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Radiographic Factors for Progression of Thoracolumbar Kyphosis in Achondroplasia Patients after Walking Age: A Generalized Estimating Equation Analysis

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Background: This study aimed to analyse the trends in changes of radiologic parameters according to age to predict factors affecting the progression of thoracolumbar kyphosis (TLK).

Methods: Records of patients with achondroplasia were retrospectively reviewed from July 2001 to December 2020. We measured imaging parameters (T10–L2 angle, sagittal Cobb angle, width, height, and number of wedge vertebrae, and apical vertebral translation [AVT]) of 81 patients with radiographically confirmed TLK. Based on the angle on X-ray taken in 36 months, 49 patients were divided into the progression group (P group, TLK angle ≥ 20°) and resolution group (R group, TLK angle < 20°). The mean values between the groups were compared using Student *t*-test, and the pattern of changes in each radiologic parameter according to age was analysed using a generalized estimating equation.

Results: Some imaging parameters showed significant differences according to age between P group and R group: T10–L2 angle ($p < 0.001$), sagittal Cobb angle ($p < 0.001$), AVT ($p = 0.025$), percentage of wedge vertebral height (WVH) ($p = 0.018$), and the number of severely deformed wedge vertebral bodies (anterior height less than 30% of posterior) ($p = 0.037$). Regarding the percentage of wedge vertebral widths (superior and inferior endplates), the difference between the two groups did not significantly increase with age, but regardless of age, it was higher in P group than in R group.

Conclusions: The difference in the TLK angle between P group and R group of the achondroplasia patients gradually increased with age. Among the imaging parameters, AVT and WVH could be factors that ultimately affect the exacerbation of kyphosis as the difference between the groups increased significantly over time.

Keywords: *Achondroplasia, Thoracolumbar kyphosis, Radiologic parameter*

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Achondroplasia is the most common skeletal dysplasia, occurring in 1 in 26,000 live births annually.[1)] It is a representative disease of rhisomelic short-limb dwarfism due to endochondral ossification defects. Genetically, it shows autosomal dominant inheritance due to a glycine-to-arginine substitution mutation at codon 380 (G380R) in the transmembrane domain of fibroblast growth factor receptor 3 (FGFR3).[2-4)] In the spine, FGFR3 mutations cause premature syncondrosis closure and interfere with enchondral ossification of the superior and inferior epiphyseal plates. As a result, achondroplasia patients show characteristic morphological features in the spine, including a short pedicle, spinal stenosis, lumbar hyperlordosis, and thoracolumbar kyphosis (TLK) with an occasional anterior wedging vertebra.[4-6]

TLK in achondroplasia is associated with fixed anterior convergence involving a thoracolumbar lesion, with or without an anterior wedging vertebra, usually involving L2 or L1. The prevalence of TLK was reported differently according to age: 94% in < 1 year, 39% in 2–5 years, and 11% in 5–10 years.[7] The persistence or progression of TLK can increase the risk of neurological sequelae in adolescence and adulthood.[8,9] In order to prevent TLK from progressing, Pauli et al.[8] recommended avoiding unsupported sitting and applying a brace early.[10] Because the extent of surgical treatment generally depends on the severity of the deformity and the presence of neurological symptoms, it is critical to identify risk factors for the progression of TLK in achondroplasia and provide timely surgical treatment.[11,12]

Studies have reported that apical vertebral translation (AVT), apical vertebral wedging for vertebral height, and developmental motor delay (DMD) are radiological and clinical risk factors for TLK progression.[13,14] However, many of these studies did not sufficiently consider the changes in these radiological parameters over time when comparing patients with or without TLK progression. The purpose of this study was to identify the trend of changes in radiologic parameters with age and to predict the factors that ultimately affect the progression of TLK.

METHODS

This study was approved by the Institutional Review Board (IRB No. 2011-174-1175), and the need to obtain informed patient consent was waived due to the retrospective nature of the study.

