

Research Article

# Salivary vitamin D levels in children with autism in relation to oral health status and disease severity

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**Abstract:** Background: Autism spectrum disorder is characterized by difficulties with social interaction and communication, as well as limited patterns of behavior and atypical sensory sensitivity. Although vitamin D insufficiency has previously been observed in autistic children, evidence on the link between vitamin D deficiency, oral health condition, and autism severity is scarce. The purpose of this study was to investigate vitamin D levels in relation to oral health status of children with autism, as well as the relationship between vitamin D and disease severity. Materials and methods: Two groups were included in this study: 40 institutionalized autistic children as a study group and 40 apparently healthy children as a control group with age range (3-12) years. Depending on the severity of autistic symptoms, the group was classified into three subgroups: mild, moderate, and severe. The oral examination was performed using simplified oral hygiene and decayed, missing and filled tooth indices to measure oral health status for both groups. Three millilitres of un-stimulated salivary sample was taken by drooling technique, the salivary level of vitamin D assessed by enzyme-linked immunosorbent assay. The data from the current study were analysed using SPSS version 21. Results: Salivary vitamin D levels were found to be significantly lower in the study group than in the control group. This reduction was not correlated with the severity of autism. 37.5% of the autistic patient group had fair oral hygiene, compared to 20% of the control group; simplified oral hygiene index shows negative significant correlation with vitamin D level while caries experience was significantly higher in patient group and there was a negative non-significant correlation with vitamin D level. Conclusion: The vitamin D level was significantly lower in the patient group with no correlation with disease severity, fair oral hygiene and more caries in both primary and permanent dentition was observed in autistic patients with significant negative correlation between the simplified oral hygiene index and vitamin D, while negative non-significant correlation with dental caries.

**Keywords:** Autism spectrum disorder, vitamin D, oral health, neurodevelopmental disorder, autism severity.

## Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired social interactions, communication difficulties, and repetitive, stereotyped behaviors as core symptoms. Genetic, epigenetic, and environmental factors all contribute to these symptoms <sup>(1,2)</sup>. Effective therapy is generally delayed because a reliable diagnosis is usually not made until the child is at least 2 years old; when the disease begins to emerge <sup>(3)</sup>. Autism spectrum disorder has a complicated and diverse etiology that involves both genetic and environmental factors. The interplay of genetic and environmental effects has received considerable attention <sup>(4)</sup>. Genetic mutations account for more than half of the chance of having ASD, with unknown environmental factors accounting for the other 40% <sup>(2)</sup>. Despite early evidence of ASD heritability, the largest twin population-based studies found that concordance rates for dizygotic twins were actually higher than previously reported, and that a shared prenatal environment

accounted for the majority of ASD risk in twins, with only a minor genetic contribution <sup>(5)</sup>. Autism's stated incidence and prevalence have increased considerably since decades. It is estimated that worldwide about one in 100 children has autism <sup>(6)</sup>.

According to previous studies, autism usually manifests itself in the second and third years of life. Most toddlers have no known sources of vitamin D at this age. In *vitro*, *in vivo*, and animal studies provide substantial evidence for vitamin D's function in brain proliferation, differentiation, neurotrophism, neuroprotection, neurotransmission, and neuroplasticity <sup>(7)</sup>. Vitamin D is considered a neuroactive steroid that affects general brain function. It is essential for myelination, which is crucial for brain connectivity <sup>(8)</sup>. Vitamin D also possesses remarkable antioxidant, anti-inflammatory, and anti-autoimmune properties, and it has been found to play an important role in the etiology of ASD <sup>(7,8)</sup>. Vitamin D is a multifunctional hormone generated primarily in the skin in response to ultraviolet (UV) B sunlight exposure. Exogenous sources (foods and supplements) provide a negligible amount as well. Despite the fact that vitamin D production is molecularly well-regulated in a limited number of organs, it can travel via the circulatory system to distant organs and act on most cells due to the presence of vitamin D receptors. It regulates all physiological functions by modulating calcium and phosphate metabolism, promotes growth, and induces necessary remodeling of the bones and teeth <sup>(9)</sup>. The rising incidence of ASD has sparked interest in their oral health problems, which coincides with one of the global oral health goals to improve oral health within this population group. Individuals with special needs, particularly those with mental and behavioral impairments, are affected regarding their oral health, with caries and periodontal disease being the most prevalent disorders <sup>(10)</sup>. Oral health and dental needs of autistic children with vitamin D deficiency have been evaluated by multiple global and Iraqi studies <sup>(11-16)</sup>.

