Calcified Tissue International (2019) 105:37–50
https://doi.org/10.1007/s00223-019-00542-z

ORIGINAL RESEARCH

Serum Sclerostin and Bone Morphogenetic Protein-2 Levels in Patients with Ankylosing Spondylitis: A Meta-Analysis

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Received: 20 December 2018 / Accepted: 16 March 2019 / Published online: 25 March 2019

Abstract

Various studies have investigated the serum sclerostin and bone morphogenetic protein-2 (BMP-2) levels in patients with ankylosing spondylitis (AS), but the results were inconsistent. The aim of this meta-analysis was to synthetically assess the associations of serum levels of sclerostin and BMP-2 with AS. Multiple electronic databases were searched to locate relevant articles published before November 2018. Pooled standard mean difference (SMD) with 95% confidence interval (CI) was calculated by the random-effect model. Totally, 21 studies were included. Meta-analysis results showed no significant difference between AS group and control group in serum sclerostin levels (SMD = 0.098, 95% CI − 0.395 to 0.591, $p = 0.697$). Nevertheless, serum BMP-2 levels in AS patients were higher than that in controls (SMD = 1.184, 95% CI 0.209 to 2.159, $p = 0.017$). Subgroup analysis demonstrated that European and South American AS patients had lower serum levels of sclerostin than controls. AS patients with age ≥ 40 years, erythrocyte sedimentation rate (ESR) ≤ 20 mm/h and Bath Ankylosing Spondylitis Functional Index (BASFI) < 4 had statistically significant lower serum sclerostin concentrations compared to controls. Chinese and Korean AS patients as well as patients with lower CRP had higher serum BMP-2 levels than controls, and country may be a source of heterogeneity across the studies. No publication bias existed and sensitivity analysis confirmed the stability of results. Serum BMP-2, but not sclerostin levels may be closely related to the development of AS.

Keywords Sclerostin · Bone morphogenetic protein-2 · Ankylosing spondylitis · Meta-analysis

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory autoimmune disease which predominantly involves the spinal column and sacroiliac joint [1]. AS is characterized by chronic inflammation and new bone growth which is usually associated with syndesmophyte formation and joint ankylosis, leading to restriction of mobility [2]. The existing relevant researches have made great progress, nevertheless, the exact pathogenesis of AS is not clear. Since new bone formation is confirmed to be the main cause of spinal deformity and function loss in AS, there has been substantial interest in investigating the role of biomarkers that are implicated in osteoblastogenesis, such as sclerostin and bone morphogenetic proteins (BMPs), in AS development [3, 4].

Sclerostin is primarily expressed and secreted by osteocytes and some terminally differentiated cells embedded within mineralized matrix such as cementocytes, chondrocytes, and osteocytes [5]. Sclerostin is regarded as a

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natural inhibitor of the Wnt/β-catenin signaling pathway, which plays a significant part in bone formation by regulating the development and differentiation of osteoblasts and osteoclasts [6]. Substantially, the activated Wnt proteins bind to the frizzled receptor and the low-density lipoprotein receptor-related protein 5 or 6 (LRP5/6), which makes part of β-catenin enter the cell nucleus and combine with the nuclear transcription factors, thus activating the transcription of downstream osteoblast-related genes and increasing bone formation [7]. Sclerostin is capable of competitively binding to LRP5/6, which restricts the Wnt proteins to reach LRP5/6, leading to the blocking of Wnt signaling pathway and consequently reducing the bone formation [6].

Bone morphogenetic proteins (BMPs), are crucial members of the transforming growth factor superfamily, which can induce embryonic development, cell lineage determination and osteoblastic differentiation [8]. Recombinant human BMPs have been demonstrated to be effective in enhancing bone healing and promoting spinal fusion [9]. BMP-2 is especially an important and active factor in the BMP family. BMP-2 is capable of independently inducing the expression of markers related to osteoblast and chondroblast differentiation by activating Smad signaling and regulating the transcription of osteogenic genes, thus promoting the formation of bone and cartilage [10, 11]. Furthermore, BMP-2 and Wnt/β-catenin signaling pathways have dependent and/or synergistic effects on regulating osteoblast differentiation and bone formation [12, 13]. BMP signaling regulates gene expression of the Wnt pathway, likewise, Wnt/β-catenin signaling can activate BMP-2 expression in osteoblasts [14].

Recently, the association of serum sclerostin or BMP-2 levels with AS have been investigated by plenty of studies, however, the results were inconsistent [4, 15–17]. Therefore, we conducted this meta-analysis to obtain the more comprehensive and accurate results quantificationally.

Materials and Methods

Publication Search

The current meta-analysis was carried out based on a standard guideline [18]. To obtain relevant publications, several electronic databases including PubMed, Medline, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), WANFANG (Chinese Database) and VIP (Chinese Database) were retrieved until November 2018. Search keywords and strategy were as follows: ("sclerostin" or "SOST" or "bone morphogenetic protein-2" or "bone morphogenetic protein2" or "BMP-2" or "BMP2") and ("ankylosing spondylitis" or "Bechterew's disease" or "AS"). The corresponding Chinese terms were adopted in Chinese databases. Furthermore, we manually reviewed the references cited in the related articles.

Inclusion Criteria and Exclusion Criteria

Included study must meet the following criteria: (1) used a case–control, cohort or cross-sectional design; (2) provided detailed data regarding serum concentrations of sclerostin or BMP-2 in AS patients and healthy controls; (3) published in English or Chinese. If there were duplicate studies in different publications, only one was selected according to the sample size and publication date.

