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Caries Resistance in Children with Chronic Renal Failure: Plaque pH, Salivary pH, and Salivary Composition

S. PETERSON, J. WOODHEAD, AND J. CRALL

University of Iowa College of Dentistry [S.P., J.C.] and Medicine [J.W.], Iowa City, Iowa 52242

ABSTRACT. We studied properties of saliva and of dental plaque which affect the caries process in an effort to understand the low prevalence of caries in patients with chronic renal failure. Plaque pH, before and following carbohydrate exposure, saliva pH, and saliva composition were evaluated in children and adolescents with chronic renal failure ($n = 10$) and successful renal transplantation ($n = 11$), and in two comparison groups of healthy children with few caries ($n = 15$) and numerous caries ($n = 15$). Salivary urea nitrogen concentration was elevated in all subjects with elevated serum urea nitrogen concentration. Chronic renal failure subjects had significantly higher salivary urea nitrogen concentration than transplanted subjects. Plaque pH correlated directly with salivary urea nitrogen concentration and was significantly more alkaline in chronic renal failure than transplant or comparison groups. Salivary urea nitrogen concentration accounted for the majority of variability in plaque pH; salivary pH and salivary phosphorous contributed negligibly. Absolute pH drop following carbohydrate exposure did not differ among groups, but because baseline plaque pH was elevated for chronic renal failure subjects, minimum pH did not attain cariogenic levels. Our data support the hypothesis that the relative paucity of caries in patients with chronic renal failure results from alteration of plaque by metabolic end products of urea metabolism. Our data further suggest that transplanted patients whose renal function is normal may be at increased risk of caries, especially if enamel hypoplasia is present and oral hygiene is poor. (*Pediatr Res* 19: 796–799, 1985)

Abbreviations

CRF, chronic renal failure
SalUN, salivary urea nitrogen concentration

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Address reprint requests to Jerold C. Woodhead, M.D., 2559 JCP, Department of Pediatrics, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.
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Children with CRF have relatively few dental caries (1, 2) despite common occurrence of conditions which should increase risk of caries. Poor oral hygiene (3, 4) and enamel hypoplasia (1, 2) are prevalent in CRF, and dietary supplementation of calories (5) results in cariogenic diets for many CRF patients. In an effort to explain low caries prevalence we designed a study to evaluate properties of plaque and saliva which might affect the caries process.

Demineralization and erosion of enamel by organic acid are major factors in caries development (6). Plaque bacteria produce organic acid as a product of carbohydrate metabolism (7). In

contrast, nitrogenous substances are metabolized by plaque to form ammonia which has an alkalinizing effect on plaque (7, 8). Since salivary urea, the principle nitrogenous substrate of plaque (8), is elevated in subjects with decreased renal function (9), we hypothesized that plaque pH would be more alkaline in subjects with CRF than in healthy controls. We also expected to see an altered response of plaque to carbohydrate since metabolism of urea by plaque is more rapid than that of glucose or sucrose (7).

METHODS

We planned the study to allow comparison of salivary composition, salivary pH, and plaque pH among groups of children and adolescents with and without renal disease. All study subjects had the following measured: salivary concentrations of urea nitrogen, calcium, phosphorus, and fluoride; salivary pH; and plaque pH at baseline and following carbohydrate exposure. Serum concentrations of urea nitrogen, calcium, phosphorus, and total CO_2 were determined for patients with renal disease only.

We identified four study groups: patients with CRF; patients who had functioning renal transplants; healthy children with no or few caries; and healthy children with numerous caries. The two renal groups were selected from the patient population of the Renal Failure Clinic, University of Iowa Department of Pediatrics. The two healthy comparison groups were selected from the patient population of the University of Iowa Department of Pedodontics.

All children and adolescents seen between December 3, 1982 and April 27, 1983 in the Renal Failure Clinic were eligible for study. Four eligible subjects did not participate: two were being dialyzed and were excluded, one transplanted patient declined to participate for personal reasons, and one CRF patient declined because of illness. In all, 21 subjects participated: 10 with CRF (5 to 18 yr of age) and 11 with functioning renal transplants (7 to 18 yr of age).

The CRF group included 10 patients with chronic renal disease and serum creatinine concentrations ranging from 3.4 to 10.1 mg/dl. None of these patients was undergoing dialysis therapy. All required restriction of dietary protein and phosphorus, supplements of vitamin D and calcium, and phosphate binder (aluminum hydroxide). The majority was receiving bicarbonate orally and several required a variety of other medications including antihypertensive and anticonvulsant agents.

