IJPSR (2016), Vol. 7, Issue 3 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 19 September, 2015; received in revised form, 19 November, 2015; accepted, 17 December, 2015; published 01 March, 2016

VITAMIN D INTAKE AND SUN EXPOSURE IN AUTISTIC CHILDREN

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Keywords:

Autistic Disorder,
Autism Spectrum Disorders,
Dietary Vitamin D, Sun Exposure.

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ABSTRACT: It is well known that main sources of Vitamin D are sun exposure and diet. There is a gap in our knowledge about the contribution of these factors to Vitamin D level among autistic children in Egypt. **Aim:** To determine Vitamin D dietary intake and sun exposure and their impact on vitamin D level. **Methods and procedures:** Serum Vitamin D levels were measured in 42 autistic and 40 healthy matched children. Dietary Vitamin D intake and sun exposure hours were collected using an adapted pre-validated food frequency questionnaire. Vitamin D intake was compared with recommended dietary intake (600 IU). **Results and outcomes:** Autistic children had significantly lower serum levels of 25- hydroxy Vitamin D than healthy children ($P < 0.001$) with 54.7% and 28.6% being Vitamin D deficient and insufficient, respectively. Dietary Vitamin D intake of both groups was significantly lower than recommended dietary intake. No correlations between serum Vitamin D level and dietary Vitamin D intake or Childhood Autism Rating Scale. **Conclusion and implications:** Vitamin D deficiency was found in autistic children and this may contribute to pathogenesis of the disease. There is a need to increase awareness about Vitamin D importance in children's diet.

INTRODUCTION: Autism spectrum disorders (ASDs) are a heterogeneous group of complex, biologically based neurodevelopmental disorders. Their etiology is still unknown and somewhat controversial. Although there is a large consensus regarding a key genetic role in the condition, an increasing body of evidence suggests that environmental factors may also be implied, in conjunction with the genetic factors and acting very early in development [1-3]. The gene-environment interaction hypothesis [4] investigated for several other medical and psychiatric conditions [5], has been recently suggested for ASD a putative role of Vitamin D deficiency has been proposed [6-8].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.7(3).1043-49

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.7 (3).1043-49

Vitamin D has important role in brain homeostasis as well as gene regulation modulation of immune function [9], cell proliferation and apoptosis, and brain development and function as well as many neuroprotective properties [10], with important protection against cognitive impairment and neurological conditions in general [11-13].

Vitamin D, whose main sources in humans are sun exposure and food intake [11, 14], is well- known to have several positive effects. An apparent epidemic of Vitamin D deficiency is now being recognised [10, 15] as a major public health problem worldwide in all age groups despite abundant sunshine in many countries [16].

Children with ASDs often exhibit behaviours that result in feeding problems and, in turn, may impact nutrient intake. They tend to desire sameness in daily routines including eating the same foods that result in a diet that lacks variety [17]. Additionally,

disturbances in routine may lead to disruptive mealtimes, and, thus poor intake. Other possible factors that may affect nutritional status include gastrointestinal (GI) complications as well as differences in metabolism and utilization of nutrients. Difficulties in dietary intake of nutrients such as calcium and Vitamin D in children with ASD have been found [18-20].

Researchers have begun to explore the importance of Vitamin D which forces the American Academy of Pediatrics (AAP) in 2008 to recommend higher intakes based on evidence from clinical trials and the history of safe use of 400 IU/day of Vitamin D in paediatric and adolescent populations which increased in 2010 to reach 600 IU per day for children aged above 1 year [21].

All these factors make it imperative to examine the adequacy of nutrient intake in children with autism. Few studies have compared food and nutrient intake of children with AD to children with typical development or to standard values. Thus, the purpose of this study was to determine Vitamin D status of autistic children as well as the adequacy of their Vitamin D dietary intake and compare it to dietary reference intake.

SUBJECTS AND METHODS:

1. Study population: [1]

This cross sectional study was conducted on 42 children with autism. They were recruited from the autism clinic in paediatric genetics unit, Ain Shams University hospital, Cairo, Egypt.