Excluded points were (1) case reports, letters, editorials, meeting abstracts, reviews or other non-original articles, (2) studies without available or extractable requisite information, (3) animal or in vitro studies.

Literature Quality

The Newcastle-Ottawa Quality Assessment Scale (NOS) was used by two researchers (JY and SX) to independently assess and score the selected studies. NOS consists of eight questions with nine items which evaluate participants' selection, group comparability and ascertainment for the exposure. The NOS score ranges from 0 to 9, and a higher score means better quality in methodology.

Data Extraction

The following characteristics were collected from each eligible articles: name of first author, publication year, country, sample size, mean and standard deviation (SD) of serum sclerostin and BMP-2 levels in AS group and control group. When significant information was missing in the original articles, we tried to send an email to the corresponding authors for available data.

Statistical Analysis

Because of the discrepant units of serum sclerostin concentrations, the standardized mean difference (SMD) with its confidence interval (CI) was calculated for every study, and described by a forest plot. Mean values and standard deviations (SDs) were provided in most studies, but in a minority of articles, only the median values with maximum and minimum values or the median values with 25th and 75th percentiles were presented. In such case, we transformed initial data to the estimated mean and SD through the latest and accurate methods [19, 20] (http://www.comp.hkbu.edu.hk/~xwan/median2mean.html). Cochrane Q test (Chi square test, χ^2) and I^2 test ($I^2 = [(Q - \mathrm{df})/Q] \times 100\%$) were used to evaluate the statistical heterogeneity amongst the incorporated studies. The random-effect model was used if there

was significantly statistical heterogeneity ($p < 0.10$ for the Q test or $I^2 > 50\%$), otherwise the fixed-effect model was selected. To ascertain the source and effect of heterogeneity, we conducted subgroup analyses and meta-regression analyses. Begg's and Egger's tests were performed to detect the potential publication bias within studies. Sensitivity analysis was adopted to assess the reliability and robustness of the overall result if there was a high heterogeneity. All statistical analyses were carried out using Stata 14.0 (StataCorp, College Station, TX, USA) software. Statistical significance was set at a two-sided $p < 0.05$.

Results

Publication SEARCH and Study Characteristics

Initially, 327 publications were retrieved, of which 22 articles (included 17 articles for sclerostin [3, 15, 16, 21–34], four articles for BMP-2 [4, 17, 35, 36], and one article covers both sclerostin and BMP-2 [37]) met the inclusion criteria and were incorporated in the present meta-analysis (Fig. 1). Totally, 18 studies including 1186 AS patients and 719 controls researched the serum sclerostin levels, and five studies investigated the serum levels of BMP-2 in 300 AS patients and 155 controls. All the studies were published from 2008 to 2018. Patients were diagnosed with AS according to the modification of the New York criteria (19 studies) and Assessment of SpondyloArthritis International Society (ASAS) criteria (one study), and one study included AS

