



The implications of Phenylketonuria on oral health

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Abstract

Purpose: This study was performed to evaluate the oral health of children with PKU and to assess, *in vitro*, the erosive potential of 5 amino acid supplements commonly prescribed in the management of these children.

Methods: Forty children with phenylketonuria underwent a full dental examination and were compared with an age and sex matched control group. The erosive potential of the supplements was assessed by comparing their pH and titratable acidity to those of Coca Cola and orange juice.

Results: There was no significant difference between the affected and control groups in the level of dental caries, with over 75% of the children examined being caries free. However significantly more (33%) children with phenylketonuria exhibited signs of tooth wear compared with 24% of the controls ($P < 0.05$). While Coca Cola had the lowest pH (2.46), the titratable acidity of the flavoured supplements (92.86-126.8 mEq/l) was significantly higher than both their unflavoured counterparts (4.18-14.0mEq/l) and Coca Cola (38.56mEq/l).

Conclusions: Despite the potentially damaging nature of their diet, significantly less children with PKU had ever seen a dentist. Health professionals involved in the care of these patients should be aware of the implications of management and provide appropriate dental advice and referral. (*Pediatr Dent* 21:433-437, 1999)

Phenylketonuria (PKU) is an autosomal recessive genetic disorder with a birth incidence of between 1:5,000 to 1:20,000.¹ Individuals affected by this inborn error of metabolism have a deficiency in the liver enzyme phenylalanine hydroxylase, which converts phenylalanine to tyrosine. The resulting abnormally high concentration of plasma phenylalanine will, if not treated within the first few weeks of life, lead to progressive intellectual disability. With neonatal screening currently available in many countries, affected children are usually treated from early infancy; these children can grow and develop normally, and may be expected to lead a relatively normal, healthy life into adulthood.

The management of these patients involves adherence to a low protein diet, which is essential to restrict the intake of phenylalanine to only the amount necessary for normal protein synthesis. To make up the energy requirements, the diets of these children are often high in carbohydrates, which are usually taken frequently throughout the day. To ensure suffi-

cient intake of essential amino acids, phenylalanine-free protein supplements (available in powder form to be made up as drinks) are necessary. These too are consumed at regular intervals throughout the day and occasionally during the night.

Dental caries is a multifactorial disease of bacterial origin. However, the role of fermentable carbohydrates in providing a substrate from which the cariogenic bacteria can produce acid, which in turn causes demineralization (and eventual cavitation) of susceptible tooth surfaces, is well recognized.² Furthermore not only is the total amount of sugar consumed an important factor influencing the development of caries but also the frequency of intake, with increased snacking related to increased caries incidence.^{3,4}

Erosion is the progressive loss of dental hard tissues not involving bacteria.⁵ Dental erosion has been attributed to the presence of acids in the mouth. The origin of these acids may be either extrinsic or intrinsic. Extrinsic acids are found principally in the diet in the form of acidic drinks and foods⁶ while intrinsic acids are found in the stomach contents and may be regurgitated back in to the mouth in gastric reflux or in certain eating disorders.⁷

Given the combination of the frequent intake of carbohydrates and the potentially acidic nature of the protein supplements, children with PKU are on a diet which appears to place them at risk of developing either or both dental caries and erosion. The potential sequelae to both dental caries and erosion is loss of tooth structure, cavities, pain, infection, need for extensive (and expensive) restorative dental treatment, and even dental extractions. To date there have been very few reports on oral health of children with PKU.⁸⁻¹⁰ These studies suggest that affected children do not experience significantly greater amounts of dental caries. To date, there has been no assessment of the potential problem of dental erosion in these children. The aims of this study were twofold; to evaluate the oral health of children with PKU and secondly to assess, *in vitro*, the erosive potential of the amino acid supplements taken by children with PKU.

