Original Article

The Effects of Psychostimulants on Oral Health and Saliva in Children with Attention Deficit Hyperactivity Disorder: A Case-Control Study

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Abstract

Introduction: This study investigated the dental health problems and saliva characteristics of children under psychostimulant therapy for attention-deficit hyperactivity disorder (ADHD). **Materials and Methods:** One hundred and twenty children aged 7–12 years were divided into three groups. Groups 1–2 comprised children diagnosed with ADHD: those who had not yet started psychostimulant therapy (Group 1) and those already receiving long-term psychostimulant therapy (Group 2). Group 3 comprised healthy, nonmedicated children. Possible side effects of psychostimulants were investigated at the beginning of study in Group 2 and after 3 months drug use in Group 1. Bruxism and dental erosion prevalence, salivary *Streptococcus mutans* count, buffering capacity, and stimulated salivary flow rate (SSFR) were measured, and salivary α-amylase, calcium, total protein, and proline-rich acidic protein (PRAP) levels were quantified in the beginning of the study. Data were analyzed using the Kruskal–Wallis test. **Results:** The most frequently reported side effects of psychostimulants were decreased appetite, dry mouth, and increased fluid consumption. The prevalence of bruxism and dental erosion was higher in Groups 1 and 2 than in Group 3, but the differences were not significant ($P > 0.05$). In Group 2, subjective dry mouth feel was reported by 32.5% of patients and 17.5% had a very low SSFR. Salivary α-amylase, calcium, total protein, and PRAP levels were lower in Group 2 than the others, but the differences were not significant ($P > 0.05$). **Conclusions:** ADHD and psychostimulant therapy do not appear to be significantly related to decreasing SSFR or protective saliva components against dental caries. However, a systematic investigation of the long-term safety of psychostimulants is needed. The most effective method of maintaining dental health of children with ADHD is frequent appointments focusing on oral hygiene practices accompanied by dietary analyses.

Keywords: *Attention-deficit hyperactivity disorder, bruxism, dental erosion, dry mouth, psychostimulants, saliva biochemical components, salivary flow rate*

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a childhood psychiatric disorder characterized by inattention, hyperactivity, and impulsivity.[1] ADHD has been reported to be among the most frequent diagnoses in patients referred to child psychiatry clinics worldwide, and male children are affected more than the females.[2-4] Psychostimulants are currently the most commonly used psychotropic drugs to treat ADHD in psychiatric patients under the age of 18 years, and psychostimulant usage has increased in recent years.[5,6]

Numerous studies describe several side effects of psychostimulants that threaten oral and dental health,

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including dry mouth, gingival overgrowth, dental erosion, awake bruxism, and sleep bruxism.[7] It was reported that signs and symptoms of temporomandibular joint dysfunction may be influenced by the use of medications prescribed for ADHD.[8] In a recent systematic review, psychostimulants were shown to induce xerostomia, salivary gland hypofunction, and sialorrhea.[9] In children and young adults with ADHD, unstimulated salivary flow rate (SSFR) was found to be lower, and microbial dental plaque scores were higher than non-ADHD[10] Obtained data from current research such as inappropriate oral health behaviors, excessive consumption of sugary snacks and beverages, and an increased number of meals in children with ADHD suggest that ADHD may be a risk factor for the development of dental decay.[10-14] It was concluded in a study that the risk of dental caries is higher in children with attention deficits independently of their socioeconomic status than in healthy children.[15] In such instances, protective properties of saliva become pivotal in preventing tooth decay and gum diseases. When the saliva flow rate is decreased, there may be changes in the organic and inorganic components of the saliva (e.g., proteins, enzymes, and calcium), which are responsible for protecting enamel integrity.[10] Furthermore, the biochemical composition of saliva may be directly affected by the side effects of psychotropic drugs.[16,17] Furthermore, some researchers found that there is a significant increase in the salivary protein thiols and pseudocholinesterase levels in ADHD children when compared to controls.[18] However, few studies have clinically investigated these effects of psychotropic drugs in school-aged children with ADHD.

