The association of disproportionate skeletal growth and abnormal radius dimension ratio with curve severity in adolescent idiopathic scoliosis

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Abstract Abnormal anthropometric measurements during the peripubertal growth spurt have been documented in adolescent idiopathic scoliosis (AIS). Magnetic resonance (MR) imaging studies of the spine have suggested a disproportionate endochondral and membranous ossification in AIS. The present study aimed at investigating whether disproportional ossification and skeletal growth occurred in the peripheral bone of AIS patients using the radius as the target bone. Skeletally mature AIS girls with different severity ($n = 290$) and age-matched control healthy girls ($n = 80$) were recruited. The anthropometric parameters were recorded. The midshaft of non-dominant radius was scanned with peripheral quantitative computed tomography (pQCT) and the radius diameter was calculated from the cross-sectional area. Radius dimension ratio was derived from the ratio of radius diameter to radius length. The anthropometric parameters were compared between AIS

and control with adjustment for age. The radius dimension ratio was further correlated with curve severity in AIS girls using Pearson's correlation test. The analysis showed that the arm span and radius length were slightly longer in AIS girls. The BMI of AIS girls was significantly lower than the controls. The radius dimension ratio in severe AIS girls was significantly lower than the controls and the ratio of AIS girls correlated with the curve severity ($r = -0.120$; $p = 0.039$). The abnormal radius dimension ratio supported the presence of systemic growth abnormalities in AIS. Disproportional endochondral-membranous ossification could explain for the observation. The observation of the association of radius dimension ratio with curve severity provides an important potentially clinically measurable parameter for further longitudinal studies on the prognostication of curve progression in AIS.

Keywords Adolescent idiopathic scoliosis · Skeletal growth · Curve severity · Bone geometry · Association study

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Introduction

Adolescent idiopathic scoliosis (AIS) is a complex three-dimensional deformity of the spine that most commonly occurs in girls between ages 10 and 16 during the pubertal growth spurt. The general incidence of AIS has been reported to range from 2 to 4% [1–4]. Among the different causes suggested in the literature [5, 6], abnormal skeletal growth in AIS has been shown to associate with the development and progression of scoliotic curves [7, 8]. In our previous study [9], AIS girls were found to be significantly taller and leaner, and had longer arm span similar to other reports [10–12]. Studies on the morphology of the

vertebral column with magnetic resonance (MR) imaging showed that the anterior vertebral columns of AIS patients are longer than the normal controls [13]. The differential growth between the anterior and the posterior elements of each thoracic vertebra in the patients with AIS was significantly different from that in the normal controls. It was suggested that AIS is associated with disproportionate and asynchronous growth between the anterior endochondral and posterior membranous ossification during the growth spurt. Relative anterior spinal overgrowth in AIS has also been suggested. However, the study [13] has its limitation in the measurement of the MR images of the scoliotic spine. It may not fully represent the true length of individual vertebra without a full volumetric image of the vertebra unless a comprehensive three-dimensional image is obtained for analysis. Moreover, the measurement may also represent the secondary effect of the spine deformity. Therefore, to follow up with the findings from previous study [13], we think it would be meaningful to try identifying a site other than the spine to test the hypothesis of systemic disproportionate endochondral and membranous ossification. The radius of the non-dominant forearm was selected because it is a non-weight bearing part of the skeleton and relatively easy to be measured longitudinally. Similar to the vertebral body, the growth in length of the radius results from endochondral ossification while the increase in width is mainly through membranous ossification. The radius dimension ratio of AIS girls and normal controls was investigated and the association between the radius dimension ratio and curve severity was also studied.

Subjects and methods

Subjects

Two hundred and ninety (290) AIS girls aged 16–20 were recruited. The patients were grouped into moderate (Cobb's angle 20°–40°) and severe groups (Cobb's angle > 40°) according to their curve severity at skeletal maturity. All the subjects underwent full clinical and radiological examinations to rule out other causes of scoliosis and to ascertain the diagnosis of AIS. The subject exclusion criteria were scoliosis of congenital, neuromuscular, metabolic etiology, and others with skeletal dysplasia and known endocrine and connective tissue abnormalities. Eighty age-matched healthy girls were recruited from local communities as control for comparison. They were confirmed without any associated medical diseases, spinal deformities, or neurological problems when entered to the study. The study protocol was approved by the Clinical Research Ethics Committee of the University. Informed consents were obtained from all the subjects and their parents before entering the study.