In this study, we retrospectively reviewed all patients with achondroplasia who visited our institution between July 2001 and December 2020. TLK was defined as a sagittal Cobb angle or T10–L2 angle of 20° or more.[13-15] Simple radiographs were taken in the standing position at the age where standing was possible and in the supine position otherwise. We included only patients who had a T-L spine lateral or whole spine lateral view obtained before age 10 years. Exclusion criterion were (1) previous surgery for spinal disease other than kyphosis correction and (2) incomplete radiographic data.

Radiographic parameters were measured based on the study reported by Borkhuu et al.[14] (Fig. 1). The values of the most apical or the most severe wedge vertebral bodies (WVBs) were determined as follows: the wedge vertebral height (WVH), which is the percentage of decrease in the height of WVB, was calculated as the ratio of the posterior maximum vertical height to the anterior minimum vertebral body height; the wedge vertebral width (WVW) relative to the width or sagittal diameter of the adjacent normal vertebral body was measured on the superior (WVW-S) and inferior (WVW-I) endplates; and the AVT was measured as the percentage of the degree of deviation from the arc obtained from vertebral bodies above and below the apical vertebra.

In addition, the numbers and ratios of severely deformed WVBs were calculated as follows: N-WVH50%, the number of WVBs with anterior height of 50% or less; R-WVH50%, the ratio of the N-WVH50% to the total number of WVBs; N-WVH30%, the number of WVBs with anterior height of 30% or less; R-WVH30%, the ratio of the N-WVH30% to the total number of WVBs.

Finally, we divided and analysed two groups, a progression group (P group) and a resolution group (R group), according to the TLK angle among patients who had standing X-rays after 36 months of age; 49 patients in these groups had at least two good quality simple radiographs after the age of 3 years. The R group was composed

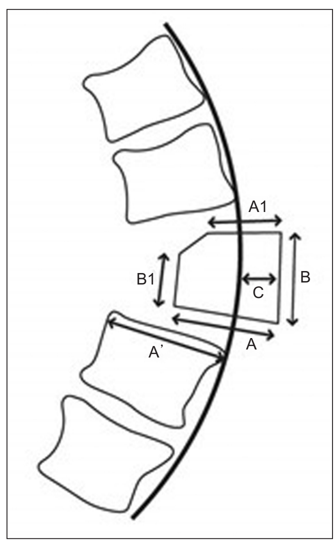

Fig. 1. The measurement of radiological parameters. Wedge vertebral height (WVH, %) = (B – B1) / B x 100. Wedge vertebral width on the superior endplate (WVW-S, %) = (A′ – A1) / A′ x 100. Wedge vertebral width on the inferior endplate (WVW-I, %) = (A′ – A) / A′ x 100. Apical vertebral translation (AVT, %) = (1 – (A′ – C) / A′) x 100.

of patients who had a TLK angle of less than 20° at the final follow-up, whereas the P group consisted of patients with a TLK angle of 20° or greater at the final follow-up.[13,14)]

A Student *t*-test was used to compare the mean values between the P group and the R group. The changes in each radiological parameter over time were depicted with a scatter plot, and a generalized estimating equation (GEE) was used to compare the trends of changes in these radiological parameters over time between the two groups. A GEE is a statistical technique that can analyse repeated measurement time series data that are difficult to handle in a general linear model, such as censored data and dichotomous variables. Using a GEE, we identified factors that ultimately affected the progression of TLK. Statistical analyses were performed using IBM SPSS ver. 25.0 (IBM Corp., Armonk, NY, USA), and a *p*-value < 0.05 was considered statistically significant.

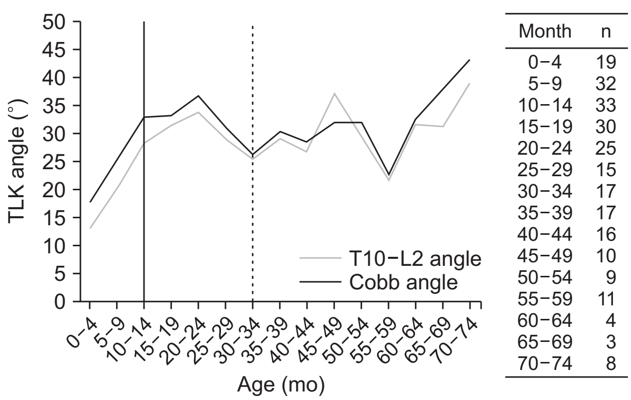

Fig. 2. The changes of T10–L2 and sagittal Cobb angle over time. The graph shows the tendency of the thoracolumbar kyphosis (TLK) angle to increase until the sitting age (perpendicular line) and then decrease as patients start standing (perpendicular dotted line).

