ORIGINAL RESEARCH PAPER

Medical Science

A Relation in between Metabolic Diseases and Oral Health: Phenylketonuria

KEY WORDS: Phenylketonuria ,Dental cavity; Serum calcium, phosphate, fluoride and lactic acid,.

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ABSTRACT

Introduction:,

The present study aims to provide an insight into the oral status of children& adults suffering from two different metabolic diseases. At the same time it seeks to answer questions on whether the dietary regulations of the children have an effect on their dental health and whether there is an alteration in their oral microflora, putting the children at a higher or lower risk for developing dental caries and periodontal disease. Diabetes is a metabolic disorder i.e. principally classified into type 1 and type 2 diabetes. Traditionally, children suffering from type 1 diabetes had to follow a diet restricted in carbohydrates In order to maintain normal blood sugar levels. The intake of carbohydrates was aligned with the insulin regime. Advancements insulin therapy regimes have led to the relaxation of dietary restrictions &type 1 diabetics are now able to follow a diet .And also the results of the present research for children's showed that the mean dmfs index value in the group of children's suffering from PKU was statistically significantly higher than in the healthy children and the diabetic children. Thus the study is of great practical importance In Phenylketonuria, the metabolic disorder is the inability to convert a substance called phenylalanine to tyrosine due to deficiency of an enzyme called phenylalanine hydroxylase.

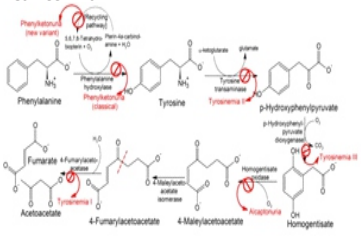
INTRODUCTION

The present study aims to provide an insight into the oral status of children& adults suffering from two different metabolic diseases. At the same time it seeks to answer questions on whether the dietary regulations of the children have an effect on their dental health and whether there is an alteration in their oral microflora, putting the children at a higher or lower risk for developing dental caries and periodontal disease. Diabetes is a metabolic disorder i.e. principally classified into type 1 and type 2 diabetes. Traditionally, children suffering from type 1 diabetes had to follow a diet restricted in carbohydrates [1] in order to maintain normal blood sugar levels. The intake of carbohydrates was aligned with the insulin regime. Advancements insulin therapy regimes have led to the relaxation of dietary restrictions &type 1 diabetics are now able to follow a diet quite similar to normal healthy individuals [2] The percentage of the population & diabetes is approximately 8-12%. The fraction is increasing with age, reported.

Total children's are selected between the ages of 3 and 18 years were recruited for each group in the study. The total sample consisted of 238 children. The PKU group had 38 children and both the diabetic and healthy control group comprised of 100 children each. Demographic data was collected with the help of a standard questionnaire.

The dental status was assessed by the dmfs / DMFS Index and the gingival health and oral hygiene was evaluated using the Papillary Bleeding Index (PBI) . i.e. the aim of this study was to investigate the oral parameters that influence the caries risk and risk of developing periodontal disease in children with phenylketonuria (PKU) and type 1 diabetes. The parameters to be assessed were the dental and oral hygiene status, gingival health and oral microorganisms in children with diabetes, PKU and healthy children.

The findings of present study, it can be concluded for adults that the adequate level of calcium, phosphate and fluoride is responsible for the significant deposition of these minerals in plaque which greatly reduces the developmental caries in the adjacent enamel i.e. the diabetic patients are more prone to develop dental caries with



In figures shows the defect in phenylketonuria can be represented as above:

calcium, phosphorus levels decreases and alkaline phophatase level increases. but in diabetic females with dental caries serum phosphorus levels

are very low in comparision to diabetic male. And also the results of the present research for children's showed that the mean dmfs index value in the group of children's suffering from PKU was statistically significantly higher than in the healthy children and the diabetic children. A statistically significant difference in the dmfs Index value was found between the three groups. The mean dmfs index value for the PKU children (4.18) was found to be relatively high as compared to the other two groups.[3] No statistically significant difference was found in the mean DMFS values between the children and adolescents in the three groups. : Children with PKU possess a higher caries rate in their primary dentition. While diabetic children have a lower caries rate in their primary dentition, they show a higher risk of developing periodontal disease.

It has been suggested that patients with PKU are more likely to have dental caries and or dental erosion as their diets tend to include more sugary foods and acidic drinks. As mentioned above, children with PKU derive less protein from foods; [4] hence it is necessary for them to consume more carbohydrates and fats to

supplement their energy [5] It is, therefore, proposed that both groups of child patients, i.e. PKU and type 1 diabetics be encouraged to seek early dental advice and be incorporated in a meticulous prevention programme.

