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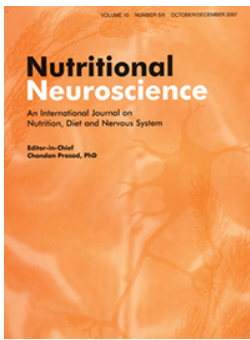
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Blunted serum 25(OH)D response to vitamin D₃ supplementation in children with autism

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Introduction: Data suggest a potential role for vitamin D in autism spectrum disorder (ASD) prevention and treatment. It is likely that the serum response to vitamin D supplementation contributes to its effectiveness. Multiple factors affect serum vitamin D 25(OH)D response to supplementation.

Methods: We conducted post-hoc analysis of two double-blind, randomized, placebo-controlled trials (RCT) of vitamin D₃ supplementation, one RCT involving children with ASD and another involving children with asthma. Both trials were conducted in the same geographic location (Dublin, Ireland, 53°N), conducted over Winter season and utilized the same vitamin D₃ dose (2000 IU/day).

Results: We included 18 children with ASD and 17 children with asthma. There was no significant difference in 25(OH)D or age at baseline, however, BMI was significantly lower in ASD ($P = 0.03$). Compliance with vitamin D supplementation was high in both trials. Despite a significantly longer intervention period (20w vs. 15w; $P < 0.0001$), ASD children had a significantly lower absolute increase (+26 vs. +45 nmol/l) in 25(OH)D ($P = 0.04$).

Conclusions: Despite similar demographics, children with ASD had a lower increase in 25(OH)D levels with supplementation. Potential mechanisms include altered absorption/metabolism as well as well genetic factors. Clinical and research work relating to vitamin D in ASD should measure 25(OH)D response to supplementation to assess therapeutic doses.

Keywords: Vitamin D, Asthma, Autism, Absorption

Introduction

One potential environmental contributing risk factor for ASD is vitamin D deficiency (VDD). While VDD has detrimental effects on bone health, recent reports suggest implications for neurological, immune, and inflammatory disorders due to its unique role in brain homeostasis, neurodevelopment and immunological modulation, and gene regulation.¹⁻⁴

A 2016 meta-analysis demonstrated significantly lower 25-hydroxyvitaminD (25(OH)D) in children with ASD compared to controls.⁵ Further, recent reviews have detailed the associations between vitamin D and ASD.¹⁻⁴ However, there is inconsistent evidence regarding vitamin D supplementation in ASD. A single case report,⁶ two open label studies,⁷ and a double-blind, randomized, placebo-controlled trial (RCT) reported the benefit of supplementation in ASD.⁸ In contrast, our group has published a well conducted trial which noted no benefit of vitamin D supplementation in ASD.⁹

Some reports have demonstrated the 25(OH)D level obtained following supplementation is a major influencer of any therapeutic effect in multiple clinical scenarios.⁷⁻¹⁰ However, there is evidence of decreased 25(OH)D response to vitamin D supplementation in adults with certain clinical conditions including non-alcoholic fatty liver disease¹⁰ and also the neurological disorder, multiple sclerosis.¹¹ Although, no data exist suggesting a similar phenomenon in ASD, a recent case-control study reported significantly decreased 25(OH)D levels in children with ASD compared to typically developing children despite very similar sun exposure and oral intake.¹²

Interest in vitamin D and ASD is growing. However, the optimal dosing to achieve target serum 25(OH)D levels in ASD has not yet been established. Our group has previously conducted two separate RCTs of vitamin D supplementation in children with either asthma or ASD. We wanted to assess the effect of daily vitamin D₃ supplementation on 25(OH)D amongst those with ASD⁹ compared to those without ASD.¹³

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Methods

We conducted separate parallel, randomized, double-blind, placebo-controlled trials of vitamin D supplementation in children with asthma (from September 2014 to April 2015)¹³ or ASD (September 2015 to April 2016).⁹ The asthma RCT was designed to be ~15 w intervention while the ASD RCT was ~20 w. This report refers to the post-hoc analysis of only the children randomized to vitamin D₃ intervention in these trials.

