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Does the nutritional intake in children with Phenylketonuria have an impact on their growth?

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Abstract

Objective: The objective of the present study was to assess the nutritional intake and its relation to growth of children diagnosed with Phenylketonuria between the ages of 1.2-8 years. **Materials and Methods:** 8 participants were enrolled in this Cross- sectional study and their nutritional intake, growth was assessed using a dietary survey, stadiometer and digital weighing scale. Out of the 8 participants- 5 were girls and 3 were boys. The study participants were enrolled based on their disease condition using purposive sampling and an informed consent was obtained from the parents of these participants. The study was continued for a period of 4 months at Mediscan Systems, Department of Genetics, Chennai, India. Both inferential and descriptive statistics was used to quantify and digest the study parameters. **Results:** The study results suggested that 85% of the study participants were consuming an energy and protein deficient diet which was below 60% of the Recommended Dietary Allowance (RDA). Also, 80% of the participants had a lower than 10th percentile of Mid-Arm Circumference (MAC). About 75% study participants ranged between -2 to -3SD in terms of their weight. 90% participants attained a height of about -2 SD. The BMI/Weight for height ranged between -2 to -3 SD for 69% of the study population. **Conclusion:** This cross- sectional study highlights that there may be an influence of the nutritional intake on the nutritional status of the children diagnosed with PKU.

Key Words: Phenylketonuria, Nutritional intake, Inborn errors of Metabolism, Genetic disorders

Background

Phenylalanine is an essential amino acid that is both ketogenic and glucogenic in nature. Phenylalanine must be consumed from the diet to meet its daily requirements. Phenylalanine hydrolyzes to synthesize the non- essential amino acid tyrosine in the body in the presence of the enzyme Phenylalanine hydroxylase. This is an irreversible reaction. Together Phenylalanine and tyrosine are finally metabolized into fumarate and acetoacetate to produce acetyl Co- A and glucose for energy synthesis (*Harper's Illustrated Biochemistry (EBook, 2018*).

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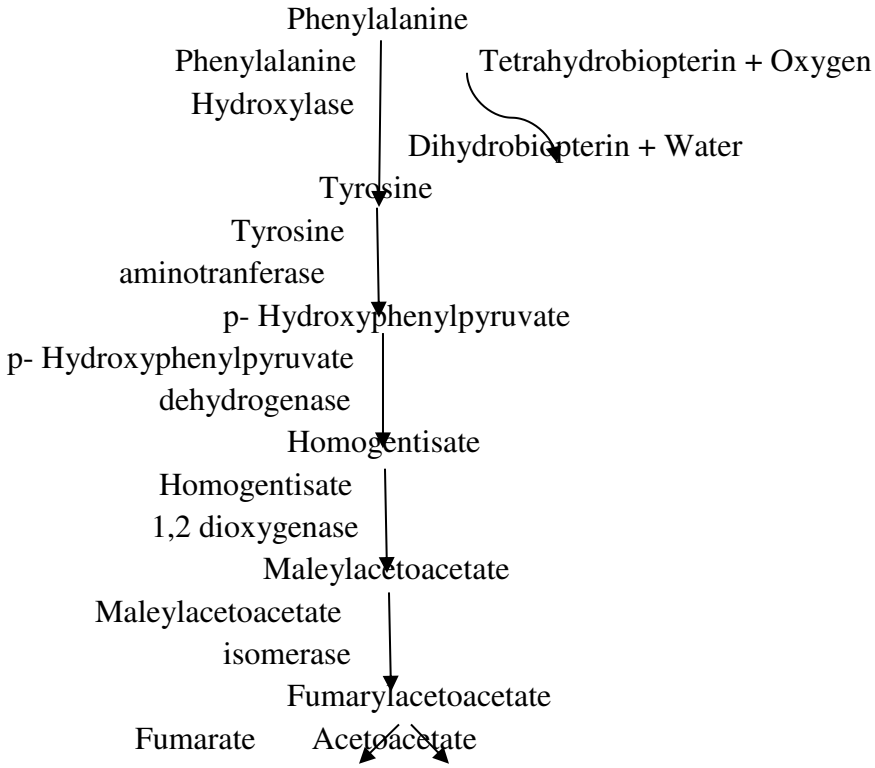
Figure Degradation of Phenylalanine



