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Effect of circulating 25-hydroxyvitamin D and antioxidant capacity level on cognitive function parameters of children with idiopathic short stature

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Abstract

Background: An optimal level of vitamin D is necessary for normal bone growth. Recently, vitamin D has been linked to many neurological disorders, changes in antioxidant capacity levels, and cognitive function decline in old age; thus, the aim was to evaluate the effect of vitamin D and antioxidant levels on the cognitive function parameters of children with idiopathic short stature (ISS).

Results: A prospective case-control study was conducted with 60 primary school-aged children with ISS who were compared to 60 unrelated healthy age- and sex-matched children as a control group. A complete clinical evaluation; anthropometric measurements; neurocognitive function parameters using the Stanford-Binet test, fifth edition; vitamin D level; total antioxidant capacity (TAC); total oxidative stress (TOS); and oxidative stress index (OSI) were measured. A total of 83.3% of children with ISS had a vitamin D level < 30 ng/ml with significantly lower vitamin D levels than the control group. The TAC level was significantly lower in children with ISS than in healthy children. Children with ISS had an average level for all of the cognitive function parameters but a lower non-verbal IQ, full-scale IQ, fluid reasoning, knowledge, quantitative reasoning, and working memory than healthy controls. A positive correlation was found between vitamin D level and all anthropometric measurements, all IQ parameters, and TAC levels in the studied children. A positive correlation was found between TAC and all IQ parameters.

Conclusion: Vitamin D level and antioxidant capacity level have a major impact on cognitive function parameters in children with ISS.

Keywords: Vitamin D, Idiopathic short stature, Antioxidant capacity, Cognitive functions

Background

Vitamin D is an important fat-soluble vitamin that is required for bone health and calcium homeostasis [1]. Vitamin D has a well-recognized role in bone formation, skeletal growth, development, and normal bone mineralization [2–4]. Vitamin D deficiency may negatively affect bone mineralization during childhood [5].

Idiopathic short stature (ISS) in children is a clinical description of a child with a height of more than 2 standard deviations below the corresponding mean height for their age and sex, without evidence of a cause and with a normal stimulating growth hormone test [6–8].

Vitamin D deficiency is a major public health problem, and vitamin D deficiency and insufficiency are also common in sunny areas such as Asia-Pacific, Africa, and Middle East regions [9, 10]; the estimated prevalence rates of levels less than 30 ng/ml in the USA, Turkey, Iran, and India were 47%, 89%, 93%, and 99%, respectively [10], while Cashman et al [11] estimated that vitamin D deficiency with levels less than 20 ng/ml in the European population had a prevalence of 40.4%.

Vitamin D deficiency, in addition to its well-established musculoskeletal effects, is linked to and associated with the development and progression of many

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different neurological disorders [12]. Experimental studies have shown that active vitamin D may influence the brain and neuronal development and have neuroprotective and antioxidant effects [13]. The widely distributed vitamin D receptors (VDR) in the brain [14] and the ability of the brain to synthesize active vitamin D locally are highly suggestive of its involvement in the normal development and function of the brain [15].

The aim of this current study was to evaluate vitamin D levels and oxidative stress levels in children with ISS and to evaluate their effect on cognitive function parameters of children with ISS.

Methods

Study design

A prospective case-control study was conducted with 60 school-aged children 6–12 years of age who were seen as outpatients at the pediatric endocrinology clinic from January 1, 2018, to December 31, 2018. These children were compared to 60 healthy age- and sex-matched children as a control group. We adjusted the size of the sample to achieve 80% power and 5% confidence of significance (type 1 error). All participants were informed about the aim of our study, and written informed consent was obtained from their parents after approval of the ethics committee.

Patient evaluation

A detailed history of age, sex, residence, nutritional history, family history, history of musculoskeletal pain, chronic fatigue, and headache was obtained.