Table 1. Characteristics of Patients in the Progression (P) and Resolution (R) Groups

Variable	P group (n = 31)	R group (n = 18)	*p*-value
Sex			0.108*
Female	14 (45.16)	4 (22.22)	
Male	17 (54.84)	14 (77.78)	
Follow-up period (mo)	41.74 ± 21.69	55.67 ± 26.35	0.051†
Initial follow-up age (mo)	17.65 ± 19.51	14.72 ± 19.13	0.113†
Last follow-up age (mo)	59.23 ± 21.74	70.39 ± 25.92	0.613†

Values are presented as number (%) or mean ± standard deviation.
*Chi-square test. †Student *t*-test.

RESULTS

Among patients under 10 years of age, 81 patients with TLK confirmed in simple radiography at any time point were included. A total of 81 patients (men: 49, women: 32) were included in this study with a mean follow-up period of 32.69 ± 26.16 months, a mean initial follow-up age of 14.57 ± 16.40 months, and a mean final follow-up age of 47 ± 27.97 months. The average TLK angle over time (Fig. 2) showed a tendency to increase until the sitting age and then decreased as patients started standing.

Among the 81 patients, 49 (men: 31, women: 18) underwent standing radiography after 3 years of age and were further divided into the P group and R group (P group: T10–L2 or sagittal Cobb angle ≥ 20°; R group: T10–L2 or sagittal Cobb angle < 20°). Of the 49 patients, 31 patients (63.27%) were in the P group and 18 patients (36.73%) were in the R group. There was no statistically significant difference between the P and R groups with

Table 2. Comparison of Radiological Parameters between the Progression (P) and Resolution (R) Groups at the Last Follow-up

Variable	P group (n = 31)	R group (n = 18)	*p*-value
T10–L2 angle (°)	32.93	10.35	< 0.001*
Sagittal Cobb angle (°)	33.97	11.07	< 0.001*
AVT (%)	7.83	0.34	< 0.001*
WVH (%)	71.55	54.62	0.005*
WVW-S (%)	40.62	31.97	0.026*
WVW-I (%)	28.31	24.30	0.490
Number of total WVB	2.97	2.72	0.469
N-WVB50%	2.42	1.61	0.020*
N-WVB30%	1.65	0.56	< 0.001*
R-WVB50%	0.79	0.53	0.011*
R-WVB30%	0.54	0.19	0.001*

AVT: apical vertebral transition, WVH: wedge vertebral height, WVW-S: wedge vertebral width of the superior endplate, WVW-I: wedge vertebral width of the inferior endplate, WVB: wedge vertebral body, N-WVB50%: the number of wedge vertebral body with anterior height of 50% or less, N-WVN30%: the number of wedge vertebral body with anterior height of 30% or less, R-WVB50%: the ratio of the number of WVH (50%) to the total number of WVB, R-WVB30%: the ratio of the number of WVH (30%) to the total number of WVB.
*Statistically significant ($p < 0.05$).

regards to the mean follow-up period, the initial follow-up age, and the final follow-up age (Table 1).

When radiological parameters were compared between the P and R groups at final follow-up using student *t*-test, there was a significant difference in all radiological parameters except for the number of WVBs and WVW-I (Table 2). However, when the changes in radiological parameters over time were compared between the two groups using scatter plots, the difference in the TLK angle, WVH, and AVT significantly increased with age (Fig. 3).

