## Title
Diffuse idiopathic skeletal hyperostosis association with thoracic spine kyphosis: a cross-sectional study for the Health Aging and Body Composition Study.



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DEFORMITY

# Diffuse Idiopathic Skeletal Hyperostosis Association With Thoracic Spine Kyphosis

*A Cross-sectional Study for the Health Aging and Body Composition Study*

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**Study Design.** A descriptive study of the association between diffuse idiopathic skeletal hyperostosis (DISH) and kyphosis.

**Objective.** To investigate the association of DISH with Cobb angle of kyphosis in a large cohort of older subjects from the Health Aging and Body Composition Study.

**Summary of Background Data.** DISH and thoracic kyphosis are well-defined radiographical findings in spines of older individuals. Characteristics of DISH (ossifications between vertebral segments) reflect changes of spine anatomy and physiology that may be associated with Cobb angle of kyphosis.

**Methods.** Using data from 1172 subjects aged 70 to 79 years, we measured DISH and Cobb angle of kyphosis from computed tomographic lateral scout scans. Characteristics of participants with and without DISH were assessed using the $\chi^2$ and *t* tests. Association between DISH and Cobb angle was analyzed using linear regression. Cobb angle and DISH relationship was assessed at different spine levels (thoracic and lumbar).

**Results.** DISH was identified on computed tomographic scout scan in 152 subjects with 101 cases in only the thoracic spine and 51 in both thoracic and lumbar spine segments. The mean Cobb angle of kyphosis in the analytic sample was 31.3° (standard deviation = 11.2). The presence of DISH was associated with a greater Cobb angle of 9.1° and 95% confidence interval (95% CI) (5.6–12.6) among African Americans and a Cobb angle of 2.9° and 95% CI (0.5–5.2) among Caucasians compared with those with no DISH. DISH in the thoracic spine alone was associated with a greater Cobb angle of 10.6° and 95% CI (6.5–14.7) in African Americans and a Cobb angle of 3.8° and 95% CI (1.0–6.5) in Caucasians compared with those with no DISH.

**Conclusion.** DISH is associated with greater Cobb angle of kyphosis, especially when present in the thoracic spine alone. The association of DISH with Cobb angle is stronger within the African American population.

**Key words:** Cobb angle, kyphosis, hyperkyphosis, diffuse idiopathic skeletal hyperostosis, DISH, aging, spine, computed tomography, spine ligament, race, bone metabolism.

**Level of Evidence:** 3

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Diffuse idiopathic skeletal hyperostosis (DISH), often referred to as Forestier disease,[1] is a condition diagnosed by the presence of ossification of the soft tissue of the anterolateral thoracolumbar spine during at least 4 contiguous segments, with flowing vertebral bony bridges in absence of frank degenerative changes in the intervertebral discs.[2] Currently, the cause of DISH is unclear, however there are studies that support a genetic association with an allele variant in the *COL6A1* gene, hormonal mechanisms including IGF-1 and growth hormone, medications (vitamin A), and mechanical factors that could activate different cell-signaling pathways such as Wnt-B-catenin, NFkB, bone morphogenic protein 2, prostaglandin I2, and endothelin.[1,3,4] Also, studies have reported associations between DISH and diabetes mellitus type 2, obesity, hyperuricemia, and male sex.[5,6]

DISH is a prevalent radiographical finding in the spines of older individuals. Other prevalent radiographical findings in older individuals include kyphosis and vertebral fractures. The spinal curvature that results in kyphosis is assessed by Cobb angle measurement obtained from a lateral spine radiograph.[4] Kyphosis increases with age and has been associated with decreased bone mineral density (BMD),[5,6] decreased lumbar paraspinal muscle density,[7] vertebral fractures,[8] and is a predictor of poor physical function.[9–11] Although both kyphosis and DISH are prevalent in aging populations, we hypothesized that the characteristic ossification of the ligaments between the vertebras in DISH may alter the architecture of the spine and affect spinal curvature resulting in greater kyphosis. To investigate the possible association between DISH and kyphosis, we used a large cohort of older subjects from the Health Aging and Body Composition (Health ABC) Study.[12]