The focus of this study is to decide if any evidence exists to verify that ADHD itself or stimulant therapy in children threatens the oral and dental health by virtue of its effects on the saliva physical and biochemical properties. The authors hypothesized that salivary flow rate, pH, buffering capacity, and salivary biochemical components which are responsible for protecting tooth tissues from decay in ADHD children medicated with psychostimulants are lower than in nonmedicated ADHD children and healthy controls. Furthermore, the hypotheses that the prevalence of bruxism and dental erosion is higher in ADHD children with or without medication than healthy peers are tested. By the virtue of obtained data, it was aimed to determine the measures must be taken to maintain dental health of children with ADHD.

Materials and Methods

Study population

The study protocol was approved by the Clinical Research Ethics Committee of the Medical Faculty (No. 173/2014). Informed consent was obtained from parents of all children who participated in the study. The children with ADHD had been diagnosed based on inattention, hyperactivity, and impulsivity symptoms as described in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition[1] and treated by child psychiatrists in the Child and Adolescent Psychiatry Department of Medical School.

A total of 120 children, aged 7–12 years, were divided into three groups of 40 each. Groups 1 and 2 comprised children diagnosed with ADHD: those about to start psychostimulant therapy (Group 1) and those already under long-term (≥6 months) psychostimulant therapy (Group 2). Group 3 comprised healthy, nonmedicated children (control group). Inclusion criteria were as follows: (1) Patients in Groups 1 and 2 were diagnosed with ADHD and did not have any disorders other than ADHD. (2) In Group 2, no other medication than psychostimulants were taken. (3) Children in the control group were healthy and did not use any medication regularly in the month before the study. Exclusion criteria were as follows: (1) Exposure to any infection that could cause dehydration in the 1 month before the saliva analysis. (2) Use of antibiotics in the 3 weeks before the analysis. (3) Topical application of fluoride in the last 48 h before analysis. (4) Gingival bleeding. (5) Fixed or removable appliance or a dental crown in the mouth.

Study design

The flow chart of the study is as follows:

- Medical history and medication data for all participants were gathered from Child Psychiatry Department records
- Parents of children were questioned regarding possible psychostimulant side effects such as appetite changes, thirst or dry mouth, and increased consumption of liquid (water, soft drinks) in Group 1 after 3 months drug use and in Group 2 at the beginning of the study
- Information was obtained from all parents on whether their children were experiencing either awake or sleep bruxism
- Children's behavior during dental examinations was scored according to the Frankl behavior scale (1: Definitely negative, 2: Negative, 3: Positive, 4: Definitely positive)[19]
- Intraoral examinations were performed based on oral health surveys and basic methods specified by the World Health Organization,[20] and dental erosion scores were recorded by the basic erosive wear examination (BEWE) scoring system.[21] For grading erosive wear of each tooth, four scores (Score 0:no

erosive tooth wear, Score 1:initial loss of surface texture, Score 2:distinct defect, hard tissue loss is less than 50% of the surface area, Score 3: hard tissue loss is more than 50% of the surface area) are used in this scoring system. After the estimation of dental scores the individual risk of erosive tooth wear (none, low, medium, high) is determined for each patient.[21]

- Quantifying of salivary *Streptococcus mutans* count with the Saliva-Check Mutans test (GC Europe N. V. Leuven, Belgium)
- Collection and storage of unstimulated saliva samples for biochemical analysis of salivary amylase, calcium, total protein, and proline-rich acidic protein (PRAP). Unstimulated saliva was obtained by asking children to collect saliva in their mouths and spit it into a test tube
- Measurement of saliva viscosity, pH, and buffering capacity from unstimulated saliva samples with Saliva-Check Buffer test (GC Europe N. V. Leuven, Belgium). Salivary viscosity was evaluated by visually assessing the resting salivary consistency in the oral cavity in accordance with the instructions of the manufacturers. Salivary pH and buffering capacity were measured with stripes from test content
- Collection of stimulated saliva samples by having the children chew paraffin gum for 5 min and spit into a scaled cup and measurement of SSFR
- Saliva analyses were performed at the beginning of the study in all groups. To avoid possible effects of circadian rhythm, saliva was collected from all participants under the same conditions between 09:00 AM and 11:00 AM. Children refrained from eating, drinking, brushing teeth, and rinsing for at least 2 h before saliva analyses.