Height was measured by a standard stadiometer to the nearest 0.1 cm. Weight was measured by an electronic scale to the nearest 0.1 kg. Body mass index (BMI) was calculated as kg/m^2. All anthropometric measurements were then expressed as Z scores (standard deviation scores), which express the anthropometric value as a number of standard deviations or Z scores below or above the reference mean or median value, which was calculated from the following formula [16]:

Z score (or SD–score)
$$= (\text{observed value–median value of the reference population}) / \text{standard deviation value of reference population}$$

Cases had ISS with a height > 2 SD below the corresponding mean height of a given age, sex, and population group without evidence of systemic, endocrine, or chromosomal abnormalities and normal stimulated growth hormone (GH) levels [6].

Complete cardiac, respiratory, abdominal, and neurological examinations of the patients were performed with the exclusion of cases with a chronic parasitic infestation, severe anemia, chronic disease as thyroid, celiac disorders, or inflammatory bowel disease. Cases suspected to have

chromosomal disorders, cases with neurological disorders, and children who were taking vitamin D supplements in the last 3 months were also excluded.

Bone age (BA) was determined by the radiograph of the left hand and wrist according to the method of Greulich and Pyle [17].

Cognitive assessment

Neurocognitive functions were evaluated using the Arabic version of Stanford-Binet test [18], the fifth edition, which is a standardized and well-validated psychometric test used to evaluate intelligence quotient (IQ) level (non-verbal, verbal, and full-scale IQ), fluid reasoning, knowledge, quantitative reasoning, visuospatial skills, and working memory.

Laboratory workup

Blood samples were collected into two empty and anticoagulated tubes containing ethylene diamine tetraacetic acid (EDTA). The serum was then separated from the cells by centrifugation at 3000 rpm for 10 min. Serum samples for measurement of serum 25(OH) D3, total oxidative stress (TOS), and total antioxidant capacity (TAC) levels were stored at − 80 °C until they were used.

Vitamin D assessment

The assessment of vitamin D was conducted using a commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kit supplied by Chongqing Biospes Co., Ltd. (Chongqing, People's Republic of China) with the catalog number BYEK1472 using a microplate ELISA reader (EMR -500, USA). Vitamin D deficiency was defined as a 25-OHD level of ≤ 20 ng/ml and vitamin D insufficiency as 21 to 29 ng/ml and normal level as ≥ 30 ng/ml [19].

The TAC and TOS levels

The TAC and TOS levels were evaluated spectrophotometrically using a commercially available colorimetric assay kit supplied by Bio-Diagnostic Co. Cairo, Egypt, catalog no. TA 25 13.

The level of TAC < 1 mmol/L was considered too low, 1–1.3 mmol/L indicated a borderline level and TAC > 1.3 mmol/L showed sufficient antioxidant capacity [20].

Determination of the OSI

The ratio of TOS to TAC was accepted as the Oxidative Stress Index (OSI). The OSI value was calculated according to the following formula: OSI (arbitrary unit) = TOS (µmol H_2O_2 Eq/l)/TAC (mmol Trolox Eq./L) × 100 [21].

Statistical analysis

Data analysis was performed using SPSS version 20 (Statistical Package for Social Science). Data are presented as a number, percentage, mean, and standard

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deviation. A chi-square test was used to compare qualitative variables. Independent t tests were used to compare quantitative variables between the two groups. Pearson correlation was performed to measure the correlations between quantitative variables. P values were considered statistically significant when $P < 0.05$.

Results

This current study included 60 children with ISS with a mean age of 10.16 ± 1.98 years: 32 males (53.3%) and 28 females (46.7%). These children were compared to 60 healthy age- and sex-matched children as a control group, with a mean age of 10.23 ± 1.54 years: 34 males (56.7%) and 26 females (43.3%). There were no significant differences between the two groups with regard to age or sex (Table 1).

All anthropometric measurements were significantly different between patients and controls; the patients' weight, height, and BMI were (23.46 kg ± 6.17, 120.83 cm ± 12.4, and 16.0 kg/m^2 ± 3.16) versus the control group (33.7 kg ± 7.68, 138.43 cm ± 9.12, and 17.36 kg/m^2 ± 2.14, respectively) (Table 1).