## MATERIALS AND METHODS

### Subjects

Health ABC is an ongoing longitudinal cohort of 3075 African American (42%) and Caucasian (58%) participants, with relatively equal numbers of males (48%) and females (52%). At baseline, participants aged 70 to 79 years were recruited from a random sample of Caucasian Medicare-eligible residents and all age-eligible African American residents of selected areas of Pittsburgh, Pennsylvania, and Memphis, Tennessee. Participants were independent in activities of daily living, able to walk ¼ of a mile and up 10 steps without resting. Protocols were approved by institutional review boards and written informed consent was collected for each participant.

### Covariates

Self-reported history of vertebral fractures, doctor-diagnosed gout, and a medication inventory were assessed by an interviewer-administered questionnaire at the baseline visit. Osteoporosis medication use (bisphosphonates, calcitonin, raloxifene hydrochloride, and fluoride) was coded using the Iowa Drug Information System ingredient codes. Height and weight were measured using a Harpenden stadiometer and a calibrated balance beam scale. Body mass index was calculated and reported as kilograms/meters squared. Diabetes was determined from any of the following 3 criteria: self-reported diabetes, medication use, or fasting glucose 7 mmol/L or more. BMD of the proximal femur was assessed by dual-energy x-ray absorptiometry (Hologic QDR 4500A; Hologic Inc., Bedford, MA). Lumbar paraspinal muscle density was measured using a previously reported protocol[7] from axial computed tomographic (CT) scans at the L4–L5 disc space on a 9800 Advantage Scanner (General Electric, Milwaukee, WI). The regions defined as left and right lumbar paraspinal muscles in the axial CT scan were measured, and lumbar paraspinal muscle density was expressed as the average of these 2 measures. Gait speed was performed by timing participants walking at their usual pace along a 6-m walking course twice, and reported as the average in meters per second. Chair stands were performed with arms crossed at the chest, and recorded as number of chair stands completed in 10 seconds.

The sample for this study included 1172 males and females from the Pittsburgh site for whom baseline scout CT scans and Cobb angle of kyphosis measurements were available. Of the 1172 participants with CT scans and kyphosis measurements, 1128 (96.2%) were read for presence and location of DISH, 44 scans were excluded for poor-quality image and inability to assess for presence of DISH.

### Radiological Assessment: Cobb Angle and DISH Definition

Using the scout CT of the spine (lateral view), Cobb angle[13] was calculated using a modified 6-point vertebral morphometry technique widely used for osteoporotic fracture assessment on radiographs.[14] Specifically, 3 points were placed on the superior endplate of the fourth thoracic (T4) vertebral body, and 3 on the inferior endplate of T12, corresponding to the midpoint and most anterior and posterior points of the vertebra. Linear regression was used to estimate the orientation of each endplate, and then orientation lines were superimposed over the image. Cobb angle was calculated as the angle between the intersecting orientation lines (Figure 1). Repeated Cobb angle measurements from 50 scans was reproducible (intraclass correlation coefficient = 0.9).[10]

DISH was assessed on the same scout CT scan. Prerequisites for the diagnosis of DISH included flowing calcification along the anterolateral aspect of at least 4 contiguous vertebral bodies (Figure 2)[2]; preservation of the intervertebral disc height, absence of severe degenerative disease in the involved

