When *Ankylosing Spondylitis* and *Takayasu Arteritis* walking into a bar named Syndesmophytes

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Abstract

Objectives

This study was to describe the characteristics of syndesmophytes in different inflammatory and non-inflammatory diseases aiming to reflect the aortic-vertebrae interaction.

Methods

We conducted a cross-sectional study including four group of patients, ankylosing spondylitis (AS, n=52), Takayasu's arteritis (TKA, n=31), diffuse idiopathic skeletal hyperostosis (DISH, n=30), coronary artery disease (CAD, n=100), and also age-matched healthy controls (HC, n=143). All subjects underwent a chest CT and images of the upper and lower border of seven adjacent thoracic vertebrae (T5 to T12) were captured. An ‘aorta ipsilateral ratio’ (AIR) of the syndesmophyte was calculated as the area crossed the midline toward aorta side divided by the total syndesmophyte area.

Results

The frequency of subjects with syndesmophyte and syndesmophyte counts increased with age across the board. Frequencies of syndesmophyte in AS and TKA were much higher than age-matched HCs. The AIRs were significantly elevated in AS, TKA and CAD compared with DISH or age-matched HCs. In addition, the AIR of patients with higher CRP levels (>8mg/L) were greater than that of those with lower levels, both among AS and CAD patients.

Conclusions

Our findings indicate that, in an inflammatory niche, regardless the origin or the grade of the inflammation, syndesmophyte formation will be facilitated and screwed toward aorta. There is a possible mechanistic connection between large vessel and new bone formation in the context of inflammation.

Introduction

Syndesmophytes are the new bone formation developed in the enthesis at the annulus bone junction of the vertebral body. Alike other oesteophytes, the formation of syndesmophytes is attributed to aging, mechanical stress and local inflammation; however, the precise pathophysiology remains to be clarified[1–4]

A well-conceived intriguing observation is that syndesmophytes are tend to spare the aorta side, as characterized in a non-inflammatory disease, diffuse idiopathic skeletal hyperostosis (DISH), with prominent continuous right-sided syndesmophytes away from aorta (left-sided)[5]. In a recent report using a semiautomated method based on CT scans, Tan S et al. illustrated that in ankylosing spondylitis (AS), syndesmophytes are also less frequent and smaller in the area of the vertebral rim adjacent to the aorta than in neighboring regions in the lower thoracic and upper lumbar spine[6]. This “aorta-privileged”

phenomenon was merit to the mechanical effects of aortic pulsations on the vertebrae and surrounding tissue[7,8] ,the specific mechanism, particularly in the context of inflammation, is yet to be explored.

In order to investigate this aortic-vertebral interaction, several disease models should be taken into consideration. First, enthesitis from the vertebral side which drives subsequent new bone formation through the process of tissue metaplasia[9] is a common knowledge in AS. Indeed, anti-inflammatory treatments such as tumor necrosis factor (TNF) inhibitors, interleukin-17 (IL-17) antagonists, and even non-steroidal anti-inflammatory drugs (NSAIDs) have shown the effects of retarding AS radiographic progression[10–13]. Second, Takayasu's arteritis (TKA) is a representative large-vessel vasculitis involving aorta and its branches. It will be a good candidate to evaluate the aortic-vertebral interaction from the aortic perspective. Moreover, coronary artery disease (CAD) is considered to be a chronic low-grade inflammatory disorder, as evidenced by CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) and COLCOT (Colchicine Cardiovascular Outcomes Trial) trials, showing anti-inflammatory approaches eventually mitigate cardiovascular events[14,15]. Therefore, CAD may serve as an excellent example to address our question.

With all these diseases on board, we hypothesized that inflammation originated either from the vertebral side or from the aortic side may facilitate syndesmophyte formation and leads to “aorta-privilege” breaching.

Methods

Participants and study design

We conducted a cross-sectional study including four group of patients, AS (n=52), TKA (n=31), DISH (n=30), and CAD (n=100). 143 healthy controls (HC) were also enrolled and subsequently divided into 2 groups (<=50 years of age vs. >50 years of age) to match different disease groups. All AS[16], TKA[17], DISH[18] patients fulfilled their respective classification criteria. All TKA patients were with thoracic aorta involvement confirmed by either CT angiography or magnetic resonance angiography or ^{18}F-FDG PET/CT. All CAD patients collected were those with a documented percutaneous coronary intervention (PCI) procedure. The disease duration was defined as the time since the diagnosis for AS and TKA, or the time since the first PCI for CAD. Patients with scoliosis or a history of thoracic vertebrae fractures were excluded. The data from all subjects, including age-matched HCs (from the health check-up center), were retrospectively collected via the electronic medical records system of Shanghai Renji Hospital (from 1 January 2013 to 31 May 2021). All participants willing to join the study gave written informed consent. This study was conducted based on the ethical guidelines of the 1975 Helsinki Declaration[19] and was approved by the ethics committee of Renji Hospital, Shanghai Jiao Tong University School of Medicine (2018093).