Inclusion criteria for children to participate included that they be 3-15 years of age and have a diagnosis of autistic disorder based on DSM-IV criteria of the American Psychiatric Association. [22]

Exclusion criteria for the study included:

Diagnosis of Asperger's syndrome or pervasive developmental disorder-not otherwise specified.

Patients who had associated neurological diseases (such as cerebral palsy and tuberous sclerosis) and metabolic disorders (for example, phenylketonuria)

Patients on casein-free diet.

Children received calcium and/or Vitamin D therapy in the past 6 months. In addition, none of them had a concomitant infection, photosensitivity, used photo protection (such as broad-spectrum sunscreens) or treatment known to affect serum 25 hydroxy Vitamin D levels (such as antiepileptic drugs, corticosteroids, and other immunosuppressive drugs).

Children were randomly chosen and lab analysts were blinded about status of participants (autistic or control). The autistic group comprised of 34 boys and 8 girls. Their ages ranged between 4 and 13.5 years. The control group comprised 40 age and sex matched healthy children of similar age, gender, and geographic distribution, tested currently under identical conditions to the autistic group. They were the healthy siblings of autistic group with no clinical findings suggestive of immunological or neurological disorders as recommended by the study physician who conducted a physical exam to determine that the children were in adequate health for participating in the study. They included 19 boys and 21 girls. All subjects were studied from March to August to avoid effect of seasonal variation on serum 25 hydroxy Vitamin D levels.

Methodology:

The study protocol received approval of Faculty of Pharmacy, Ain Shams University Ethical Committee in Cairo, Egypt and has therefore been performed in accordance with the ethical standards laid down in the 1975 Declaration of Helsinki, as revised in 2000. All parents had signed consent before enrolment in study and received a copy of it.

Study measurements:

Clinical evaluation of autistic patients:

This was based on clinical history taking from caregivers, clinical examination, and neuropsychiatric assessment. In addition, the degree of the disease severity was assessed by using the Childhood Autism Rating Scale (CARS) [23].

Biochemical Measurements:

Fasting blood samples were obtained from all patients by single venipuncture into 2 vacutainers (serum plain).

Sera were allowed to clot for 30 min at RT and then centrifuged at 3000xg for 10 min. immediately following centrifugation, all specimen were analyzed within 30 min for following analytes using appropriate spectrophotometric methods (Total calcium, phosphorous , alkaline phosphatase, AST, ALT, Blood urea nitrogen, Serum Creatinine). All assays were performed using kits supplied from Stanbio Laboratory (Stanbio laboratory Diagnostics company, Texas, USA) according to manufacturers specifications by using proprietary reagents at department of biochemistry laboratory of Ain Shams University Hospitals, Cairo, Egypt.

Assay of serum 25-hydroxy Vitamin D:

Serum level 25OH Vitamin D was quantatively analyzed by 25OH Vitamin D ELISA kit: Immunodiagnostic AG, Germany. Normal level of Vitamin D is defined as 25OH concentration >than 75 nmol/l, Vitamin D insufficiency (50-74nmol/l) and Vitamin D deficiency (< 50 nmol/l).

Dietary assessment and sun exposure:

The data collection method was based on an interview in which medical history, personal data, lifestyle factors were documented. This is followed by administration of prevalidated food frequency questionnaire to determine the Vitamin D intake [24]. The food frequency questionnaire was adjusted to reflect the local food items known to contain Vitamin D and the various types of local fish consumed in the country. The intake of Vitamin D was calculated by multiplying the frequency of consumption of each unit of food by Vitamin D content of the specified portions. Values for non-local foods (tuna and salmon) were obtained from the US Department of Agriculture data [25]. Low Vitamin D intake is defined as the daily intake of <600 IU as recommended by the IOM [21] . Hours of sun exposure per week were recorded for all studied subjects.