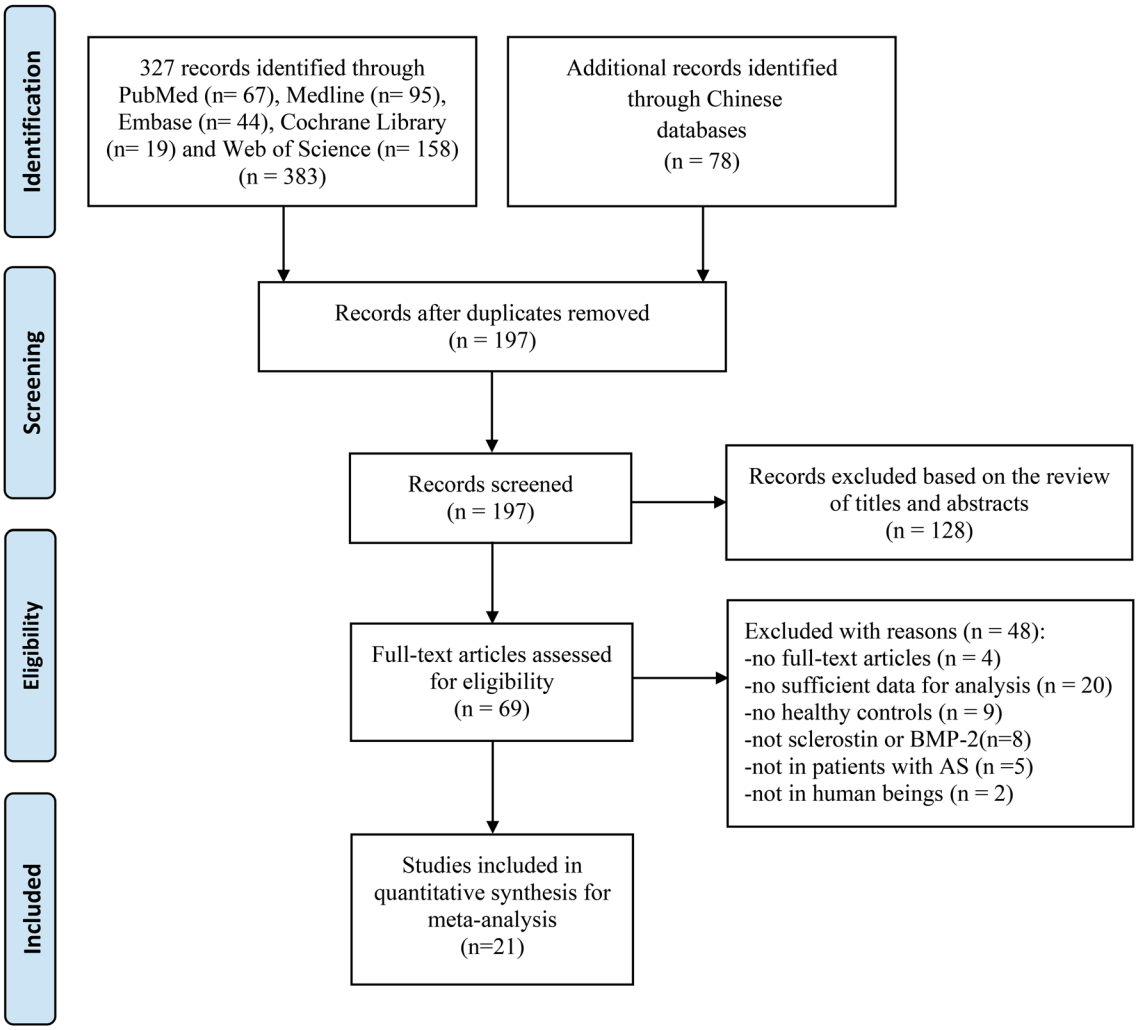

Fig. 1 Flow chart of the study selection process

patients based on their clinical and imaging characteristics. Serum levels of sclerostin and BMP-2 were measured by enzyme-linked immunosorbent assay (ELISA) in most studies except one with an enzyme immunoassay (EIA). The NOS scores of all studies ranged from 6 to 8, meaning the satisfactory quality in methodology. Table 1 details the general characteristics of all included studies.

Results of Meta-Analysis

Test of Heterogeneity

Significant heterogeneity was observed among the studies of sclerostin and BMP-2, respectively (sclerostin: $I^2 = 95.7\%$, $p < 0.001$; BMP-2: $I^2 = 94.7\%$, $p < 0.001$), thus the random-effect models were applied (Figs. 2, 3).

Overall Results

The overall pooled results indicated that there were no statistical difference in serum sclerostin concentrations between AS patients and controls (SMD = 0.098, 95% CI − 0.395 to 0.591, $p = 0.697$) (Fig. 2). Nevertheless, AS group had significant higher serum levels of BMP-2 compared to control group (SMD = 1.184, 95% CI 0.209 to 2.159, $p = 0.017$) (Fig. 3).

Subgroup Analysis

For sclerostin, we carried out the subgroup analyses based on region, age, erythrocyte sedimentation rate (ESR), C-reaction protein (CRP), bath ankylosing spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), modified stoke ankylosing spondylitis spinal score (mSASSS) and ELISA kit, and the results are shown in Table 2. In Europe and South America, AS patients had lower serum levels of sclerostin than controls (Fig. 4). Furthermore, in the subgroups of age ≥ 40 years, ESR ≤ 20 mm/h as well as BASFI < 4, serum sclerostin concentrations in AS group were significantly lower than that in control group. Additionally, in CRP ≤ 10 mg/L subgroup, marginally significant difference existed in serum sclerostin levels between AS patients and controls. In addition, serum levels of sclerostin were not different between AS group and control group when using kits from Biomedica, R&D Systems and BD Biosciences. However, when using kits from AUROGENE srl, ICL Lab Inc, TECO*medical*, NovaTeinBio and from Rapidbio, serum sclerostin levels in AS patients were strikingly lower as compared with controls.

Regarding BMP-2, due to the limited number of studies and the lack of some data, subgroup analyses by country and CRP stratification were performed. The results showed that both Chinese and Korean patients with AS had significantly higher serum BMP-2 levels when compared to controls, and country may be a source of heterogeneity for the studies (Fig. 5). In addition, serum levels of BMP-2 in AS patients were higher than that in controls in the lower CRP subgroup rather than the higher CRP subgroup.

Random-Effects Meta-Regression Analyses

Meta-regression analyses were implemented to further detect the sources of heterogeneity for the studies on sclerostin. Publication year, total sample size and NOS score were respectively incorporated as covariates, however, none of them could explain for the heterogeneity of studies (Table 3).

Publication Bias and Sensitivity Analyses

Both egger's and Begg's tests showed no statistically significant publication bias whether across the overall studies or subgroup studies (all $p > 0.05$, Table 2). Sensitivity analyses suggested that the pooled results did not significantly alter when the data of any single study are deleted in turn, indicating the overall effect sizes of the included studies were robust (data not shown).

Discussion

Sclerostin emerges as a potent negative regulator of bone formation [23], while BMP-2 is an important promoting factor for osteogenesis and cartilage homeostasis [4]. Previous studies reported that sclerostin antibody administration to ovariectomized rats resulted in increased bone growth, bone mineral density and bone mass, and the increment of exogenous sclerostin suppressed differentiation and proliferation of human and mouse osteoblastic cells [38, 39]. Wildemann et al. demonstrated that BMP-2 had a powerful role in inducing the transformation of mesenchymal cells into osteoblasts [40]. Katagiri et al. held the view that implantation of BMP-2 into muscular tissues induced ectopic bone formation at the implantation site [41]. Literature evidence indicated that the cycles of bone resorption coupled with subsequent bone formation were typical processes during the development of AS [42]. Multiple studies have investigated the association of serum sclerostin or BMP-2 levels with AS, nevertheless, the results were discrepant. Hence, we conducted the present meta-analysis to probe into the role of serum levels of sclerostin and BMP-2 in AS development.