The vitamin D level in the ISS group (20.63 ng/ml ± 7.35 SD) was significantly lower than that in the control group (32.18 ng/ml ± 9.2 SD). There was also a significant difference between the two groups with regard to the percentage of children with vitamin D deficiency and insufficiency, with 28 children (46.7%) and 22 children (36.6%) in the ISS group having vitamin D deficiency and insufficiency, respectively (total 50/60 children 83.3%), while 22 children (36.7%) in the control group

had only vitamin D insufficiency, and no one in the control group had deficiency (Table 1).

The TAC level was significantly lower in the ISS group (1.50 mmol/L ± 0.6 SD) than in the control group (2.27 mmol/L ± 1.31 SD). OSI was significantly higher in the ISS group (21.1 ± 12) than in the control group (17.94 ± 14.77), while there was no significant difference in TOS between the two groups (Table 1).

The cognitive function parameters of ISS children were within the average range of IQ classifications [18], but non-verbal IQ (98.9 ± 8.85), full-scale IQ (102.13 ± 7.43), fluid reasoning (99.47 ± 10.65), knowledge (101.26 ± 7.96), quantitative reasoning (105.9 ± 7.51), Visuospatial (101.83 ± 7.9), and working memory (99.13 ± 8.7) were significantly lower than in the control group with P values < 0.05 (Table 2).

Children with ISS and vitamin D deficiency in comparison to ISS children without deficiency had significantly lower non-verbal IQ (97.54 ± 9.36), full-scale IQ (101.08 ± 7.71), knowledge (99.92 ± 7.97), quantitative reasoning (104.54 ± 7.47), visuospatial (100.54 ± 8.22), and TAC (1.36 mmol/L ± 0.57) with P value < 0.05 and without significant difference as regard total oxidant status and oxidative stress index with P value > 0.05 (Table 3).

There was a positive correlation between vitamin D level and weight Z score ($r = 0.581$, $P = 0.000$), height Z score ($r = 0.588$, $P = 0.000$), and BMI Z score ($r = 0.325$, $P = 0.011$) in the studied children (Fig. 1a–c).

There was a positive correlation between vitamin D level and all cognitive function parameters: non-verbal IQ ($R = 0.474$, $P = 0.000$), verbal IQ ($r = 0.327$, $P = 0.011$), full-scale IQ ($r = 0.446$, $P= 0.000$), fluid reasoning

Table 1 Characteristics data of the studied groups

Variable	Patients with ISS $N = 60$	Control $N = 60$	P value
Age (years)	10.16 ± 1.98	10.23 ± 1.54	0.83
Sex	32 (53.3%) male 28 (46.7%) female	34 (56.7%) male 26 (43.3%) female	0.71
Weight (kg)	23.46 ± 6.17	33.7 ± 7.68	0.0001**
Weight z score	− 2.63 ± 1.33	− 0.078 ± 0.72	0.0001**
Height (cm)	120.83 ± 12.4	138.43 ± 9.12	0.0001**
Height z score	− 3.0 ± 0.86	− 0.23 ± 0.86	0.0001**
BMI (kg/m^2)	16.0 ± 3.16	17.36 ± 2.14	0.006*
BMI z score	− 0.89 ± 1.62	0.05 ± 0.76	0.0001**
Vit D (ng/ml) level	20.63 ± 7.35	32.18 ± 9.2	0.0001**
Percentage of vitamin D deficiency %	50(83.3%)	22 (36.7%)	0.0001**
TAC (mmol/L)	1.50 ± 0.6	2.27 ± 1.31	0.0001**
TOS (µmol/L)	0.29 ± 0.19	0.27 ± 0.19	0.57
OSI	21.1 ± 12	17.94 ± 14.77	0.20

