Association of taste receptor gene polymorphisms with dental caries

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Abstract: This study was performed to evaluate the interplay between dental caries, nutritional status, and genetic polymorphisms in *TAS1R1* and *TAS1R2* (taste receptor, type 1, member 1 and 2) in preschool children and pre-adolescents. We included 525 subjects (306 preschool children and 219 pre-adolescents). Parents/caregivers answered a self-administered questionnaire about their children's systemic health, characteristics, oral hygiene habits, and diet. Clinical examination was performed to evaluate dental caries and nutritional status. Saliva samples were collected for DNA extraction. The genotyping of rs17492553 (*TAS1R1)*, rs3935570, and rs4920566 (*TAS1R2) polymorphisms* was performed using real-time PCR with Taqman Genotyping Master Mix and SNP assay. Both univariate and multivariate Poisson regression analyses with robust variance were used for the data analysis. In preschool children, consumption of sweets between meals increased the prevalence of dental caries by 85% (PR_c = 1.85; 95%CI 1.39–2.46; p < 0.001), whereas in pre-adolescents, this prevalence increased by 34% (PR_a = 1.34; 95%CI 1.11–1.62; p = 0.002), regardless of genetic polymorphisms. Moreover, individuals carrying at least one allele C in rs17492553 presented 23% more prevalence of dental caries (PR_a = 1.23; 95%CI 1.02–1.49 p = 0.030). Nutritional status was not associated with dental caries, neither with genetic polymorphisms. Consumption of sweets between meals increased the prevalence of dental caries. In pre-adolescents, rs17492553 genetic polymorphism in *TAS1R1* was associated with dental caries.

Keywords: Polymorphism, Genetic; Child; Genetics; Dental Caries; Diet.

Introduction

Dental caries is one of the most common chronic childhood diseases. It is a major oral health problem in most industrialized countries, affecting many children and pre-adolescents.[1] Many studies have explored its multifactorial etiology and complex interaction with several variables, including environmental factors,[2] and the host genetic background.[3] It has been well demonstrated that dietary habits are related to the development and risk of dental caries,[4] in particular, the intake frequency of sugar[5] that is metabolized by oral microorganisms,[6] and contributes to the formation of the dental biofilm matrix.[7]

The perception of sweet taste is believed to have an influence on sugar intake,[8] therefore affecting the predisposition to dental carie.[9] Evidence exists supporting that taste has a genetic component since some genetic polymorphisms in taste receptors have been associated with food preferences and consumption.[8,10] Sugar intake and taste preferences have been associated with genetic polymorphisms in sweet taste receptors in humans.[8,11,12,13] Interestingly, previous studies have also demonstrated that genetic polymorphisms in taste receptors such as rs35874116, rs3935570, rs9701796, and rs307355[14,15,16,17,18,19] were associated with dental caries and also with obesity.[20]

The association between dental caries and children's nutritional status, such as underweight, overweight, and obesity have been also reported recently by many investigators and revised by two recent systematic reviews,[21,22] therefore, it is reasonable to assume that the association between dental caries and obesity involves dietary factors. On the other hand, it is also possible that genetic background, such as genetic polymorphisms in taste receptor genes, could be common etiologic factors for both conditions.

Although it is well established that sugar intake is highly associated with the development of dental caries,[4,5] the role of genetic polymorphisms, mainly genetic polymorphisms in genes that codify taste receptors, is poorly studied. Taste receptors, including hT1R1 (taste receptor, type 1, member 1) and hT1R2 (taste receptor, type 1, member 2), are encoded by *TAS1R1* and *TAS1R2*, which reside in a small region of chromosome 1.[23] To date, few studies have explored the role of genetic polymorphisms in *TAS1R1* and *TAS1R2* in dental caries experience.[14,15,16,17,18,19] Wendell et al.[14] evaluated families recruited from the Center for Oral Health Research in Appalachia in the United States and concluded that *TAS1R2* was associated with dental caries. Kulkarni et al.[15] also demonstrated that *TAS1R2* was associated with dental caries in Canadian adults. Holla et al.[16] evaluated Czech teenagers and associated a genetic polymorphism in *TAS1R2* with dental caries experience. Haznedaroğlu et al.[17] found a significant association with *TAS1R2* in Turkish schoolchildren. Robino et al.[18] also found an association between *TAS1R2* and dental caries in Italian adults. Recently, Eriksson et al.[24] found that TAS1R1 and TAS1R2 were associated with dental caries in young Swedish individuals. To the best of our knowledge, genetic polymorphisms in taste receptor genes have never been evaluated in a Brazilian population. Therefore, the present investigation was performed in order to evaluate the interplay between dental caries, nutritional status, and genetic polymorphisms in *TAS1R1* (rs17492553 and rs3935570) and *TAS1R2* (rs4920566) in Brazilian preschool children and pre-adolescents.