Seventeen studies as for sclerostin were included in this meta-analysis. The pooled results revealed that serum sclerostin levels in AS patients were not significant different with that in healthy controls. This result is similar to the result previously reported by Shi et al. who conducted a meta-analysis synthesized seven studies, but they only retrieved English articles from limited databases, and did not

Table 1 Characteristics of including studies regarding serum sclerostin and BMP-2 levels of AS

References	Year	Country	Cases			
			N	Age (years), mean ± SD	Sex ratio (M/F)	Mean ± SD (pg/ml)/(pmol/L)
Sclerostin						
Perrotta et al	2018	Italy	40	49.72 ± 3.77	30/10	7.41 ± 5.07
Genre et al	2018	Spain	119	44.9 ± 11.9	73/46	350 ± 110
Luchetti et al	2018	Italy	20	NA	NA	126.4 ± 36.93
Sun et al	2018	China	88	36.5 ± 13.5	66/22	106 ± 6.75
Niu et al	2017	China	6	54.0 ± 19.1	5/1	368.7 ± 143.9
Tian et al	2017	China	58	36.5 ± 13.5	38/20	65.9 ± 21.7
Lu et al	2017	China	54	39.2 ± 1.3	51/3	353.4 ± 37.2
Sakellariou et al	2016	Greece	57	39.1 ± 1.4	53/4	357.4 ± 280.85
Rossini et al	2015	Italy	71	44.01 ± 12	59/12	25.2 ± 79.21
Xie et al	2015	China	75	37.3 ± 11.8	67/8	55.6 ± 23.4
Chen et al	2015	China	47	37.62 ± 8.34	39/8	51.93 ± 22.13
Klingberg et al	2014	Sweden	204	48.90 ± 11.13	87/117	35.66 ± 31.64
Tuylu et al	2014	Turkey	94	42.23 ± 9.29	65/29	137.97 ± 113.80
Ustun et al	2014	Turkey	44	40.06 ± 9.51	34/10	427.69 ± 368.10
Korkosz et al	2013	Poland	78	35.72 ± 69.07	NA	293.33 ± 634.61
Taylan et al	2012	Turkey	55	36.66 ± 9.21	48/7	75.31 ± 17.11
Saad et al	2012	Brazil	30	35.70 ± 11.00	24/6	60.5 ± 32.7
Appel et al	2009	Germany	46	NA	30/16	240.78 ± 1083.12
BMP-2						
Liao et al	2017	China	72	36.82 ± 11.67	58/14	121.53 ± 63.05
Xie et al	2015	China	21	35.3 ± 12.5	14/7	60.12 ± 8.63
Chen et al	2015	China	47	37.62 ± 8.34	39/8	352.83 ± 123.09
Chen et al	2010	China	120	35.65 ± 10.67	97/23	92.3 ± 164.0
Park et al	2008	Korea	40	31.4 ± 10.1	34/6	109.7 ± 26.4

References	Year	Country	Control				*p*	Criteria for diseases	Measurement	NOS
			N	Age (years), mean ± SD	Sex ratio (M/F)	Mean ± SD (pg/ml)/(pmol/L)				
Sclerostin										
Perrotta et al	2018	Italy	20	NA	15/5	18.59 ± 8.30	< 0.01	New York (1984)	ELISA	7
Genre et al	2018	Spain	63	50.9 ± 15.3	28/35	430 ± 170	< 0.05	New York (1984)	ELISA	6
Luchetti et al	2018	Italy	20	NA	NA	263.6 ± 75.5	< 0.001	ASAS criteria	ELISA	6
Sun et al	2018	China	26	NA	NA	62.78 ± 6.39	< 0.05	New York (1984)	ELISA	7
Niu et al	2017	China	9	55.9 ± 15.9	2/7	261.1 ± 111.4	NS	Clinical features	ELISA	7
Tian et al	2017	China	25	NA	16/9	51.2 ± 25.7	0.0349	New York (1984)	ELISA	6
Lu et al	2017	China	31	38.7 ± 2.0	30/1	271.4 ± 16.8	0.518	New York (1984)	ELISA	7
Sakellariou et al	2016	Greece	34	38.8 ± 1.0	32/2	276.4 ± 103.79	NS	New York (1984)	ELISA	7
Rossini et al	2015	Italy	71	NA	59/12	38 ± 144.93	< 0.001	New York (1984)	EIA	8

Table 1 (continued)