A flat polyethylene tube with absorbent cotton and screw cap (Salivette®, Sarstedt AG and Co., Nümbrecht, Germany) was used for biochemical analyses. The absorbent cotton in the tube was not used because it can stimulate the flow of saliva. For biochemical analyses, the tubes of saliva samples were stored at −80°C (Wise Cryo. Aachen, Germany). Before the analyses, the samples were thawed, cool centrifuged at 4000 g for 4 min (Eppendorf MR5415, Wesseling-Berzdorf, Germany), and the supernatants were then separated into aliquots. The levels of salivary α-amylase, calcium, and total protein were measured using a colorimetric assay kit (Beckman Coulter, Brea CA, USA) and an autoanalyzer device (AU 5800; Beckman Coulter). The PRAP measurement was made using a human PRAP1 enzyme-linked immunosorbent assay kit (Hangzhou Eastbiopharm Co., Ltd., Hangzhou, China).

Statistical analysis

All data were entered into the SPSS Statistics Version 20.0 software package (IBM, SPSS Inc., USA). The Chi-square independence test was applied for nominal data. The Kruskal–Wallis test was used to evaluate differences between groups because the data did not satisfy the preconditions for parametric tests. As a result of the Kruskal–Wallis test, differences between the medians of groups were evaluated using the Bonferroni–Dunn test.

Results

Mean ages of the children participated in the study were 8.81 ± 1.83 (Group 1), 9.07 ± 1.44 (Group 2), 8.78 ± 1.38 (Group 3), and there was no statistically significant difference in gender between the groups ($P > 0.05$).

All patients in Groups 1 and 2 were prescribed methylphenidate. Only 14 patients (35%) in Group 1

Table 1: Patients with drug side effects in attention-deficit hyperactivity disorder groups

Groups	Appetite			Dry mouth, *n* (%)	Increased fluid consumption, *n* (%)
	Decreased, *n* (%)	Unaffected, *n* (%)	Increased, *n* (%)		
Group 1 (*n*=14)*	5 (35.7)	8 (57.2)	1 (7.1)	3 (21.4)	1 (7.1)
Group 2 (*n*=40)	22 (55.0)	13 (32.5)	5 (12.5)	13 (32.5)	17 (42.5)

*Patients who continued to use psychostimulants for at least 3 months in Group 1. *n*=Number of children

Table 2: The prevalence of awake and sleep bruxism in each group

Bruxısm	Group 1, *n* (%)	Group 2, *n* (%)	Group 3, *n* (%)	*P**
Awake bruxism	8 (20)	4 (10)	1 (2.5)	0.102
Sleep bruxism	9 (22.5)	13 (32.5)	5 (12.5)	0.161
Total number of patients with bruxism	14 (35)	14 (35)	6 (15)	0.159

*P<0.05 means statistically significant difference. *n*=Number of children

Table 3: Basic erosive wear examination findings of the groups

Groups	Mean	Erosive tooth wear risk (*n*)			
		None	Low	Medium	High
Group 1	0.75±0.76	17	18	4	1
Group 2	0.73±0.59	14	23	3	-
Group 3	0.51±0.67	24	13	3	-
*P**			0.161		

*P<0.05 means statistically significant difference. *n*=Number of children

Table 4: Salivary viscosity, pH, stimulated salivary flow rate, and buffering capacity findings of the groups

