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Association between calcium-phosphorus balance and adolescent idiopathic scoliosis: A meta-analysis

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ABSTRACT

Study design: A systematic review and meta-analysis.
Objective: The objective of this meta-analysis was to evaluate the association between calcium-phosphorus balance and adolescent idiopathic scoliosis (AIS).
Methods: Databases, including PubMed, OVID database, Web of Science, CBM database and CNKI database were searched for the relevant case control studies and cross-sectional studies. Two authors selected studies and extracted data independently. Data analysis was performed by Review Manager Software 5.0. Subgroup analysis was performed on the serum level of vitamin D according to gender and menstruation.
Results: Five studies were included, with a total of 646 cases of AIS and 791 controls. AIS group had a lower serum level of vitamin D compared to control group [MD = −6.74, 95% CI (−9.47, −4.00)]. Gender and menstruation condition were thought to have no effect on the primary outcome of vitamin D level by subgroup analysis [MD = −5.97, 95% CI (7.61, −4.34)]. The AIS group had a lower calcium level [SMD= −0.77, 95% CI (−1.51, −0.02)] and calcitonin level compared to control group. There was no statistical difference in phosphorus level [SMD=0.5, 95% CI (−0.46, 0.57)] and parathyroid hormone level [SMD = −0.11, 95% CI (−0.54, −0.31)]. Meanwhile, the observational indexes, including serum levels of calcium, phosphorus, parathyroid hormone and calcitonin were within normal limits.
Conclusion: Vitamin D deficiency may be involved in the pathogenesis of AIS by influencing the regulation of calcium-phosphors metabolism on human bone. Therefore, we suggest to screen vitamin D level in AIS patients.
Level of Evidence: Level III, Therapeutic Study

Introduction

Scoliosis is one of the most common forms of spinal deformity. However, in most patients with scoliosis, the underlying cause of the condition cannot be identified.[1] Scoliosis that develops during adolescence is termed adolescent idiopathic scoliosis (AIS), which is the most common diagnosis. In total, 2%–3% of all children develop AIS, among whom approximately 10% will need conservative treatment. Furthermore, as much as 0.1%–0.3% of all patients eventually require surgical intervention.[2] According to a large sample, observational, cross-sectional study in China, most patients were girls and aged 12–13 years.[3] Although AIS itself does not cause any health problems, the resulting deformity can result in the development of psychological disorders or mental illness.[4]

Bone metabolism is influenced by various factors and maintains the dynamic equilibrium between bone formation and destruction. Once this dynamic equilibrium is disturbed, a variety of skeletal diseases can develop. Calcium-phosphorus metabolism and balance, which are affected by many factors, such as vitamin D, parathyroid hormone (PTH), and calcitonin levels, have important roles in bone formation and destruction.[5]

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Although the etiology of AIS has not been fully elucidated, previous studies have indicated that the causes are often systemic in nature. In this study, we performed a systematic review and meta-analysis to assess the association between calcium–phosphorus balance and AIS, which may further clarify the relationship between calcium–phosphorus balance and AIS.

Materials and methods

Study design

A systematic review and meta-analysis based on case-control study. Our review was not registered to any institution.

Criteria for studies

Included criteria: 1. Case–control studies or cross-sectional studies. 2. Studies that assessed the association between calcium–phosphorus balance and AIS. 3. The subjects of study were adolescents.

Exclude criteria: 1. Republished research. 2. Non-primary literature. 3. Study without control group.

Types of participants

Patients with AIS, regardless of sex, or ethnicity, were included as research subjects.

Outcomes

The primary outcome was serum vitamin D level, which was determined by measuring serum 25-hydroxyvitamin D levels.[6] The secondary outcomes included serum levels of calcium, phosphorus, PTH, and calcitonin, as well as the correlations between Cobb's angle and the aforementioned indices.

Search strategy

The PubMed, OVID, Web of Science, Chinese Bio-medicine, and China National Knowledge Internet databases were independently searched by two authors. The search strategy described below was used in PubMed and similarly applied to other databases. All databases were searched until January 2017. Additionally, Google Scholar was used to search for relevant articles. The references of each included study were investigated to identify other eligible studies. There was no language restriction.

Search strategy in PubMed.
#1 “scoliosis” [Mesh]
#2 adolescent idiopathic scoliosis
#3 OR/#1-2
#4 vitamin D
#5 25-hydroxyvitamin D
#6 25(OH) vitamin D
#7 dihydnxycholecalcifero
#8 parathyroid hormone
#9 PTH
#10 calcitonin
#11 calcium
#12 phosphorus
#13 phosphorus–calcium
#14 calcium-phosphorus
#15 OR/#4-14
#16 #3 AND #15

Data extraction and analysis

Two authors independently extracted data from all eligible studies. The extracted information included study characteristics and main outcome results. The authors were contacted by e-mail if any required information was unavailable.

