14)
< -2	0(0)	0(0)	0(0)	0(0)
-2 to < -1	7(28)	2(14)	7(28)	2(14)
-1 to < 0	6(24)	4(29)	7(28)	2(14)
0 to < 1	11(44)	8(57)	11(44)	9(64)
1 to < 2	1(4)	0(0)	0(0)	1(7)
⩾2	0(0)	0(0)	0(0)	0(0)
P value*	0.741		0.180	

Note: *Using Fisher's exact test.

3 Discussion

When assessing the health of children and adolescents, anthropometric measures are crucial, particularly for those who require specific dietary care.

The current study involved monitoring the growth in 39 children with PKU diagnosed by NBS over the first 3 years of their lives. It focused on the relationship between the children's height/weight and dietary control degree. Poor adherence to Phe-restricted diets is a major concern in our practice, as limited family socioeconomic status often leads to inconsistent access to specialized dietary products and supplements.

Many earlier studies have investigated the impact of dietary management on linear growth in PKU children, with mixed results. Evans et al.[6] stated that growth parameters in both non-PKU and PKU groups fell within the normal range. While several studies have reported that individuals with PKU are at increased risk of impaired linear growth[7-10]. For example, Ilgaz et al.[7] and Aldámiz-Echevarría et al.[8] observed suboptimal anthropometric outcomes in PAH-deficient individuals, as did Manti et al.[9] and Giovannini et al.[10], who both emphasized the need for early dietary interventions to support growth. Shakiba et al.[14], Thiele et al.[15], Huemer et al.[16] and Weng et al.[17] all concluded that adequate metabolic control, normal linear growth can be maintained in PKU patients.

This current study displayed that both poorly-controlled and well-controlled groups had a steady increase in the height during the time frame of the study. The heights were consistently higher in the well-controlled group than the poorly-controlled group, however, there were no significant differences at various time points except at 3 months of age. This could be explained by the small sample size and the limited follow-up duration. Genetic factors can be a cause of height variations among individuals.

The current study showed that between 6 and 36 months of age, children in the well-controlled group had significantly higher mean weight Z-scores compared to the poorly-controlled group. Similarly, the well-controlled group demonstrated significantly higher mean weight at most time points within this period. However, at 12, 24, and 36 months, the differences in mean weight were not statistically significant, possibly due to greater variation in weight within each group at older ages, which can reduce statistical power. In addition, some children in the poorly-controlled group may have shown partial catch-up growth. At the same time, the well-controlled group may have reached a natural slowing in weight gain after earlier rapid growth. Nonetheless, we emphasize the need for ongoing nutritional assessment beyond infancy in children with PKU.

Despite these variations both well-controlled and poorly-controlled groups had their height and weight Z-scores were in the normal range. These findings were consistent with those of the study by Shakiba et al.[14], a cross-sectional Iranian study conducted from 2015 to 2017, which compared the anthropometric indices of PKU patients with those of the normal population. The study found no significant differences in anthropometric indices between the cases (PKU patients aged ⩽ 2 years) and controls, and mean Phe levels were not associated with any of these indices. In the study by Evans et al.[6], 20 children with PKU were observed monthly from 4 to 24 months of age for growth indices, energy intake, and macronutrient intake, and compared to non-PKU children. At all ages, growth parameters in both groups fell within the normal range. By two years of age, no PKU child had Z-scores less than -2 for any growth parameter. Our findings are consistent with theirs.

The study by Thiele et al.[15] systematically evaluated height development and growth patterns in PKU patients throughout their first eighteen years of life. The findings revealed consistent growth retardation across developmental stages: (1) PKU patients exhibited significantly shorter stature compared to healthy German references from infancy through adolescence; (2) At birth, their length already fell below national standards, suggesting intrauterine growth restriction despite all being term deliveries. The growth trajectory showed biphasic characteristics: initial stabilization approaching reference percentiles between ages 2-12 years, followed by secondary deceleration during puberty. This pattern ultimately resulted in a final height deficit of 5-6 cm (negative SDS at growth completion). Notably, weight SDS demonstrated parallel reductions, becoming significantly lower than healthy German controls from age 2 years onward.

In the study by Huemer et al.[16], growth and body composition measurements of 34 treated PKU patients were recorded over 12 months and compared with those of healthy peers and the general

population. While the study by Aldámiz-Echevarría et al.[8] showed that the mean weight Z-score gradually decreased during the first 2 years of life, and decreased to a nadir of -0.59 ± 0.95 *SD* and -0.51 ±0.99 *SD* in male and female PKU patients, respectively. The study found that from ages 2 to 3.5 years, mean weight Z-scores for both boys and girls showed steady increases. These scores then remained relatively stable until age 16.5 years, with females maintaining a mean Z-score of approximately -0.2 and males remaining near zero.

Weng et al.[17] selected 22 PKU patients (8-27 years) and 22 age- and gender-matched healthy controls (8-39 years) for their study. During follow-up, PKU patients showed comparable growth and development to controls, with no significant differences in height. These findings contrast with other studies reporting growth impairments in PKU populations. Tanaka et al's[18] study of 18 treated PKU children (5-18 years) found 44% were overweight/obese despite only 6% having height-for-age deficits. Similarly, Ahmadzadeh et al.[19] observed stunting in 17.5% of PKU children (4-18 years), with 37.5% overweight and 43.8% obese. The 2020 study by de Almeida et al.[20] also noted significant overweight/obesity prevalence, particularly in female PKU patients (2-19.9 years).

Recent evidence provides alternative perspectives. Paterno et al's[21] 2024 Italian longitudinal data demonstrated normal body mass index Z-scores in PKU children, suggesting proper dietary management can maintain healthy growth parameters. The observed discrepancies may arise from methodological differences, including study designs (cross-sectional vs longitudinal), sample sizes, and assessment protocols. Growth variations could also reflect the complex interaction of genetic, endocrine and nutritional factors across developmental stages (fetal, infantile, childhood, and pubertal). Current guidelines recommend total protein intake at 1.3 g/(kg·day) (110% of dietary reference intakes) for PKU patients undergoing low-Phe therapy[17,22].

Our retrospective cohort study at a Baghdad teaching hospital, while limited by sample size and follow-up duration, contributes to this ongoing discussion. Future multicenter studies with larger cohorts and extended observation periods are needed to better understand the long-term effects of dietary interventions on PKU patients' growth and nutritional status. Although Z-scores were used to standardize growth parameters across age intervals, a limitation of this study is the use of independent samples *t*-tests for comparing the differences of growth parameters between different diet control groups, which do not account for longitudinal correlation patterns. Therefore, more advanced statistical methods (e. g., mixed-effects models) are recommended for future studies.

Maintaining optimal dietary control remains crucial in PKU management, serving dual purposes: preserving neurological/cognitive function and supporting healthy physical development. The conflicting evidence underscores the need for standardized growth monitoring protocols and personalized nutritional approaches in this population.

Contribution statement: Basma Adel IBRAHIM designed the study and developed the research methods and protocols. Wasnaa Hadi ABDULLAH and Nabeeha Najatee AKRAM collected patient data and performed clinical assessments. Basma Adel Ibrahim and Wasnaa Hadi ABDULLAH analyzed and interpreted the data. Wasnaa Hadi ABDULLAH drafted the initial manuscript. Nabeeha Najatee AKRAM reviewed and revised the manuscript.

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Conflict of interest: All authors declare no conflicts of interest.

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