Statistical analysis:

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) vs. 21. Numerical data were summarized using means and standard deviations or medians and ranges. Categorical data were summarized as percentages. Data were explored for normality using Kolmogrov-Smirnov test and Shapiro-Wilk test. Comparisons between the numerical variables and normal values were performed by the one sample t-test. Comparisons between 2 groups for normally distributed numeric variables were done using the Student's t-test. For non normally distributed variables, comparisons between the groups were done by Mann-Whitney test. Chi-square test was used to compare between the groups with respect to categorical data. To measure the strength of association between the numerical variables, the Spearman's correlation coefficients were calculated. All p-values are two-sided. P-values < 0.05 were considered significant.

RESULTS:

Table 1 showed analyses conducted on 42 autistic children and 40 healthy children. There was no significant difference between studied groups in demographic data with uneven gender distribution that reflects the increased prevalence of males in autistic group.

TABLE 1: DEMOGRAPHICS OF STUDIED GROUPS

Demographics		Groups: Autistic Mean ±SD	Groups: Controls Mean±SD	p-value
Age(years)		7.1 ± 2.3	7.6±3.1	0.403
weight(Kg)[a]		27.7±9.3	26.4±12.5	0.613
Height (cm)[a]		120±14.9	123.5±20.1	0.385
BMI(Kg/cm2)$_a$		27.7±9.3	26.4±12.5	0.613
sex [b]	Female	8(19 %)	21(52.5%)	<0.001*
	male	34(81%)	19(47.5%)	

X[a]= analyzed by two tailed T-test ,X[b]= chi square test , *significant difference ,BMI : body mass index

We also measured Serum Vitamin D and sun duration of autistic and healthy children as represented in **Table 2**. Autistic children had significantly lower serum levels of 25 hydroxy Vitamin D (median 46.5 nmol/l) than healthy children (median 70.89 nmol/l) with P-value

<0.001, with 54.7% and 28.65 % being Vitamin D deficient and insufficient, respectively. While only 15% of healthy children were Vitamin D deficient and 45% were Vitamin D insufficient.

TABLE 2: VITAMIN D LEVEL (SERUM AND DIETARY) AND DURATION OF SUN EXPOSURE OF STUDIED GROUPS

Clinical data	Autistic	Control	P-value
Vitamin D serum level [a]	46.5	70.89	<0.001*
Median (min-max)	(14-120)	(16-149)	
Vitamin D deficiency (<50 nmol/l)	54.7% (23/42)	15%(6/40)	
Vitamin D insufficiency (50-74 nmol/l)	28.6% (12/42)	45% (18/40)	
Vitamin D sufficiency (> 75 nmol/l)	16.7% (7/42)	40%(16/40)	
Dietary vitamin D (IU) [b]			
mean ± SD	164.7 ± 71.5	177.9 ± 75.9	0.42
The duration of sun exposure (minutes/week)[b]	44.4 ± 20.7	47.3 ± 23	0.559

X^a : Mann-whitney test ,X^b: two tailed T-test

There was no significant difference between autistic and healthy children in either duration of sun exposure (minutes per week) (P=0.559) or dietary Vitamin D content (P=0.42) as presented in **Table 2** and by comparing these values to dietary reference intake of 600 IU using one sided t-test , both groups had much less than recommended daily intake (P-value <0.001*) with no correlations between Dietary Vitamin D intake and serum Vitamin D level in both groups as shown in **Table 3**. Also there were no correlations between CARS and Vitamin D level in autistic group.

TABLE 3: SPEARMAN CORRELATION BETWEEN SERUM AND DIETARY VITAMIN D LEVEL

Serum Vitamin D level	Dietary vitamin D					
	Autistic			Control		
	r	R^2	P-value	r	R^2	P-value
	-0.171	0.0292	0.278	-0.009	0.000081	0.956

The results represented in **Table 4** showed low serum calcium levels in both groups and highly significant differences in Alkaline Phosphatase level (P= 0.001) and aspartate transaminase level (P=0.013) in healthy than autistic children.