Groups	Group 1	Group 2	Group 3	P*
Viscosity *n* (%)				
Normal viscosity (watery clear saliva)	19 (47.5)	20 (50)	22 (55)	0.350
Increased viscosity (frothy bubbly saliva)	21 (52.5)	15 (37.5)	15 (37.5)	
Residues (sticky frothy saliva)	-	5 (12.5)	3 (7.5)	
pH (mean)	6.89	6.97	7.19	0.055
SSFR, *n* (%)				
<0.7 ml/dk	6 (15)	7 (17.5)	4 (10)	0.249
0.7-1.0 ml/dk	19 (47.5)	18 (45)	14 (35)	
>1.0 ml/dk	15 (37.5)	15 (37.5)	22 (55)	
Buffering capacity				
Normal	28 (70)	24 (60)	28 (70)	0.406
Low	10 (25)	14 (35)	12 (30)	
Very low	2 (5)	2 (5)	-	

*$P<0.05$ means statistically significant difference. *n*=Number of children; SSFR=Stimulated salivary flow rate

Table 5: Salivary biochemical analysis findings in each group

Saliva components	Groups	Mean±SD	Median	P*
α-Amylase (U/ml)	1	163.28±28.05	154.95	0.126
	2	154.01±31.74	144.63	
	3	160.33±7.97	159.72	
Calcium (mg/dl)	1	1.85±0.67	1.73	0.155
	2	2.08±0.94	1.74	
	3	2.21±0.60	2.10	
Total protein (g/dl)	1	0.115±0.082	0.105	0.592
	2	0.129±0.130	0.085	
	3	0.108±0.030	0.110	
PRAP (ng/ml)	1	19.95±6.44	18.52	0.742
	2	17.57±7.48	15.93	
	3	17.61±2.32	17.27	

*$P<0.05$ means statistically significant difference.
PRAP=Proline-rich acidic protein; SD=Standard deviation

began and continued to use methylphenidate for 3 months; 26 of them began but stopped drug therapy after a few doses because of various reasons. The most common parent-reported side effects of methylphenidate were decreased appetite, increased fluid consumption, and feeling of dry mouth, respectively. Subjective dry mouth feel was reported by 32.5% of the children in Group 2, and 42.5% of the children in this group have been found to increase fluid consumption. Data on patients with drug side effects in Group 1 after 3-month usage and Group 2 are presented in Table 1.

Mean Frankl behavior scale scores were 3.44 ± 0.65 (Group 1), 3.36 ± 0.73 (Group 2), 3.90 ± 0.30 (Group 3), and significantly lower in both Group 1 and Group 2 ($P = 0.000$) than in Group 3.

Awake bruxism is most frequently seen in Group 1 (20%), and sleep bruxism is the most frequently seen in Group 2 (32.5%). The prevalences of awake and sleep bruxism in Group 1 and Group 2 were higher than those in Group 3, but the differences were not statistically significant ($P > 0.05$) [Table 2]. The highest BEWE index scores were found in Group 2. Mean BEWE index score of Group 1 (0.75 ± 0.76) and Group 2 (0.73 ± 0.59) were higher than Group 3 (0.51 ± 0.67) although the difference was not significant ($P = 0.161$). BEWE findings of the study are presented in Table 3.

The saliva *S. mutans* count was higher than 5×10^5 CFU/mL, which indicates the high caries risk in all children participated in the study. The highest salivary viscosity and lowest salivary flow rate and buffering capacity values were measured in Group 2. However, differences in salivary viscosity ($P = 0.350$), pH ($P = 0.055$), flow rate ($P = 0.249$), and buffering capacity ($P = 0.406$) among the groups were not statistically significant. Salivary viscosity, pH, SSFR, and buffering capacity values are presented in Table 4.

Salivary biochemical analyses were performed on 20 saliva samples in each cohort. The lowest median values of α-amylase, calcium, total protein, and PRAP were determined in Group 2, and the highest median values of α-amylase, calcium, and total protein were in control group. However, the differences in evaluated biochemical components of the saliva between all groups were not statistically significant ($P > 0.05$) [Table 5].