CT scanning and image analysis

All subjects underwent a chest CT with or without contrast using multidetector CT scanner (United Imaging, Shanghai, China). The CT slice thickness was 1.0 to 1.5mm at 10mm intervals. The non-enhanced images of the upper and lower rim of thoracic vertebrae, namely T5-T6, T6-T7, T7-T8, T8-T9, T9-T10, T10-T11 and T11-T12 were captured.

The syndesmophyte areas, if any, were measured at the aforementioned 14 slices. We further defined an 'aorta ipsilateral ratio' (AIR) of the syndesmophyte, calculated as the area crossed the midline toward aorta side divided by the total syndesmophyte area (Fig 1A). The segmentation of the area of syndesmophyte in a given slice was drawn manually and the AIR was calculated automatically by the picture archiving and communications system (PACS). Two trained readers (J.C. and L.G.) were participated independently. One of the readers was masked to diagnosis during imaging analysis and then cross-over. The measurement was highly replicable as the inter-rater agreement of the AIR readout between the two readers were excellent as measured by Cronbach's alpha test (p=0.998).

Statistical analysis

Syndesmophyte frequency (presence of syndesmophyte at any slice) and syndesmophyte count of all subjects with syndesmophyte were presented. Then non-parametric Mann Whitney U test was applied to compare AIR between groups. R programs were used for analysis (version 4.1.1). $P<0.05$ was considered statistically significant.

Results

The clinical characteristics of all 356 subjects were provided (Table 1). Of note, HLA-B27 was positive in 78.8% of AS patients and the mean ASDAS-CRP level was 2.97. Overall, 240 subjects (67.4%) had syndesmophytes on CT. The frequency of subjects with syndesmophyte and syndesmophyte count increased with age across the board. Frequencies of syndesmophyte in AS and TKA were much higher than age-matched HCs.

The median of AIR in DISH and HCs (both <=50 and >50 years of age) were zero which confirmed syndesmophytes predominance at right-sided spine, away from aorta (left sided). Interestingly, the AIR (median [quartile]) were significantly elevated in AS and TKA (0.247 [0, 0.485], 0.323 [0, 0.511], respectively) compared with age-matched HCs. Furthermore, the AIR of syndesmophytes in patients with CAD was also elevated compared with DISH or age-matched HCs (Fig. 1B). In subgroup analysis, AIR of subjects with higher CRP levels (>8mg/L) was greater than those with lower levels, both among AS and CAD patients (Fig. 1C).

Discussion

Our observation is based on and confirmatory to the notion that syndesmophytes of thoracic vertebrae spare aorta side ("aorta-privilege") in the aging general population and patients with DISH[5–7]. The novel finding is that whenever there is inflammation, regardless its origin either from vertebrae (AS) or aorta

(TKA), syndesmophyte formation will be facilitated and screwed more toward aorta side, as measured by AIR. Similar elevation of AIR was observed in CAD suggesting that low-grade inflammation might well follow this hypothetical rule. In addition, the effect is apparently ‘dose-dependent’ to the extent of inflammation, as measured by the level of CRP.

Our data help to shape the perception of vertebrae-aorta interaction. There is a conceptual interface or ‘matrix’ between vertebrae and aorta to maintain their independence and integrity (Figure 2). The ‘matrix’, constituted by connective tissues and stromal cells surrounding the bone and aorta, can be breached by inflammatory stimuli and switch on tissue remodeling. For example, adipocytes located in the enthesis at the annulus bone junction, orchestrated by TNFα and IL17, are crucial in terms of promoting syndesmophyte formation in AS[9,10]. Similarly, adventitia and periaortic fat tissue might be responsible for perpetuating inflammation and tissue remodeling in large vessel vasculitis and atherosclerosis[20,21]. It is known that with the Th1 and Th17-dominant immune response, up-regulation of interferon gamma (IFNγ), IL-6, IL-12 and IL-17 are evident in TKA[22,23], which might in turn exert impact on adjacent bone through aorta-vertebrae interface. Likewise, IL-1β might play a fundamental role in the scenario of atherosclerosis. Furthermore, in a latest milestone study, a secreted extracellular matrix protein, tenascin-C (TNC), is proved to be aberrantly induced by TNFα, IL17A and IL22 in ligament and entheseal tissues in AS patients. The inhibition of TNC could significantly suppress new bone formation both *in vitro* and *in vivo*[24,25]. Interestingly, TNC also actively participates in atherosclerotic plaque/aneurysm formation[26], which suggested that TNC might be a key molecule to align aorta-vertebrae remodeling.