Subsequently, a GEE was performed with the age set as a covariate to determine if there were differences between the P and R groups for each parameter with increasing age. We found that with age, T10–L2 angle, sagittal Cobb angle, AVT, WVH, and N-WVH30% differed significantly between the P and R groups (Table 3). Among parameters without significant interactions with age, WVW-S, WVW-I, and R-WVH50% were significantly different between the P and R groups when a GEE was performed after excluding the interaction term (independent variable × age) (Table 4).

DISCUSSION

TLK in patients with achondroplasia can cause significant health-related problems due to deformity and neurological deficits. It is essential to investigate the natural course of TLK in early childhood and to identify patients who

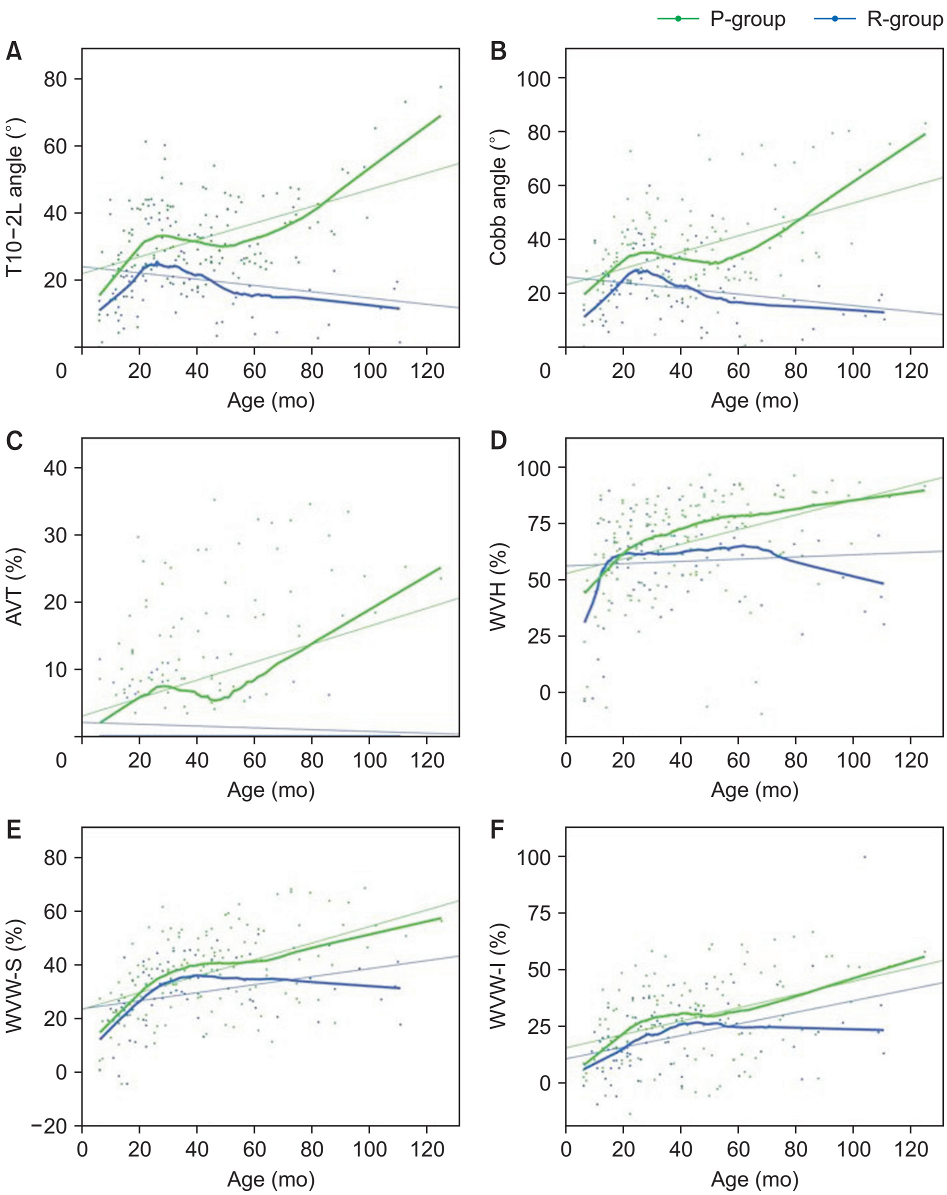

Fig. 3. The changes of radiological parameters over time. (A) T10–L2 angle. (B) Sagittal Cobb angle. (C) Apical vertebral translation (AVT, %). (D) Wedge vertebral height (WVH, %). (E) Wedge vertebral width on the superior endplate (WVW-S, %). (F) Wedge vertebral width on the inferior endplate (WVW-I, %). With age, the difference between the two groups increased significantly for the thoracolumbar kyphosis angle, WVH, and AVT. The age-related difference margins were not significantly increased for WVW-S and WVW-I.

Table 3. Result of GEE Analysis (Age as a Covariate)

Variable	0 mo	36 mo	72 mo	108 mo	120 mo	*p*-value*
T10–L2 angle (°)	–11.15	8.07	27.30	46.52	52.93†	< 0.001
Sagittal Cobb angle (°)	–10.11	8.97	28.05	47.13	53.49	< 0.001
AVT (%)	1.53	4.62	7.72	10.81	11.85	0.025
WVH (%)	–1.61	7.82	17.26	26.69	29.83	0.018
N-WVB30%	0.05	0.70	1.35	2.00	2.21	0.037