Anthropometric assessment

Anthropometric measurements included body weight, arm span, and radius length. The radius length was measured according to the standardized anthropometric measurement techniques. Briefly, it is the distance between the radiale and the stylium. The end pointers of the segmometer were placed on the radiale and dactylion while keeping the segmometer parallel to the long axis of the radius [14]. In the present study, arm span was used for the calculation of the BMI as previous studies [15, 16] have shown that the different equations for correction of height loss had its limitation and might not fit every curve. Moreover, it has been shown that there is a significantly high linear correlation between arm span and standing height in healthy children and adolescents ($r^2 = 0.99$) [17]. Hence, to avoid the height correction problem with different equations [15], arm span was used for the calculation of body mass index (BMI) by dividing the body weight (kg) by squared arm span (m^2).

Cross-sectional area and average diameter of midshaft of non-dominant radius

The cross-sectional area of midshaft of the non-dominant radius was derived from the image acquired from the peripheral quantitative computed tomography (pQCT) (Densiscan 2000, Scanco Medical AG, Bruttisellen, Switzerland). The radius was positioned in a radiolucent splint anatomically adapted for the subject during the pQCT scanning. The midpoint of the radius was defined as half the length of radius and marked on the skin with radiolucent marker. With the projectional scout view of the midshaft of radius, the reference line for scanning was set at the radiolucent marker corresponding to the midpoint and a single slice of pQCT image with a scan resolution of 0.3 mm was taken for the evaluation of the cross-sectional area of midshaft radius (Fig. 1) with the built image analysis program (IPL, Scanco, Medical AG, Bruttisellen, Switzerland). The average diameter of the radius midshaft of individual was calculated based on the assumption of a cylindrical shape of the midshaft of radius [18]. A radius dimension ratio was obtained by dividing the radius midshaft diameter by the radius length.

Statistical analysis

All the parameters were presented as mean and standard deviation. The inter-group difference of anthropometric parameters was tested by one-way ANOVA. Post hoc test was done using Bonferroni method. For the correlation between different parameters was analyzed by multiple regressions. For the correlation of the anthropometric

Fig. 1 Peripheral quantitative computed tomography image of the midshaft of radius

parameters with arm span, the arm span of individual AIS subject was standardized as *z*-score according to the arm span of the control subjects. Multiple regression analysis was used to delineate if curve severity and arm span had effect on the radius dimension ratio. In all the tests, an alpha level $<5\%$ was considered statistically significant. SPSS/PC 13.0 (SPSS Inc., Chicago, USA) was used on all statistical computations.

Results

Anthropometric measurements versus radius dimension ratio

The average age of the three groups of subjects was similar between age 17.1 and 17.3 (Table 1). Among the three groups, the body weight and BMI in the severe AIS group were significantly lower than the control group. For the

moderate AIS group, only the BMI was significantly lower than the control subjects. In this series, the arm span of girls with AIS was longer than the control though not statistically significant. The radius length was also similar between different groups.

Based on image analysis result for the pQCT, the cross-sectional area of the midshaft radius showed a decreasing trend from largest area in the control group ($92.3 \pm 11.5 \text{ mm}^2$) to smallest in the severe group ($88.6 \pm 10.7 \text{ mm}^2$) although it is not statistically significant. For the radius midshaft diameter, a similar decreasing trend among the three groups was also observed (Table 1).

Using the radius dimension ratio (RD/RL), significant differences were found in AIS girls when compared with control ($p = 0.008$). In the post hoc test, the ratios of the severe AIS girls were significantly smaller among groups in the post hoc test.

Correlation between anthropometric parameters and curve severity

The correlation analysis of different anthropometric parameters with curve severity in AIS subjects is shown in Table 2. The RD/RL ratio was significantly associated with the curve severity in Cobb's angle (Correlation coefficient: -0.120 ; $p = 0.039$; Fig. 2). The correlation indicated that a decrease in the RD/RL ratio was associated with increase in the Cobb's angle. Other anthropometric measurements were not found to correlate with curve severity in AIS subjects in this series.