References	Year	Country	Control					Criteria for diseases	Measurement	NOS
			N	Age (years), mean ± SD	Sex ratio (M/F)	Mean ± SD (pg/ml)/(pmol/L)	*p*			
Xie et al	2015	China	70	NA	61/9	84.7 ± 32.5	< 0.01	New York (1984)	ELISA	7
Chen et al	2015	China	25	36.24 ± 9.98	19/6	75.45 ± 28.57	< 0.001	New York (1984)	ELISA	7
Klingberg et al	2014	Sweden	80	47.61 ± 10.75	26/54	37.71 ± 17.68	0.014	New York (1984)	ELISA	7
Tuylu et al	2014	Turkey	68	44.2 ± 10.6	48/20	151 ± 158	NS	New York (1984)	ELISA	8
Ustun et al	2014	Turkey	41	NA	32/9	656.32 ± 643.51	0.037	New York (1984)	ELISA	7
Korkosz et al	2013	Poland	23	32.3 ± 35.97	NA	120 ± 431.62	NS	New York (1984)	ELISA	6
Taylan et al	2012	Turkey	33	38.21 ± 6.01	24/9	77.56 ± 14.67	0.2	New York (1984)	ELISA	7
Saad et al	2012	Brazil	30	35.70 ± 11.00	24/6	96.7 ± 52.9	0.002	New York (1984)	ELISA	7
Appel et al	2009	Germany	50	NA	33/17	522.26 ± 1,097.92	< 0.05	New York (1984)	ELISA	7
BMP-2										
Liao et al	2017	China	30	NA	24/6	77.43 ± 37.37	0.004	New York (1984)	ELISA	7
Xie et al	2015	China	20	NA	NA	57.13 ± 11.09	0.509	New York (1984)	ELISA	7
Chen et al	2015	China	25	36.24 ± 9.98	19/6	257.93 ± 104.11	0.01	New York (1984)	ELISA	7
Chen et al	2010	China	40	34.8 ± 9.4 ± 9.4	36/4	49.4 ± 20.3	0.07	New York (1984)	ELISA	8
Park et al	2008	Korea	40	31.9 ± 8.8	34/6	32.1 ± 9.6	< 0.01	New York (1984)	ELISA	7

BMP-2 bone morphogenetic protein-2; *AS* ankylosing spondylitis; *N* number of studies; *M/F* male/female; *NA* not available; *NS* no significant difference; *ASAS* Assessment of Spondyloarthritis International Society; *ELASA* enzyme-linked immunosorbent assay; *EIA* enzyme immunoassay; *NOS* Newcastle–Ottawa scale

implement further subgroup analyses [43]. The current study that included more studies had a large sample size and high statistical power. Subgroup analysis indicated that in Europe and South America, AS patients had lower serum sclerostin levels than controls, but there were no difference in serum levels of sclerostin between AS patients and controls in Asia, suggesting that region may have influence on the serum sclerostin levels. Indeed, populations from different regions have different physical qualities, genetic and environmental characteristics, and all of these may be associated with serum levels of sclerostin. Furthermore, AS is a complex autoimmune disorder involving a series of complicated pathological processes which include but are not limited to bone resorption and formation, and sclerostin mainly regulates the processes of bone remodeling [44]. In addition, one pivotal point should be noted that although sclerostin plays an important regulatory role in the osteogenesis process mediated by the Wnt/β-catenin signaling pathway, it is only one of many Wnt inhibitors. Dickkopf-1 (Dkk-1), another potent antagonist of Wnt signaling, has been proven to be implicated in the pathogenesis of AS [45]. Multiple lines of evidence have shown that the low levels of DKK-1 could lead to the overexpression of Wnt, thus inducing the new bone formation in AS [46, 47]. Diarra et al. [48] observed that by inhibiting DKK-1, the bone-destructive pattern of a mouse model of rheumatoid arthritis could be reversed to the bone-forming pattern of osteoarthritis, which suggested the effect of DKK-1 on regulating bone remodeling. Sclerostin cooperates with other inhibitors of Wnt signaling to involve in AS progression, and the amount of sclerostin in serum may be influenced by Dkk-1 [26]. Based on the above-mentioned issues, no significant difference in serum sclerostin levels between AS patients and healthy controls might be observed.

