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ORIGINAL SCIENTIFIC ARTICLE

Related factors of dental caries and molar incisor hypomineralisation in a group of children with cystic fibrosis

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Abstract
Aim To investigate dental caries and molar incisor hypomineralisation (MIH)-related factors such as treatment, diet, brushing and salivary factors in children with cystic fibrosis (CF) compared with healthy peers.
Study design A cohort study was performed.
Methods This study was performed on 30 CF children comprising patients at the Faculty of Medicine and 30 control children recruited from the Dental School. Salivary factors, dental caries, MIH, daily diet, brushing habits were analysed. Statistical analysis was calculated by SPSS for Windows.
Results Decay missing filled teeth (DMF-T) score was 4.6 ± 4.0 in CF and 7.7 ± 2.7 in control ($p = 0.001$). 43 % of CF children with MIH were found to use antibiotics, but no significant difference in the caries experience was found with antibiotic usage ($p > 0.05$). DMF-T of CF adolescents (23 %) who use Tobramycin was 7 ± 3.5. DMF-T of CF children (20 %) who take other antibiotics was 2.5 ± 3.5, but no statistical difference was found ($p = 0.054$). Saliva pH, salivary flow rate, and buffering capacity were not found statistically significant ($p > 0.05$).
Statistics Percentage arithmetic mean value, standard deviation, independent sample *t* test, Fisher's exact test, Chi-square test and Mann–Whitney *U* test were used, while a *p* value of <0.05 was considered statistically significant.
Conclusions Medication and diet could be considered as a risk factor for dental caries and factors such as salivary pH, good oral hygiene could play a protective role for oral health CF children. MIH frequency and lower caries experience seen in CF children could be due to salivary factors or pharmacological treatment they take. The multidisciplinary approach team would be advantageous in the management of children with CF and oral health should be under control during early years of life by paediatric dentists.

Keywords Cystic fibrosis · Children · Dental caries · Saliva · Molar incisor hypomineralisation

Introduction

Cystic fibrosis (CF) is characterised with chronic airway inflammation, mucus plugging, and bronchial infection with specific bacterial pathogens (Welsh et al. 2001). Cystic fibrosis transmembrane conductance regulator (CFTR) gene abnormalities decreasing the expression of other epithelial proteins in in vitro models are the primary causes of disease despite its complex pathophysiology (Schwiebert et al. 1999).

CF therapy includes treatment of bronchial inflammation and infection with antibiotics and physiotherapy, pancreatic enzyme replacement therapy, and fat-soluble vitamin supplementation. Also β_2 agonists and corticosteroids are parts of pharmacological treatment. For these patients, a high calorie diet is recommended, and high sugary foods are often consumed to maintain the increased calorific intake needed (Kinirons 1989, 1992; Atar and Körperich 2010).

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The production of acids by oral bacteria after carbohydrate consumption gives rise to dental caries following demineralisation during cycles of de- and remineralisation (Catalán et al. 2011). Salivary changes, including the pH and buffering capacity, build up a protective mechanism for oral health (Narang et al. 2003). CFTR gene is highly expressed in salivary glands, but the reported effects of CF on salivary gland function and the incidence of dental caries are inconsistent. The basis for these discrepancies is unknown (Catalán et al. 2011).

An indirect role of CFTR gene for mineral composition of incisors probably by maintaining a normal salivary environment for continuous tooth eruption is suggested by a study in mice (Gawenis et al. 2001). Also it is claimed that CFTR plays an important role in enamel formation (Chi 2013). The high prevalence of enamel defects such as hypoplasia in CF patients could be due to the metabolic disease, and above all to long-term pharmacological therapies (Rosenstein and Cutting 1998).

A direct association between prevalence of carious lesions and decreased saliva production is well documented (Edgar et al. 1981), but the role of specific salivary constituents in the pathogenesis of dental caries is not well understood, particularly in diseases such as CF (Catalán et al. 2011). Cystic fibrosis patients have been reported to have abnormal dentitions, with dental effects related either to the disease itself or as a consequence of treatment (Kinirons 1989, 1992).