Thus the study is of great practical importance. The present study aims to provide an insight into the oral status of adults & children's which is suffering from two different metabolic diseases i.e. diabetes mellitus & phenylketonuria

(PKU) with references to macro-minerals elements such as calcium, phosphorous, fluoride & pH and alkaline phosphatase.

SUMMARY:

Dental caries, also known as tooth decay or a cavity, is an infection, bacterial in origin, that causes demineralization and destruction of the hard tissues (enamel, dentin and cementum), usually by production of acid by bacterial fermentation of the food debris accumulated on the tooth surface. If demineralization exceeds saliva and other remineralization factors such as from calcium and fluoridated toothpastes, these hard tissues progressively break down, producing dental caries (cavities, holes in the teeth).[6] The bacteria most responsible for dental cavities are the mutans

streptococci, most prominently Streptococcus mutans and Streptococcus sobrinus, and lactobacilli. If left untreated, the disease can lead to pain, tooth loss and infection. Today, caries remain one of the most common diseases throughout the world. The systemic effects of periodontal diseases have been of increasing interest during the past two decades. Periodontitis is an inflammatory response to a bacterial challenge and represents a portal of entry for periodontal pathogens, bacterial endotoxins, and proinflammatory cytokines . Thus, the local oral inflammatory disease, periodontitis, may induce and perpetuate a systemic inflammation that may aggravate systemic diseases such as cardiovascular disease , pulmonary disease , rheumatoid arthritis and diabetes mellitus .[7]

It is often essential for children suffering from metabolic diseases to follow a strict diet to keep the disorder under check and to be able to develop and function normally. Phenylketonuria (PKU) is a metabolic disorder in which the patients present with an absence or deficiency of the enzyme phenylalanine hydroxylase which is essential to metabolise the amino acid phenylalanine into the amino acid tyrosine. Uncontrolled, the disease can lead to the accumulation of phenylalanine in the blood and brain causing disabilities. In order to keep the ingestion of phenylalanine to a minimum, children with PKU follow a special low protein diet. At the same time, their diet is rich in carbohydrates and the phenylalanine -free formula drinks have a high pH[8] The frequency of ingestion of these carbohydrates is high and therefore, the risk for the development of caries in children suffering from PKU is considered to be high.

Literature Review

The ISPAD (International Society for Pediatric and Adolescent Diabetes) has defined Diabetes as follows:

"Diabetes is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The abnormalities in carbohydrate, fat, and protein metabolism that are found in diabetes are due to deficient action of insulin on target tissues. If ketones are present in blood or urine, treatment is urgent, because ketoacidosis can develop rapidly."[9]

Patients with hyperglycemia present with the symptoms of polyuria, polydipsia, blurred vision and weight loss associated with polyphagia. Chronic hyperglycemia may be accompanied by impairment of growth and susceptibility to certain infections. Inadequacy due impairment of insulin secretion and defects in insulin action may exist in the same patient, making it difficult to define which of the above is truly responsible for the hyperglycemia.

Diabetes can be mainly classified in type 1 and type 2 diabetes. Further classification of diabetes includes cases of hyperglycemia due to genetic defects of the -cells or in insulin action, endocrinopathies, infections, induced by drugs or chemicals, pancreatic diseases, associated with syndromes and gestational diabetes.

Heterogeneous epidemiological data about the prevalence of periodontal diseases are available in the dental literature. Due to the advanced age of the subjects examined in the present study, the following epidemiological data predominantly focus on the prevalence of chronic periodontitis in adults and older subjects.

Cariology is the study of dental caries. Dental cavity is a multifactorial disease, which has affected people throughout the ages. Many constituent of serum and saliva, both organic and inorganic have potentially protective role. These include calcium, phosphate, fluoride ions and bicarbonate buffer systems . Epidemiological studies have supported the view that raised level of calcium, phosphate, and Fluoride in plaque might inhibit dental caries . It is commonly thought that the organic acid produced in dental plaque is responsible for caries, but this is only partly true because it is a complex effect of pH, calcium, phosphate and fluoride, which brought about minerals dissolution . In theory, continuous saturation of plaque fluid with mineral ions should completely over come the harmful effect of plaque pH depressions, and thus should be more effective than fluoride therapy. In low concentration, fluoride alone only partially inhibits the net dissolution of enamel and the production of acid by plaque organisms, while demineralization requires the presence of calcium and phosphate .The present study is done to estimate serum calcium, phosphate, and fluoride in the patients of dental caries in diabetes and to see and compare their level with the severity of disease and control.