Adequate doses of vitamin D can have a therapeutic effect on the basic symptoms of autism <sup>(7)</sup>. The reduction in vitamin D levels in patients, the reduction of vitamin D levels in the mother during pregnancy, and the reduction in exposure to UVB solar radiation may increase the incidence of symptoms of AD and autism. However, autism symptoms can be improved with vitamin D supplementation <sup>(8)</sup>. Children between the ages of 1 and 18 need 200 to 600 IU of vitamin D daily <sup>(17)</sup>. Vitamin D deficiency is defined as 25(OH)D of 20 ng/mL, vitamin D deficiency as 25(OH)D of 20–30 ng/mL and vitamin D deficiency as 25(OH)D of >30 ng/mL <sup>(18)</sup>.

Vitamin D has been shown to raise the seizure threshold by upregulating glutathione and a set of DNA-repair genes <sup>(19)</sup>. It has also been found that it binds to over 2700 genes, with over 200 of them influencing gene expression. Several studies have previously reported vitamin D deficiency in autistic children <sup>(20,21,22)</sup>.

The null hypothesis states that there are no differences in vitamin D level and oral health states between autistic patients and healthy children therefore the aim of this study was to look at vitamin D levels in children with autism and their dental health, as well as the link between vitamin D and disease severity and the association of vitamin D with oral health status.

## Materials and Methods

The study was carried out on 80 Iraqi children, 40 patients (31 male and 9 female) aged 3–12 years old with autistic disorder who were registered in Iraqi Institutions of Autism Care/Baghdad. The diagnosis was made by the medical staff responsible at the institute on the basis of international criteria. They were divided into three groups according to the severity of the disease (mild, moderate, and severe). The control group included 40 children (25 male and 15 female), from same geographical area where patient group was selected. All subjects were not under drugs, and they did not suffer from any other disease. This study was conducted during the period from January to March 2022. Furthermore, an informed written consent for participation in the study was signed by the parents or legal guardians of all studied subjects.

### Oral examination

The diagnosis of children with autistic disorder was carried out using a dental mirror and a dental explorer, a portable source of light, with the aid of their school teacher. The simplified oral hygiene index (S-OHI) was used to assess debris and calculus, score 0–1.2 is regarded as Good; 1.3–3.0 considered fair; and 3.1–6.0 is Poor <sup>(23)</sup>, while the Decayed, Missing, and Filled Teeth Index (dmft and DMFT) was used to record caries experience <sup>(24)</sup>.

### Saliva collection

The drooling technique was used to obtain 2–3 ml of un-stimulated saliva from each participant. Children are given clear, simple, direct instructions to lift their heads and place plane tubes near their lips to help them breathe saliva to promote saliva flow <sup>(25)</sup>. The collected saliva was transferred to a plain tube and left to clot at room temperature (20–25°C) for 15 minutes. The saliva sample was centrifuged at 2000 rpm for 15 minutes, and by then, the supernatant was collected and frozen at -20°C until laboratory assessments.

### Vitamin D level detection

The detection of saliva D levels was determined by commercially available ELISA kits, and was conducted in accordance with the guidelines outlined in the attached booklet (Shanghai/China). In summary, this test uses a quantitative sandwich enzyme immunoassay method to evaluate vitamin D levels. It is a 96-well microplate pre-coated with a vitamin D specific monoclonal antibody. The streptavidin-peroxidase combination detects vitamin D in samples and standards sandwiched by the immobilized antibody and a biotinyl monoclonal antibody specific to vitamin D. After the unbound material has been washed, the substrate of the peroxidase enzyme is administered. The optical density (OD) value of each well was determined immediately using a 450 nm microplate reader within 10 minutes of adding the stop solution.