Methodology

This study was approved by the Human Ethics Committee of the Amazon State University - Brazil (process #923.569) and by the Human Ethics Committee of the Fluminense Federal University (process #02463012.1.0000.5243). The research was conducted in accordance with the Declaration of Helsinki. All parents or caregivers were informed about the study and signed an informed consent. For the population from Manaus, age-appropriate assent documents were used for children aged 7 to 14 years (with parents' consent).

All parents or caregivers from both subsets answered a self-administered questionnaire with open- and closed-ended questions. Questions about the children's systemic health and characteristics (age and ethnicity) were open-ended. Questions about children's oral health were mainly multiple choice (closed-ended questions), as follows: Does your child brush his/her teeth before going to bed? (yes or no); You're your child eat cakes, cookies, and other sweets between meals? (yes or no); and How often does your child eat sweets between meals? (quite often or rarely). The question about how many times a day the child brushed his/her teeth was open-ended. The frequency of oral hygiene was considered appropriate when teeth were brushed at least twice a day (including before bedtime).

Inclusion criteria were biologically-unrelated preschool children and pre-adolescents. Children and pre-adolescents who had any syndromes or severe systemic disease or who were wearing orthodontic appliances were excluded from the study.

Convenience sampling was used for both subsets. The first subset comprised preschool children aged 3 to 5 years recruited from public daycare centers in Nova Friburgo, Rio de Janeiro State, Brazil[25]. The second subset included pre-adolescents aged 9 to 12 years recruited from four public schools in Manaus, state capital Amazonas, Brazil.[26,27] All children who met the inclusion criteria and whose the parents/legal guardians agreed to participate, were included. During the clinical examination, those preschool children with dental treatment needs were referred to dental treatment. Those pre-adolescents with dental treatment needs received dental treatment at school-based health centers.

Sample size was calculated according to minor allele frequency (higher than 20%) and an expected 30% genotype difference among the groups, with an alpha of 5% and power of 80%. The characteristics of this population have been previously described.[26,27]

Determination of caries experience

The oral examination was performed at the daycare centers and at schools. Clinical examinations were performed by experienced pediatric dentists and were previously described by Antunes et al.[25] and Arid et al.[27] The modified World Health Organization protocol[28] recommended for oral health surveys was used to diagnose caries in primary and permanent teeth, using the dmft and DMFT index (decayed, missing teeth, filled teeth). The patients were classified according to their caries experience into 'caries experience' (DMFT/dmft ≥ 1) or 'caries- free' (DMFT/dmft = 0) groups.

Determination of the nutritional status

The children's and pre-adolescents' heights were recorded in meters. The children's and pre-adolescents' weight was measured on a scale and expressed in kilograms. The body mass index (BMI) z-score was calculated by the pediatric z-score calculator of the Children's Hospital of Philadelphia (http://zscore.research.chop.edu/index.php) using individual height, weight, age, and sex as variables. Therefore, the nutritional status was established according to the World Health Organization[29] and the patients were classified as 'well-nourished', 'underweight,' and 'overweight + obese.'

DNA extraction and polymerase chain reactions

Oral cells were collected from the saliva of all patients. Genomic DNA was extracted from the cells for genotyping, as previously described by Küchler et al.[30] Genetic polymorphisms were selected as follows: rs17492553 C>T (catalog number: 4351379; global minor allele frequency = 0.482) in *TAS1R1* and rs3935570 G>T (catalog number: 4351379; global minor allele frequency = 0.261) and rs4920566 A>G (catalog number: 4351379; global minor allele frequency = 0.494) in *TAS1R2* in intronic regions. The selection was based on global minor allele frequency equal to or higher than 25%.

Genotyping was blinded and performed by polymerase chain reactions (PCR) using the TaqMan assay with an endpoint real-time PCR system (Applied Biosystems® Prism QuantStudio 6 Flex PCR System Thermo Fisher Scientific, Foster City, USA). The probes and the master mix were purchased from Applied Biosystems (Foster City, USA). Real-time PCR reactions were performed in a total final volume of 3 μL (1.5 μL Taqman genotyping master mix, 0.075 μL SNP assay; Applied Biosystems, Foster City, USA and 4 ng DNA/reaction in 1.5 of water). The thermal cycling was carried out with an initial hold cycle of 95ºC for 10 minutes, followed by 40 amplification cycles of 92ºC for 15 seconds and 60ºC for 1 minute.