The major limitation of this cross-sectional study was that the natural courses of syndesmophytes development in different diseases were unavailable. Only CT images were analyzed without other approaches such as MRI, which would be more sensitive to capture inflammation and fat tissue changes. The observation is descriptive; nevertheless, our data provide insights to better understand the possible connection between large vessel and bone in the context of inflammation.

Declarations

Competing Interests

The authors declare no competing interests.

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Tables

Table1 Subject characteristic

	HC≤50 (n=75)	AS (n=52)	TKA (n=31)	CAD (n=100)	DISH (n=30)	HC>50 (n=68)
Age, years	45.6±3.6	44.4±14.9	41.7±17.3	67.8±9.4	67.4±6.9	64±5.5
Male(%)	37(49.3)	34(65.4)	12(38.7)	70(70)	18(60)	33(48.5)
Duration of disease, months	/	8.9±8.8	39.5±72.1	4.5±20	NA	/
CRP (mg/L)	/	38.2±44.0	29.5±47.7	9.4±13.5	NA	/
Subjects with Syndesmophyte(%)	11(14.7)	41(78.8)	11(35.4)	90(90)	30(100)	57(83.8)
Syndesmophyte counts	52	231	84	447	192	361

Data are presented as either mean±SD or number (percent). HC, healthy control; AS, ankylosing spondylitis; TKA, Takayasu's arteritis; CAD, coronary artery disease; DISH, diffuse idiopathic skeletal hyperostosis. The disease duration was defined as the time since the diagnosis for AS and TKA, or the time since the first percutaneous coronary intervention for CAD.