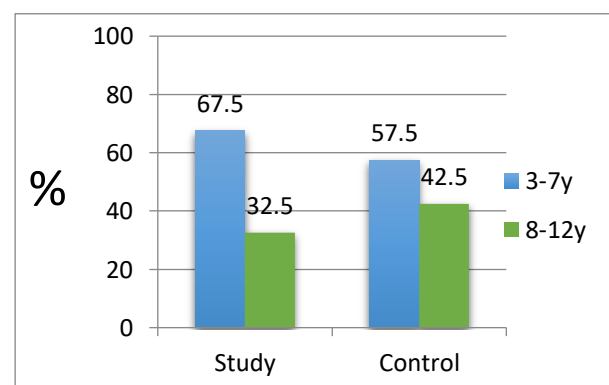
### Statistical analysis

Data were entered and analyzed using SPSS (Statistical Social Sciences Package) version 21.0 for Windows. Description statistics (sequences, percentages, tables, graphs) and implicit statistics were used. Independent T tests are used to compare the mean between a case and a control. p values equal to or less than 0.05 were statistically significant<sup>(26)</sup>.

## Results

The results of the current study were based on the diagnosis of 40 autistic patients, compared with 40 apparently healthy children. As shown in figure 1, this result was a basic requirement for conducting such a case control study. The most frequent age group was (3–7 years), which comprised 67.5%, while the age group of (8–12 years) constituted (32.5%) of the patients.

**Figure 1:** Distribution of the study and control groups according to the age groups.



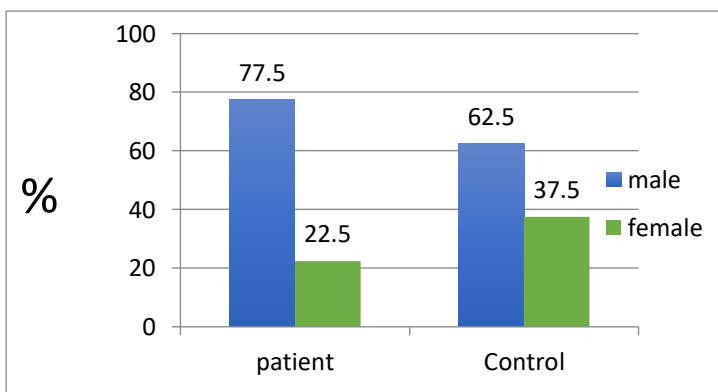
Regarding gender distribution, there was a male predominance among patients. (77.50%) of autistic patients were males, and only (22.50%) were females. Whereas in the control group, there were (62.5%) males and (37.5%) females. As seen in table 1 and figure 2.

**Table 1:** Distribution of the study and control group according to gender

Gender	Study Groups		Chi square test (p-value)
	Patients Group N=40	Control Group N=40	
Males	N.	31	0.143 <sup>NS</sup>
	%	77.50	
Females	N.	9	
	%	22.50	

NS:non-significant; N=Number ; %= Percent.

**Figure 2:** Gender distribution in study and control groups.



According to the severity of disease, this study found that 8 (20%) of patients have mild autism, 15 (37.5%) have moderate autism, and the remaining 17 (42.5%) have severe autism, as shown in figure 3.

**Figure 3:** Frequency distribution of patients (study group) according to clinical features severity.

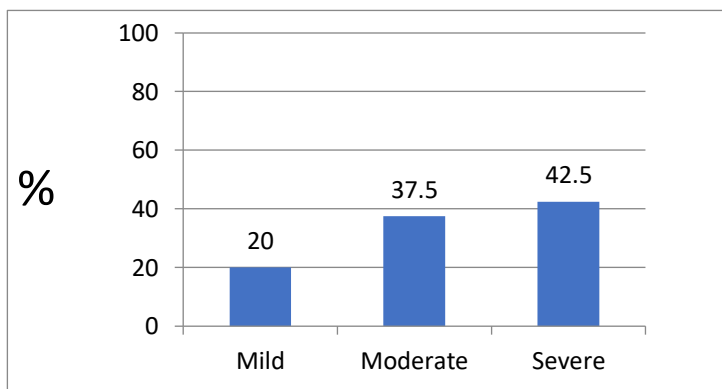


Figure (4) shows the differences in oral hygiene index between study and controls. The findings revealed that 15 (37.5%) of the patients had fair oral hygiene and 25 (62.5%) had good oral hygiene, while 8 (20%) of the control group had fair oral hygiene and 32(80%) had good oral hygiene.