Diet, supplement use and particularly exposure to ultraviolet B radiation contribute to vitamin D status. We conducted both trials at high latitude (53° N) during the respective Winter seasons when skin vitamin D synthesis is minimal. Further, we advised recruits not to change dietary/supplemental behaviours during the trial. We assessed behaviour relating to vitamin D status with the VIDSun questionnaire at baseline and endpoint.¹⁴ Both trials utilized the same dose of vitamin D₃ (2000 IU/day) and participants were instructed to administer the vitamin D supplement with a meal, daily. Compliance was assessed by counting remaining vitamin D preparations and also with a compliance diary.

Both RCTs excluded children with conditions/medications that influence vitamin D metabolism or absorption including liver, renal, and gastrointestinal issues such as inflammatory bowel disease, coeliac disease, and cystic fibrosis as well as children taking anti-seizure drugs or vitamin A supplements (including cod liver oil). Written parental/guardian consent was obtained prior to both trials and both RCTs were registered on clinicaltrials.gov prior to patient enrolment (Identifier: NCT02508922 for ASD and NCT02428322 for asthma). Further details regarding each trial has been published previously.^{9,13}

Biochemistry

Venous blood samples were collected at baseline and endpoint of each RCT and analysed locally for complete blood count, 25(OH)D and C-reactive protein (CRP), as well as renal, liver, bone profiles.

We assessed vitamin D status by measuring total 25(OH)D, which is currently considered the best circulating biomarker of vitamin D status. 25(OH)D levels were measured by liquid chromatography–tandem mass spectrometry on an AB SCIEX API 4000 liquid chromatography–tandem mass spectrometer (Applied Biosystems Life Technologies, Foster City, CA, USA). This method has been shown to provide results that are in close agreement with the National Institute of Standards and Technology (NIST) target values for 25(OH)D₂ and 25(OH)D₃ for Standard Reference Material 972, levels I–III. The within-run coefficient of variation (CV) was 4.1% at 60.7 nmol/L for vitamin D₂ and 3.4% at 27.7 nmol/L for

vitamin D₃. The between-run CVs were <6.3% for both tests for two levels of quality controls.

25(OH)D values were reported as nmol/L. Here we use the 2011 Endocrine Society guidelines to define serum 25(OH)D status, whereby 25(OH)D <50 nmol/L equates to VDD, while <75 nmol/L equates to vitamin D insufficiency (VDI) and >75 nmol/L denotes vitamin D sufficiency (VDS).¹⁵

Statistics

We used independent sample, one tailed *t*-tests to assess differences between the asthma group to the ASD group. *P* < 0.05 was considered statistically significant. Statistical analysis was performed using a software package (SPSS, version 18; SPSS, Inc., Chicago, IL).

Results

Although, 39 children completed the asthma trial, only 17 were randomized to the vitamin D intervention. Similarly, 38 children completed the ASD trial, only 18 were randomized to the vitamin D intervention. As per of original ASD report, one of these 18 ASD children refused blood testing and therefore is not included here.

Table 1 compares the demographics of these children. There was no significant difference in age, however, BMI was significantly lower. Table 2 compares the vitamin D parameters of these children. There was no significant difference in baseline 25(OH)D, whereas VIDSun score was significantly higher in ASD. Further, supplementation compliance was higher in the ASD compared to asthma. Additionally, the intervention period was significantly longer for the ASD trial.

Nevertheless, post-supplementation 25(OH)D level as well as average change in 25(OH)D and percent change in 25(OH)D were greater in the asthmatic children compared to ASD children (Table 2, Figures 1 and 2).