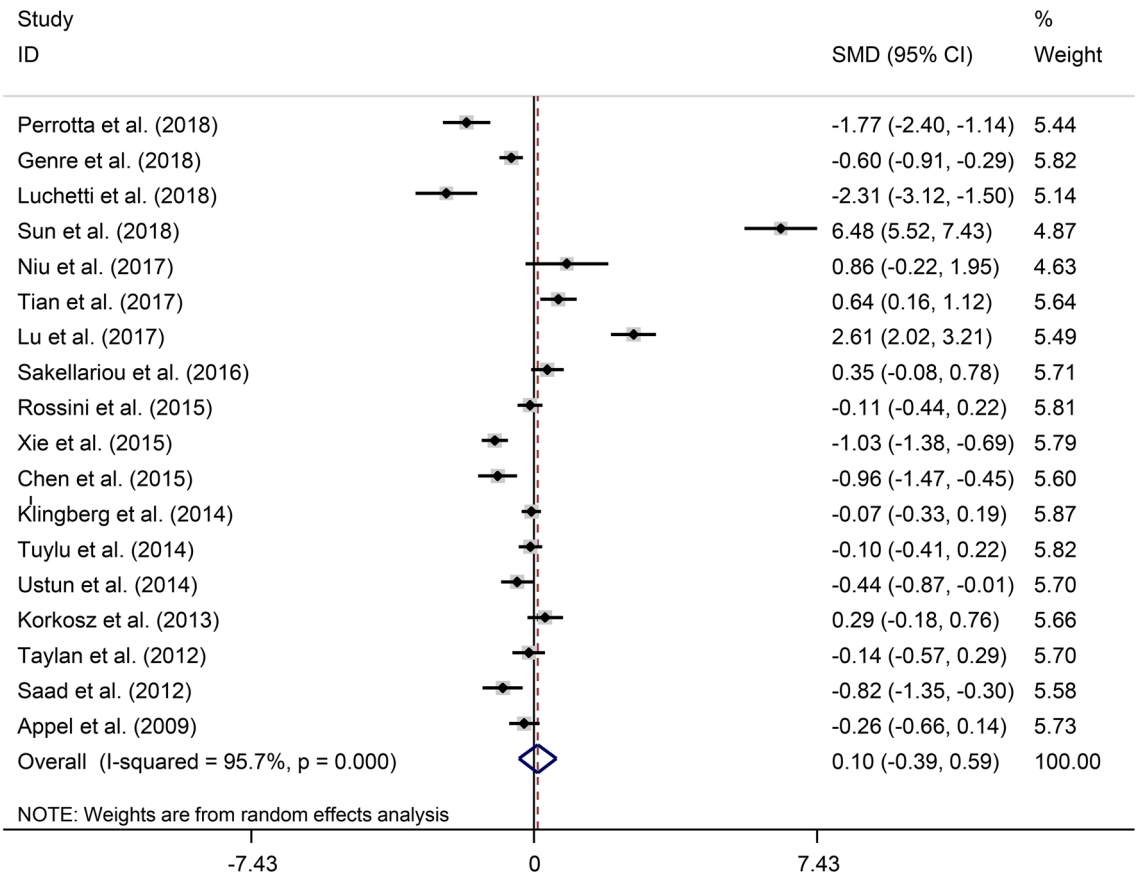

Fig. 2 Forest plot for AS patients versus healthy controls based on sclerostin serum levels

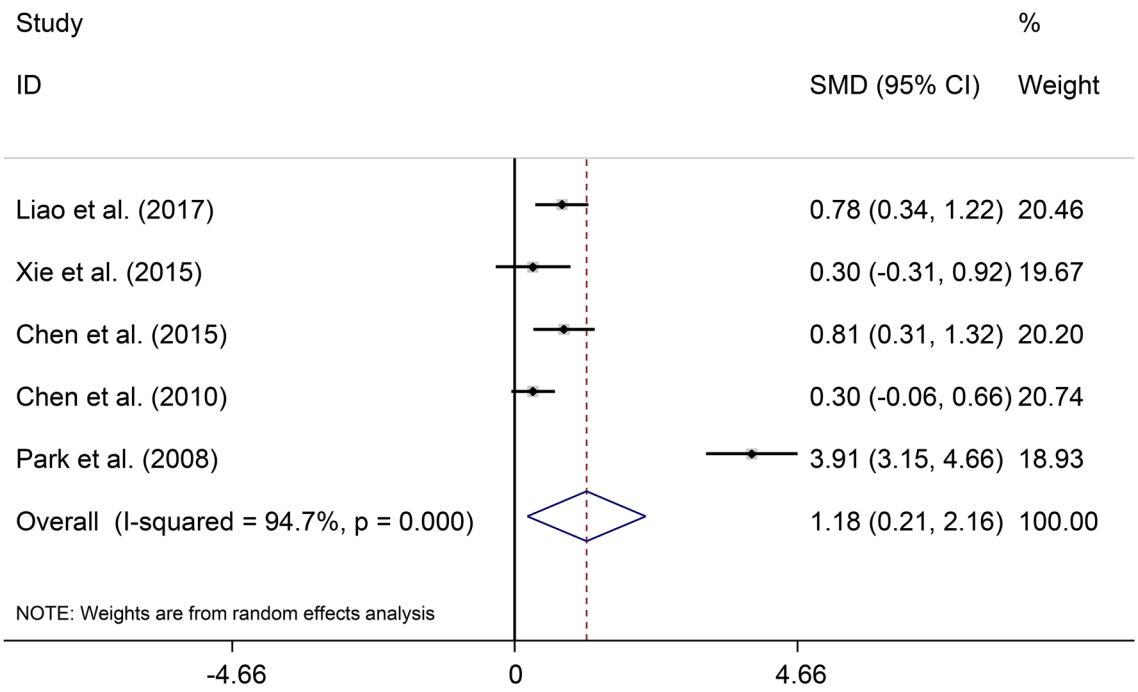

Fig. 3 Forest plot for AS patients versus healthy controls based on BMP-2 serum levels