Discussion

The number of ADHD cases and the use of psychostimulant therapy have increased in recent years, but the literature remains unclear both on the short-/long-term drug side effects and the impact of the disease on the dental health of the children.

It has been reported that the majority of patients referred to the Child Psychiatry Clinics range in age from 7 to 12 years.[22,23] In pediatric dentistry, school age

(7–12 years) is a period when nutrition and toothbrushing habits decline, while elements that threaten anatomical and physiological aspects of dental health increase. Therefore, the current study included children aged 7–12 years. The majority of children with ADHD in our study group were male (82.5%), in concurrence with the literature.[2,4]

Due to the characteristic symptoms of the disease, such as overactivity and impulsivity, children with ADHD may have difficulties in interacting with the dentist and in staying focused on dental procedures, and so the dental treatments could be challenging.[24,25] However, children with ADHD and healthy children are reported to experience similar levels of dental anxiety.[26] In the present study, children in Groups 1 and 2 were found to have difficulty in communicating with the dentist during the dental examinations, and the Frankl scale scores of these children were significantly lower than were those of the control group. Furthermore, treatment of some ADHD patients was often delayed or completed under sedation.

Side effects of psychostimulant drugs are frequently discussed in the literature.[9,27] Some authors have reported that methylphenidate causes subjective dry mouth,[28] while others have not found any effect on salivary flow rate.[29,30] Wolff *et al*. (2017) reported in a recent study that psychostimulants induce xerostomia.[9] In the present study, we found that 32.5% of children receiving long-term methylphenidate use had subjective dry mouth and that 17.5% had a markedly low SSFR level (<0.7 ml/min). At the beginning of the study, it was hypothesized that the SSFRs of medicated ADHD children are lower than those of not yet on medication ADHD cases and of healthy controls. The similar measurement of SSFRs in Groups 1 and 2 weakened the opinion that methylphenidate may cause xerostomia.[31] The findings of Medori *et al*. that children with ADHD using methylphenidate have more cases of xerostomia than the control group were based on subjective complaints of participants.[31] In contrast, this study objectively measured the amount of stimulated saliva.

In this study, saliva pH, viscosity, and buffering capacity were similar in all three groups. This finding is compatible with the results of a similar study by Hidas *et al*.[12] Hence, it is not possible to conclude that medicated ADHD children are at a dental disadvantage compared with nonmedicated ADHD children or those without ADHD, based on salivary pH, viscosity, and buffer capacity, which are the major mechanisms by which saliva protects against tooth decay.

Salivary defense systems including salivary calcium, total proteins, and PRAP play significant roles in maintaining the health of the oral cavity and preventing caries.[29,32-34] It has been reported that PRAP levels are significantly correlated with lower caries scores.[29] In addition, salivary amylase is one of the building blocks of the acquired pellicle and therefore serves as a receptor for the adhesion of microorganisms to the tooth surface.[35,36] Moreover, α-amylase levels have gained increasing interest as indicators of bodily changes following stress, specifically under autonomic activation.[37] However, a low salivary flow rate can alter the biochemical composition of saliva.[38] In addition, some psychotropic drugs have also been reported to change salivary biochemical content.[16-18] To the best of our knowledge, no prior study has investigated the effect of stimulant drugs on salivary amylase, calcium, total protein, and PRAP in children with ADHD. The current investigation found that the salivary calcium, total protein, and PRAP levels were lower in children who used psychostimulants on a long-term basis than in the other groups. This could indicate that these children, particularly those with low salivary flow rates, may be susceptible to tooth decay, but further researches are needed about this subject.