Quality assessment in included studies

The study quality was assessed by the 9-star Newcastle-Ottawa Scale,[7] as follows: adequate definition of cases, representativeness of cases, selection of controls, definition of controls, control for important factor or additional factor, exposure assessment, same method of ascertainment for cases and controls, and nonresponse rate.

Data analysis

Review Manager Software 5.0 was used for statistical analysis. Heterogeneity among studies was assessed using the $\chi 2$ test, with $P < 0.10$ and $I^2 > 50\%$ being assumed to indicate statistical significance.[8] The meta-analysis was applied using a fixed-effect model if there was no statistical heterogeneity ($P \geq 0.10$, $I^2 \leq 50\%$); otherwise, a random-effect model was used ($P < 0.10$, $I^2 > 50\%$). When data could not be extracted for meta-analysis, the data were descriptively analyzed and reported in the Results section. Subgroup analysis of the primary outcome (i.e., the serum level of vitamin D) was performed according to sex and menstruation status.

Results

Description of studies

As presented in Fig. 1 and as described in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement,[9] 614 articles were identified by searching through the relevant databases and 9 articles were identified by searching Google Scholar. After screening and reading the remaining articles, five articles[10–14] were finally included, which comprised a total of 646 AIS cases and 791 control cases. Further information about the characteristics of the included studies was shown in Table 1. E-mails were sent to the corresponding authors to obtain any missing information, except for two studies with no contact information provided. No responses were received.

The results of the quality assessment according to the 9-star Newcastle-Ottawa Scale was summarized in Table 2. Lam's conference paper[12] had insufficient information for extracting data and assessing the study quality. Therefore, it was considered a pending literature and excluded from the analysis of the results. All other articles were scored >6 stars, which was considered to be high quality.

A study could be awarded a maximum of one star for each numbered item except for the item control for important factor or additional factor. A maximum of two stars could be awarded for control for important factor or additional factor. Studies that controlled for sex and age received one star, whereas studies that controlled for menstruation received one additional star.

Serum vitamin D level

Three of the included trials reported the serum level of vitamin D,[11,13,14] with the 25-hydroxyvitamin D level as an indicator. There was statistical heterogeneity among the three studies (heterogeneity test = 14.01, $P = 0.003$, $I^2 = 79\%$). The causes of heterogeneity

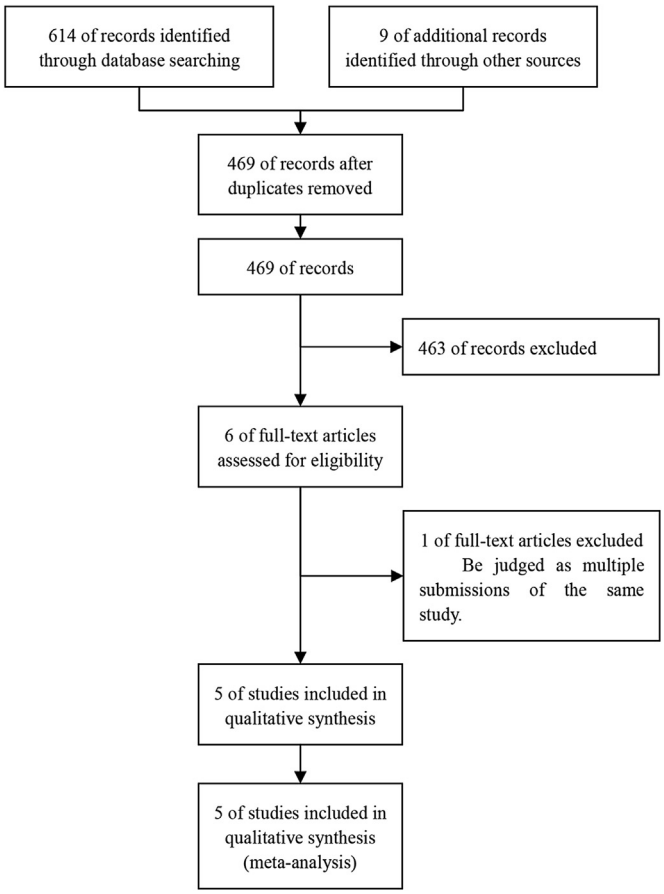

Fig. 1. The flowchart of literature screening.

were hypothesized to be sex and menstruation status. Therefore, a random-effects model was applied for serum vitamin D level and a subgroup analysis was performed. The pooled data analysis showed that the AIS group had a lower serum vitamin D level than the control group [MD = −6.74, 95% CI (−9.47, −4.00)] (Fig. 2).