Table 2 Subgroup analysis of serum sclerostin and BMP-2 levels of AS

Subgroups	N	SMD (95% CI)	*z*	*p*	Heterogeneity test		Egger's test		Begg's test	
					I^2 (%)	*p*	*t*	*p*	*z*	*p*
Sclerostin										
Region										
Europe	**8**	**− 0.482 (− 0.922 to − 0.042)**	**2.15**	**0.032**	89.6	<0.001	− 1.71	0.139	0.87	0.386
Asia	9	0.827 (− 0.167 to 1.821)	1.63	0.103	97.4	<0.001	2.47	0.059	1.77	0.076
South America	**1**	**− 0.823 (− 1.351 to − 0.295)**	**3.06**	**0.002**	NA	NA	NA	NA	NA	NA
Combined	18	0.098 (− 0.395 to 0.591)	0.39	0.697	95.7	<0.001	1.25	0.229	0.23	0.820
Age (mean, years)										
< 40	9	0.776 (− 0.242 to 1.795)	1.49	0.135	97.5	<0.001	1.80	0.122	1.56	0.118
≥ 40	**7**	**− 0.362 (− 0.720 to − 0.004)**	**1.98**	**0.048**	83.0	<0.001	− 0.56	0.601	0.30	0.764
Combined	16	0.261 (− 0.266 to 0.787)	0.97	0.332	95.9	<0.001	1.84	0.087	0.86	0.392
ESR (mean, mm/h)										
≤ 20	**6**	**− 0.626 (− 1.043 to − 0.209)**	**2.94**	**0.003**	95.0	<0.001	− 2.19	0.093	1.50	0.133
> 20	5	0.448 (− 0.514 to 1.410)	0.91	0.361	87.8	<0.001	1.10	0.353	− 0.24	1.000
Combined	11	− 0.164 (− 0.639 to 0.312)	0.67	0.500	93.6	<0.001	0.50	0.628	0.00	1.000
CRP (mean, mg/L)										
≤ 10	**5**	**− 0.204 (− 0.407 to − 0.000)**	**1.96**	**0.050**	50.0	0.092	− 0.16	0.884	0.73	0.462
> 10	7	− 0.120 (− 1.005 to 0.766)	0.26	0.791	96.0	<0.001	0.74	0.494	0.00	1.000
Combined	12	− 0.159 (− 0.583 to 0.266)	0.73	0.464	93.0	<0.001	0.47	0.649	0.21	0.837
BASDAI										
< 4	7	− 0.343 (− 0.690 to 0.004)	1.94	0.053	84.7	<0.001	− 1.40	0.221	0.90	0.368
≥ 4	4	0.477 (− 0.809 to 1.762)	0.73	0.467	96.2	<0.001	1.11	0.382	0.34	0.734
Combined	11	− 0.077 (− 0.511 to 0.358)	0.35	0.729	92.5	<0.001	0.39	0.705	0.31	0.755
BASFI										
< 4	**5**	**− 0.488 (− 0.932 to − 0.044)**	**2.15**	**0.031**	85.6	<0.001	− 1.66	0.196	0.73	0.462
≥ 4	3	0.707 (− 1.083 to 2.496)	0.77	0.439	97.3	<0.001	0.54	0.685	0.00	1.000
Combined	8	− 0.075 (− 0.699 to 0.548)	0.24	0.813	94.5	<0.001	0.42	0.690	0.12	0.902
mSASSS										
< 20	4	1.184 (− 0.881 to 3.249)	1.12	0.261	98.6	<0.001	0.82	0.499	0.34	0.734
≥ 20	5	0.205 (− 0.824 to 1.234)	0.39	0.696	96.0	<0.001	0.53	0.631	0.24	0.806
Combined	9	0.614 (− 0.319 to 1.548)	1.29	0.197	97.4	<0.001	1.25	0.252	0.31	0.754
ELISA kit										
Biomedica	5	0.972 (− 0.270 to 2.214)	1.53	0.125	97.9	< 0.001	1.54	0.222	0.73	0.462
R&D systems	4	0.956 (− 0.326 to 2.238)	1.46	0.144	95.1	< 0.001	0.77	0.521	1.02	0.308
BD biosciences	2	− 0.045 (− 0.819 to 0.729)	0.11	0.910	84.6	< 0.001	0.00	1.000	0.00	1.000
Other kits	**6**	**− 1.010 (− 1.592 to − 0.428)**	**3.40**	**0.001**	89.4	< 0.001	0.22	0.836	1.50	0.133
Combined	17	0.115 (− 0.419 to 0.649)	0.42	0.673	95.9	< 0.001	1.24	0.234	0.37	0.711
BMP-2										
Country										
China	**4**	**0.543 (0.259 to 0.828)**	**3.74**	**< 0.001**	33.3	0.212	0.38	0.743	− 0.34	1.000
Korea	**1**	**3.907 (3.153 to 4.660)**	**10.16**	**< 0.001**	NA	NA	NA	NA	NA	NA
Combined	**5**	**1.184 (0.209 to 2.159)**	**2.38**	**0.017**	94.7	< 0.001	1.89	0.155	1.22	0.221
CRP (mean, mg/L)										
≤ 10	**2**	**0.521 (0.056 to 0.986)**	**2.20**	**0.028**	62.9	0.101	0.00	1.000	0.00	1.000
> 10	1	0.302 (− 0.314 to 0.918)	0.96	0.337	NA	NA	NA	NA	NA	NA
Combined	**3**	**0.466 (0.144 to 0.787)**	**2.84**	**0.004**	33.3	0.223	0.08	0.950	0.00	1.000

BMP-2 bone morphogenetic protein-2; *AS* ankylosing spondylitis; *N* number of studies; *SMD* standardized mean difference; *CI* confidence interval; *NA* not available; *ESR* erythrocyte sedimentation rate; *CRP* C-reaction protein; *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index; *BASFI* Bath Ankylosing Spondylitis Functional Index; *mSASSS* modified stoke ankylosing spondylitis spinal score; *ELISA* enzyme-linked immunosorbent assay