ISS idiopathic short stature, *BMI* body mass index, *TAC* total antioxidant capacity, *TOS* total oxidant status, *OSI* oxidative stress index
*P value < 0.05
**P value < 0.001

Table 2 Cognitive function parameters in studied groups

Variable (mean ± SD)	Patients(N = 60)	Control (N = 60)	P value
Non-verbal IQ	98.9 ± 8.85	106.78 ± 7.8	0.0001**
Verbal IQ	104.36 ± 8.3	106.52 ± 9.43	0.186
Full-scale IQ	102.13 ± 7.43	107.19 ± 8.21	0.0006 **
Fluid reasoning	99.47 ± 10.65	105.56 ± 8.15	0.0006**
Knowledge	101.26 ± 7.96	106.82 ± 11.49	0.003*
Quantitative reasoning	105.9 ± 7.51	109.52 ± 9.86	0.025*
Visuospatial	101.83 ± 7.9	105.19 ± 6.62	0.012 *
Working memory	99.13 ± 8.7	107.2 ± 8.42	0.0001**

IQ intelligence quotient
*P value < 0.05
**P value < 0.001

($r = 0.346$, $P = 0.007$), knowledge ($r = 0.363$, $P = 0.004$), quantitative reasoning ($r = 0.350$, $P = 0.006$), visuospatial processing ($r = 0.340$, $P = 0.008$), and working memory ($r = 0.504$, $P = 0.000$) (Table 4).

There was a positive correlation between TAC level and all cognitive function parameters: non-verbal IQ ($R = 0.737$, $P = 0.000$), verbal IQ ($r = 0.691$, $P = 0.000$), full-scale IQ ($r = 0.769$, $P = 0.000$), fluid reasoning ($r = 0.697$, $P = 0.000$), knowledge ($r = 0.691$, $P = 0.000$), quantitative reasoning ($r = 0.615$, $P = 0.000$), visuospatial processing ($r = 0.644$, $P = 0.000$), working memory ($r = 0.653$, $P = 0.000$), and a negative correlation between OSI and all cognitive function parameters (Table 4).

There was a positive correlation between vitamin D levels and TAC ($r = 0.546$, $P = 0.000$) and a negative correlation with OSI ($r = -0.0317$, $P = 0.014$), but we could not demonstrate a correlation between the vitamin D level and total oxidative stress level (Table 4).

Discussion

An adequate level of vitamin D has been known for its positive impact on bone metabolism and bone turnover [22–25] and is required to achieve normal genetic growth potential among children [26]; vitamin D deficiency has become very common in both children and adults [27]. Zhu et al. [28] showed that 40% of school-aged children had vitamin D levels of 20 ng/ml, and Roh et al. [29] demonstrated that vitamin D deficiency in children aged 6 to 12 years is very common, with 59.1% in his study found to have vitamin D deficiency. In the current study, we found that 36.7% in the healthy children group had vitamin D insufficiency, while 46.7% and 36.6% in the ISS group had vitamin D deficiency and insufficiency, respectively.