Another commonly reported side effect of psychostimulants is bruxism. Investigations have shown that bruxism can be pharmacologically modulated by substances that act on the neurotransmission of the brain, supporting the concept that bruxism is primarily a central nervous system phenomenon.[39-41] Some studies suggest that the prevalence of bruxism is higher in children with ADHD than in those without ADHD and that bruxism can occur as a side effect of stimulant therapy.[42-44] A recent study concluded that ADHD signs had a significant effect on sleep bruxism in school-age children.[45] Chau *et al*. found that children with ADHD had a significantly higher frequency of parent-reported bruxism than did children without ADHD.[30] Another investigation showed that medicated ADHD children were more likely to develop bruxism than were nonmedicated children with ADHD or children in the control group.[43] The same study found that the number of worn teeth was 2.5 times higher in the children who used psychostimulants than in those who did not.[43] However, Hidas *et al*. found no significant difference between children with ADHD and healthy children in the prevalence of bruxism.[10] Our study showed that the prevalence of bruxism was higher in Groups 1 and 2 than in the control group, but the differences were not statistically significant for either awake or sleep bruxism. In addition, the similar prevalences of bruxism in Groups 1 and 2 suggest that bruxism may occur due to the neuropsychiatric disease itself, rather than to drug side effects.

There are few studies in the literature investigating the prevalence of dental erosion, which has been reported to be a side effect of psychostimulant therapy in children with ADHD. Chau *et al*. found no significant differences in tooth wear between children with and without ADHD.[30] In the present study, dental erosion was found to be higher in Groups 1 and 2 than in the control group, but it was thought that the number of eroded teeth may be increased because of the higher prevalence of bruxism in these groups. Furthermore, in our study, the high prevalence of dental erosion in ADHD patients who did not use psychostimulants yet was similar to that of psychostimulant users, weakening the argument that dental erosion may be a side effect of psychostimulant therapy. However, dry mouth, one of the reported side effects of the psychostimulants, has been associated with increased frequency of consumption of acidic beverages and poor oral hygiene.[46] Therefore, it should be considered that children with ADHD who have dry mouths and/or reduced salivary flow rates may be at high risk for dental erosion and caries.

All children in the study recorded high counts (≥5.105 CFU/mL) of salivary *S. mutans,* one of the most important etiological factors of dental caries. Even though children with ADHD had *S. mutans* counts that were similar to those of healthy children, children with ADHD have been found to be at high risk of caries and should have regular dental examinations.[15,47]

The literature remains inconclusive regarding the dental effects of ADHD and its related factors. A systematic investigation of the long-term safety of psychostimulant drugs is needed. The current opinion is that ADHD children have lower un-SSFRs, worse oral health behaviors, higher plaque indices, and more frequent snacking habits than do children without ADHD.[10,12]

The most effective methods for maintaining dental and oral health in ADHD children are more frequent appointments focusing on home oral hygiene practices and dietary analyses to reduce the consumption of cariogenic foods and beverages. In one study, parents of children with developmental disorders such as ADHD reported that their children's oral and dental health care needs were not adequately satisfied.[48] As did previous investigations, our study indicated that dental treatment for ADHD children should include an understanding of their behavior management needs. Children with ADHD are considered patients who need special attention in pediatric dentistry. Increased awareness is needed regarding ADHD and the dental health problems of ADHD patients, as is coordination between child psychiatrists and pediatric dentists.

Limitations of the study

This study was also intended to compare the initial and 3-month salivary analysis findings of children in Group 1. However, for various reasons, the parents did not fully support their children's medication regimens. Consequently, most (65%) of the children discontinued medication before 3 months. Thus, saliva evaluations could only be performed at the beginning in Group 1, not after 3 months of drug use as intended.

Conclusions

This study found that methylphenidate use had no significant effect on salivary pH, stimulated flow rate, buffering capacity, or biochemical content of the saliva. Bruxism and dental erosion prevalence were higher in the ADHD groups, but the findings were not statistically significant. ADHD and psychostimulant therapy do not appear to be significantly responsible for decreased salivary flow rates or changes in saliva pH, viscosity, buffering capacity, or examined biochemical components. However, further studies with larger samples are needed to clarify alterations in saliva characteristics of children with ADHD, as well as to confirm previous findings regarding the possible side effects of psychostimulant drug use in children.

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Conflicts of interest

There are no conflicts of interest.

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