Another aims of study to provide an insight into the oral status of children suffering from two different metabolic diseases. At the same time it seeks to answer questions on whether the dietary regulations of the children have an effect on their dental health and whether there is an alteration in their oral microflora, putting the children at a higher or lower risk for developing dental caries and periodontal disease.

A number of studies have been dedicated to the investigation of oral health in diabetics. The majority of these studies have been focused on the relationship between periodontal disease and diabetes and fewer on dental caries and diabetes. Although the risk of developing periodontal disease in diabetics is well established, the association of dental caries and diabetes is still debated[10]. *Dental cavity; Serum calcium, phosphate, fluoride and lactic acid, phenylketonuria. Dental cavity; Serum calcium, phosphate, fluoride and lactic acid, phenylketonuria. [11]*

It is, however, difficult to interpret the significance of the results in relation to children as a large amount of the studies regarding oral health in diabetics have been carried out with type 2 diabetic adult patients. In the oral health of forty children with PKU and the erosive potential of 5 amino acid supplements commonly prescribed in their management[12] They found no significant difference in the level of dental caries between the PKU children and the healthy children. [13] PKU children did, however, show more signs of tooth wear. Supporting this finding, the study did reveal that the titratable acidity of the flavoured supplements was significantly[14].

MATERIALS AND METHODS

A total of 200 subjects of either sex aged >30 years adults and <10yrs children's were selected from the Naraina Medical college &Hospital. Kanpur. All the subjects were free from any systemic illness and were not taking any caries preventive regimen like fluoride toothpaste, fluoride rinses or NaF/calcium tablets. Subjects who gave improper history about missed tooth or suffering from any type of Xerostomia or having any oral inflammatory problems were not included in the study. Dental examination is done with the assistance of dentist under natural light source. Decayed, missed and filled teeth (DMFT) were used as index for scoring the dental caries . All subjects were distributed into 5 groups (Table-1) each having twenty individuals. Like group 1 with DMFT index 30-40, group 2 with DMFT index 41-50, group 3 with DMFT index 51-60 and group 4 with DMFT index more than 60, while the control subjects have the DMFT index equal or less than 3.

A cross-sectional study for children's was conducted and involved the examination of patients from 3 groups Children suffering from PKU (Group A) und type 1 diabetes (Group B) . The control group (Group C) consisted of healthy children. Children between the ages 3 and 18 years were recruited for the study. The total sample consisted of 238 children. Both Group B and C comprised of 100 children and Group A had 38 children. The patients were matched for gender and age.

10 mL of venous blood sample was drawn after applying a tourniquet, followed by proper aseptic precautions with a sterile disposable plastic syringe without any anticoagulant. A drop of blood was put on the electrode of pH meter from the novel of syringe carefully for blood pH determination. 0.5 mL of blood was immediately put into sterile bottle containing 0.5 mg of EDTA (Ethylene Diamine Tetra Acetic acid) powder, shaken gently and

stoppered. This blood is used within 24 hours for the estimation of lactic acid.

The blood in the syringe was covered, labeled and transferred in an ice box to the laboratory. Blood sample was centrifuged for 15 minutes at 3000 rpm. The hemolyzed samples were discarded. The supernatant layer of serum was then separated and poured in labeled glass bottles and stored in deep freezer at -20oC.The serum pH was measured electrometrically with the glass electrode by digital pH meter HI 8014 (Hanna Instrument, USA). After calibration and

temperature adjustment the bulb of glass electrode was immersed in a drop of rum sample and pH was noted from the screen of digital pH meter. The serum calcium was estimated calorimetrically by using kit (Ref # 995936) supplied by Quimica Clinical Aplicade SA Aposta Spain. Serum inorganic phosphorus was measured by colorimetric method using kit, cat # KC 120 supplied by Clonital Italy. Serum fluoride was also measured by colorimetric method using alazerine and zirconium dye. The fluoride was analyzed by the Magregian, Haier method cited by Farber in which the fluoride reacts with dye lake, dissociating a portion of it into a colorless complex anion (ZrF-6) and the dye. As the amount of fluoride increased, the color produced becomes progressively lighter or different in hue depending on the reagent used.

The student's "t-test" was used to compare the serum calcium, phosphate and fluoride among the control and diseased groups.

RESULT AND DISCUSSION:

Two hundred individuals were divided into five groups according to their DMFT index (table-1). The distribution of sex is approximately equal in all groups. The base line comparison of mean values of age, DMFT, index and number of brushing per day (Table-2) shows a significant decrease in number of brushing and significant increase in DMFT index in all groups when compared to control.