Methods

Clinical study

Ethical approval was gained from the ethics committee at the New Children's Hospital, Westmead, Sydney, Australia. The

Table 1. A Summary of the Dental History of the Test and Control Children

	Gender (%)		Mean age in years (+/-SD)	Fluoridated water (%)	Dental attendance (%)			Toothbrushing (%)		
	Male	Female			Regular	Occasional	Never	1/day	2/day	Occasional
PKU (N = 40)	23 (56)	17 (43)	8.76 (5)	37 (93)	14 (35)	12 (30)	14* (35)	16 (40)	20 (50)	4 (10)
Control (N = 33)	15 (46)	18 (56)	8.98 (3)	29 (88)	17 (50)	12 (35)	5* (15)	13 (40)	18 (55)	2 (6)

*Signifies statistical significance ($P < 0.05$).

children involved in the study were among those who attended the PKU clinic held weekly at the hospital and whose parents had given written consent for their participation. A control group made up of unaffected siblings and healthy children enrolled from the general outpatient clinic waiting area was also examined. The age of the children ranged from two years and two months to 17 years and 10 months. A standard questionnaire was completed by all participating parents to establish information concerning their child's oral hygiene practices, exposure to fluoride, and dental attendance history.

All children were examined in the dental chair, using overhead dental lighting, a mouth mirror, and a probe by one of the authors (HA). A full dental examination was carried out; caries diagnosis was based on the criteria set down by the World Health Organization,¹¹ in which diagnosis was made only where there was a visible cavity involving dentine. Radiographs were not taken as part of the study protocol. If there was a clinical indication radiographs were arranged for a subsequent visit as part of routine dental care or the patient was referred to their general practitioner for care. Assessment of oral hygiene levels was done using Modified Plaque Index¹² and Gingival Inflammation Index.¹³ The presence of tooth wear was recorded using the Tooth Wear Index of Smith and Knight.¹⁴ Intraoral photographs were taken for recording/scoring tooth wear and an assessment was made of whether the wear resembled dental erosion or had the appearance of tissue loss caused by other wear processes such as attrition or abrasion.

Statistical analysis was conducted using SPSS for Windows. All numeric scores were compared between PKU and control groups using the Mann-Whitney test while discrete characteristics, such as age, were compared using the Pearson Chi-Square test. The impact of PKU on several clinical outcomes, dental attendance, probability of being caries-free, and incidence of tooth wear, was examined through logistic regression.

In vitro study

For the in vitro study, the pH and titrateable acidity (TA) of five amino acid supplement drinks (XP Maxamaid, XP

Maxamaid Orange Flavoured, XP Maxamum, XP Maxamum Orange Flavoured, and Novamix Flavoured; SHS International Ltd., Liverpool, England.) and two control drinks (orange juice and Coca Cola) were determined. The amino acid supplement drinks were each freshly prepared according to the manufacturer's instructions prior to testing. Measurement of pH was done using a PHM 83 Autocal pH meter (Radiometer, Copenhagen); the pH of five different samples of each drink was measured and the mean pH was noted. One hundred ml of each drink was titrated to neutrality (pH 7.0) against 0.1M NaOH solution, and the volume of sodium hydroxide required was recorded in mEq/l. Mann-Whitney U tests were conducted to compare the pH and titrateable acidity of Coca Cola and amino acid supplement drinks.

Results

Clinical Study

A total of 40 PKU children and 33 healthy controls were seen and examined during the six month study period. Table 1 describes the characteristics of the two groups, there being no significant difference in the age, sex, or numbers resident in areas with water fluoridation. There was little difference in the oral hygiene practices of the two groups, with all children brushing their teeth with fluoridated toothpaste either on their own or with the help of their mothers. Almost all the healthy control children (94%) and slightly less in the PKU group (90%) brushed at least once a day. Significantly more of the healthy control children (85%) had seen a dentist at least once while 35% of the PKU children had never seen a dentist ($P < 0.05$). However, there was no difference in the number of children who were reported to see a dentist regularly as opposed to just occasionally.