The effect of arm span on radius dimension ratios

To explore the relationship between the arm span and the radius dimension ratio, multiple regression analysis was carried on RD/RL ratio with respect to the *z*-score of the

Table 1 Comparison of anthropometric parameters and radius morphology

	Control ($n = 80$) Mean $\pm$ SD	Moderate ($n = 150$) Mean $\pm$ SD	Severe ($n = 140$) Mean $\pm$ SD	<i>p</i> value
Age	17.3 $\pm$ 0.9	17.2 $\pm$ 1.0	17.1 $\pm$ 1.1	0.375
BW (kg)	50.2 $\pm$ 5.6	48.4 $\pm$ 5.9	47.8 $\pm$ 6.4	0.014
BMI (kg/m^2)	19.9 $\pm$ 1.8	18.9 $\pm$ 2.0	18.4 $\pm$ 2.0	<0.001 (a, b)
AS (cm)	158.8 $\pm$ 7.2	160.3 $\pm$ 6.8	160.9 $\pm$ 6.9	0.087
RL (cm)	24.6 $\pm$ 1.3	24.6 $\pm$ 1.2	24.7 $\pm$ 1.3	0.420
XA (mm^2)	92.3 $\pm$ 11.5	90.2 $\pm$ 11.3	88.6 $\pm$ 10.7	0.053 (b)
RD (mm)	1.08 $\pm$ 0.07	1.07 $\pm$ 0.07	1.06 $\pm$ 0.06	0.055 (b)
RD/RL	4.41 $\pm$ 0.26	4.36 $\pm$ 0.26	4.29 $\pm$ 0.31	0.008 (b)

BW body weight, AS arm span, BMI body mass index, RL radius length, XA cross-sectional area of midshaft radius, RD radius diameter

a post-hoc Bonferroni test: $p < 0.05$ (moderate vs. control)

b post-hoc Bonferroni test: $p < 0.05$ (severe vs. control)

Table 2 Correlations between anthropometric parameters and curve severity

log (Cobb's)	RD/RL	Arm span	Radius length	Radius diameter
Pearson correlation	−0.128*	0.019	0.056	−0.091
Sig. (2-tailed)	0.030	0.752	0.344	0.124

* $p < 0.05$ **Fig. 2** Scatter plot of ratio of radius diameter and radius length against the Cobb's angle of the girls with adolescent idiopathic scoliosis (Pearson's correlation: coefficient (r): −0.128; $p = 0.03$)

arm span and the curve severity. Arm span was found to be a significant independent variable to the RD/RL ratio (Table 3). The regression model also showed the negative association of curve severity with RD/RL ratio.

Discussion

Abnormal systemic growth has been implicated in AIS patients from different reports in the literature. As suggested in a previous study [13], AIS girls might have disproportionate growth between endochondral and membranous ossification, the present study provided additional piece of evidence to support the presence of disproportionate growth as part of a systemic phenomenon. The lower radius dimension ratio in AIS girls when compared with healthy control subjects indicates that the growth in length by endochondral ossification and width of the radius by membranous ossification was discordant. The radius dimension ratio was also found to correlate with curve severity in AIS subjects when other linear measurement of arm span and

Table 3 Effect of arm span on different dimensional ratio of radius among different curve severity groups of AIS and control

Group	Estimate	Std. error	p value
RD/RL			
Control	4.38	0.02	<0.001*
Severe AIS ^a	−0.07	0.03	0.014*
z-arm span	−0.07	0.01	<0.001*

RD/RL ratio of radius diameter to radius length, *Control* The reference value of the RD/RL of the control subjects. *Severe AIS* AIS girls whose Cobb's angle was greater than 40°. *z-arm span*: the z-score of the arm span with reference to the control subjects

* p value <0.05 indicating the variable was significant involved in the regression analysis

^a During the regression analysis, moderate curve severity (Cobb's angle between 20° and 40°) was tested in the model. However, moderate curve severity is not significantly correlated with the RD/RL. Thus, it is not shown in the present model

radius length could not show the correlation with Cobb's angle. Although it is a subtle change, the systemic disproportionate growth between endochondral ossification and membranous ossification in AIS patients has important implication in the etiopathogenesis of AIS [13, 19].