The effect of vitamin D level on growth was demonstrated in different age groups, and multiple studies demonstrated that vitamin D status affects growth outcome and is associated with stunted growth in the pediatric age group [22, 30, 31]. Liu et al. [32] revealed a positive correlation between serum 25(OH)D concentration and BMI-for-age Z score in school-aged children. Miguel [33] stated that serum levels of vitamin D varied significantly between different BMI groups with the lowest levels in individuals with either high or low BMI, demonstrating a curvilinear, U-shaped association. The current study revealed that children with ISS had significantly lower weight, height, and BMI than healthy children and
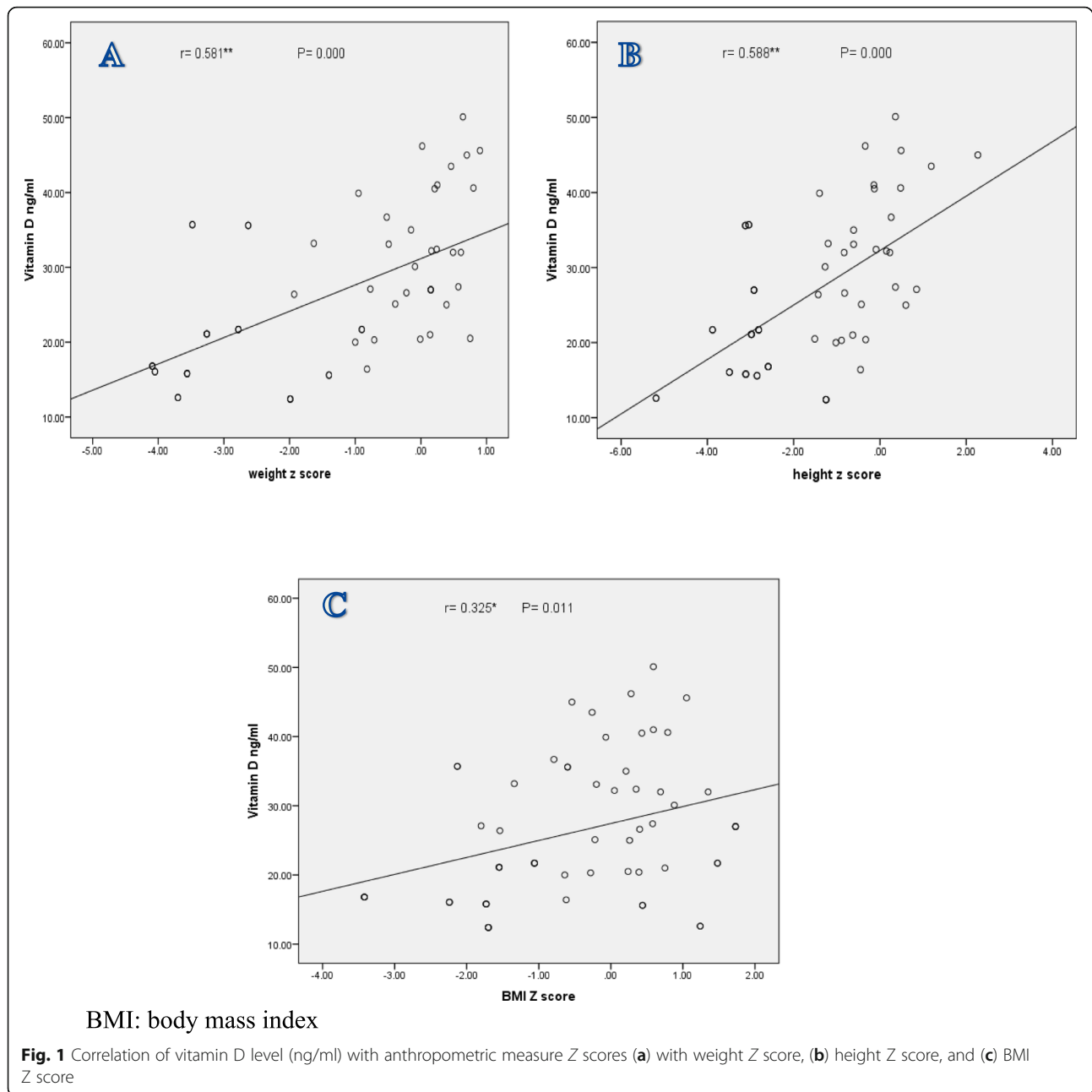
Table 3 Cognitive functions and oxidative stress parameters among children with idiopathic short stature subgroups with and without vitamin D deficiency