Molar incisor hypomineralisation (MIH) is defined as the developmentally derived dental defect that involves hypomineralisation of 1–4 permanent first molars that are frequently associated with similarly affected permanent incisors. Hypomineralisation can be caused by disorders occurring in the calcification or maturation stage (Gawenis et al. 2001). The defect clinically presents as demarcated enamel opacities of different colours in the affected teeth that can occasionally undergo post-eruptive breakdown due to soft and porous enamel. This may result in atypical cavitation or even to complete coronal disturbance, requiring extensive restorative treatment (Arquitt et al. 2002). MIH is the result of a variety of environmental factors acting systematically, including prenatal, perinatal, natal and childhood medical conditions affecting the developing enamel, while an underlying genetic predisposition should not be excluded (Ferrazzano et al. 2009).

Respiratory disease, high fever diseases such as chicken pox, low birth weight and frequent use of antibiotics in early childhood are linked to MIH in literature (Costa-Silva et al. 2011). Aetiological associations with systemic conditions or environmental insults during the child's first 3 years have been implicated (William et al. 2006).

There is insufficient information on MIH prevalence and caries experience among children affected by CF. The aim of this study was to investigate salivary, oral hygiene habits, diet and treatment-related risk factors with prevalence of dental caries and MIH in CF children.

Material and methods

Ethical approval

Ethical approval was taken from Marmara University Medical Faculty Clinical Researches Ethics Committee. The informed consent was obtained from all parents/caregivers.

Sample groups

This cohort study was undertaken in children with and without CF. The case group was composed of children with CF at the Faculty of Medicine and the control group was composed of healthy peers recruited from the dental school. The study population included 30 children with CF, compared with a control group of 30 healthy peers all under 18 years of age with no systemic disorders recorded and taking no medication (Edgar et al. 1981; Costa-Silva et al. 2010). Medical conditions of patients were followed up by two experienced paediatric pulmonologists. Study population numbers were determined according to the recordings of population of children with CF diagnosis who attended respiratory outpatient clinic.

Oral examinations were undertaken by an experienced dentist (SM) to assess dental caries (WHO criteria) and MIH in children attending respiratory outpatient clinic. The Kappa statistics was used for intra-examiners agreement calibration. After one week, the same patients were examined again by the same examiner and k values were found to be 0.96 and 0.93 for the variables dental decay and MIH, respectively. Systemic or topical fluoride exposure criteria for both study and control groups were regarded to be similar. Diagnosis of MIH was clinically based on the criteria established by Weerheijm (2003).

In our study, the severity of MIH was determined in three groups; (a) mild defect (demarcated opacities) (b) moderate defect and (c) severe defect (enamel breakdown and atypical restorations), as previously proposed by Jasulaityte et al. (2007).

Clinical assessment

Following a professional coronal polishing of the teeth, a clinical examination of each child was performed in a dental chair using mirror, probe and dental light; salivary flow rates were expressed as the volume of saliva (mL) secreted per minute. Besides flow rate, buffering capacity and pH value of the saliva samples were analysed by

Saliva-Check BUFFER kit (GC, Europe). To investigate associations between carious lesions and salivary properties, Saliva-Check BUFFER kit was used as an easy-to-use chairside saliva-testing examination tool (Costa-Silva et al. 2010, 2011). Prior to any visit where a saliva diagnostic procedure was planned, instructions were given to patients not to smoke, consume food or drink, brush the teeth or use a mouth wash for at least 1 h prior to the scheduled appointment time.

For pH measurements, the patients were instructed to expectorate any pooled saliva into the collection cup. Then a pH test strip was placed into the sample of resting saliva for 10 s, and then checked the colour of the strip. This was then compared with the testing chart available in the package. Neutral saliva pH ranges between 6.8 and 7.8.