The present study compared the radius dimension ratio of the length and the radius diameter between AIS girls and controls. The finding showed that AIS girls have lower value than the control subjects while severe AIS girls have the lowest. This is similar to the observation in the previous study [13] on the ratio of the anteroposterior diameter of vertebral body to the vertebral height which was shown to be significantly smaller in AIS subjects. In the present study, the difference in the ratio between severe AIS girls and controls is 4.5%. In a recent study on humeral dimension ratio measured by dual energy X-ray absorptometry in adolescence [20], the dimension ratios of normal girls in different pubertal stages were not statistically different. It was shown that the ratio was relatively constant in different pubertal stages, ages, and height of the normal girls [20]. Moreover, the gender difference shown in the previous study [20] was only 3.7% which was lower than the present finding of 4.5% difference. Therefore, the present study showed a 4.5% difference in the radius dimension ratio between AIS subjects and controls bears a significant meaning on the problem of AIS related to the coordinated growth by endochondral ossification for bone elongation and membranous ossification for circumferential growth. It suggested a possible discordant between two modes of ossification in AIS subjects during their pubertal growth. Furthermore, our previous study [21] showed that the physical activity, nutrition intake especially calcium, protein, and energy were similar between AIS girls and controls at age above 15 years. Therefore, the influence of these possible covariates on the dimension ratio difference

between AIS patients and controls would be minimized. Taken together with our previous observation [13], the present results clearly provide an important piece of evidence to the presence of systemic disproportionate growth in AIS girls. Since this dimension ratio is relatively constant, it is possible that this ratio could be developed to one of the clinical prognostication factors for the curve progression in the future.

The dimension ratio of radius was more sensitive in detecting the difference between AIS girls and control subjects as shown in the results that all the linear measurements such as arm span, radius length, and radius diameter alone were not exhibited to be different between AIS girls and controls. Although the previous studies demonstrated that the AIS girls were taller [9, 22], another study [23] suggested that even though younger girls with AIS seem taller, their normal peers catch up and by the end of growth period they are indistinguishable. In the light of this, the present study seems to agree with Goldberg's observation [23]. Moreover, the post hoc power test of the present measurement on the linear measurements indicated that the effect size is small. It requires a large sample size to detect the difference as in the previous study [9]. The dimension ratio (RD/RL, Table 2) in this study showed significant correlation with the Cobb's angle of AIS girls and could provide a more sensitive parameter for documenting disproportionate skeletal growth in AIS.

One of the major concerns in the management of AIS patient with initial small curve is whether one can identify the curve that will progress into significant deformity and would require early treatment. In current clinical practice, prognostic indicators of curve progression such as Risser grade, age, and sexual maturity are all related to remaining growth potential of the affected patient [7]. However, there is lack of simple clinically reliable parameter of proven prognostic significance that can be measured longitudinally and non-invasively. Although bone mineral density has been shown to be another objective and quantifiable prognostic factor [24], it is costly and not readily available in most of the clinics. The measurements of BMD are also sensitive to many other environmental factors and life style factors overtime. As suggested in Clark et al.'s longitudinal study [20], the peripheral bone dimension ratio was relatively constant and not affected by puberty, age, and height, the present radius dimension ratio would potentially be a new parameter to add into the prognostic equation along with other factors. Further longitudinal study on the radius dimension ratio of AIS patients is warranted to validate its clinical applicability.

In the present study, the lower radius dimension ratio in AIS subjects points to the possibility of abnormal control and modulation of skeletal growth and development. It supports the speculation that etiopathogenesis of AIS

would likely be related to the skeletal development during puberty. The mechanism of disproportionate skeletal growth affecting the structure of the spine to cause a structural deformity in AIS subjects merits further study.