GEE: generalized estimating equation, AVT: apical vertebral transition, WVH: wedge vertebral height, N-WVN30%: the number of wedge vertebral body with anterior height of 30% or less.
*Statistically significant ($p < 0.05$). †As the age increases, the difference in thoracolumbar kyphosis angle, WVH, AVT, N-WVH30% between group P and R gradually increase. When the follow-up was observed without surgery, the difference between the two groups around 10 years of age is expected to be 52.93°.

Table 4. Result of GEE Analysis (Excluding Interaction Term; Independent Variable × Age)

Variable	B*	*p*-value
WVW-S (%)	6.135	0.012†
WVW-I (%)	6.375	0.048†
Number of total WVB	0.114	0.726
N-WVB50%	0.570	0.063
R-WVB30%	0.142	0.065
R-WVB50%	0.207	0.007†

GEE: generalized estimating equation, WVW-S: wedge vertebral width of the superior endplate, WVW-I: wedge vertebral width of the inferior endplate, WVB: wedge vertebral body, N-WVB50%: the number of wedge vertebral body with anterior height of 50% or less, R-WVB50%: the ratio of the number of WVH (50%) to the total number of WVB, R-WVB30%: the ratio of the number of WVH (30%) to the total number of WVB.
*B: regression coefficient. †Statistically significant ($p < 0.05$).

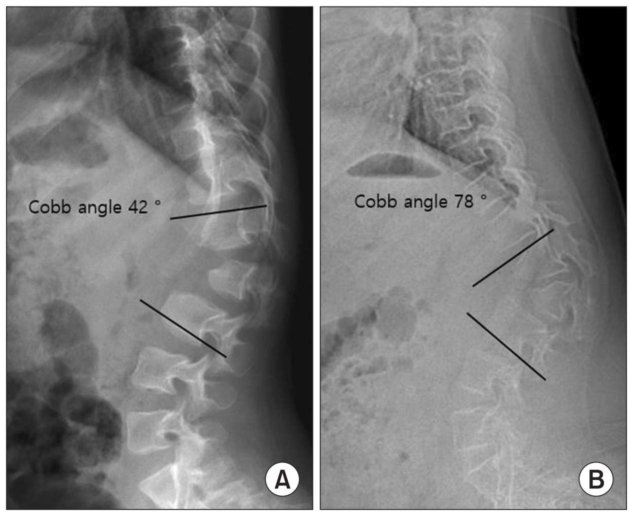

Fig. 4. Progression case. (A) Sagittal Cobb angle at 36 months. (B) Sagittal Cobb angle at 93 months: deformation of the apical vertebral body became more severe and the angle increased.

have a higher risk of progression and who require an early surgical intervention and an orthosis.[12,16,17] In this study, we measured both sagittal Cobb angle and T10–L2 angle in patients with achondroplasia to describe the differences in the natural course between the P and R groups. And, radiologically, we identified WVH, AVT, and the number of severly deformed WVBs as critical factors.