Table 1: Distribution of control and patients in groups. (According to the DMFT index)

Group	DMFT index	Distribution of subjects	Sex	
			Male	Female
Control	<30	40	13	7
Group - I	30-40	40	11	9
Group – II	41-50	40	11	9
Group – III	51-60	40	10	10
Group – IV	> 60	40	10	10

Table 2: Baseline comparison of personal data of the control and patients.

Groups	Age (years)	DMFT Index	Brushing (No. of times/day)
Control (n=20)	23.9 +1.623	1.35 +0.208	2.05 +0.05
Group – I (n=20)	27.75 +1.680	6.3* +0.291	1.6* +0.11
Group – II (n=20)	28.25 +1.769	12.15* +0.099	1.05* +0.135
Group – III (n=20)	31.7* +1.818	19.8* +0.47	0.5* +0.114
Group – IV (n=20)	31.95* +1.59	26.95* +0.364	0.15* +0.08

Values are expressed as mean + SEM, * P < 0.001 as compared to control.

Table 3 shows the comparison of the mean values of serum pH, calcium, phosphate, fluoride and lactic acid between control and all groups. In group I there is a significantly decreased level of serum, calcium and fluoride and significantly increased level of lactic acid when compared to control subjects (P<0.001). in group II, III and IV serum, calcium, phosphate and fluoride observed decreased significantly and a significant increased in serum lactic acid when compared to control subjects (P<0.001). No significant change is observed in serum pH of all groups when compared to control group.

Table 3: Comparison of serum pH, calcium, phosphate, fluoride and lactic acid between control and groups.

Parameters	Control (n=20)	Group I (n=20)	Group II (n=20)	Group III (n=20)	Group IV (n=20)
PH	7.412 +0.005	7.407 +0.006	7.417 +0.005	7.419 +0.004	7.418 +0.005
Calcium (mg/dl)	10.275 +0.154	9.72** +0.128	9.1** +0.127	8.6** +0.139	7.955** +0.115
Phosphate (mg/dl)	4.22 +0.117	4.03 +0.099	3.59** +0.047	3.005** +0.032	2.295** +0.059
Fluoride (mg/dl)	4.4 +0.393	2.295** +0.317	1.615** +0.713	0.76** +0.044	0.58 +0.069
Lactic acid (mg/dl)	7.45 +0.413	11.765** +0.809	15.32** +0.695	18.14** +0.794	22.875** +0.956

Values are expressed as mean + SEM., ** P<0.001 as compared to control.

Table 4 shows the intergroup comparison of mean values of serum pH, calcium, phosphate, fluoride and lactic acid. A significantly decreased serum calcium and phosphate and increased lactic acid were observed in group II, III and IV when compared to group I whereas fluoride was significantly decreased in group II and IV when compared to group I. When group III and IV were compared with group II, the decreased serum calcium, phosphate and increased lactic acid were observed. In contrary when group IV compared with group III, significantly decreased level of calcium, phosphate, fluoride and increased lactic acid were observed. In group II serum calcium and phosphate were significantly decreased while lactic acid was significantly increased when compared to group I (P<0.001). In group III and IV serum calcium, phosphate and fluoride were decreased significantly while lactic acid was increased significantly when compared to group I (P<0.001). In group III serum calcium and phosphate were significantly decreased and lactic acid is significantly raised when compared to group II (P<0.05).

Table 4: Inter group comparison of serum pH, calcium, phosphate, fluoride and lactic acid.

Parameters	Group I (n=20)	Group II (n=20)	Group III (n=20)	Group IV (n=20)
PH	7.7407 +0.006	7.417 +0.005	7.419 +0.004	7.418 +0.005
Calcium (mg/dl)	9.72 +0.128	9.1** +0.127	8.6**† +0.139	7.955**††ÅÅ +0.115
Phosphate (mg/dl)	4.03 +0.09	3.59** +0.047	3.005**†† +0.032	2.295**††ÅÅ +0.059
Fluoride (mg/dl)	2.295 +0.317	1.615 +0.713	0.76** +0.044	0.58**Å +0.069
Lactic acid (mg/dl)	11.765 +0.809	15.32** +0.69	18.14**† +0.794	22.875**††ÅÅ +0.956

Values are expressed as mean + SEM.* P < 0.05, ** P < 0.001 as compared group I vs. all groups. † P < 0.005, †† P < 0.001 as compared group II vs. III and IV. Ĺ P < 0.02, ĹĹ P < 0.001 as compared group III vs. IV.