Table 2 describes the oral health indices of the two groups of children. There was no significant difference in the caries levels in either group of children, with 83% of the PKU and 79% of the control groups children being decay free. Interestingly, while there was no significant difference in the amount

Table 2. The Oral Health Indices of the PKU Compared With the Healthy Control Group of Children

	Caries free (%)	Mean plaque index (+/-SD)	Mean gingival inflammation (%)*	Presence of tooth wear (%)*	Wear typical of erosion*
PKU	33 (83)	0.70 (.44)	0.54 (1)	13 (33)	9
Control	26 (79)	.75 (.46)	.23 (.28)	8 (24)	2

*Signifies a significant difference ($P < 0.05$).



Fig 1. An example of the wear pattern seen in a child with PKU. This is typical of dental erosion.

of plaque and debris on the teeth of the two groups of children, those with PKU had significantly more gingival inflammation ($P < 0.05$). A total of 33% (13) of the children with PKU had tooth wear. In four of the cases the type of wear, as indicated by the clinical appearance and affected sites, appeared to be mainly due to attrition. However, in the other nine there was distinctive occlusal “cupping” or “ditching” characteristic of erosion (Fig 1). In the control group, wear was seen in eight (24%) children, but in only two cases was it characteristic of erosion.

In vitro testing

The pH and TA of the phenylalanine free amino acid supplement drinks and the two control drinks are shown in Table 3. The pH scores of all the drinks tested were significantly different to each other ($P = 0.008$), with that of Coca Cola being the lowest (2.46). The addition of flavoring to the protein supplements significantly lowered their pH from 6.76 to 4.48 for XP Maxamaid and from 6.44 to 4.90 for XP Maxamum. Unflavored Novamix was not available for testing, however, the pH of the flavored Novamix was 4.87, which is closer to the other flavored drinks. The TA of both unflavored supplements, 4.18 and 14.40 mEq/l, was significantly lower than those of their flavored counterparts, 126.8 and 92.86 mEq/l respectively ($P = 0.008$). Furthermore, the TA of all the flavoured drinks, including the orange juice, was significantly greater than that of Coca Cola ($P = 0.008$).

Discussion

The caries experience of the children with PKU in this study was generally low, with over 80% of children being caries free.

This is somewhat surprising given the potentially cariogenic nature of the PKU diet, in which protein is severely restricted and even the intake of fruit and vegetables must be calculated in the dietary prescription. The remainder of the recommended energy intake is provided by foods which are low in protein content but high in carbohydrate and fat. Daytime snacks may consist of small amounts of fruit, crisps, low protein biscuits, fruit sticks, sweet confectionery or sweetened beverages which are very low in phenylalanine. At times of intercurrent illness or poor growth, appetite is low and additional high energy snacks are encouraged. Young children may eat snacks as often as every two hours throughout the day: a diet, which might be expected to be associated with higher levels of caries. The lack of a significant increase in caries levels between children with PKU has been reported earlier.⁸⁻¹⁰ It has been suggested that phenylalanine may constitute a factor that limits the growth of plaque microorganisms and that this may explain the low caries rate in the presence of a highly cariogenic diet.¹⁰ Furthermore, in the current study there was no significant difference between the PKU children and the controls, both groups having significantly lower levels of caries than is reported for Australian children in general.¹⁵ The caries rates for this study are, in general lower than those reported earlier. This may reflect the change in pattern of use of fluoridated toothpastes and in their exposure to fluoridated water. Most (90%) of the children in the current study lived in areas supplied by optimally fluoridated water, a factor known to reduce the incidence of caries.¹⁶

Despite a slightly higher incidence of tooth wear among the PKU children compared with the controls, conclusions should be drawn with care. The dietary intake of the control children was not assessed, and yet it can be presumed that they, too, consume significant quantities of potentially erosive foods and drinks (i.e., citrus fruit, fruit juices, carbonated beverages, and sports drinks). In addition, defining the principal wear process occurring in any one mouth based upon the appearance of the teeth is somewhat subjective. Characteristic features of erosion are concave defects with smooth, rounded margins and a highly polished appearance. Attrition (tooth-on-tooth wear that may occur during grinding) results in a flatter wear facet limited predominantly to the incisal edges and molar cusps. Nevertheless, nine of the 13 PKU children who had signs of wear demonstrated features of erosion. Given the young age of the patients and hence the short time that the teeth may have been exposed to the acidic environment, these early signs are clinically significant.