Margalit et al.[13] found that unresolved TLK was associated with AVT, WVH, and DMD. In addition, Borkhuu et al.[14] suggested DMD as a significant risk factor for TLK progression, and the risk ratio was 2.65 (95% confidence interval, 1.20–5.91) in the multivariable binomial regression model of the clinical features. Previous studies are meaningful in identifying factors that influence the progression of TLK, but they include comparisons of radiological parameters and clinical factors at a specific time point (e.g., 1 year after walking starts). In our study, by analysing the change in each parameter over time, we found that TLK progression was not a factor at a specific time, but was, instead, a factor of deterioration over time. In particular, we confirmed that the difference between the specific factors increased over time and the effect on the deterioration of TLK could be more clearly explained.

In our GEE analysis, the difference between the P and R groups significantly increased over time for T10–L2 angle, sagittal Cobb angle, AVT, WVH, and N-WVH30%, whereas the changes with age in WVW-S and WVW-I were not statistically significant. These results suggest that AVT and WVH are related to the increased TLK angular difference between the two groups with age. As the difference between the anterior and posterior portions of the vertebral body grows (i.e., more severe wedging), the Hueter-Volkmann Law can act as a larger compression force in the anterior body and as a larger tensile force in the posterior body. This vicious cycle can further worsen the wedging of the apical vertebra and the overall TLK (Fig. 4).

The WVW-S and WVW-I were significantly different between the P and R groups, but the difference did not significantly increase with age. This can be interpreted as follows: initially, patients with more severe anomalies were more likely to belong to the P group. However, the width of the deformed vertebra was not a factor that accelerated the deformity. Meanwhile, the total number of WVBs was not associated with the progression of TLK, regardless of age. In contrast, N-WVH30% was significantly associated with the progression of TLK. Therefore, based on these results, the presence of even a small number of severely deformed vertebrae can have a greater influence on the progression of TLK with achondroplasia than the presence of a large number of slightly deformed vertebrae. Therefore, based on these results, it seems that the severity of deformity is more important than the number of deformed vertebral bodies in the progression of TLK in achondroplasia patients.

As in previous studies, we observed a tendency of the TLK angle in achondroplasia patients to increase until they reached the age of starting sitting and then to decrease as they started standing.[16,18] It should be noted that achondroplasia patients have different standards of developmental delay (sitting age, 14 months; walking alone, 30 months) than normal children.[19] Due to the change in angle, there has been no clear consensus on the timing of surgery, which is a critical issue. Shirley and Ain[16] did not believe surgery was appropriate before the age of 4 years, while others have suggested that surgery is more appropriate between the ages of 5 and 6 years.[20,21] In this study, after walking period, the difference in the TLK angle between the two groups became evident and increased with age, especially after the age of 5 years. Therefore, an early surgical intervention could be considered in achondroplasia patients with progressive TLK after early childhood.

This study has several limitations. First, there are limitations in explaining the causes and effects because of the retrospective design. Second, the measurement values may have been affected by the patient's position at the time of radiography. However, the difference in measured values according to patient posture would have affected indiscriminately all patients in both groups. Third, the radiological parameters in this study were the average of repeated measurements performed by one orthopedic spine specialist. The validity of the study could have been increased by having more than one specialist measure the parameters to reduce interobserver error. Fourth, there was a lack of association analysis with sagittal parameters such as pelvic incidence that could affect TLK sagittal angle. Moreover, the biggest limitation is that clinical factors, such as DMD and hydrocephalus, were not considered. Although this analysis was focused only on regional imaging parameters, future studies will help in the evaluation of patients by including clinical parameters and other global radiological parameters. Despite these limitations, this study is significant in that it evaluated the time-dependent changes in TLK and identified progression-determining factors in patients with achondroplasia with TLK.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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