The above figure explains the metabolic pathway that phenylalanine undergoes to finally yield fumarate and acetoacetate. In this pathway conversion of phenylalanine to tyrosine is an irreversible reaction. The inherited metabolic disorder that occurs due to the deficiency of the enzymes of phenylalanine metabolism is termed as Phenyketonuria (PKU). It is an inherited autosomal recessive disorder in which the ability to metabolize phenylalanine becomes impaired due to the defect in Phenylalanine hydroxylase; Dihydrobiopterin synthetase or dihydropteridine reductase enzymes (Acosta, 2001).

Phenylalanine from the diet is catabolized in the liver and is used for protein synthesis. It is crucial for the synthesis of tyrosine that is a precursor for the synthesis of thyroxine and melanin. Phenylalanine hydroxylase is the liver enzyme that helps in this pathway along with a cofactor tetrahydrobiopterin. The deficiency of Phenylalanine hydroxylase or tetrahydrobiopterin results in toxic build up of phenylalanine in the body and also its conversion to tyrosine is disrupted (Blau N, 2016). Hence, there is deficiency of tyrosine and toxicity of phenylalanine. Phenyl lactate, phenylacetate and phenylalanine get stored and appear in elevated concentrations in the blood and urine. Tyrosine levels may appear normal or lower in the blood (Flydal & Martinez, 2013). This toxic build up of phenylalanine is called hyperphenylalaninemia or Phenylketonuria. Once this inborn metabolic error occurs , it is irreversible and if left untreated or if diagnosed late can lead to mental retardation, hypotonia, epilepsy, physical disability and failure to thrive (van Spronsen et al., 2017).

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According to recent studies, the current burden of the disease has affected over 0.45 million people and about 1 in 23,900 live births get diagnosed with PKU (Hillert et al., 2020). Over 51 countries have been affected severely with 62% of people suffering from Classical PKU. In India the burden is high with an incidence of 1 in 18300 live births (Dave, 2016).

Studies have shown that the most common cause of PKU, is the mutations in the hepatic PAH gene and sometimes in the synthesis of cofactors like Dihydrobiopterin synthetase and Dihydropteridine reductase. The most affected continent is Europe wherein a lot of hetero and homozygous gene types have been identified (Hillert et al., 2020).

According to the national Institute of Health, PKU may be classified into Classical PKU that results due to complete deficiency of Phenylalanine hydroxylase with plasma serum phenylalanine levels ranging between or above 1200 umol/L in a newborn; Morbid PKU in which the residual enzyme activity is exhibited and blood plasma phenylalanine ranges between 900- 1200 umol/L ; Mild PKU is one in which plasma phenylalanine concentration ranges between 600- 900 umol/L ; mild hyperphenylalaninemia ranges between 360-600 umol/L and Benign mild hyperphenylalaninemia ranges between 120- 360 umol/L (Camp KM, 2014).

Based on the Human phenotype ontology, excessive phenylalanine is toxic to the human body and it can cross the blood- brain barrier causing organ failure and mental retardation at a very young age. The first symptoms like blond hair, mousy odor, anxiety, aggressive behavior, seizure, intellectual disability, poor reflexes, irritability, and delayed development can be observed in Children with PKU. After all conditions have been ruled out, a heel prick test can be taken and tandem mass spectrometry can be done to identify PKU. Also, plasma phenylalanine concentration that is consistently falling above 120umol/L and even the phenylalanine:tyrosine ratio shows altered values , these suggest PKU. Beyond this the Phenylalanine hydroxylase gene is examined for mutations and confirmatory diagnosis (Nelwan, 2020). The first symptoms of PKU may appear until after early infancy, once child is started on complementary feeds (Mujamammi, 2017).

Materials and Methods

Objective of the Study- The objective of the present study was to assess the nutritional intake and its relation to growth of children diagnosed with Phenylketonuria between the ages of 1.2-8 years.

Design of the Study- The study design employed was cross-sectional design.