To test stimulated saliva, patients were instructed to chew a piece of wax to stimulate salivary flow, and after 30 s expectorated into the spittoon. They continued chewing for a further 5 min, collecting all the saliva into the collection cup at regular 30 s intervals. The quantity of saliva was measured by checking the mL markings on the side of the cup. Normal stimulated saliva flow rate may vary between 1 and 1.6 mL/min. To test buffering capacity, after removal of a buffer test strip from the foil package, it was placed onto an absorbent tissue with the test side up. Using a pipette, sufficient saliva was drawn from the collection cup and one drop dispensed onto each of the three test pads, the strip was then turned 90° to soak up excess saliva on the absorbent tissue. This prevent the excess saliva from swelling on the test pad and possibly affecting the accuracy of the test result. The test pads began to change colour immediately, and after 2 min the final result was calculated by adding the points according to the final colour of each pad. Normal values range between 10 and 12.

Recommended daily diets were recorded in consideration of diet prescription of paediatric pulmonology department for children with CF. Snacking, medication and tooth brushing habits of children were also recorded.

Statistics

Data were collected, recorded, and evaluated using the Statistical Package for Social Sciences (SPSS) 20.0 for Windows. Percentage arithmetic mean value, standard deviation, independent sample t test, Fisher's exact test, Chi square test and Mann–Whitney U test were used while a p value of <0.05 was considered statistically significant.

Results

The mean age of CF children ($n = 30$) was 10.2 years (± 4.8) and that of the healthy subjects ($n = 30$) was 9.9 years (± 1.4). There was no statistically significant difference between the mean ages of the CF patients and healthy subjects ($p > 0.05$).

Table 1 DMF-T data according to gender among cystic fibrosis and control group children

	CF children ($n = 30$) Mean age (10.2 ± 4.8 years)	Healthy group ($n = 30$) Mean age (9.9 ± 1.4 years)
Boys ($n = 18$)	$n = 14$ (47 %)	$n = 18$ (60 %)
	DMF-T	DMF-T
	6.2 ± 4.31	7.5 ± 3.14
	$n = 4$ (13 %)	$N = 0$
	Caries-free	
Girls ($n = 12$)	$n = 9$ (30 %)	$n = 12$ (40 %)
	DMF-T	DMF-T
	5.4 ± 4.24	7.91 ± 2.96
	$n = 3$ (10 %)	$N = 0$
	Caries-free	

CF cystic fibrosis

DMF-T of CF children was 4.6 ± 4.0 and 7.7 ± 2.7 in control children and difference between two groups was found statistically significant ($p = 0.001$). Among the group of children with CF, 23 % of children were caries free. Table 1 shows the distribution of decayed, missing, and filled teeth.

In CF children 43 % were reported to use antibiotics to control chronic respiratory infection, 57 % were caries-free but no significant difference in the caries-experience was found with antibiotic usage ($p > 0.05$).

In CF children 23 % whose mean age was 14.7 ± 3.9 years were found to use Tobramycin and the DMF-T value of this group was 7 ± 3.5 and DMF-T value of 20 % of CF children, with mean age 10.8 ± 5.9 years, who had taken other antibiotics was 2.5 ± 3.5. No statistical difference was found between two groups ($p = 0.054$).

Of CF children 63.2 % ($n = 16$) consumed recommended daily diets for energy. Because CF children follow recommended daily diets, only 30 % of CF children were found to snack more than three times a day, while 63 % of the control group were found to snack in same frequency. The relationship of snacking and DMFT scores between CF and control groups was not statistically significant ($p > 0.05$).

Initial brushing age of 86 % of CF children was 2 years and 49 % of healthy peers started at 3–4 years of age. Sixty percent of CF children and 33% of healthy peers brushed their teeth more than once a day. The relationship between brushing and DMFT scores of CF and control groups was not statistically significant ($p > 0.05$).

Table 2 Stimulated salivary factors according to study and control groups

	Buffer capacity (mean ± SD)	Flow rate (mL/min) (mean ± SD)	Salivary pH (mean ± SD)
CF children ($n = 30$)	8.47 ± 2.7	1.30 ± 0.7	7.25 ± 0.45
Healthy group ($n = 30$)	8.20 ± 1.58	1.54 ± 0.9	7.45 ± 0.34
p	0.64 (NS)	0.09 (NS)	0.57 (NS)

NS non-significant ($p > 0.05$)

Table 3 The severity of molar incisor hypomineralisation defects among study and control groups

	Mild MIH n (%)	Moderate MIH n (%)	Severe MIH n (%)
CF children $n = 6$ (20 %)	5 (83.3)	1 (16.7 %)	0
Healthy group $n = 7$ (23.3 %)	7 (100)	0	0
p	NS	NS	NS

NS non-significant ($p > 0.05$)

For CF children with MIH and controls with MIH buffering capacities were 9.3 and 8.2, respectively ($p = 0.0816$).