Subgroup analysis

AIS is more common in young female patients. Therefore, we performed a subgroup analysis according to sex and menstruation status.

Balioglu et al[14] reported that there was no sex-based difference in serum vitamin D level in either the AIS group or the control group. For female patients, the mean vitamin D level in the AIS group and control group was 17.23 ± 8.71 and 20.96 ± 16.53 ng/mL, respectively. For male patients, the mean vitamin D level in the AIS group and control group was 16.82 ± 7.52 and 21.99 ± 13.27 ng/mL, respectively. To focus on studying female patients, the data sets of female subjects were integrated. Pooled data analysis (heterogeneity test = 11.20, $P = 0.004$, $I^2 = 82\%$) showed that the AIS group had a lower serum vitamin D level than the control group among female patients [MD = −5.97, 95% CI (−7.61, −4.34)] (Fig. 3).

Only the study by Gozdzialska et al[13] described the influence of menstruation on AIS. The trial included only female patients, divided into four groups according to menstruation status and AIS status: premenarcheal AIS, postmenarcheal AIS, premenarcheal scoliosis-free, and postmenarcheal scoliosis-free female subjects. In their study, the vitamin D level in premenarcheal AIS subjects was lower than that in premenarcheal scoliosis-free subjects. Furthermore, the vitamin D level was also lower in postmenarcheal AIS subjects than in postmenarcheal scoliosis-free subjects. Additionally, the vitamin D level in premenarcheal AIS subjects was lower than that in postmenarcheal AIS subjects, whereas the vitamin D

Table 1
Characteristics of included studies.

First author	Year	Country	Groups	Age, mean (SD), yrs	N (male/female)	BMI, mean (SD), kg/m^2	Cobb's angle, mean (SD), °	Outcomes*
Kulis	2009	Poland	AIS	11–14	0/50	NG#	31 ± 11	b, c
			Control	11–14	0/59	NG	–	
Batista	2014	Brazil	AIS	20 (7.7)	4/51	20.3	NG	a, b, c
			Control	13.6 (3.4)	12/48	19.6	–	
Lam	2015	China	AIS	12.9 (0.6)	0/212	NG	–	a
			Control	12.9 (0.5)	0/183	NG	–	
Gozdzialska	2016	Poland	AIS (premenarcheal)	12.6	0/50	19.2 (0.51)	NG	a, b, c, d
			AIS (postmenarcheal)	14.6	0/50	21.5 (0.28)	–	
			Control (premenarcheal)	11.9	0/50	19.4 (0.12)	NG	
			Control (postmenarcheal)	13.6	0/50	21.3 (0.23)	–	
Balioglu	2017	Turkey	AIS	14.7 (2.6)	112/117	NG	NG	a
			Control	13.9 (2.7)	222/167	NG	–	

*: a: serum level of vitamin D; b: serum levels of calcium and phosphorus; c: serum level of PTH; d: serum level of calcitonin. #: NG: not given.

Table 2
Quality assessment of case-control studies included in this meta-analysis.

Study	Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of controls	Control for important factor or additional factor	Exposure assessment	Same method of ascertainment for cases and controls	Nonresponse rate	Total quality scores
Kulis	☆	☆	☆	☆	☆☆	☆	☆	–	8
Batista	☆	☆	☆	☆	☆	☆	☆	–	7
Lam	–	–	–	–	–	–	☆	–	1
Gozdzialska	☆	☆	☆	☆	☆☆	☆	☆	–	8
Balioglu	☆	☆	☆	☆	☆	☆	☆	–	7

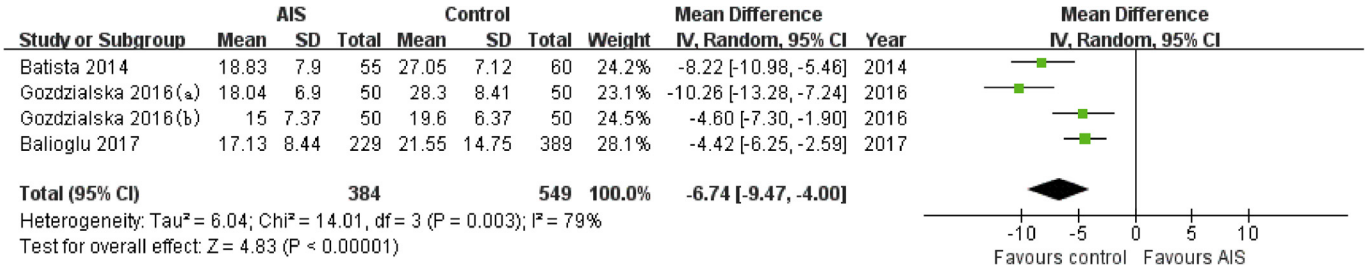

Fig. 2. Meta-analysis of serum level of vitamin D. Gozdzialska 2016(a): premenarcheal AIS group VS premenarcheal control group; Gozdzialska 2016(b): postmenarcheal AIS group VS postmenarcheal control group.