Table 1 Demographics

	Asthma	ASD	P-value
N=	17	17	—
Age (y)	9±4 (5–15)	8±3 (4–16)	0.14
BMI	21±5 (13–31)	18±3 (15–26)	0.036
Male:female	11:6	15:3	—

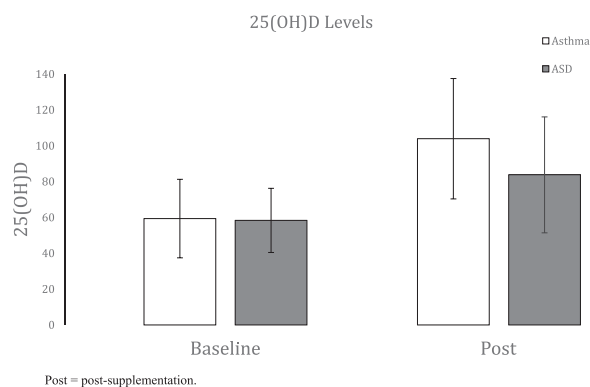
Abbreviations: ASD=autism spectrum disorder; BMI=body mass index

All comparison are 1-tailed, independent sample *t*-tests

Table 2 Vitamin D parameters

	Asthma	ASD	P-value
N=	17	17	—
Baseline 25(OH)D nmol/L	57±19 (28 to 92)	58±18 (15 to 90)	0.38
VDD at baseline n	6 (35%)	2 (11%)	—
VDI at baseline n	8 (47%)	12 (71%)	—
VDS at baseline n	3 (18%)	3 (18%)	—
Baseline VIDSun score (0–7)	3.5±0.8 (1–5)	5.1±5 (3–8)	<0.0001
Intervention period (w)	16±1 (14–19)	23±2 (20–29)	<0.0001
Compliance? >85%	>85%	>95%	—
Follow up 25(OH)D (nmol/L)	104±34 (59–175)	84±32 (17–164)	0.04
VDD at follow up n	0	2	—
VDI at follow up N	4 (24%)	3	—
VDS at follow up n	13 (76%)	9	—
Average change (nmol/L)	45±35 (–10 to 116)	26±26 (–9 to 77)	0.04
Mean 25(OH)D change (%)	97±0.1 (–12 to 279)	48.8±62 (–16 to 251)	0.04

Abbreviations: 25(OH)D=25-hydroxyvitamin D; VDD=vitamin D deficient; VDS=vitamin D sufficient.
All comparison are 1-tailed, independent sample *t*-tests.

**Figure 1** Mean 25(OH)D at baseline and post-supplementation

Discussion

Summary of main findings

We report for the first time that response to vitamin D supplementation is blunted in children with ASD. Several factors can determine response to vitamin D supplementation including compliance, body size and type of vitamin D. Here, the difference in response to supplementation could not be attributed to these factors or to seasonal/geographical variation. Another factor which determines response to vitamin D supplementation is baseline 25(OH)D. However, baseline 25(OH)D was very similar in asthmatic and ASD groups and there was no statistical difference

(57 vs. 58 nmol/L; $P = 0.38$). Further, ASD children had lower BMI as well as greater compliance and greater VIDSun score, which would all be expected to contribute to greater response to supplementation. Conversely, the response to vitamin D supplementation was almost 50% lower in ASD compared to non-ASD, asthmatic controls (+26 vs. +45 nmol/L); $P = 0.04$).

Strengths and limitations of the study

The data are derived from separate double-blind, randomized, placebo-controlled trials. Both trials utilized the same dose of vitamin D₃ (2000 IU/day), were led by the same researcher (CPK) and involved the same clinical and research teams. Further, the trials were conducted at the same, single centre (National Children's Hospital, Dublin, Ireland) at high latitude (53°N) during the Winter season when vitamin D photosynthesis is minimal. We utilized the same laboratory equipment. We controlled for supplement compliance as well as diet, non-trial supplement use and exposure to ultraviolet B radiation. Finally, both RCTs had strict entry criteria to exclude the effect of non-ASD clinical condition or medications on vitamin D. The major limitation of this study is the post-hoc nature as well as the inclusion of small sample sizes from separate trials.