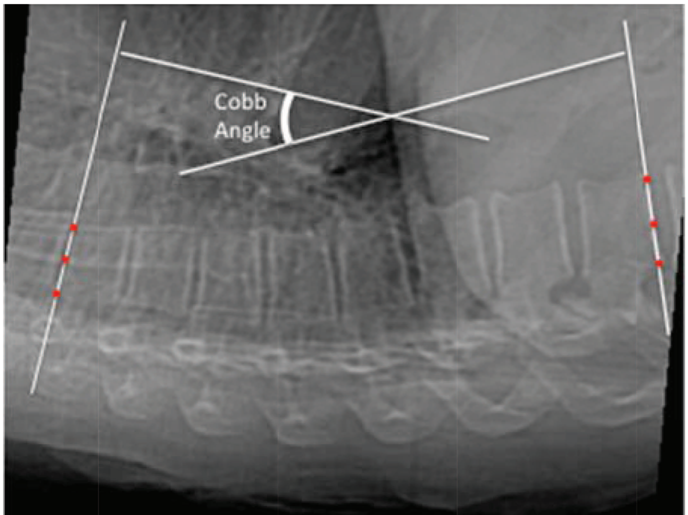


**Figure 1.** Lateral scout view of the spine. T4 and T12 were automatically detected and 3 points were placed on the superior endplate of T4 and the inferior endplate of T12 (red dots), corresponding to the anterior, middle, and posterior vertebra. Using linear regression to determine the best fit, these points were used to precisely draw 2 lines: 1 parallel to T4 vertebral body (T4) and 1 parallel to T12 vertebral body (T12); Cobb angle was calculated as the angle between these 2 lines.

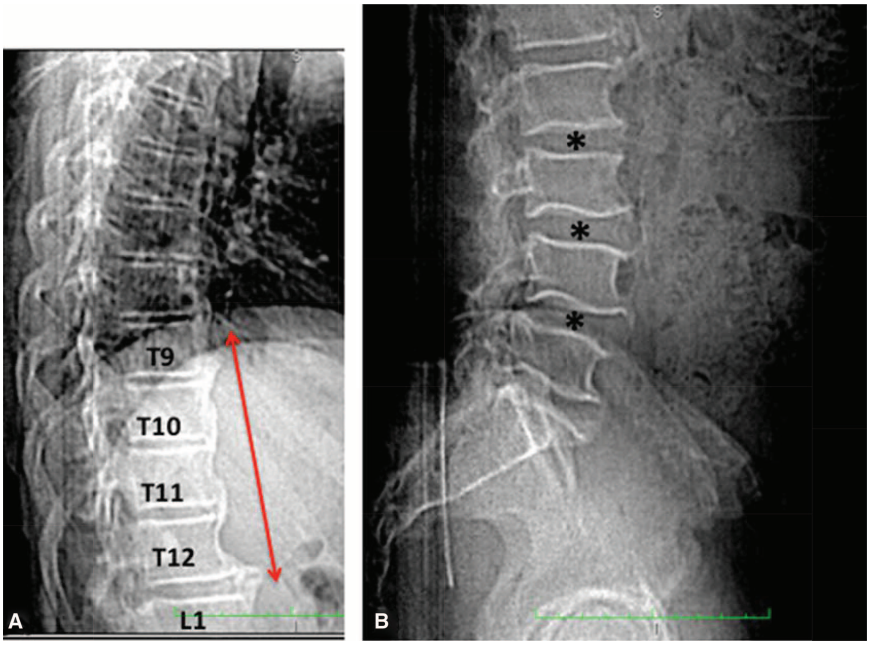


**Figure 2.** Lateral scout image. At the middle and lower thoracic spine, abnormal confluent hyperostosis (arrow) is noted in the anterior longitudinal ligaments from T9 to L1 (**A**); this finding is not present in the lumbar segment of the spine (**B**). The intervertebral disc spaces are relatively maintained (*) in both lumbar and thoracic spine. These findings are hallmarks of diffuse idiopathic skeletal hyperostosis.

vertebral segments[15]; and absence of apophyseal joint ankylosis, costovertebral joint fusion, sacroiliac joint erosions, or intra-articular osseous fusion in the synovial portion of the joints.[16]