The transplant group included 11 patients with functioning renal grafts. A patient was defined as having a functioning graft if dietary protein restriction was not necessary and if serum creatinine concentration was below 3 mg/dl. Serum creatinine for the transplant group ranged from 0.7 to 2.8 mg/dl. All subjects in the transplant group were receiving prednisone and azathioprine (Imuran) for immunosuppression. Some patients were also receiving bicarbonate, calcium, vitamin D, phenobarbital, and multiple vitamins.

Comparison subjects with no history of chronic illness, especially renal disease, and with no dental problems other than caries, were selected from the patient population of the Department of Pedodontics. Fifteen subjects with history of zero or one carious lesion comprised the inactive caries group. An additional 15 subjects with history of five or more carious lesions were enrolled in the active caries group. Comparison subjects were examined by the pediatric dentist only; no medical examination or blood tests were performed.

The study protocol was reviewed and approved by the University of Iowa Human Subjects Review Committee. The purpose of the study and the procedures to be followed were discussed with the children and adolescents and their parents and written consent was obtained.

All subjects were contacted before a scheduled clinic visit and asked not to brush teeth for the 48 h immediately preceding the visit. All subjects were examined by the same pediatric dentist (S.P.) and underwent a standard dental screening examination with results entered onto the form developed by the National Institute of Dental Research (10). Caries, as defined by the National Institute of Dental Research criteria, were identified by clinical examination and with two bitewing radiographs, where indicated. All subjects were examined between 09.50 and 12.50 h to minimize effects of the diurnal variability in salivary composition (11).

We measured plaque pH on the buccal surface of the first maxillary permanent molar with an MI-405 glass electrode (Microelectrodes, Inc., Londonderry, NH) by the method of Wei *et al.* (12) using an Orion model 701-A pH HV meter (Orion Research, Inc., Cambridge, MA). After baseline pH measurement, each subject rinsed for 10 s with a 10% sucrose solution. Plaque pH was then measured at 1-min intervals for 5 min, then at 5-min intervals until baseline pH was reattained. The lowest pH attained after sucrose rinse was identified and designated "minimum pH." Time from the completion of the sucrose rinse until baseline pH was reattained was measured and identified as "time to baseline." Absolute pH drop following sucrose rinse was calculated as the difference between baseline and minimum pH.

After completion of plaque pH measurements, salivary flow was stimulated by lemon candy and isolated parotid saliva was collected by the method of Schaeffer *et al.* (13). Saliva was transported on ice to the laboratory where aliquots were frozen at −4° C for later analysis. Salivary components remained stable when frozen for up to 4 months, thus all analyses were made at the completion of the study.

Salivary composition was determined in the microchemistry laboratory of the University of Iowa Department of Pediatrics: urea nitrogen by the microdiffusion technique (14); calcium by atomic absorption spectrophotometry (15), and phosphorus by a minor modification of the method of Fiske and Subbarow (16).

Salivary fluoride concentration was measured in the fluoride laboratory of the Department of Pedodontics with the Orion fluoride-specific electrode (Orion Research).

Data analysis was done using SAS (17) (general linear models program: one-way analysis of variance with Duncan's multiple range test, and multiple regression analysis). The four groups (CRF, transplant, inactive caries, active caries) were compared with respect to salivary concentrations of urea nitrogen, calcium, phosphorus and fluoride, salivary pH and plaque pH (baseline pH, minimum pH after sucrose rinse, time to return to baseline pH, and absolute pH drop).

RESULTS

SalUN differed significantly among groups ($p < 0.001$) (Table 1). CRF subjects had highest SalUN (mean 83.8 mg/dl), transplanted subjects were intermediate (mean 40.0 mg/dl), and the two comparison groups were lowest (means 10.6 and 12.5 mg/dl). CRF and transplant groups differed significantly from each other and from comparison groups (Table 1).

SalUN correlated strongly with serum urea nitrogen concentration in CRF and transplant groups ($r = 0.86$, $p = < 0.001$). Serum urea nitrogen concentration was highest in CRF subjects (102.1 ± 26.5 mg/dl) and significantly greater than that of transplant subjects (33.5 ± 27.4 mg/dl).