Figures

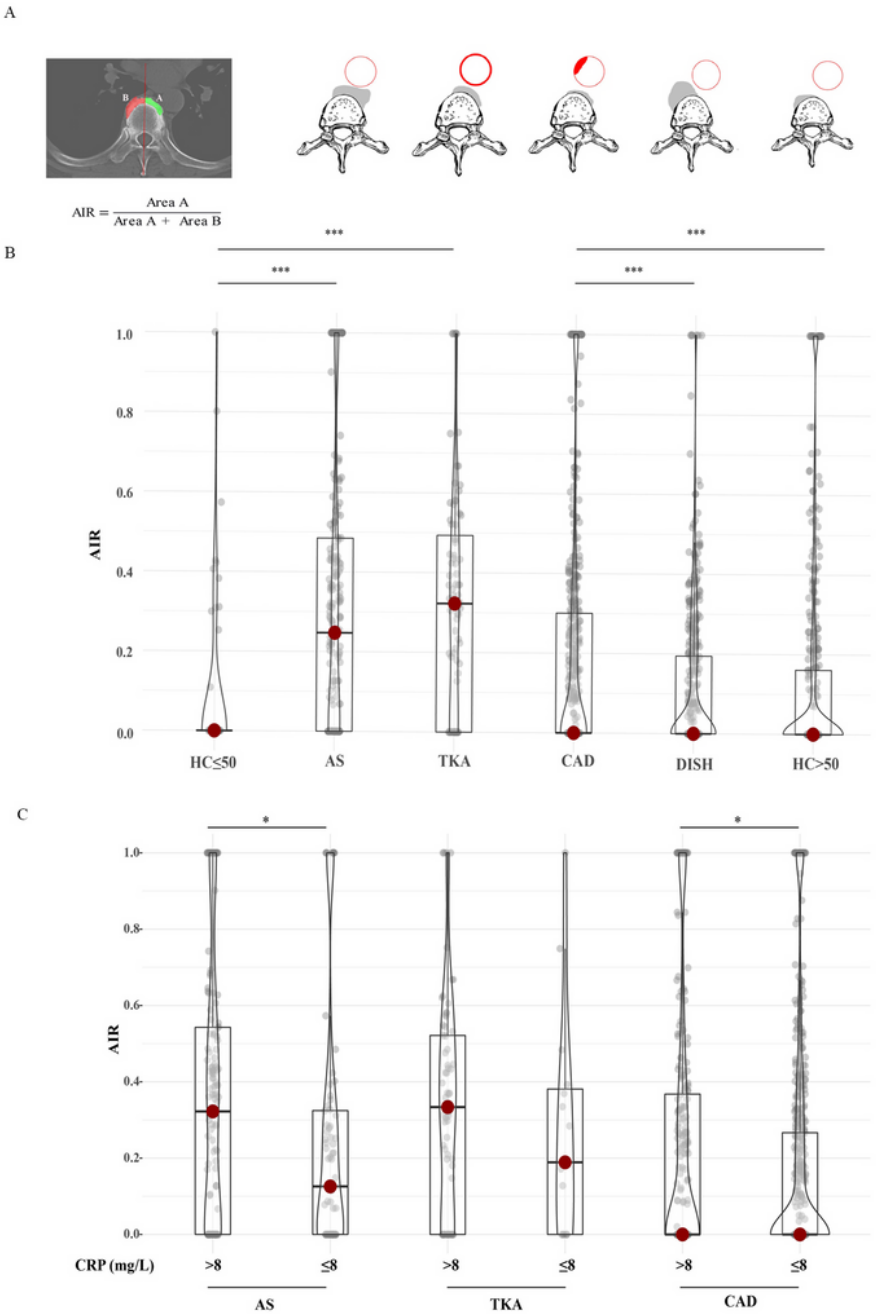

Figure 1

(A) Representative CT image with segmentation of syndesmophyte and the calculation of ‘aorta ipsilateral ratio’ (AIR). A set of cartoon representing the patterns of different disease or condition is also presented.

(B) Each dot represents the AIR of a given syndesmophyte. Values beyond 1 are rounding to 1.

(C) The AIR of syndesmophytes were elevated for AS and CAD patients with CRP >8mg/L compared to those with lower levels (p=0.015 and p=0.01, respectively).

Median and interquartile levels are shown. P values are calculated using non-parametric Mann Whitney U test. ***p<0.001,*p<0.05

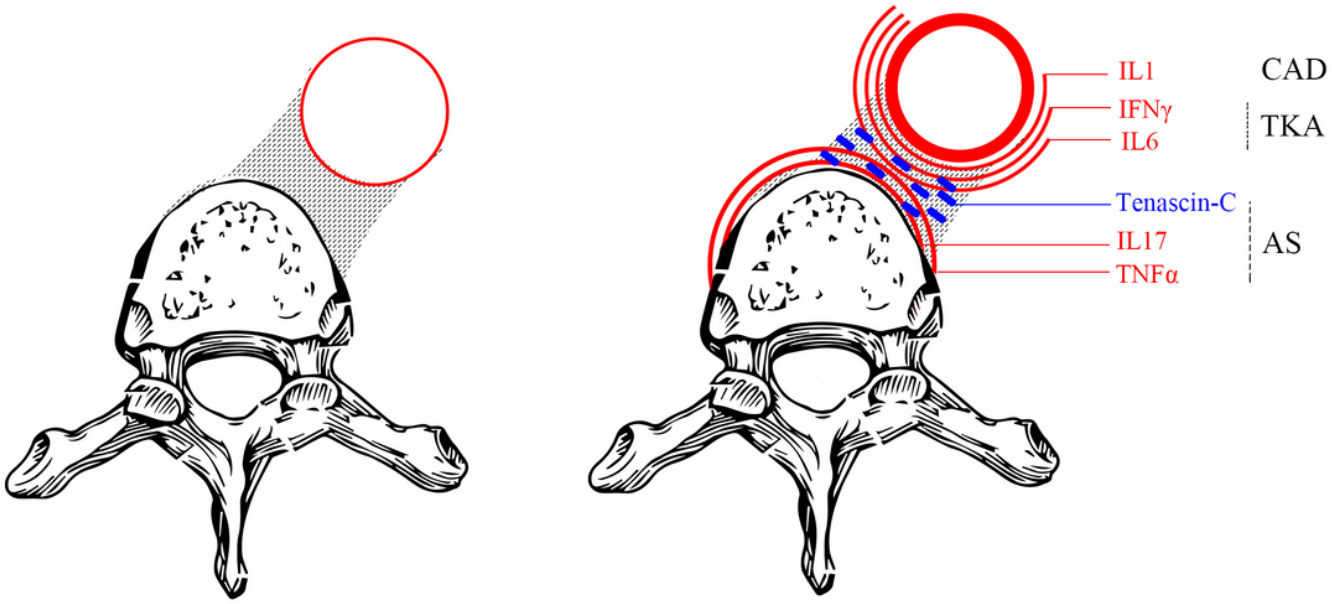

Figure 2

A schematic model represents a conceptual interface or ‘matrix’ between vertebrae and aorta (shadow area) which maintains their independence and integrity. Inflammatory stimuli can breach the ‘matrix’ and switch on tissue remodeling (right), facilitating symdesmophyte formation.