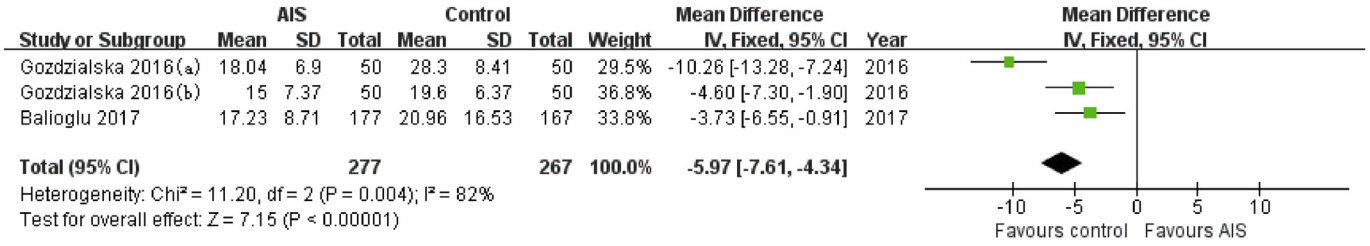

Fig. 3. Meta-analysis of serum level of vitamin D (female only). Gozdzialska 2016(a): premenarcheal AIS group VS premenarcheal control group; Gozdzialska 2016(b): postmenarcheal AIS group VS postmenarcheal control group.

level in premenarcheal scoliosis-free subjects was also lower than that in postmenarcheal scoliosis-free subjects.

Our meta-analysis of four studies that assessed vitamin D levels produced similar results to those of two studies in subgroup analysis. Therefore, sex and menstruation status likely have no effect on vitamin D level.

Serum calcium and phosphorus levels

The serum level of calcium was reported in three of the included trials.[10,11,13] Kulis et al[10] reported that there was no difference in calcium levels between the AIS and control groups. Furthermore, the levels of calcium in each included subject were within the normal range. Their article did not provide specific values of means and standard deviations. Thus, an e-mail was sent to the author for missing data; however, there was no response. Batista et al[11] reported that the level of calcium in the AIS group was lower than that in the control group, although the calcium levels in both groups were within normal limits. In the study by Gozdzialska et al,[13] which included a cohort divided into four groups, the calcium levels in the two AIS groups were lower than those in the two control groups. The difference in calcium levels between the two premenarcheal groups was not statistically significant. A random-effects model was applied to evaluate the outcome measure, which indicated that the AIS group had a lower calcium level than the control group [SMD = −0.77, 95% CI (−1.51, −0.02)].

The serum phosphorus level was reported in two of the included trials.[11,13] Batista et al[11] reported that the serum phosphorus level in the AIS group was significantly lower than that in the control group ($P < 0.05$). Gozdzialska et al[13] reported that the phosphorus levels in two AIS groups were higher than those in two control groups; however, this difference was not statistically significant ($P > 0.05$). Notably, the phosphorus concentrations in the control and AIS groups in those two trials were within normal limits. The meta-analysis indicated that there was no statistical difference between the two groups [SMD = 0.5, 95% CI (−0.46, 0.57)] by using the random-effects model.

Serum PTH level

The serum level of PTH was reported in three of the included trials.[10,11,13] Kulis et al,[10] who studied only female subjects, reported that the level of PTH in the control group was higher than that in the AIS group; however, specific values were missing. Batista et al[11] identified that the level of PTH in the AIS group was higher than that in the control group. Gozdzialska et al[13] indicated that the level of PTH in the two AIS groups were lower than those in the two control groups; however, this difference was not statistically significant ($P > 0.05$). Notably, the PTH levels of patients in the three trials were within normal limits. The meta-analysis indicated that there was no statistical difference between the AIS and control groups in both trials [SMD = −0.11, 95% CI (−0.54, −0.31)] by using the random-effects model.

Serum calcitonin level

Only Gozdzialska et al[13] reported on the serum calcitonin level. The calcitonin levels in both premenarcheal and postmenarcheal female subjects in the AIS groups were twice lower as those in the two control groups (4.56 vs. 8.64 pg/mL and 4.54 vs. 8.99 pg/mL, respectively; $P < 0.05$ for all measurements). However, all reported calcitonin concentrations across the four groups were within normal limits.