Statistical analysis

For the data analysis, the dependent variable (dental caries) was categorized as 'caries-free' and 'caries experience.'

To test the association between dental caries and genotypes, this study also included the risk factors of dental caries previously established in the literature (oral hygiene habits and consumption of sweets) as independent variables and nutritional status as a confounding factor. First, the association between dental caries and the independent variables was analyzed using univariate Poisson regression analysis with robust variance at a 5% significance level. The multiple regression model was constructed

by stepwise forward selection, including independent variables associated with dental caries with $p < 0.20$. Independent variables significantly associated with dental caries or fitted to the model [31] were kept in the multiple model.

The analysis was performed using SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, USA) and STATA (Statacorp, version 11, USA).

Results

The response rates were 95.03% (306/322) for preschool children and 95.60% (219/229) for pre-adolescents. A total of 525 pediatric subjects were included in the study. The mean DMFT/dmft in the preschool children and pre-adolescent subsets were 1.53 (SD = 2.85) and 1.68 (SD = 0.14), respectively.

Table 1 describes the distribution of independent variables among the 'caries- free' and 'caries-affected' children. The consumption of sweets between meals was associated with dental caries experience in both subsets ($p < 0.05$).

Table 2 describes the genotype distribution among the 'caries-free' and 'caries-affected' children. In the recessive model, rs17492553 genetic polymorphism was borderline associated with caries ($p = 0.048$).

In preschool children, only the consumption of sweets between meals was significantly associated with dental caries (Table 3). Children who reported the consumption of sweets between meals presented an 85% higher prevalence of dental caries ($PR_c = 1.85$; 95%CI 1.39–2.46; $p < 0.001$) (Table 3).

In the multiple regression analysis, pre-adolescents who ate sweets between meals presented a 34% higher prevalence of dental caries, regardless of genetic polymorphisms ($PR_a = 1.34$; 95%CI 1.11–1.62; $p = 0.002$). Moreover, subjects carrying at least one allele C (CC+CT) in rs17492553 presented a 23% higher prevalence of dental caries ($PR_a = 1.23$; 95%CI 1.02–1.49; $p = 0.030$) (Table 4).

Genetic polymorphisms – rs3935570 ($p = 0.211$ and $p = 0.080$), rs17492553 ($p = 0.533$ and $p = 0.858$), and rs4920566 ($p = 0.212$ and $p = 0.358$) – were not associated with nutritional status in preschool children and pre-adolescents.

Table 1. Distribution of independent variables in caries groups among preschool children and pre-adolescents.

Variables	Preschool children		p-value	Pre-adolescents		p-value
	Caries -free (n = 193)	Caries experience (n = 113)		Caries -free (n = 77)	Caries experience (n = 142)	
Sex n (%)						
Male	96 (62.3)	58 (37.7)	0.789	34 (31.8)	73 (68.2)	0.305
Female	97 (63.8)	55 (36.2)		43 (38.4)	69 (61.6)	
Consumption of sweets between meals n(%)						
No	153 (70.8)	63 (29.2)	**< 0.001**	59 (42.8)	79 (57.2)	**0.003**
Yes	39 (45.9)	46 (54.1)		16(21.9)	57 (78.1)	
Proper toothbrushing n(%)						
No	20 (74.1)	7 (25.9)	0.176	25 (36.2)	44 (63.8)	0.913
Yes	155 (60.8)	100 (39.2)		50 (35.5)	91(64.5)	
Toothbrushing before bedtime n(%)						
No	30 (63.8)	17 (36.2)	0.999	9 (37.5)	15 (62.5)	0.777
Yes	157 (63.8)	89 (36.2)		65 (34.6)	123 (65.4)	
Nutritional status n(%)						
Well-nourished	76 (62.8)	45 (37.2)	Reference	46 (41.8)	64 (58.2)	Reference
Underweight	16 (57.1)	12 (42.9)	0.578	2 (40.0)	3 (60.0)	0.932
Overweight/Obese	38 (77.6)	11 (22.4)	0.067	25 (41.7)	35 (58.3)	0.981

Values in bold indicate statistical significance according to chi-square or Fisher's exact tests.

Table 2. Genotype distributions in children and pre-adolescents according to caries experience.