Study site- The study site chosen was The Department of Genetics at Mediscan Systems, Chennai, Tamil Nadu.

Sample selection- About 350 patients were attending the genetic counseling and medical clinic at the Department of Genetics, Mediscan Systems between 1-04-2021 to 1-08-2021. Out of these 10 patients were identified as affected with Phenylketonuria and were approached for the cross-sectional study. Out of these participants only 8 consented to be a part of the study and their parents signed the informed consent. Out of these participants 5 were girls and 3 were boys. The

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mean age of the selected participants fell between 1.2 to 8 years. All the above participants had undergone TMS screening; GCMS studies and a genetic confirmation study to be diagnosed with PKU and were attending the follow up medical clinics at the centre.

Inclusion criteria - All participants suffering from only PKU were included. All participants had to get an informed consent from their parents/caregivers for participation in the study. All participants who were not willing and were diagnosed with some other disorder were excluded

Tools used for the Study- A standardized survey was used to collect the study parameters such as demographic, socio-economic, anthropometric and dietary details of all the participants.

Statistical analysis-Arithmetic mean, standard deviation, frequency distribution and pearson's correlation tests were used analyze the data.

Results

Of the 8 study participants 62.5 per cent were girls and 37.5 participants were boys. The mean calculated age of these participants was mean age of the participants was found to be 5.6 ± 2.54 SD years. In table 1 we can observe the age distribution of all the study participants.

Table 1

Age wise distribution of the study participants

S.No	Age	Sex
1	2	Boy
2	7	Boy
3	5	Girl
4	7	Boy
5	6	Boy
6	9	Boy
7	7	Girl
8	1.8	Girl

In the below table 2, the mean dietary intake and RDA for energy, protein, carbohydrate and fat intake is presented. The energy intake of study participants under the above-mentioned age groups was compared with that of the Recommended Dietary Allowances, ICMR, 2020. The mean energy intake was 1056.2 ± 205.78 Kcals which was 30% lower as compared to the RDA of 1467.5 ± 265.90 Kcals. The mean protein intake of the participants was lower at 24.45 ± 8.73 g per day. This protein intake was 110% met as per the RDA. As per the dietary guidelines for the management of inborn errors of metabolism quoted in the Ross protocol, this protein intake was 50% lower than the 1.5-2g/kg/day recommendations. This lower protein intake is arbitrated to the highly restricted nature of the diets followed with disorders of amino acid metabolism. The mean carbohydrate and fat intake were sufficiently met as per the RDA and can be observed in the below table 2.

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Table 2

Comparison of nutrient intake of the Study participants with the RDA, ICMR, 2020

S.No	Energy (KCals)	RDA	Protein (g)	RDA	Fat (g)	RDA	Carbohydrate (g)	RDA
1	809.9	1110	34.5	12.9	40.5	25	113	130
2	1060	1700	21	25.3	15.9	25	137.5	175
3	774	1360	29.4	18.3	28	25	78.9	150
4	1100	1700	28.9	25.3	37.3	25	221.7	175
5	951	1360	12	18.3	8.5	25	78.5	150
6	1372	1700	34.8	25.3	29	25	149.5	175
7	1250	1700	14.5	18.3	27.2	25	136.8	175
8	1132.7	1110	20.5	12.3	30.6	25	224.75	130

The mean calcium and iron intake were significantly lower as compared to the RDA. The mean calcium intake was 60% lower as compared to the RDA for ages of 1-3 years at 500mg, 3-6 years at 550mg and for 7-9 years at 650 mg of calcium per day. The mean iron intake was 5.5 ± 4.15 mg/day as compared to the mean RDA for age which is 12.25 ± 3.15 mg/day. These results have been presented in Table 3 below:

Table 3
Comparison of calcium and iron intake of participants with RDA, ICMR, 2020

S.No	CALCIUM (mg)	RDA	IRON (mg)	RDA
1	163.7	500	4	8
2	187.5	650	3.4	15
3	166.69	550	6.3	11
4	289.6	650	14.8	15
5	131.7	550	1.5	11
6	227	650	5.7	15
7	157	650	2.3	15
8	281.5	500	6.5	8

The Table 4 suggests the mean height and body weight indices of the study participants. The body weight of the participants was compared to the WHO z-scores for age and the mean weight of 24.24 ± 14.6 kg is 50% lower than the recommended z-scores. The mean height of the participants was 113.12 ± 28.00 cm which was 45% lower than the Z-scores of height for age.