TABLE 4: BIOCHEMICAL MEASUREMENTS OF STUDIED GROUPS

Laboratory values	Autistic	Control	P-value
	Mean ±SD		
Calcium(10-12 mg/dl) [a]	9±1.3	9.2±1	0.468
Phosphorous (4.5-5.5 mg/dl) [a]	4.9±0.4	4.9±0.5	0.475
Alkaline Phosphatase (up to 250 U/L)[a]	54.2±20.5	76.8±38	0.001*
Blood urea nitrogen [b] (8-23mg/dl)	14.7±4.1	14.2±2.6	0.299
Creatinine [b**]	0.93±0.21	0.96±0.21	0.54
Aspartate transaminase [b] (8-33 U/L)	19.7±6	21.9±4.6	0.013*
Alanine transaminase [b](3-35U/L)	16.5±6.2	15.5±3.5	0.613

X^a : two tailed t-test , X^b: Mann-Whitney test,* significance difference

** Serum Creatinine normal levels (male:0.9-1.5 mg/dl, female:0.7-1.4 mg/dl)

DISCUSSION: This is the first study to examine Vitamin D in Egyptian diets revealed that autistic and normal children had diets lower than recommended intakes of Vitamin D. Several studies from United States have reported the inadequacy of dietary Vitamin D intake among children with autism or compared their intake to that of control children [17-19, 26-28]. All these studies concluded that Vitamin D in autistic children were lower than daily recommended intake. Herndon and Neumeyer were the only two studies who compared diet intake with control group with different results [27, 28].

Herndon found that both autistic and control groups had comparable inadequacy of Vitamin D in their diet which was similar to our findings. However, Neumeyer reported that autistic children was much lower than control group with both less than daily recommended allowance [28]. Furthermore, there were many studies reported that even healthy children did not reach the recommended Vitamin D intake in their diets as in Europe, Saudi Arabia, Beirut and Israel [29-32].

Despite the comparable dietary intake of Vitamin D between autistic and normal children found in this study, the median serum 25 (OH) D levels was significantly lower in autistic children compared to normal controls.

Vitamin D deficiency was found in different geographical area with completely different ethnic distribution. In an Egyptian study , it was reported that children with autism had lower Vitamin D and calcium [33] levels with mean Vitamin D value of 28.5 ng/ml and which was described as "Vitamin D inadequate ".

In a recent study conducted from Assiut, Egypt, the mean Vitamin D level were lower (18ng/ml) in 122 autistic children than healthy controls [34]. Mostafa and Al-Ayadhi from Saudi Arabia and Gong et al. from China reported Vitamin D plasma levels in children with ASD, 18.5 ng/mL and 19.9 ng/mL, respectively, were similar by showing significantly lower levels than normal controls. [35, 36]. Another study from Brazil reported lower level of Vitamin D in children with ASD than controls and a mean serum value of 26.5 ng/mL [28, 37]. In a study conducted in the Faroe Islands as part of a population based study, lower Vitamin D levels (mean : 9.9 ng/mL) were reported in 40 individuals (aged 15–24 years) with ASD, as compared to their normally developing siblings, parents, and age- and gender-matched healthy controls [38].

In contrast, another study from the USA, reported no difference in Vitamin D levels between children with ASD and a control group, despite a relatively low level (19.6 ng/mL) in the ASD group [39] and insufficient Vitamin D level (25.2 ng/ml) as reported by Ugur et al [40]. It is of note that that levels of 25 hydoxy Vitamin D found in autistic children of the present study (18.7 ng/mL=46.5 nmol/l) are similar to the levels found in four other studies from Molloy (USA),china, Saad Egypt and Saudi Arabia. [34-36, 39] .

This value seems lower than those reported in the studies conducted in Egypt, brazil, USA and Turkey [28, 33, 37, 40] ,but greater than that reported from Faroe islands [38]. Vitamin D levels for normal controls in our study were 70.5 nmol/l which was less than that reported in Meguid (Egypt), Saad (Egypt), Brazil, and Saudi Arabia [33-35, 37] but greater than faroe islands [38] and turkey [40].