How and why it agrees with existing literature

A 2016 meta-analysis of 11 studies, including 870 ASD children and 782 typically developing children, demonstrated significantly lower 25(OH)D in children with ASD compared to controls.⁵ Tryptophan hydroxylase 2 (THP2) gene and selected neurotransmitters (e.g. serotonin) and brain hormones (e.g. oxytocin and vasopressin) are associated with ASD.^{4,16} Executive function, sensory gating, and prosocial behaviour are regulated by serotonin and ASD are associated with tissue-specific aberrant serotonin concentrations.^{4,16} THP2 gene helps control brain serotonin synthesis.¹⁶ Oxytocin, which acts synergistically with serotonin, is associated with ASD social deficits⁴ and ASD is associated with low oxytocin.⁴ Detailed *in vitro* and *in silico* work has demonstrated these factors are directly regulated by the hormonal form of vitamin D (calcitriol)^{4,17} implying that VDD may have a role in ASD. An early case study reported improvement of core ASD symptoms following 150 000 IU/month for 2 months+400 IU/day in a 32 month old Chinese male with VDD and ASD.⁶ Subsequently, two open label studies were published. An Egyptian study reported that 67 of 83 VDD children with ASD (81%) had improved ABC and childhood autism rating scale following vitamin D₃ supplementation (300 IU/d per kilogram of body weight) for 12 weeks.¹⁸ Another open label study from China,

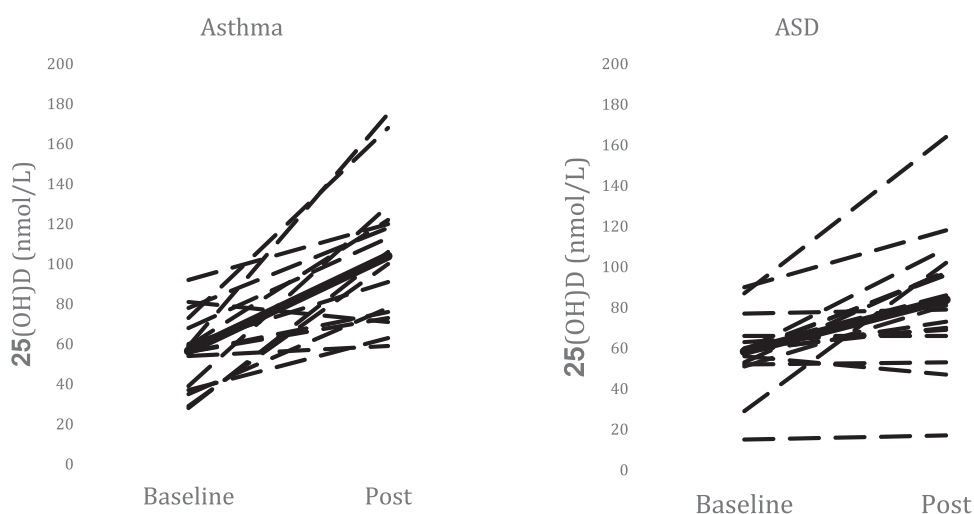


Figure 2 Individual and mean 25(OH)D at baseline and post-supplementation. Post=post-supplementation. Dashed lines represent individuals, bold lines represent mean values

assessed 37 VDD children before and after monthly intramuscular vitamin D₃ (150 000 IU) and daily oral vitamin D₃ (400 IU). Total ABC and SRS scores were reduced significantly after 12 weeks.⁷ Additionally, a very recent, double-blind, randomized, placebo-controlled trial consisted of 109 ASD children (3–10 y) randomized to daily vitamin D (300 IU per kg of body weight but ≤ 5000 IU) or placebo for 4 months. Vitamin D supplementation significantly improved ABC, SRS, childhood autism rating scale, and Autism Treatment Evaluation Checklist scores.⁸ However, the results of this RCT have proved controversial, resulting in several letters to the Editor of the publishing journal (*Journal of Child Psychology and Psychiatry*).^{19,20} These letters resulted in a letter to the author from the editor-in-chief seeking clarifications on 10 separate points.²¹ The response to these from the study author did not fully address these 10 points,²² leaving many in the field sceptical, particularly regarding sample size powering, questionable consistency in the evaluations, criticisms of statistical tests used^{19,20} and the unforeseen remarkable response.¹⁹ In contrast to these preliminary and controversial results, our group have published a well conducted trial which noted no benefit of vitamin D supplementation in ASD.⁹