Concentration of phosphorus was higher in saliva of CRF subjects than of all other groups ($p < 0.05$) (Table 1). Transplant and comparison groups did not differ. Serum phosphorus concentration was greater in CRF than transplant group subjects (4.99 *versus* 3.88 mg/dl) ($p < 0.01$). There was no significant group effect for salivary or serum calcium or salivary fluoride, although mean salivary fluoride values for CRF and active caries groups differed significantly from values for transplant and inactive caries groups by Duncan's test. Salivary pH was significantly more alkaline for CRF group subjects than subjects of all other groups ($p < 0.01$).

Baseline plaque pH and minimum plaque pH were signifi-

Table 1. *Saliva and plaque variables**

	Group			
CRF	Transplant	Inactive caries	Active caries	
Saliva				
Urea nitrogen (mg/dl)†	83.8[a] ± 0.64	40.0[b] ± 30.1	10.6[c] ± 3.7	12.5[c] ± 2.9
Phosphorus (mg/dl)‡	20.1[a] ± 5.1	15.0[b] ± 5.4	14.5[b] ± 4.0	14.9[b] ± 4.7
Calcium (mg/dl)	41.8[a] ± 29.7	36.6[a] ± 17.1	39.9[a] ± 12.6	31.5[a] ± 8.9
Fluoride (μg/ml)	0.97[a] ± 0.053	0.056[b] ± 0.03	0.063[b] ± 0.041	0.073[a] ± 0.030
pH§	7.64[a] ± 0.57	7.11[b] ± 0.50	7.04[b] ± 0.53	6.99[b] ± 0.23
Serum				
Urea nitrogen (mg/dl)†	102.1[a] ± 26.5	33.5[b] ± 27.4		
Calcium (mg/dl)	9.8[a] ± 0.5	9.6[a] ± 0.7		
Phosphorus (mg/dl)	5.0[a] ± 0.9	3.9[b] ± 0.5		
Total CO_2 (mEq/liter)	23.1[a] ± 3.2	23.6[a] ± 3.6		
Plaque				
Baseline pH†	7.87[a] ± 0.64	6.67[b] ± 0.42	6.58[b] ± 0.20	6.27[b] ± 0.35
Minimum pH†	7.04[a] ± 0.83	5.80[b] ± 0.66	5.68[b] ± 0.50	5.45[b] ± 0.37
Absolute pH drop	0.83[a] ± 0.61	0.87[a] ± 0.36	0.90[a] ± 0.42	0.83[a] ± 0.49
Time to return to baseline (min)§	15.5[a] ± 5.5	22.7[b] ± 7.2	21.3[b] ± 4.8	24.7[b] ± 6.7

* Data are expressed as mean ± SD. Test for group effects was performed by one-way analysis of variance. Means with the same superscript letter do not differ by Duncan's test at $p = 0.05$.

† $p < 0.001$.

‡ $p < 0.05$.

§ $p < 0.01$.

cantly more alkaline for the CRF group than for all other groups ($p < 0.001$ for both measurements). The other groups did not differ significantly among themselves. Absolute pH drop from baseline to minimum after sucrose rinse did not differ among groups ($p > 0.05$). However, time to return to baseline was significantly shorter for CRF than for all other groups ($p < 0.01$).

Figure 1 depicts graphically the relationships between baseline plaque pH and SalUN for the study groups. Active and inactive caries groups are combined in this figure as "control" and show no correlation between plaque pH and SalUN. Both CRF and transplant groups show positive correlations ($r = 0.59$ and 0.58, respectively). When data were analyzed across groups, plaque pH and SalUN showed a strong positive correlation ($r = 0.81$, $p < 0.001$). Minimum plaque pH demonstrated similar correlations ($r = 0.88$ for CRF and $r = 0.66$ for transplant). Both CRF and transplant correlations for minimum pH were statistically significant ($p < 0.001$ and < 0.05, respectively). Across groups, minimum pH showed a positive correlation with SalUN with $r = 0.79$, $p < 0.001$.

Multiple regression analysis identified SalUN as the factor which explained the majority of the variation in baseline plaque pH (66.8%; $R^2 = 0.668$). Salivary pH accounted for only 3.3% of variation ($R^2 = 0.033$) and phosphorus for less than 1% ($R^2 = 0.008$). The same was true for minimum plaque pH: SalUN accounted for 63.5% of pH variability, salivary pH for 1.9%, and phosphorus for 3.2%.