Correlation between Cobb's angle and measurement outcomes

Only one study reported on the correlation between Cobb's angle and vitamin D level. Balioglu et al[14] reported that the vitamin D level was negatively correlated to Cobb's angle ($P < 0.026$, $r = -0.147$). Meanwhile, using a Cobb's angle of 45° as a cutoff produced no difference in vitamin D levels among patients with Cobb's angles that were greater than, equal to, or less than 45°.

Publication bias

As the included studies were relatively few, publication bias was not assessed.

Discussion

This systematic review and meta-analysis summarized the results of five studies that evaluated the association between calcium–phosphorus balance and AIS. Our study found that the AIS group had lower levels of vitamin D and calcium, whereas the levels of phosphorus and PTH were the same between the AIS and control groups. However, as few relevant studies have been conducted to date, further research is likely to change the estimate of this effect.

The physiology of calcium–phosphorus metabolism is complex and related to bone physiology. Vitamin D is known to contribute in maintaining calcium–phosphorus homeostasis. Thus, vitamin D deficiency could lead not only to bone defects but also to several other diseases.[15–17] Our meta-analysis showed that the vitamin D level in the AIS group was lower than that in the control group. In addition, it was negatively correlated to Cobb's angle. This indicate that vitamin D is associated with the pathogenesis of AIS, which provides new ideas for further research into AIS from both mechanistic and clinical perspectives. The hormone PTH, along with vitamin D, is involved in the regulation of calcium–phosphorus homeostasis. Our study found no statistical difference in PTH or in serum phosphorus level between the AIS and control groups. Meanwhile, the calcium levels in the AIS group were lower than those in the control group. Moreover, the observational indices, including serum levels of calcium, phosphorus, PTH, and calcitonin, were within normal limits. On the one hand, the normal results of those outcomes may be explained by different mechanisms.[18] On the other hand, those indices that were within normal limits could suggest precluding the existence of renal metabolic disorder interfering with the metabolic pathway of vitamin D in patients with AIS.

We performed a subgroup analysis to consider the effect of menstruation on vitamin D levels and AIS. We compared premenarcheal AIS subjects to premenarcheal scoliosis-free subjects, as well as postmenarcheal AIS subjects to postmenarcheal scoliosis-free subjects. We found that the levels of serum vitamin D in premenarcheal and postmenarcheal female patients with AIS were lower than those in premenarcheal and postmenarcheal scoliosis-free female subjects, respectively. This subgroup analysis agrees with the results of the meta-analysis. Thus, the menstruation status did not affect the metabolism of vitamin D between the two groups. We performed a similar subgroup analysis of sex and found that it had no effect on the vitamin D level between the two groups.

The etiology of AIS is likely to be multifactorial. Studies have shown that abnormalities in the vestibular reflex usually lead to asymmetric contraction of paravertebral muscles, thereby resulting in abnormal development of vertebral cartilage as well as skeletal structure, and eventually leading to scoliosis.[19] Additionally, animal studies and clinical case–control trials have indicated that melatonin and melatonin pathway dysfunction are widely believed to contribute to the pathogenesis of scoliosis.[20] Furthermore, researchers have assessed the role of genetic predisposition in AIS.[21]

A review on 2018,[22] the relationship among vitamin D and different factors, such as genetics, central nervous system, skeletal growth, menarche, osteopenia and hormones were analyzed respectively, and suggested that vitamin D deficiency may produce an effect on the development of AIS by the influence of the regulation of fibrosis, posture control and bone metabolism.

As shown in our study, the balance between calcium and phosphorus also has a vital function in AIS. While these hypotheses have widely implicated these factors in AIS, the central etiology of AIS remains unknown.

There are several limitations to this study, which may have resulted in potential bias that should be addressed in further studies. First, the systematic nature of this review and meta-analysis required the use of data whose authenticity was determined by the original research team. Second, as only a few studies were included in our review, the number of the included subjects was low, which may have produced imprecise results. Third, subgroup analysis was not performed for all factors that might contribute to the existence of heterogeneity. Last, the interactions between multiple pathogenic factors were not analyzed.

In conclusion, vitamin D deficiency may be involved in the pathogenesis of AIS by influencing the regulation of calcium-phosphors metabolism on human bone. Therefore, we suggested the vitamin D level should be assessed in AIS patients. However, further studies are needed to fully elucidate the pathogenic mechanism of AIS.

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Conflict of interest

We declare that we have no conflicts of interest.

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