While pH is considered to be important, the amount of tritrateable acid in a product is thought to give a more accurate indication of the erosive potential as it provides an

Table 3. Mean pH and Titratable Acidity of the Test Drinks and Controls

Drinks (n=5)	MD	MDF	MM	MMF	NXF	OJ	CC
Mean pH (+/- SD)	6.76 (0.01)	4.48 (0.01)	6.44 (0.01)	4.90 (0.02)	4.87 (0.02)	3.75 (0.02)	2.46 (0.01)
Titratable acidity in mEq/l (+/- SD)	4.18 (0.58)	126.80 (1.64)	14.40 (0.58)	92.86 (0.35)	86.80 (1.60)	109.50 (0.86)	38.56 (2.90)

(MD=XP Maxamaid, MDF=XP Maxamaid Orange Flavoured, MM=XP Maxamum, MMF=XP Maxamum Orange Flavoured and NXF=Novamix Flavoured, OJ=Orange Juice, CC=Coca Cola) All results are statistically significantly different ($P < 0.05$).

indication of the amount of free acid available.¹⁷ The higher the TA and the more free acid, the greater the erosive potential. A previous study compared the erosive potential of orange juice (pH=4.5) with a cola drink (pH=2.4). Over the short term (five minutes), the amount of erosion (as measured by the amount of calcium dissolved out of tooth structure) was the same for both drinks. However, after 40 minutes the orange juice had caused significantly more calcium dissolution than the cola drink.¹⁸ In the current study, all of the amino acid supplements had higher pH values than both the orange juice and the Coca Cola. However all three flavored supplements had pH values below the critical pH (5.5), at which point enamel starts to demineralize. When these pH values are considered together with the TA values, it is possible that all three flavored supplements have significant erosive potential, particularly XP Maxamaid Orange Flavored, which had the lowest pH (4.45) and highest TA (126.8 mEq/l). It is unfortunate that the flavored supplements are potentially more erosive, as the unflavored supplements are relatively unpalatable. The newly introduced Novamix Flavored does offer some improvement, as the TA is significantly less than that of either of the two flavored drinks.

There are many factors other than pH and TA that are thought to influence the erosive potential of a drink. These include the chemical composition of the drink, specifically the calcium and phosphate content¹⁹ and host response in terms of flow rate and buffering capacity of saliva.²⁰ However, frequency of exposure to the acid attack is also likely to be as significant in the development of dental erosion as frequency of exposure to fermentable carbohydrates is in dental caries. Children with PKU may take these supplements as often as every four hours for life and as such this group of children is undoubtedly at risk of developing dental erosion during their lives.

Children with PKU are potentially at risk of oral pathology. Their management includes dietary therapies which aim to promote normal growth and development, but which are often highly cariogenic and potentially erosive. Despite this, significantly more children with PKU had never seen a dentist compared with the healthy controls. The general oral health of the children with PKU was not clinically very different from the healthy controls. However, the higher levels of gingival inflammation and of tooth wear should be noted. Children with chronic medical conditions and their families have many pressures placed upon them. Awareness of oral health may not be high and there is often a delay in seeking dental care resulting from the preoccupation with their more immediate medical needs.²¹ Additionally, the medical profession in general has a poor appreciation of oral health issues, with little time in either general medical or specialist pediatric training being devoted to dental education. Hence, the medical profession may not counsel patients appropriately. Often there are conflicting interests: the maintenance of normal growth and development must be balanced against concern about the potential damage to the dentition. However, the potential sequelae of untreated dental disease—namely that of pain and infection—can have implications on the child's metabolic stability and treatment may be complicated by the underlying disorder.