Variable (mean ± SD)	ISS with vitamin D deficiency (N = 50)	ISS without vitamin D deficiency (N = 10)	P value
Non-verbal IQ	97.54 ± 9.36	104.33 ± 2.73	0.0275*
Verbal IQ	103.54 ± 8.57	107.67 ± 6.71	0.156
Full-scale IQ	101.08 ± 7.71	106.33 ± 4.50	0.0425*
Fluid reasoning	98.67 ± 11.77	102.67 ± 2.25	0.2918
Knowledge	99.92 ± 7.97	106.67 ± 5.68	0.0136*
Quantitative reasoning	104.54 ± 7.47	111.33 ± 5.09	0.0081*
Visuospatial	100.54 ± 8.22	107 ± 3.22	0.0180*
Working memory	98.5 ± 8.99	101.67 ± 7.6	0.3021
TAC (mmol/L)	1.36 ± 0.57	2.025 ± 0.47	0.001**
TOS (μmol/L)	0.3 ± 0.15	0.4 ± 0.27	0.1
OSI	21.26 ± 11.65	20.53 ± 14.7	0.86

ISS idiopathic short stature, IQ intelligence quotient, TAC total antioxidant capacity, TOS total oxidant status, OSI oxidative stress index
*P value < 0.05
**P value < 0.001

BMI: body mass index

Fig. 1 Correlation of vitamin D level (ng/ml) with anthropometric measure *Z* scores (**a**) with weight *Z* score, (**b**) height *Z* score, and (**c**) BMI *Z* score

significantly lower vitamin D levels (20.63 ng/ml ± 7.35 SD) than (32.18 ng/ml ± 9.2 SD) the control group; a positive correlation between vitamin D level and all anthropometric measurements was detected.

In early life, vitamin D is essential for normal neuronal development; vitamin D regulates the expression of calcium-binding proteins and L-type voltage-sensitive calcium channels, which play important roles in intracellular calcium balance. Vitamin D regulates the expression of neuron growth factor (NGF), neurotrophin-3 (NT-3), neurotrophin-4 (NT-4), and glial cell-derived neurotrophic factors. Additionally, the existence of vitamin D metabolic enzymes in addition to the VDR in the central nervous system suggests its participation in the cognitive functioning process [34]. Yates et al. [35] in an animal study revealed that rats born to vitamin D3-deficient mothers had marked brain alterations with some disabilities in early life, including learning and memory problems, with some evidence of increased lateral ventricle volume and altered neural expression of genes involved in dopamine and glucocorticoid-related pathways [35].

Table 4 Correlation between cognitive function parameters, Vitamin D level, and oxidative stress parameters in all studied children

Variable	Statistics	Vitamin D	TAC	TOS	OSI
Non-verbal IQ	Pearson correlation	0.474**	0.737 **	0.091	− 0.654**
	P value	0.000	0.000	0.487	0.000
Verbal IQ	Pearson correlation	0.327*	0.691**	0.251	− 0.633**
	P value	0.011	0.000	0.053	0.000
Full-scale IQ	Pearson correlation	0.446**	0.769**	0.177	− 0.714**
	P value	0.0000	0.000	0.177	0.000
Fluid reasoning	Pearson correlation	0.346**	0.697**	0.128	− 0.722**
	P value	0.007	0.000	0.330	0.000
Knowledge	Pearson correlation	0.363**	0.691**	0.299*	− 0.311*
	P value	0.004	0.000	0.020	0.015
Quantitative reasoning	Pearson correlation	0.350**	0.615**	0.272*	− 0.498**
	P value	0.006	0.000	0.036	0.000
Visuospatial	Pearson correlation	0.340 **	0.644**	0.147	− 0.720**
	P value	0.008	0.000	0.263	0.000
Working memory	Pearson correlation	0.504**	0.653**	− 0.053	− 0.729**
	P value	0.000	0.000	0.687	0.000
Vitamin D	Pearson correlation		0.546**	0.041	− 0.317*
	P value		0.000	0.757	0.014
TAC	Pearson correlation	0.546**		0.212	− 0.623**
	P value	0.000		0.104	0.000
TOS	Pearson correlation	0.041	0.212		0.366**
	P value	0.757	0.104		0.004
OSI	Pearson correlation	− 0.317*	− 0.623**	0.366**	
	P value	0.014	0.000	0.004	