Both dental cavity (periodontitis) and diabetes mellitus are frequent chronic diseases and generate enormous costs for the public health care system. Numerous studies ,review articles and meta-analyses indicated a mutual influence between periodontitis and diabetes mellitus.The mechanisms, whereby diabetes may negatively influence periodontal health, are primarily based on the impaired local immune defense and a reduced renewal of the periodontal tissues. Moreover, higher levels of advanced glycation end products (AGE) can be found in the dental cavity of diabetics

compared to non -diabetic subjects . The interaction between AGEs and collagen generates highly stable collagen macromolecules, that are resistant to physiologic enzymatic degradation.Hence, the renewal of all periodontal tissues is effectively compromised in diabetic subjects, especially when glycemic control is poor. These phenomena explain in part why diabetic patients are three times more likely to develop periodontitis than non-diabetic subjects.

The role of serum calcium, phosphate and fluoride& pH in dental caries has been the point of interest since the mid of this century by many oral hygienist in the field of oral biochemistry. The early work of Stephan regarding the estimation of salivary pH had showed that the pH of saliva remained below the critical level of 5.5 in dental caries of diabetic patients, than the caries free people. Another study carried out by Abelson and Mandel demonstrated that the saliva exert its major influence on caries initiation by means of plaque formation rather than by direct contact on the tooth surface, they showed that plaque pH fall was greater in caries susceptible subjects. However this study did not show any significant change in the blood pH with the progression of disease.

The study is carry on by previous workers revealed that the calcium ions are present normally in dental plaque bound to matrix and other proteins attracting phosphate and fluoride as counter ion, other phosphate and fluoride occurs intracellularly. All three ions occur as an inorganic mineral in serum and are in continuous exchange phase with the saliva over the dental plaque. This is responsible for the "pool" or "reservior" of calcium, phosphate and fluoride in dental plaque and also maintains their saturation. These observations are quite identical with our study as levels of serum calcium, phosphate and fluoride are significantly low in dental caries patient in comparison to the control.

Table no. 5 Dmfs Index

A comparison of the dmfs index for the primary dentition revealed that the children in group A had an astonishingly high value as compared to the other two groups. A statistically significant difference was found between the three groups. Primary teeth of the children in group A showed a mean (± Standard deviation) dmfs index value of 4.18 (±7.46) whereas those of group B and C showed values of 1.38 (± 5.33) and 3.86 (±7.68), respectively. Thus the children in group B demonstrated the lowest mean dmfs index values (Table 05).

Group	N	Minimum	Max.	Mean	Standard Deviation
A	37	0	32	4.18*	7.46
B	100	0	50	1.38*	5.33
C	100	0	56	3.86*	7.68

Table 5: dmfs index values for groups A, B and C. * indicates statistically significant difference between the groups, $p \leq 0.05$

The results of the present research showed that the mean dmfs index value in the group of children suffering from PKU was statistically significantly higher than in the healthy children and the diabetic children.

Our study quite clearly gives the information that there is significant fall in serum calcium, phosphate and fluoride as the disease process advances. This observation is in complete agreement with the study is carry on by Pearce explained that salt dissolution is governed by the concentration of calcium, phosphate and OH- ions in the surrounding fluid. These results are also supported by the research study of previous investigators who explained the process of caries on the basis of ionic product and solubility product. They explained that these ions are the main constituent of the enamel apatite lattice. The study carried out by Murray on "fluoride in caries prevention" observed that the crystals formed in the presence of fluoride dissolved more slowly in acid as they have lower intrinsic rate of dissolution, particularly of F- are taken up during remineralization and the crystals formed in the presence of F- are large, dense and more perfect Another observation made in this study was that, the rate of remineralization was raised in the presence of F- in early carious lesion at those time when the pH has risen so that remineralization is the dominant process and he also demonstrated the antibacterial property of F- as it has a tendency to bind with the active metal of enzyme system e.g. in case of enolase, an enzyme that require magnesium (Mg^{++}) which can be inhibited up to 100% by F- with the level of 95 ppm in the solution.

Conclusion

The study is carry on by previous workers revealed that the calcium ions are present normally in dental plaque bound to matrix and other proteins attracting phosphate and fluoride as counter ion, other phosphate and fluoride occurs intracellularly. All three ions occur as an inorganic mineral in serum and are in continuous exchange phase with the saliva over the dental plaque. This is responsible for the "pool" or "reservior" of calcium, phosphate and fluoride in dental plaque and also maintains their saturation. These observations are quite identical with our study as levels of serum calcium, phosphate and fluoride are significantly low in dental caries patient in comparison to the control..

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