It is known that serum 25(OH)D response to vitamin D supplementation can vary between individuals^{23,24} which may partially explain the discrepancies in ASD vitamin D interventions. Previous data have demonstrated that response to vitamin D supplementation may be blunted in certain clinical disorders. A study of 42 adults with non-alcoholic fatty liver disease reported a low response rate to vitamin D supplementation (2000 IU/day for 6 m).¹⁰ A potential explanation among this cohort may be altered hepatic metabolism of exogenous vitamin D.

Further, a separate case-control trial noted decreased 25(OH)D response to vitamin D supplementation (5000 IU/day for 3 m) in females, with the neurological disorder multiple sclerosis, compared to controls, even accounting for putative confounders.¹¹ Although we are not aware of any similar data specific to ASD a recent case-control study reported significantly decreased 25(OH)D levels in 42 children with ASD compared to 40 typically developing children (46.5 compared to 70 nmol/L; $P < 0.001$), despite very similar demographics (age, BMI), sun exposure (44 vs. 47 min/week; $P = 0.559$) and oral intake (164 vs. 177 IU/day; $P = 0.42$).¹² These authors suggest that ‘some underlying pathogenic mechanism involved in the underlying biology of autism altering the metabolism of Vitamin D in some way’.

There are several potential explanations for decreased 25(OH)D response in ASD. In addition to body composition and supplement compliance, 25(OH)D responses to vitamin D supplementation can be influenced by altered renal and hepatic metabolism, absorption, as well as vitamin D-binding protein concentrations and expression of vitamin D receptor (VDR). We are not aware of any data suggested altered the renal and hepatic metabolism of vitamin D in ASD. Antiepileptic drugs, which are known to decrease both dietary fat and fat-soluble vitamin absorption (e.g. vitamin D), have been associated with increased ASD risk.²¹ Presence of epilepsy and use of antiepileptic drugs were strict exclusion criteria in both of our RCTs for this reason. However, there is growing evidence that ASD may be associated with gastrointestinal issues, including dietary malabsorption.^{25,26} Another possibility may be the alteration of the gut microbiome in ASD, which can alter bile acid metabolism,²⁷ and fat-soluble vitamin absorption (e.g. vitamin D).²⁸ Additionally, there is evidence that

VDR variants (e.g. Taq-I, Apa-I) are present in ASD.^{28,29} Since VDR regulates both transcriptional and post transcriptional mechanisms, these variants may influence the response to vitamin D and subsequent effects, particularly regarding the innate immune system, which is involved in ASD. Further, there is evidence that vitamin D metabolic gene variants are associated with ASD risk.³⁰ Additional evidence suggests that vitamin D-related genes are subjected to significant de novo mutation burdens in ASD.³¹ These de novo mutations can influence uptake and utilization and therefore effects of vitamin D. Finally, ASD is associated with inflammation and oxidative stress, both of which may decrease 25(OH)D.^{32,33} Therefore, it is plausible that response to vitamin D supplementation may indeed be blunted in ASD. However, our preliminary findings require confirmation in additional studies.

Implications for future research or clinical practice

Interest in vitamin D and ASD is growing. Our data provide the first evidence that 25(OH)D response to vitamin D supplementation may be blunted in ASD. Confirmation of a blunted response to vitamin D supplementation in ASD would require a specific trial(s) comparing 25(OH)D response to vitamin D supplementation in ASD compared to matched, healthy controls. Nevertheless, it is possible that longer duration and higher dose vitamin D supplementation and perhaps individualization may be required to target hypovitaminosis D in ASD. We suggest that future clinical and research work relating to vitamin D in ASD should measure 25(OH)D response to supplementation to assess therapeutic doses.

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