### Reliability of DISH Readings

CT scans were studied by 2 musculoskeletal radiologists. For intra-rater reproducibility, the first reader studied all scans for DISH twice, 8 weeks apart. The second reader evaluated a random sample of 490 (43%) from each quartile of Cobb angle for inter-rater reproducibility. A senior rheumatologist (N.E.L.) was consulted in cases of disagreement or doubt. Intra- and inter-rater agreement determined by calculation of κ value was 0.9 and 95% confidence interval (95% CI) (0.8–0.9), and 0.6 and 95% CI (0.5–0.7), respectively.

### Statistical Methods

Characteristics of participants with and without the presence of DISH were assessed using the $\chi^2$ tests for categorical variables and *t* tests for continuous variables. The association between DISH and Cobb angle was analyzed using linear regression. β estimates and 95% confidence intervals (CI) were calculated for the difference in Cobb angle in participants with DISH compared with those without DISH. Analyses were also performed in subjects with DISH in the thoracic spine only and those with DISH in both the lumbar and thoracic spine (none had DISH localized only in the lumbar spine).

Statistical models were initially adjusted for age and then further adjusted for race and sex. We tested for an interaction of DISH and age, DISH and race, and DISH and sex. All subsequent analyses presented were stratified by race. To obtain final multivariable risk estimates for the association between Cobb angle and DISH stratified by race, we added covariates to models including age, sex, and BMD. Factors associated with DISH or Cobb angle at $P < 0.1$ were considered for inclusion in the final multivariable model (Table 1). Data collected from the study were compiled and analyzed using SAS software (version 9.2; SAS Institute Inc., Cary, NC).

## RESULTS

### Demographics

Among participants with DISH measurements (n = 1128), DISH was diagnosed in 152 subjects (13.5%) with 101 (66%) cases located in the thoracic spine and 51 (34%) in both the thoracic and lumbar regions (Table 1). Participants diagnosed with DISH were more likely to be males of older age, Caucasian, and have higher body mass index, lumbar paraspinal muscle density, hip BMD, and Cobb angle compared with those without DISH. Doctor-diagnosed gout and diabetes were more prevalent among participants with DISH compared with those without DISH (Table 1). There were no significant differences between DISH categories in self-reported prior vertebral fractures, gait speed, chair stands, and use of osteoporosis medication, $P > 0.05$.

### Association of DISH With Cobb Angle

There was a significant interaction of race and DISH with Cobb angle ($P$ for interaction = 0.003), and all analyses were subsequently stratified by race. The mean Cobb angle of kyphosis in the analytic sample was 31.3° (standard deviation = 11.2). In the model adjusted for age and sex, the presence of DISH among African Americans was associated with an increase in the Cobb angle of 8.9° and 95% CI (5.4–2.4) compared with those without DISH (Table 2). This association was strengthened to 9.4° and 95% CI (6.0–12.9) in models adjusted for hip BMD. The addition of other covariates to the model, including body mass index, diabetes, gout, and lumbar paraspinal muscle density, did

**TABLE 1. Baseline Characteristics**

| Baseline Characteristics | Patients With No DISH (N = 976) | Patients With DISH (N = 152) | *P* |
|---|---|---|---|
| **Mean ± SD** | | | |
| Age (yr) | 73.5 ± 2.9 | 74.2 ± 2.9 | 0.01 |
| Cobb Angle (°) | 31.0 ± 11.2 | 33.7 ± 10.8 | 0.006 |
| Gait speed (m/s) | 1.2 ± 0.3 | 1.2 ± 0.3 | 0.69 |
| Chair stands completed in 10 seconds (n) | 3.7 ± 1.1 | 3.8 ± 1.2 | 0.41 |
| BMI (kg/m$^2$) | 27.0 ± 4.4 | 28.8 ± 4.1 | <0.001 |
| Hip BMD (g/m$^2$) | 0.9 ± 0.2 | 1.1 ± 0.2 | <0.001 |
| Lumbar paraspinal muscle density (HU) | 23.7 ± 2.9 | 24.4 ± 2.9 | 0.007 |
| **N (%)** | | | |
| Caucasian | 539 (55.2) | 110 (72.4) | <0.001 |
| Males | 468 (47.9) | 131 (86.2) | <0.001 |
| Self-reported vertebral fractures | 24 (2.5) | 6 (4) | 0.28 |
| Self-reported gout | 81 (8.4) | 22 (14.5) | 0.02 |
| Diabetes | 169 (17.3) | 46 (30.3) | 0.001 |
| Osteoporosis medication use | 39 (4.0) | 3 (2.0) | 0.22 |