The results of our study showed 54.7% of autistic children and 15% of controls were Vitamin D deficient. While 28.65% and 45% were Vitamin D insufficient in autistic and control children respectively. This high percentage of Vitamin D deficiency in autistic group was also reported in a study from Egypt (Assiut), 57% (122 autistic cases) was Vitamin D deficient and 30% was Vitamin D insufficiency [34].

A study conducted on 254 autism children in Qatar reported that 14.2% of autistic children had severe Vitamin D deficiency (<10 ng/ml), 43.7% had moderate insufficient levels (between 10 and 20 ng/ml), 28.3% had mild insufficient levels (between 20 and 30 ng/ml. While only 8.3% in healthy controls had severe Vitamin D deficiency , 37% had moderate insufficient levels , 37.4% had mild insufficient levels [41]. In contrast a study from turkey reported higher percentage of 38.9%controls than 29.6% autistic children were Vitamin D deficient with no significance difference between both groups [40].

Some of the studies mentioned previously [33, 35, 36] reported a negative correlation between autism severity and Vitamin D serum level, while others found no correlation [40]. In our study, there were no correlations between scores of autism severity and vitamin d serum level and between dietary vitamin D intake (IU) and serum Vitamin D level.

Additionally there was no difference between autistic and control children in terms of calcium, phosphorous, parathyroid hormone, blood urea nitrogen, creatinine and alanine transaminase

levels. The majority of participants had normal reference values for these measurements except for calcium were low than normal reference values in both groups.

Conversely to bener et al [41], who reported that calcium, phosphorous was higher in controls than autistic group and alkaline phosphatise was higher in autistic than controls. Our findings showed that alkaline phosphatise and aspartate transaminaase level was higher in controls than autistic children inspite of low serum Vitamin D levels in autistic than control children. This may due some sort of decreased liver performance in autistic children than healthy children through Cytochrome P450 enzymes polymorphisms in enzymes responsible for Vitamin D metabolism as CYP24A1 gene [42] and CYP27B1 in kidney [43] Moreover, this low alkaline phosphatise levels may be due to GIT inflammation and abnormality occurred in ASD children that result from increased TPH1 expression as a consequence low Vitamin D hormone levels in autistic children [44].

Sunlight is an important source for vitamin D synthesis. The mean duration of sun exposure in our study was short (44.4 min/week in autistic children and 47.8 min /week in controls. In Saudi Arabia, it was reported that mean duration of sun exposure 6.48 ± 1.29) hours/week which is much greater than ours with no significant difference between autistic and healthy children [35].

Another study from Jeddah Saudi Arabia reported very short sun exposure duration (mean 7.64 ± 7.49 min/day) in healthy children [29]. The same finding was found with Malaysians who generally avoid being outdoor during the day as the weather can be very hot and humid [45].

Considering our findings, both autistic and healthy children didn't achieve the recommended dietary intake of Vitamin D and duration of sun exposure was too short inspite of that autistic children had lower Vitamin D level than healthy children this may suggests some underlying pathogenic mechanism involved in the underlying biology of autism altering the metabolism of Vitamin D in some way or Vitamin D deficiency itself contributing to the pathogenesis of ASD. Moreover, it may be due to genetic polymorphism in Vitamin D receptors that may lead to a type of Vitamin D resistance in autistic children.

In conclusion, Vitamin D deficiency was found in autistic children and this deficiency may contribute to pathogenesis of the disease in these children irrespective to their dietary intake or sun exposure. However, future studies looking at a potential role of Vitamin D in the pathophysiology and treatment of autism are warranted.

CONFLICT OF INTERESTS: No conflict of interests

ACKNOWLEDGEMENT: This is self funded research the authors gratefully thank all children who participated in this study, parents of children for their supports, and research assistants who helped with data collection and other contributions.

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How to cite this article:
Fahmy SF, Sabri NA, El Hamamsy MH, El sawi M and Zaki OK: Vitamin D Intake and Sun Exposure in Autistic Children. Int J Pharm Sci Res 2016; 7(3): 1043-49.doi: 10.13040/IJPSR.0975-8232.7(3).1043-49.