**Figure 4:** Oral hygiene distribution in study and control groups.

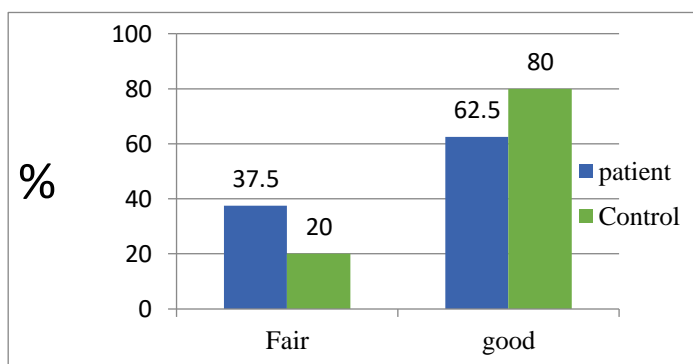


Table 2 shows the caries experience in both groups of children. The dmft index for primary teeth shows a significant difference ( $P < 0.05$ ) between the two groups. The mean value for study group was  $(4.87 \pm 0.71)$  while for the control group was  $(2.82 \pm 0.51)$ . The result of dt illustrates a non-significant difference between patients and control where the mean value of the patient group was  $(3.95 \pm 0.71)$  while in control it was  $(2.25 \pm 0.51)$ . The mt also showed non-significant differences between the two groups, with a mean value for study group was  $(0.67 \pm 0.22)$  while the control group was  $(0.25 \pm 0.08)$ . Likewise, the ft showed a non-significant difference with a mean value  $(0.25 \pm 0.10)$  for the study group and  $(0.32 \pm 0.11)$  for the control group. According to permanent dentition, this study found a significant increase in DT and DMFT in the study group  $(1.07 \pm 0.26; 1.90 \pm 0.37)$  than that in the control group  $(0.37 \pm 0.11; 1.02 \pm 0.16)$  respectively. However, there is no significant difference in MT and FT between groups.

**Table 2:** Caries experience of primary and permanent teeth in study and control groups.

Variables	Groups		T test	P-value
	Control N=40 Mean ± SD	patient N=40 Mean ± SD		
dt	2.25±0.51	3.95 ± 0.71	1.944	0.056
mt	0.25±0.08	0.67 ± 0.22	1.767	0.083
ft	0.32±0.11	0.25 ± 0.10	0.492	0.624
dmft	2.82±0.51	4.87 ± 0.71	2.328	0.023*
DT	0.37±0.11	1.07 ± 0.26	2.442	0.018*
MT	0.30±0.10	0.67 ± 0.19	1.708	0.093
FT	0.35±0.13	0.15 ± 0.08	1.278	0.206
DMFT	1.02±0.16	1.90 ± 0.37	2.133	0.038*

\*=significant  $P \leq 0.05$  ; SD: Standard Deviation; N=Number

Regarding the level of Vitamin D in study and control groups, the current results found that the mean level of salivary Vitamin D in the study group was lower  $(28.64 \pm 4.70)$  than that in the control group with a significant difference ( $P \leq 0.05$ ), as observed in table 3.

**Table 3:** Salivary levels of vitamin D (ng/ml) in study and control group.

Groups	Minimum	Maximum	Mean ± SD	T test	P value
patient	22.028	39.960	28.649±4.700	8.049	0.000*
Control	28.371	96.478	56.519±21.389		

The present findings reveal that there are no significant differences ( $P > 0.05$ ) in vitamin D levels among the study groups. According to severity of autism, mild patients had a mean value of  $(30.55 \pm 3.51)$ , moderate patients had a mean value of  $(27.96 \pm 4.84)$ , and severe patients had a mean value of  $(28.35 \pm 5.05)$ , as shown in table 4.

**Table 4:** Salivary levels of vitamin D (ng/ml) in study group according to disease severity

Severity	Minimum	Maximum	Mean±SD	F	P value
Mild	25.746	36.137	30.554±3.518	0.842	0.439 NS
Moderate	22.740	39.960	27.965±4.840		
Severe	22.028	38.379	28.357±5.059		

NS: non-significant; SD: Standard Deviation

There was a significant negative correlation between Vitamin D and S-OHI ( $r = -0.399, p = 0.011$ ), calculus index of S-OHI ( $r = -0.332, p = 0.037$ ), and dt ( $r = -0.328, p = 0.039$ ), in study group, as shown in table (5). Regarding the correlation with (DT, MT, FT, DMFT, dmft, and Debris index of S-OHI), week negative non-significant relationships were found, with the exception of (mt and ft), where positive non-significant relationships were observed.