An important objective in health management is the prevention of disease initiation and progression. Identification of

groups of children at risk of oral disease is important; children with PKU are, by the nature of their diet and dietary supplement, at risk of developing dental caries and tooth erosion. The management of these children and children with other inborn errors of intermediary metabolism has recently been reviewed.²² However, it is important for all health professionals involved in the care of these patients to be fully aware of these implications, to provide appropriate advice and to refer early for dental consultation. Good communication between the pediatrician, pediatric dentist and particularly a specialist dietitian, is essential for effective management. Prevention in the form of appropriate use of fluoridated toothpastes and supplements, plus reducing the frequency of between meal snacks, will help to reduce the risk of dental disease. Furthermore, the consumption of water rather than soft drinks should be encouraged. However, it is important that any advice received by the patient/parent does not contradict advice received from other careworkers and that help is enlisted from both pediatricians and dietitians in reinforcing the need for daily preventive oral health measures in these children.

Conclusions

Based on the results of this study:

1. Children living in a water fluoridated area with phenylketonuria did not have significantly higher levels of dental caries than healthy controls. While the levels of plaque deposits were not significantly different, the children with PKU did exhibit more gingival inflammation.
2. Children with phenylketonuria did have a significantly higher incidence of tooth wear, of which erosive wear appeared to be the predominant process. However, the numbers involved in this study were small. Further study is required.
3. The amino acid supplements used in the management of children with phenylketonuria are potentially erosive with the flavored varieties in particular having a low pH and high titrateable acidity.
4. There is a need for those responsible for the general care of children with phenylketonuria to be aware of the potential oral health problems.

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RESEARCH ABSTRACTS PRESENTED AT THE 1999 ANNUAL SESSION WERE PRINTED IN THE SPECIAL ISSUE REFERENCE MANUAL. INADVERTENTLY ONE WAS OMITTED AND IT APPEARS BELOW.

PREVALENCE OF PRIMARY DENTITION CARIES IN HIV-INFECTED CHILDREN: A LONGITUDINAL STUDY.

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The purpose of this longitudinal clinical study was to determine primary dentition caries prevalence in HIV-infected children, and to compare caries prevalence with CD4 percentage (CD4%) and immune suppression category. Forty-five children with vertical HIV transmission were evaluated for caries in the primary dentition at baseline and at 6 month intervals over a 24 month period. Caries prevalence was also compared with CD4% (>25%, 15-24%, <15%) and immune suppression category (immune suppression: none, moderate, severe). Caries in the primary dentition was expressed as dfs and dft. With primary dentition caries, comparisons were made among all children (2-9 yr-olds) 2 to 4 yr-olds, and 5 to 9 yr-olds and compared with NHANES III data. Caries-free status was also determined.

Baseline Data				CD4%			Immune Suppression		
	2-9 yr-olds	2-4 yr-olds	5-9 yr-olds	>25%	15-24%	<15%	None	Mod	Severe
dfs(mean)	9.2	2.7	14.4	4.9	6.4	9.5	1.9	4.4	10.4
dft (mean)	4.3	3.0	4.5	3.8	3.5	3.6	na	3.2	4.1
caries-free	57%	65%	32%	54%	71%	52%	57%	64%	52%
24 Month Data									
dfs (mean)	10.5	10.6	10.5	6.3	15.3	19.5	3.3	6.8	18.3
dft (mean)	3.1	3.0	3.3	2.1	6.0	4.7	1.0	2.6	5.0
caries-free	41%	52%	30%	50%	0%	42%	50%	43%	39%

NHANES III (1988-1991): National Survey of Primary Dentition Caries in US Children (*J Dent Res* 1996;75:633)

dfs(mean)	3.1	1.2	4.1
dft (mean)	1.4	0.6	1.9
caries-free	62%	83%	50%

Caries prevalence in HIV-infected children is considerably greater than in the US pediatric population, and increases with decreased CD4% and moderate to severe immune suppression. NIH-NIDR 1-RO1-DE11363