*m/s indicates meters/second; n, number; kg/m$^2$, kilograms/meter$^2$; HU, Hounsfield units; DISH, diffuse idiopathic skeletal hyperostosis; BMI, body mass index; BMD, bone mineral density; SD, standard deviation.*

not substantially alter the association between DISH and Cobb angle (Table 2).

The association of DISH with Cobb angle among Caucasians differed from that in African Americans (Table 2). In Caucasians, DISH was not significantly associated with Cobb angle in the age- and sex-adjusted model, however the results were statistically significant after further adjustment for hip BMD and the addition of clinical covariates (Table 2). Nevertheless, the magnitude of the association in African Americans, with a Cobb angle of 9.1° and 95% CI (5.6–12.6), was substantially higher than in Caucasians, Cobb angle of 2.9° and 95% CI (0.5–5.2), in the multivariate model.

### Location of DISH and Cobb Angle

The presence of DISH in the thoracic region alone was significantly associated with an increase in the Cobb angle of 10.6° and 95% CI (6.5–14.7) in African Americans and a Cobb angle of 3.75° and 95% CI (1.0–6.5) in Caucasians compared with those without DISH, adjusted for all covariates (Table 3). DISH in both the thoracic and lumbar regions was

**TABLE 2. Difference in Cobb Angle and Presence of DISH by Race**

| | Caucasians (N = 649) (110 Patients With DISH) Difference in Cobb Angle (95% CI) | African Americans (N = 479) (42 Patients With DISH) Difference in Cobb Angle (95% CI) |
|---|---|---|
| Base model | 1.8 (−0.5 to 4.1) | 8.9 (5.4–12.4) |
| Base + BMD | 2.7 (0.4–5.0) | 9.4 (6.0–12.9) |
| Multivariate model | 2.9 (0.5–5.2) | 9.1 (5.6–12.6) |

*Base model adjusted for age and sex.*

*Multivariate model adjusted for Base, BMI, total hip BMD, diabetes, gout, and lumbar paraspinal muscle density.*

*P for interaction for race and DISH in the base model = 0.003.*

*Note: There are 9 patients with missing lumbar paraspinal muscle density values. These include 8 patients without DISH and 1 with DISH. These are not included in the multivariate models.*

*CI indicates confidence interval; DISH, diffuse idiopathic skeletal hyperostosis; BMI, body mass index; BMD, bone mineral density.*

**TABLE 3. Difference in Cobb Angle With the Location of DISH by Race**

| | Caucasians | | African Americans | |
|---|---|---|---|---|
| | Thoracic only | Lumbar and thoracic | Thoracic only | Lumbar and thoracic |
| | 72 patients with DISH | 38 patients with DISH | 29 patients with DISH | 13 patients with DISH |
| | 539 patients with no DISH | 539 patients with no DISH | 437 patients with no DISH | 437 patients with no DISH |
| | Difference in Cobb angle (95% CI) | Difference in Cobb angle (95% CI) | Difference in Cobb angle (95% CI) | Difference in Cobb angle (95% CI) |
| Base model | 3.0 (0.3–5.7) | −0.5 (−4.1 to 3.1) | 10.5 (6.4–14.6) | 5.3 (−0.7 to 11.2) |
| Base + BMD | 3.7 (1.0–6.4) | 0.6 (−3.0 to 4.3) | 10.9 (6.8–14.9) | 6.1 (0.2–12.1) |
| Multivariate | 3.8 (1.0–6.5) | 0.9 (−3.0 to 4.7) | 10.6 (6.5–14.7) | 5.7 (−0.3 to 11.7) |