IQ intelligence quotient, *TAC* total antioxidant capacity, *TOS* total oxidative stress, *OSI* oxidative stress index
**Correlation is significant at the 0.01 level (2-tailed)
*Correlation is significant at the 0.05 level (2-tailed)

An adequate vitamin D level is necessary to preserve neurological function development and protect the adult brain [15]. Multiple studies have shown a correlation between vitamin D level and cognitive function decline in elderly persons, with an effect on brain health and memory [14, 36–40], but few studies have evaluated this effect in children. Nassar et al. [41] stated that the vitamin D level was significantly lower in children with delayed school achievement, with a positive correlation between vitamin D level and Wechsler Intelligence Scale values for Children. Another cross-section study by Liu et al. [32] conducted on 563 children (9.5 ± 1.6 years) from 6 areas of China, showed that serum vitamin D concentration was positively associated with the intelligence score. In the current study, cognitive function parameters of ISS children were within the average range of IQ classifications, but non-verbal IQ, full-scale IQ, fluid reasoning, knowledge, and working memory were significantly lower than those in the control group, with a positive correlation between vitamin D level and all cognitive function parameters.

Vitamin D also has an antioxidant effect that controls the process of detoxification in the brain by regulating the activity of γ glutamyl transpeptidase [42], and multiple studies have demonstrated the presence of an association between vitamin D level, TOS, and antioxidant capacity in various diseases [43, 44]. In this current study, serum levels of TAC showed statistically significantly higher levels among healthy children than among children with ISS, with a positive correlation between vitamin D and TAC and a positive correlation between TAC and all cognitive function parameters in the studied children, but we could not find an association between vitamin D and TOS without any significant difference in serum levels of TOS between the two studied groups, which was in concordance with Wang et al. [45] whose results did not manifest a clear link between vitamin D status and oxidative stress markers in the

absence of obesity, chronic disease, or advanced age. This finding may explain why all children included had no detectable chronic obesity.

Limitations

Brain imaging studies such as magnetic resonance image (MRI) because of limited financial resources for the exclusion of associated brain disorders may affect cognitive function parameters.

Conclusion

Vitamin D deficiency is highly associated with ISS and additional stunted growth in those children; vitamin D deficiency is also linked to decreasing antioxidant capacity and decreasing cognitive function parameters. Recommendations for continuous screening of vitamin D levels in all age groups to ensure normal physical and mental development in children and further prospective studies after correcting vitamin D levels to assess changes in growth and cognitive functions are needed.

Abbreviations

BA: Bone age; BMI: Body mass index; EDTA: Ethylene diamine tetraacetic acid; ELISA: Enzyme-linked immunosorbent assay; IQ: Intelligence quotient; ISS: Idiopathic short stature; GH: Growth hormone; NGF: Neuron growth factor; NT-3: Neurotrophin-3; NT-4: Neurotrophin-4; OSI: Oxidative Stress Index; TAC: Total antioxidant capacity; TOS: Total oxidative stress; VDR: Vitamin D receptors; Z score: Standard deviation scores

Authors' contributions

OA contributed to the conception and design of the study, drafting of article, analysis and interpretation of data, and final approval of the version to be published. HS shared in putting study design, psychological and cognitive assessment of the studied population, collection of data, analysis and interpretation of data writing the manuscript, and final approval of the version to be published. HA shared in laboratory work of the study, analysis and interpretation of data, and final approval of the version to be published. LA helped in the collection of data, analysis and interpretation of data, and final approval of the version to be published. All authors read and approved the final manuscript.

Availability of data and materials

All data generated and analyzed during this study are available from the corresponding author upon request.

Ethics approval and consent to participate

All participants' parents were informed about the aim of our study and written informed consent was obtained from parents after approval of the Ethical committee of Qena Faculty of Medicine, South Valley University. The Ethics committee reference numbers: 02/18

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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