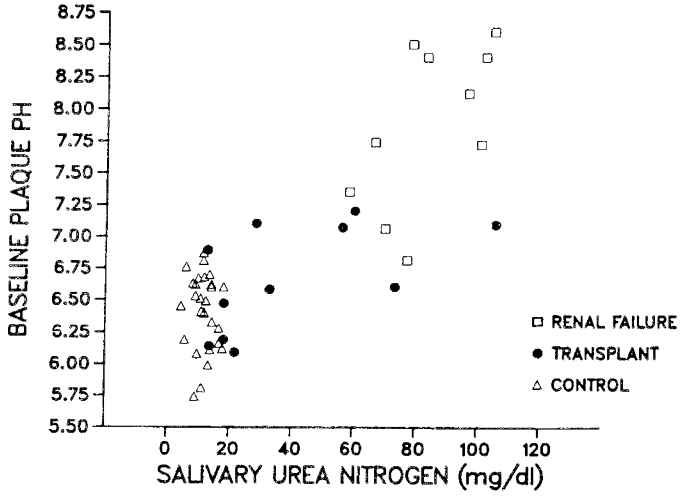

Fig. 1. Relationship between baseline plaque pH and SalUN for CRF, transplant, and control (inactive and active caries, combined) groups.

DISCUSSION

Metabolism of nitrogenous substances, especially urea, by plaque produces ammonia and elevates plaque pH (7). Since caries result in large part from acid dissolution of enamel (6), alkalinization of plaque should diminish caries formation. We have shown that children and adolescents with reduced renal function have alkaline plaque and that plaque pH correlates directly with SalUN. We suggest that salivary urea, persistently elevated in renal failure, acts as substrate for continuous ammonia production by plaque. The resultant elevation of plaque pH would account for low caries frequency in patients with renal failure since pH would not fall to levels (18) at which caries readily occur.

Although a preliminary study (Crall JJ, unpublished data) demonstrates that bacterial composition of plaque is not altered in renal failure, the possibility exists that plaque metabolic activity may be altered by continuous exposure to elevated salivary urea concentration. Acid production by plaque in absolute pH units did not differ significantly among groups, however, since pH is a log function, H^+ ion production by CRF subjects was 10-fold less than that by the other three groups. This suggests altered plaque acid production from carbohydrate.

All subjects in the CRF group required alkalinizing agents (bicarbonate in tablet form, 7/10, or Shohl's solution, 3/10) while only 3/11 transplant group subjects required alkalinizing agents. The two groups did differ significantly for mean salivary

pH (7.64 for CRF *versus* 7.11 for transplant), but not for mean serum total CO_2 (23.1 *versus* 23.6 mM/liter). As noted above, mean SalUN differed significantly in CRF and transplant groups (83.8 *versus* 40.0 mg/dl) as did mean plaque pH (7.87 *versus* 6.67). The contribution of salivary pH to variability in plaque pH is 20-fold less than that of SalUN. A local effect of bicarbonate appears unlikely since an early study (Jensen, M unpublished data) shows no local effect of bicarbonate tablets when swallowed and only a transient (10 to 15 min) effect of solutions when *rinsed* in the mouth (which probably differs from direct swallowing of solution). SalUN by itself cannot fully account for plaque pH variability, yet all other factors taken individually add only minimally to the effect of SalUN.

Our hypothesis predicts that patients with successful renal transplants may be at increased risk of caries compared with both renal failure patients and healthy subjects. SalUN decreases as renal function improves after transplantation and plaque pH should fall according to our model thus allowing plaque to reach pH levels at which caries develop. Two conditions further increase risk of caries in transplanted patients. First, preexisting hypoplastic enamel persists; this enamel is thin, irregular, difficult to clean, and has been reported by Nikiforuk and Fraser (19) as a caries risk factor. Second, patterns of poor oral hygiene, common in renal failure patients, may persist after transplantation. Plaque build-up on thin, hard-to-clean enamel, combined with low pH should greatly increase risk of caries. Our data support the suggestion that caries risk is increased after successful transplantation. Caries were identified in transplant patients only if they had low SalUN; patients with elevated salivary urea nitrogen had no evidence of active caries. This difference is not statistically significant ($p < 0.09$ Fisher exact test) (17). However, based on the potential clinical importance of the difference in active caries between CRF and transplant groups we recommended careful attention to oral hygiene, frequent dental supervision, and avoidance of cariogenic diets for patients with successful transplants.

Our caries data reflect prevalence not incidence. Ongoing evaluation of caries incidence in CRF and transplanted patients will eventually provide the information necessary to answer the question of caries susceptibility after successful renal transplantation.

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