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These results suggest that stunting and malnutrition in that undernutrion is highly prevalent among people diagnosed with disorders of amino acid metabolism.

Table 4

Measured height and body weight of the study participants

S.No	Height (cm)	Body weight(kg)
1	85	10.3
2	126	24
3	135	42
4	140	47
5	101	14
6	136	29
7	120	22
8	62	5.69

All the participants who had a poor dietary energy and protein intake were also identified to have a poor height. The participants with lower calcium and iron intake also attained lower body weight.

The above mentioned results suggest a possible link between attainment of height and weight and adequate energy and protein intake among participants with inborn errors of metabolism.

Discussion

According to many studies, the main aim of treatment is dietary restriction of phenylalanine (Guo et al., 2018). As Phenylalanine is present in all foods rich in protein, hence protein restriction in terms of milk, meat, fish, eggs and legumes is the gold standard of treatment. In order to support growth, mental and intellectual development and neuropsychological skills, supplementations of other aminoacids through metabolic formula is recommended (Yannicelli et al., 2003). Dietary phenylalanine is less restricted after child reaches adolescence (Ashe et al., 2019). Restrictions are made strictly according to the plasma phenylalanine levels to avoid over restriction that can contribute to cognitive deficits (Bruinenberg et al., 2019).

According to a recent study conducted by Sailer et al; nutrient intake, body composition and serum phenylalanine levels in children with Phenylketonuria were compared to healthy children. This study inferred that Children with Phenylketonuria consumed fewer calories from protein and fat as compared to healthy controls. Also, stunting was higher and lean body mass was observed to be lower in children affected with Phenylketonuria (Sailer et al., 2020).

In a study done by Bernstein et al; a newer simplified dietary approach to PKU was investigated. In this study, foods that contained <50-75 mg of phenylalanine per 100 g edible portion and the metabolic formula that had no phenylalanine were regarded as free foods and not included in calculating the day's phenylalanine consumed. This way patients had more variety in their diet, could consume food even outside home with peers and also had increased their fruits and vegetables intake, while still maintaining their dietary and serum phenylalanine within expected range. Thus, this study recommended a simplified diet as an approach to better the serum phenylalanine maintenance and improve patient adherence to a low phenylalanine diet (Bernstein et al., 2017).

A study conducted by Viau et al; examined the effect of phone- based Motivational Interviewing on the increase on patient activation, self efficacy and dietary adherence in individuals affected with PKU. Participants were counseled over the phone once every month for six months and dietary counseling was done using Motivational Interviewing. Their self goals, dietary and supplement goals and maintenance of phenylalanine goals were asked during the beginning of the study and these goals were also reviewed each month. At the end of six months, statistically significant increment in patient activation, achievement of all dietary and supplement goals, maintenance of phenylalanine levels and improved self efficacy were reported (Viau et al., 2016).

In a systematic review conducted by Rocha et al; current perspectives on the dietary management and interventions in PKU were discussed. The role of specialized low protein foods that are essentially made of carbohydrates, fats, essential fatty acids, vitamins and minerals was examined. Studies from Europe, Turkey, Portugal and the US have determined these foods to have a beneficial effect in lowering the serum phenylalanine levels, better palatability, improved quality of life and better dietary adherence and metabolic control. It also helps in providing variety and enhancing the overall energy intake thereby promoting growth (Rocha & MacDonald, 2016).

Therefore, we can infer that the prevalence of poor growth outcomes with PKU is alarming due to the compromised calorie and protein intake. The dietary restrictions due to the nature of the disease should be re-evaluated to compensate for the growth and development and also to combat the increasing energy demands of the disorder. Hence, this study throws light on the importance of the meeting the RDA for energy and protein levels.

Conflict of interest

All the above quoted authors have no conflict of interest.

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