MIH was observed in 20 % of CF children ($n = 6$). Among this group 83.3 % ($n = 5$) had mild defects and 16.7 % ($n = 1$) had moderate defects, none of them had severe defects (Table 2).

All CF children with MIH were found to have used antibiotics in first 3 years of life more than six times a year, but none of the children in control group with MIH was found to have used antibiotics. No difference was found between MIH and amoxycillin intake for CF children ($p > 0.05$).

As a part of pharmacological treatment of disease, among CF children with MIH, 83 % were found to use β_2 agonists and 50 % were found to use inhalation corticosteroids. Relation between MIH and β_2 agonist usage in CF children was not statistically significant ($p = 0.000$).

Aetiological factors of MIH such as ear infections and chicken pox before 3 years of age, low birth weight, mode of delivery and allergy were found to have no difference between CF children and control group with MIH ($p > 0.05$).

Table 2 shows mean saliva pH, mean stimulated salivary flow rate and mean buffering capacity values for both CF and control groups which were not statistically significant ($p > 0.05$). Table 3 shows the severity of MIH defects for the CF and control groups of children.

Discussion

Dental caries prevention plays a critical role for CF patients because of their susceptibility to infection, which influences quality of life and survival (Chi 2013). Early diagnosis and treatment are of paramount importance to help patients to see the disease as manageable, increase their life expectancy and awareness of regular dental care visits (Fernald et al. 1990). As CF is usually diagnosed in early life, involvement of paediatric dentists in the management and long-term care of these patients is essential (Atar and Körperich 2010).

According to the systematic review of Chi (2013), of the 15 studies included in the review, ten studies concluded that children and adolescents with CF have a lower caries prevalence than controls, which corresponds to our statistically significant findings ($p = 0.001$). In the study of Kinirons (1989), among 131 CF patients, significantly lower caries scores were determined compared to healthy controls. Martens et al. studied 37 CF patients aged 6–38 years, age- and sex-matched with a similar number of control individuals, and showed no difference in caries prevalence between the groups (Martens et al. 2001).

Dabrowska et al. reported that among CF patients, there is a serious risk of caries due to severe course of the disease, long-term administration of medications and high carbohydrate diet intended to overcome high energy intake (Dabrowska et al. 2006). While 63 % of the control group were found to snack more than three times a day, only 30 % of CF children were snacking in same frequency which can be attributed to their following the recommended daily diets.

Studies have shown that the addition of long-term antibiotic therapy has an effect on biofilm and reduces its cariogenicity as shown in the present study where 48 % of CF children used antibiotics. Jagels and Sweeney (1975) reported a reduced caries prevalence in 63 CF patients who were on long-term oral antibiotics, compared with 56 of their siblings. This confirmed the findings of Littleton and White (1964), who showed lower caries experience in children receiving oral penicillin for an extended period. They concluded that this finding was a result of the antibiotics, rather than a consequence of a specific disease process and could be extrapolated to any group of children on long-term antibiotic treatment (Littleton and White 1964). Kinirons claimed that antibiotic therapy may be a major cause of the lower levels of dental disease observed in CF children (Kinirons 1992). Lower caries experience can be attributable to those children and their caregivers being highly motivated and health conscious, and may be regular dental attenders, although the evidence for this is limited (Littleton and White 1964; Kinirons 1992).

For children the belief that antibiotics lower intra-oral levels of *Streptococcus mutans* and caries risk may be true, but may not be the case for adolescents with CF because at age 11 a respiratory microbiologic shift has been noted so new antibiotics were developed, including inhaled tobramycin, an aminoglycoside that targets *Pseudomonas aeruginosa*. Tobramycin does not affect *S. mutans* and thereby increased caries risk has been discussed for adolescents with CF (van Westreenen and Tiddens 2010; Bals et al. 2011; Chi 2013). Our findings showed that DMF-T scores for adolescents with CF who take Tobramycin were higher than children who take other antibiotics but the difference was not statistically significant. p value was found to be 0.054; if sample group size had been larger, results would have been found to be significant.