*Base model adjusted for age and sex.*
*Multivariate model adjusted for Base, total hip BMD, diabetes, gout, and lumbar paraspinal muscle density.*
*P for interaction with race and DISH location = 0.003.*
*Note: There are 9 patients with missing lumbar paraspinal density values. These include 8 without DISH and 1 with DISH. These are NOT included in the multivariate models.*
*CI indicates confidence interval; DISH, diffuse idiopathic skeletal hyperostosis; BMD, bone mineral density.*

not associated with Cobb angle in either African Americans or Caucasians in multivariate models (Table 3).

## DISCUSSION

We found an overall 13.5% prevalence of DISH, which was higher in Caucasians than in African Americans; however, the association of DISH with the Cobb angle of kyphosis was much stronger among the African American population. Our prevalence data were consistent with prior published studies where the prevalence of DISH varied from 4% to 52%, depending upon study population and the diagnostic criteria used to diagnose DISH. Most studies among males and females older than 50 years report 15% to 25% prevalence, whereas Holton described prevalence as high as 42%[17] in the Osteoporotic Fractures in Men Study. These discrepancies could be due to differences in race and sex of the populations studied or the criteria used to define DISH. First, the Osteoporotic Fractures in Men Study cohort is 90% Caucasian, however the Health ABC cohort is 57% Caucasian. Second, our Health ABC cohort includes both males and females, and females have lower prevalence of DISH. Also, we used the Resnick criteria[18] for defining DISH, and it requires ossifications within the anterior longitudinal ligament bridging at least 4 consecutive vertebral bodies, whereas other epidemiological studies of DISH used the Mata criteria that require incomplete bridging between only 2 vertebrae to make the diagnosis.[19] Thus, studies that use the Mata criteria tend to report a higher prevalence of DISH.[17]

We determined that DISH is associated with greater Cobb angle of kyphosis and hypothesize that the characteristic ossification of the anterior longitudinal ligament may alter the architecture of the spine and affect spinal curvatures. Spinal involvement of DISH is characterized by bridging ossification of the anterior longitudinal ligament that is normally separated from the anterior aspect of the vertebral body by a thin radiolucent line. In DISH, the ligament becomes virtually fused to the anterior aspect of the vertebral bodies, limiting the ability to straighten the spine. Ossification of the vertebral ligaments can be seen in a large number of diseases including chondrocalcinosis, acromegaly, ochronosis, hypophosphatemia, achondroplasia, and ankylosing spondylitis. In particular, in ankylosing spondylitis, there is ossification of the vertebral ligaments and fusion in the vertebrae resulting in a flexed-kyphotic posture. This ossification can be explained by alterations in the mineralization of the anterior longitudinal ligament, although the reasons for this mineralization are unknown. Recent studies in mice have determined that alteration in purine metabolism affects the regulation of biomineralization and results in ectopic mineralization of the paraspinal tissue that resembles DISH.[20] It has also been theorized that mesenchymal stem cells are responsible for ossification of the ligaments and tendons observed in DISH and ankylosing spondylitis.[20] Further investigation of these pathogenic pathways may help to explain the associations of DISH with kyphosis.