Genotypes	Preschool children			Pre-adolescents		
	Caries-free	Caries experience	p-value	Caries-free	Caries experience	p-value
TAS1R1 rs17492553						
CC	66 (66.0)	34 (34.0)		19 (33.9)	37 (66.1)	
CT	85 (64.9)	46 (35.1)	0.576*	37 (43.5)	48 (56.5)	0.072*
TT	41 (58.6)	29 (41.4)		20 (26.3)	56 (73.7)	
CC+CT	151 (65.4)	80 (34.6)	0.300**	56 (39.7)	85 (60.3)	**0.048****
TT	41 (58.6)	29 (41.4)		20 (26.3)	56 (73.7)	
TAS1R2 rs3935570						
GG	95 (67.9)	45 (32.1)		42 (35.9)	75 (64.1)	
GT	62 (59.0)	43 (41.0)	0.349*	20 (38.5)	32 (61.5)	0.455*
TT	35 (66.0)	18 (34.0)		10 (26.3)	28 (73.7)	
GG+GT	157 (64.1)	88 (35.9)	0.787**	62 (36.7)	107 (68.3)	0.261**
TT	35 (66.0)	18 (34.0)		10 (26.3)	28 (73.7)	
TAS1R2 rs4920566						
AA	48 (58.5)	34 (41.5)		25 (34.2)	48 (65.8)	
AG	88 (65.7)	46 (34.3)	0.580*	35 (42.2)	48 (57.8)	0.597*
GG	54 (64.3)	30 (35.7)		13 (42.2)	21 (61.8)	
AA+AG	136 (63.0)	80 (37.0)	0.831**	60 (38.2)	96 (61.5)	0.980**
GG	54 (64.3)	30 (35.7)		13 (38.4)	21 (61.8)	

Note: *Additive model; **recessive model. Chi-square or Fisher's exact tests.

Table 3. Crude prevalence ratio (PR_c) for dental caries experience in the preschool children subset, considering environmental and genetic variables.

Variables	PR_c	95%CI	p-value
Sex			
Male	1.04	0.77-1.39	0.789
Female	reference		
Consumption of sweets between meals			
Yes	1.85	1.39-2.46	**<0.001**
No	reference		
Proper toothbrushing			
No	0.66	0.34-1.27	0.216
Yes	reference		
Toothbrushing before bedtime			
No	1.00	0.66-1.51	0.999
Yes	reference		
Nutritional status			
Overweight/obese	0.604	0.34-1.06	0.082
Underweight	1.15	0.71-1.87	0.568
Well-nourished	reference		
TAS1R1 rs17492553			
CC+CT	1.19	0.86-1.66	0.287
TT	reference		
TAS1R2 rs3935570			
GG+GT	0.94	0.62-1.42	0.789
TT	reference		
TAS1R2 rs4920566			
AA+AG	0.96	0.68-1.34	0.832
GG	reference		

Discussion

This is the first study to evaluate the interplay between dental caries, sugar intake, nutritional status, and genetic polymorphisms in *TAS1R1* (rs17492553 and rs3935570) and *TAS1R2* (rs4920566) in Brazilian populations. Overweight, obesity, and dental caries are the biggest challenges in global health that have affected both children and pre-adolescents in this century. Overweight and obesity are increasing in different populations[32] and, although a noteworthy decline has been reported in recent decades, dental caries remains a major oral health problem in most industrialized countries.[33] However, it is important to emphasize the conflicting results for the association of these conditions.[21,22] Such results may be explained by the fact that different populations have a different food culture, which influences the prevalence of childhood overweight/obesity. The association between these two conditions has not been observed in previous studies with Brazilian children[34,35] and pre-adolescents.[35,36] We could not observe a statistical association between overweight/obesity and dental caries, nor between underweight and dental caries.

Table 4. Crude prevalence ratio (PR_c) and adjusted prevalence ratio (PR_a) for dental caries experience in the pre-adolescent subset, considering environmental and genetic variables.

Variables	PR_c	95%CI	p-value	PR_a	95%CI	p-value
Sex						
Male	1.17	0.91-1.34	0.306			
Female	reference					
Consumption of sweets between meals n(%)						
Yes	1.36	1.13-1.64	**0.001**	1.34	1.11-1.62	**0.002**
No	reference			reference		
Adequate brush teeth						
No	1.30	0.90-1.89				
Yes	reference					
Toothbrushing before bedtime						
No	1.04	0.75-1.45				
Yes	reference					
Nutritional status						
Overweight/obese	1.00	0.76-1.30	0.941			
Underweight	1.03	0.49-2.14	0.934			
Well-nourished	reference					
TAS1R1 rs17492553						
CC+CT	1.22	1.01-1.47	**0.038**	1.23	1.02-1.49	**0.030**
TT	reference					
TAS1R2 rs3935570						
GG+GT	1.164	0.93-1.45	0.180	1.23	0.98-1.54	0.069
TT	reference					
TAS1R2 rs4920566						
AA+AG	1.00	0.74-1.34	0.990			
GG	reference					

Values in bold indicate statistical significance according to chi-square or Fisher's exact tests.