**Table 5:** Correlation coefficient between salivary vitamin D (ng/ml) and oral health variables

Vars.	Vit-D			
	Patient		Control	
	r	p	r	p
<b>DT</b>	-0.170	0.295	-0.024	0.884
<b>MT</b>	-0.088	0.590	-0.125	0.441
<b>FT</b>	-0.199	0.219	0.123	0.449
<b>DMFT</b>	-0.209	0.196	0.000	1.000
<b>dt</b>	-0.328*	0.039	-0.519*	0.001
<b>mt</b>	0.065	0.689	0.285	0.075
<b>ft</b>	0.168	0.301	-0.156	0.336
<b>dmft</b>	-0.282	0.077	-0.502*	0.001
<b>Debris I</b>	-0.249	0.121	-0.199	0.218
<b>CalculusI</b>	-0.332*	0.037	-0.156	0.337
<b>S-OHI</b>	-0.399*	0.011	-0.219	0.175

\* Significant P≤0,05

## Discussion

Vitamin D insufficiency has become a serious health problem in current culture as indoor activities restrict children's sun exposure, and dietary sources cannot compensate. The results of this study provide additional evidence to support that concern. Vitamin D insufficiency has been linked to a range of developmental psychiatric disorders, including autism (27). Based on the findings of this study, the null hypothesis that there are no statistically significant differences in vitamin D level between patients and controls had to be rejected. The current findings revealed a significant decrease in the level of salivary vitamin D in autistic patients compared to the control group, which is consistent with multiple studies from around the world (28-34), all of which found that autistic children had significantly lower levels of 25-(OH) D than healthy children. These results might be attributed to some biological and lifestyle factors such as birth, kinship, body mass profile, and physical activities. Children with autism may reduce exposure to sunlight because they often spend their time after school treating their tables, usually not participating in outdoor sports, and their favorite leisure activities often involve indoor video games, computers, and television screens.

In addition, heritable vitamin D deficiency may be another factor contributing to the compromised vitamin D status, as vitamin D-related enzymes, receptors, and binding proteins are all under genetic control (17). In contrast, a study from the United States found no difference in vitamin D levels between children with ASD and a control group (35). However, this study was questioned since it only included males and used a questionable control group. Furthermore, other studies (36-38) discovered no significant differences between autistic patients and controls in their investigation.

The findings revealed that there were no significant differences in the levels of vitamin D between the groups of patients severity. Similarly, Hashemzoh et al(36) reported no significant relation between vitamin D and disease severity. Moreover, Mostafa and Al-Ayadhi (29) revealed that patients with severe autism had lower serum vitamin D than children with mild to moderate autism, although this difference did not reach statistical significance. However, studies by many researchers indicated a significant negative relationship between circulating serum vitamin D levels and the severity of autism(33,34). In general, Vitamin D can reduce the severity of autism by increasing the threshold for seizures, increasing

the regulation of T cells, protecting mitochondria, and increasing the regulation of glutathion, which destroys oxidative by-products and chesters heavy metals <sup>(17)</sup>.

In the present study, poorer oral hygiene and a higher occurrence of dental caries in autistic patients compared to controls were observed. These results go in agreement with previous studies <sup>(14,39,40)</sup> and disagree with others <sup>(15,16,41)</sup>. The authors explain that individuals with ASD enjoy delicate and sweet foods and, due to poor tongue coordination, tend to hold them inside their mouths rather than swallow them, increasing their risk of acquiring caries. Moreover, the danger of dental caries might be expected to be higher in the autistic group because of complexities in cleaning the teeth. However, the oral cleanliness of these individuals is known to be inadequate. This discrepancy is related to the fact that children with ASD are known to have a physical handicap that hinders them from doing self-oral hygiene routines such as tooth brushing. To practice it and make it a daily routine habit, they may need substantial training or guidance from their parents or caregiver.

The current study's data analysis shows a negative correlation of vitamin D with dental caries and oral hygiene index, which is consistent with others <sup>(11-13)</sup>, implying that an inadequate level of vitamin D in individuals has been linked to hypoplasia of the enamel and atrophy of the salivary glands, which contribute to poor oral hygiene and the development of dental caries <sup>(13)</sup>.