A stronger association between DISH and Cobb angle was demonstrated among African American participants than among Caucasian participants. Although the prevalence of DISH in our cohort is lower in African Americans, the impact of DISH on Cobb angle among African Americans seems to be greater. These discrepancies can be explained by anatomic differences between the 2 races. Whereas the anterior spinal ligament is histologically similar in both races, African Americans have considerably wider and thicker anterior spine ligaments compared with Caucasians.[21] The calcification of a wider and thicker ligament could have a greater effect on kyphosis than a narrower and thinner ligament. This hypothesis is supported by the study by Birnbaum *et al*,[22] that proposed that reported transection of the anterior longitudinal ligament from T3 to T7 in cadavers resulted in a mean 16° reduction of Cobb angle.

We demonstrated that when DISH is present in both thoracic (T4–T12) and lumbar (L1–L5) spine regions, Cobb angle is not significantly changed, however when DISH is present only in the thoracic spine it is associated with greater kyphosis. To explain this finding, the anatomy of the spine needs to be considered. Although the thoracic spine is characterized by a physiological kyphosis, an anterior curvature in the thoracic spine, the lumbar spine is characterized by a lordosis, a posterior curvature in the lumbar spine. Calcification of the anterior ligament of the lumbar spine may produce a force that contrasts that created by calcification of the thoracic spine ligament because of the opposing concave and convex natures of thoracic and lumbar spinal curvatures.

Although the "gold standard" measurement of kyphosis is Cobb angle from standing lateral spine radiographs, other measurements of kyphosis are used interchangeably.[23–25,26] We measured Cobb angle of kyphosis from supine CT scans because participants from the Pittsburgh site received these scans at baseline, and they had better resolution of vertebral body shape than lateral spine radiographs. Furthermore, a prior comparison of standing *versus* supine lateral spine radiographical measurements of Cobb angle of kyphosis reported that supine measurement underestimates the degree of kyphosis.[25] Standing measures were about 4° higher than supine measures, and this difference was greater among those with the most extreme kyphosis.[25] Although differences might be expected because supine measurement is not effected by gravity, among those with DISH, we would expect a more rigid spine less susceptible to differences in supine and standing measurement. Regardless, any reduction of Cobb angle in those with DISH would only underestimate our findings.

Therapeutic interventions may be considered to prevent or reduce kyphosis. Given the calcification of the anterior longitudinal ligament among individuals with DISH, novel interventions may be needed that address this abnormal mineralization of soft tissue adjacent to the vertebrae. Differences in response to targeted interventions to reduce kyphosis may depend upon the cause and warrants further investigation.

Our study is characterized by several limitations. First, selection bias may have been introduced because the Cobb angle data were available from 1 (Pittsburgh, PA) of the 2 clinical centers for Health ABC. Although this limited our potential sample size to 1172, inclusion criteria were the same for both sites and the prevalence of DISH in our study sample was similar to that reported in other studies with similar-aged participants. Second, Cobb angle was measured from supine scout CT, which is different from the standard Cobb angle measurement procedure from standing lateral spine radiographs; however, our measures of Cobb angle were very reproducible. Finally, the analysis was confined to well-functioning individuals aged 70 to 79 years and replication is needed to determine generalizability of the results in a more diverse population.

## CONCLUSION

DISH is associated with greater Cobb angle of kyphosis in the thoracic spine of older individuals. The association of DISH with Cobb angle is stronger within the African American population. These findings indicate that the presence of ossification within the anterior longitudinal ligament may alter the architecture of the spine and affect spinal curvatures. However, further investigation of this association in longitudinal studies is needed to learn whether the presence of DISH is a predictor of worsening kyphosis over time. Also, therapeutic interventions may be considered to prevent or reduce kyphosis, particularly among African Americans with thoracic DISH who may be at risk for increased Cobb angle of kyphosis.

### ➢ Key Points

- ❑ The prevalence of DISH is 13.5% in a cohort of well-functioning males and females aged 70 to 79 years.
- ❑ DISH is associated with greater Cobb angle of kyphosis in the thoracic spine of older individuals.
- ❑ The association of DISH with Cobb angle is stronger within the African American population.

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