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References

1. Kane WJ (1977) Scoliosis prevalence: a call for a statement of terms. *Clin Orthop Relat Res* 126:43–46
2. Lonstein JE, Lonstein JE, Moe JH (1995) Idiopathic scoliosis Moe's textbook of scoliosis and other spinal deformities, vol 3. W. B. Saunders, Philadelphia, pp 219–256
3. Roach JW (1999) Adolescent idiopathic scoliosis. *Orthop Clin North Am* 30(3):353 (viii)
4. Weinstein SL (1989) Adolescent idiopathic scoliosis: prevalence and natural history. *Instr Course Lect* 38:115–128
5. Lowe TG, Edgar M, Margulies JY, Miller NH, Raso VJ, Reinker KA, Rivard CH (2000) Etiology of idiopathic scoliosis: current trends in research. *J Bone Joint Surg* 82-A(8):1157–1168
6. Burwell RG, Dangerfield PH, Lowe T, Margulies JY (2000) Etiology of adolescent idiopathic scoliosis: current trends and relevance to new treatment approaches spine: state of the art reviews. Hanesley & Belfus Inc., Philadelphia
7. Lonstein JE, Carlson JM (1984) The prediction of curve progression in untreated idiopathic scoliosis during growth. *J Bone Joint Surg* 66(7):1061–1071
8. Loncar-Dusek M, Pecina M, Prebeg Z (1991) A longitudinal study of growth velocity and development of secondary gender characteristics versus onset of idiopathic scoliosis. *Clin Orthop Relat Res* 270:278–282
9. Cheung CSK, Lee WTK, Tse YK, Tang SP, Lee KM, Guo X, Qin L, Cheng JCY (2003) Abnormal peri-pubertal anthropometric measurements and growth pattern in adolescent idiopathic scoliosis—a study of 598 patients. *Spine* 28(18):2152–2157
10. Buric M, Momcilovic B (1982) Growth pattern and skeletal age in school girls with idiopathic scoliosis. *Clin Orthop Relat Res* 170:238–242
11. Nordwall A, Willner S (1975) A study of skeletal age and height in girls with idiopathic scoliosis. *Clin Orthop Relat Res* 110:6–10
12. Hagglund G, Karlberg J, Willner S (1992) Growth in girls with adolescent idiopathic scoliosis. *Spine* 17(1):108–111
13. Guo X, Chau WW, Chan YL, Cheng JCY (2003) Relative anterior spinal overgrowth in adolescent idiopathic scoliosis—result of disproportional endochondral-membranous bone growth. *J Bone Joint Surg Br* 85B(7):1026–1031
14. Ross WD, Bar-Or O (1996) Anthropometry in assessing physique status and monitoring change the child and adolescent athlete. Blackwell, Oxford, pp 538–572
15. Kono K, Asazuma T, Suzuki N, Ono T (2000) Body height correction in scoliosis patients for pulmonary function test. *J Orthop Surg (Hong Kong)* 8(1):19–26
16. Ylikoski M (2003) Height of girls with adolescent idiopathic scoliosis. *Eur Spine J* 12(3):288–291
17. Cheng JCY, Leung SSF, Lau J (1996) Anthropometric measurements and body proportions among Chinese children. *Clin Orthop Relat Res* 323:22–30
18. Schoenau E, Neu CM, Rauch F, Manz F (2002) Gender-specific pubertal changes in volumetric cortical bone mineral density at the proximal radius. *Bone* 31(1):110–113

19. Burwell RG, Dangerfield PH, Freeman BJ (2008) Concepts on the pathogenesis of adolescent idiopathic scoliosis. Bone growth and mass, vertebral column, spinal cord, brain, skull, extra-spinal left-right skeletal length asymmetries, disproportions and molecular pathogenesis. *Stud Health Technol Inform* 135:3–52
20. Clark EM, Ness AR, Tobias JH (2007) Gender differences in the ratio between humerus width and length are established prior to puberty. *Osteoporos Int* 18(4):463–470
21. Lee WTK, Cheung CSK, Tse YK, Guo X, Qin L, Ho SC, Lau J, Cheng JCY (2005) Generalized low bone mass of girls with adolescent idiopathic scoliosis is related to inadequate calcium intake and weight bearing physical activity in peripubertal period. *Osteoporos Int* 16(9):1024–1035
22. Normelli H, Sevastik J, Ljung G, Aaro S, Jonsson-Soderstrom AM (1985) Anthropometric data relating to normal and scoliotic Scandinavian girls. *Spine* 10(2):123–126
23. Goldberg CJ (2000) Skeletal growth. *Spine State Art Rev* 14(2):401–410
24. Hung VWY, Qin L, Cheung CSK, Lam TP, Ng BKW, Tse YK, Guo X, Lee KM, Cheng JCY (2005) Osteopenia: a new prognostic factor of curve progression in adolescent idiopathic scoliosis. *J Bone Joint Surg* 87:2709–2716