Many studies focusing on the association between the preference for sweets, sugar intake, and caries experience have been conducted in different populations.[18,37,38] Genetic variation determining preference for sugar consumption (and sweet taste perception) has been suggested to be risk factors for dental caries susceptibility;[15,16,17,18] however, only few studies have focused on understanding the effect of genetic factors associated with taste preferences on children's caries experience,[14,16,17,19] and our study is the first one to explore genetic factors associated with taste preferences in Brazilians. Sweet taste perception is determined by a G-protein-linked heterodimer encoded by proteins in the *TAS1R* gene family,[14,39] which is mainly effective in sweet taste perception sensitization. The taste perception mechanism of *TAS1R1* and *TAS1R2* genes operates via taste receptor proteins, expressed mostly in fungiform papillae at the tip and edges of the tongue and in palate taste receptor cells in the roof of the mouth. *TAS1R2* genetic polymorphisms (rs3935570 and rs4920566) studied herein were not associated with dental caries. However, it is important to take into consideration the differences between our study and previous studies, which include the studied populations, age of the included subjects, method for detection of dental caries, and *TAS1R2* polymorphisms. Rawal et al.[40] provided psychophysical evidence that rs17492553 in *TAS1R1* is associated with differences in overall taste intensity, which might influence the risk for dental caries. We found an association between *TAS1R1* and dental caries in pre-adolescents.

Studies performed with families estimated the heritability for dental caries ranging from 45% to 64%,

in which dental caries showed higher heritability in primary dentition than in permanent dentition.[41] However, in our study, a genetic association was only observed for permanent dentition. Genetic polymorphism rs17492553 in *TAS1R1* was borderline associated with caries experience in pre-adolescents, but not in preschool children, and, therefore, this result eventually led to three hypotheses. The first hypothesis is based on the age difference between preschool children and pre-adolescents and involves the mother-child relationship in caries experience. The genetic association with taste preference could possibly play a stronger role among pre-adolescents than among preschool children as parents (mainly the mother) have a central role in food decisions made by younger children. An important limitation of our study is the absence of DNA samples to test whether genetic polymorphisms in *TAS1R1* and/or *TAS1R2* in mothers could increase the risk of dental caries in their offspring. The second hypothesis is related to the genetic background of the studied populations. The pre-adolescent group studied here is from Manaus, located in northern Brazil, in the middle of the Amazon rainforest. Inhabitants of Manaus have mainly European and Native Amerindian ancestries.[26] On the other hand, the preschool children group is from Nova Friburgo, located in the mountain region of the state of Rio de Janeiro in southeastern Brazil. Inhabitants of Nova Friburgo are mainly of European ancestry, as Swiss citizens began to immigrate into Brazil with the foundation of Nova Friburgo colony in 1819. In fact, the differences in genotypes and allele frequencies in both studied populations support the hypothesis that the genetic background differs between both populations and could modulate dental caries susceptibility. The third hypothesis concerns the difference in the diet of each studied population, which reflects their geographical location and descendants' habits. The diet of the population from Manaus commonly includes fish and fruit that are typical of the Amazon region and that are not part of the diet in southern Brazil.

Therefore, the fact that only two Brazilian populations from different age groups were included in our study is also a limitation, for not allowing us to test whether rs17492553 is a biomarker of dental caries in older individuals from other Brazilian regions. Future studies should include children/pre-adolescents from other Brazilian regions. Other important limitations were the following: we did not use a validated questionnaire to assess individuals' diets; the protocol used to evaluate caries did not include white spot lesions as caries phenotype; there was no calibration of the multicenter team performing the clinical examination.

Although dental caries and nutritional status were not associated, it is important to emphasize that the prevalence of dental caries, obesity, and associated comorbidities is internationally high despite ongoing prevention and intervention efforts.[32] Thus, the characterization of the genetic factors that predispose to taste preferences and the incorporation of this information into dental caries and obesity prevention efforts, providing a tool to adjust eating patterns to promote a healthy diet, may be a key to the complex solution to these global problems.

Conclusion

The consumption of sweets between meals was the main factor associated with an increased prevalence of dental caries among preschool children and pre-adolescents. Genetic polymorphism rs17492553 in *TAS1R1* was borderline associated with higher dental caries prevalence in pre-adolescents.

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