## Conclusion

A decrease in vitamin D concentration in patients indicates the critical role of vitamin D in children's neurodevelopment and mental health. Because of the difficulties in cleaning the teeth, the risk of dental caries and poorer oral hygiene is considered to be greater in the autistic population. However, these people's dental hygiene is acknowledged to be deplorable since children with ASD are known to have a physical disability that prevents them from performing daily oral hygiene practices. A decreased level of Vitamin D is associated with oral conditions and has been linked to an increased incidence of dental caries and poorer oral hygiene. The beneficial effects of vitamin D on oral health are considered by modulating calcium metabolism that effects tooth mineralization.

## Conflict of interest

The authors have no conflicts of interest to declare.

## Author contributions

JYD., BH. and WA. contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript

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## Ethical approval

All of the individuals were given thorough information about the study and the procedures involved, and their informed consent was acquired on a form approved by the ethics committee of the University Of Baghdad \ College Of Dentistry.

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**مستويات فيتامين (د) اللعابية لدى الأطفال المصابين بالتوحد وارتباطها بحالة صحة الفم و شدة المرض  
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المستخلص:**

الخلفية: يتميز اضطراب طيف التوحد بصعوبات في التفاعل الاجتماعي والتواصل ، بالإضافة إلى أنماط محدودة من السلوك والحساسية الحسية غير النمطية. على الرغم من أن نقص فيتامين (د) قد لوحظ سابقاً في الأطفال المصابين بالتوحد ، إلا أن الأدلة على العلاقة بين نقص فيتامين (د) وشدة التوحد نادرة. كان الغرض من هذه الدراسة هو التحقق من مستويات فيتامين (د) في مرضى التوحد والتحقق من حالة صحة الفم والتسوسات للأطفال المصابين وعلاقتها بفيتامين دي، وكذلك العلاقة بين فيتامين (د) وشدة المرض.

المواد وطرق العمل: تم تضمين مجموعتين في هذه الدراسة 40 طفلاً مصاباً بالتوحد و 40 طفلاً يتمتعون بصحة جيدة تتراوح أعمارهم بين (3-12) سنة. وفقاً لشدة أعراض التوحد ، تم تصنيف مجموعة المرضى إلى ثلاث مجموعات فرعية: خفيفة ومعتدلة وشديدة. تم إجراء فحص الفم بواسطة مؤشر صحة الفم (S-OHI) وتسوسات الأسنان عن طريق مؤشر قياس الأسنان المتسوسة والمفقودة والمعالجة بالحشوات الدائمة (DMFT / dmft) لكلتا المجموعتين. تم جمع عينات اللعاب بتقنية سيلان اللعاب المستخدمة لجمع العينات اللعابية ، وتم فحص المستوى اللعابي من فيتامين (د) بواسطة تقنيه الفحص المناعي المرتبط بالإنزيم. (ELISA) تم تحليل بيانات الدراسة الحالية باستخدام SPSS الإصدار 21 .

النتائج: لوحظ أن مستويات فيتامين (د) في لعاب المصابين بالتوحد أقل بكثير في مجموعة الدراسة منها في مجموعة الأصحاء. لم يكن هذا الانخفاض مرتبطاً بشدة التوحد. 37.5٪ من مجموعة الدراسة لديهم نظافة فموية متوسطة ، مقارنة بـ 20٪ من مجموعة الأصحاء؛ يظهر S-OHI علاقة سلبية مع مستوى فيتامين (د). الدراسة أثبتت ان نسبة تسوس الأسنان أعلى بكثير في مجموعة الدراسة وكان هناك ارتباط سلبي غير معنوي بمستوى فيتامين (د).

الاستنتاج: كان مستوى فيتامين (د) أقل بكثير في مجموعة الدراسة مع عدم وجود علاقة مع شدة المرض. وقد لوحظ ضعف نظافة الفم والمزيد من التسوس في كل من الأسنان اللبنية والدائمة في مرضى التوحد. ووجد ارتباط سلبي معنوي بين فيتامين دي و S-OHI في حين وجد ارتباط سلبي غير معنوي مع تسوسات الأسنان .