According to Ghanim et al. only 10.8 % children with MIH had a low buffering capacity, possibly explaining the lack of correlation observed between hypomineralisation severity and buffering capacity of saliva (Ghanim et al. 2013). Although the mean buffering capacity value of CF group in the present study was higher, no difference was observed in comparison of buffering capacities between CF group and controls with MIH.

Ferrazzano et al. (2012) showed a higher prevalence of enamel defects in CF subjects in comparison to the healthy group and suggested that it could be due to the long-term pharmacological therapies that they take. For CF and healthy children in our study, no significant difference was shown.

Kuscu et al. (2013) studied the prevalence of MIH in pigs both visually and quantitatively by X-ray microtomography, and suggested a reduction in mineral density at a microscopic level. Their findings did not show an association between clinically visible MIH and amoxycillin usage. Whatling and Fearne (2008) found no significant results were found for relation between MIH and amoxycillin in children as confirmed in this study.

Kargul et al. investigated the effect of β_2 agonists and inhaler corticosteroids on saliva and plaque pH. Inhaler drugs produce a pH decrease in medicated asthmatics (Kargul et al. 1998). Decrease in saliva pH of CF children in this study could be similarly caused. In the present study results, the relationship between MIH with β_2 agonists and corticosteroids usage in CF children was not found to be statistically significant.

Children with MIH present with more medical problems and more affected teeth than controls caused by their prenatal, perinatal and postnatal period problems (Lygidakis et al. 2008). Systemic causes at time of birth such as asthma, pneumonia, upper respiratory tract infections, otitis media, antibiotics, dioxins in mother's milk, tonsillitis and tonsillectomy and exanthamatous fevers of childhood have been put forward. However, the aetiology still remains unclear (Willmott et al. 2008). Frequently found aetiological factors of MIH such as ear infections and chicken pox before 3 years of age, low birth weight, mode of delivery and allergy were not significantly different between CF and control children with MIH in this study.

Additional research is needed to evaluate aetiological factors regarding caries risk and MIH in children and adolescents with CF. Professionals who treat CF children should be alerted to promoting oral health (Azevedo et al. 2006; Chi 2013).

The underlying cause of low caries scores may be saliva-related. Salivary bicarbonate system is the main mechanism for buffering capacity of saliva that affects dental caries process. It is recognised that the association between stimulated salivary flow rate and buffer capacity is linear. According to a mouse enamel study reported by Sui et al. (2003), the pH of the whole saliva was not also significantly reduced in the CF children. Catalán et al. noted that lower saliva pH and buffering capacity observed in mice would cause an increase of acidification within the dental plaque on the tooth surface (Catalán et al. 2011). Earlier reports showed that human CF saliva pH/bicarbonate concentration had increased, with no differences found according to Aps et al. (2002a, b) or reduced as reported by Davies et al. (1990).

In a study of Aps et al. (2002c), intrinsic salivary compensatory mechanisms possibly explained the lower caries scores of Kinirons (1983) who stated that there was a link between altered saliva properties and low caries experience, but no relation between the changes in saliva and the severity of the disease process. Kinirons (1983) also concluded that the reduction in dental caries prevalence seen in the CF patients surveyed was associated with a significantly higher mean pH and buffering capacity of their stimulated saliva which supports our higher buffering capacity findings in CF children.

Conclusions

Higher pH and buffering capacity findings for saliva of CF children may be considered to explain their lower caries scores. Adolescent children with CF, who take Tobramycin, may be at higher caries risk compared to healthy peers. Future studies with larger sample size group of CF children may give favourable outcomes for aetiological factors of MIH.

Future researches should focus on effect of antibiotics, β_2 agonists, tobramycin and inhaler corticosteroids on dental caries and MIH in CF children.

The multidisciplinary approach team would be advantageous in the management of children with CF and oral health should be under control since early years of life by paediatric dentists.

Conflict of interest The authors declare that they have no conflict of interest.

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