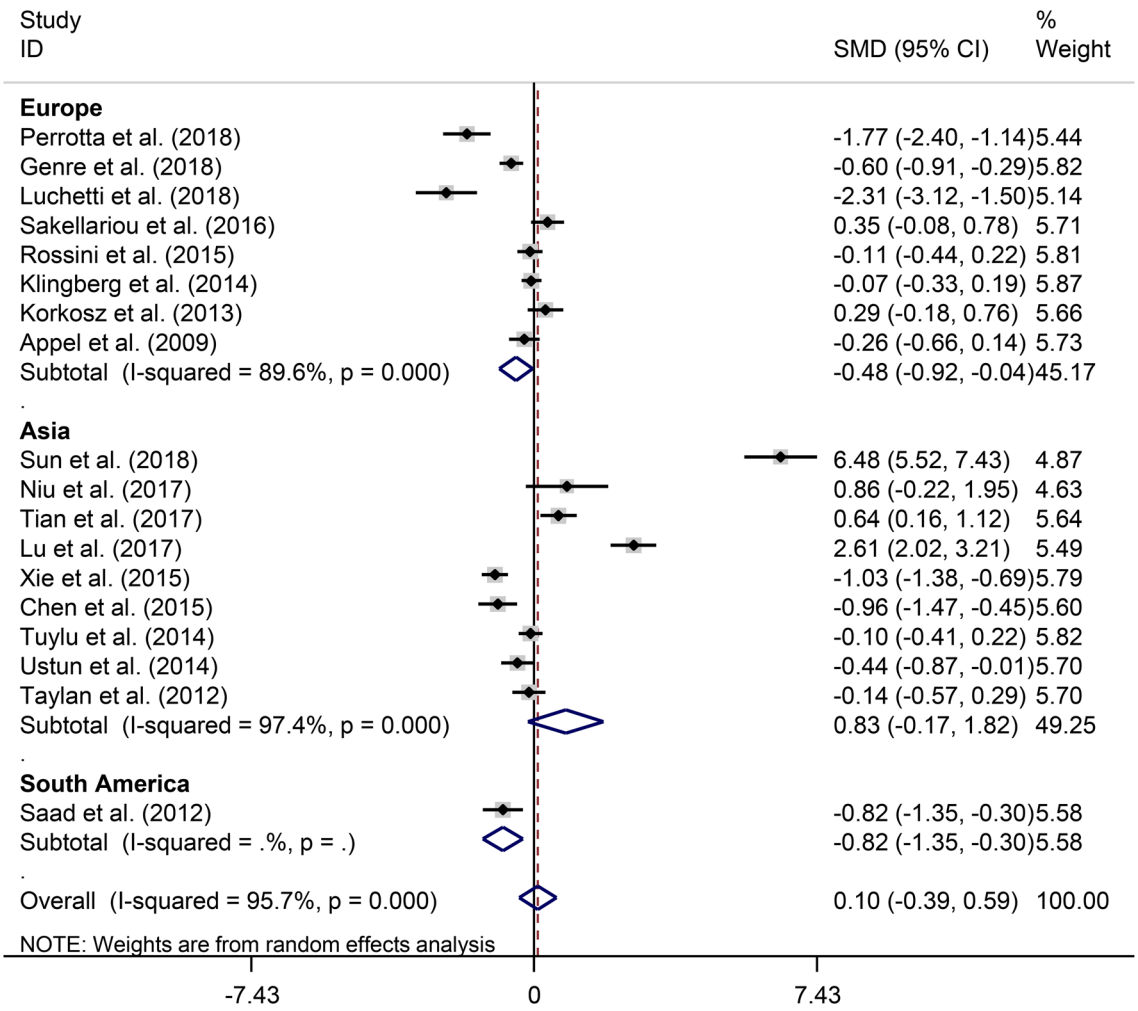

Fig. 4 Forest plot of subgroup analysis for AS patients versus healthy controls stratified by region for serum sclerostin levels

Analysis stratified by age showed that in the subgroup of age ≥ 40, serum levels of sclerostin in AS cases were lower than that in controls, suggesting that age may be associated with serum sclerostin of AS patients. Sakellariou et al. and Lu et al. have demonstrated a negative correlation between serum sclerostin levels with age in patients with AS [16, 25]. Interestingly, serum sclerostin levels have been revealed to significantly increase with age in healthy individuals [49]. However, age only accounted for a very small fraction of inter-individual variation in serum sclerostin [49]. Luchetti et al. [50] presented that the duration of articular symptoms was negatively associated with sclerostin. Hence, It can be inferred that a long-standing disease may have an effect on the sclerostin levels which is likely to be greater than the effect of age on sclerostin. In addition, stratification analyses manifested that AS patients with normal ESR (ESR ≤ 20 mm/h), lower CRP (CRP ≤ 10 mg/L) as well as lower BASFI (BASFI < 4) had lower serum concentrations of sclerostin when compared with healthy controls, revealing that ESR, CRP and BASFI may be correlated with serum sclerostin levels. ESR and CRP are widely used to evaluate systemic inflammation. Multiple studies have reported the association between sclerostin and inflammation. Plasma/serum concentrations of sclerostin were reported to be positively correlated with tumor necrosis factor (TNF)-α [51, 52], a pro-inflammatory cytokine associated with AS [53]. A recent study showed that TNF-α could increase the protein expression of SOST gene via regulating NF-κB signaling pathway [54]. BASFI is the admitted parameter to assess functional ability for AS patients [55]. Numerous studies have reported that anti-inflammatory therapy can give rise to a remarkable improvement on BASFI [56, 57]. In addition, Muntean et al. [58] revealed a positive correlation between serum sclerostin levels and BASFI values. Therefore, we speculated that serum sclerostin levels have a potential role in assessing inflammation and functional status in AS. Additionally, the results differed when different ELISA kits were used, suggesting that different immunoassay kits can

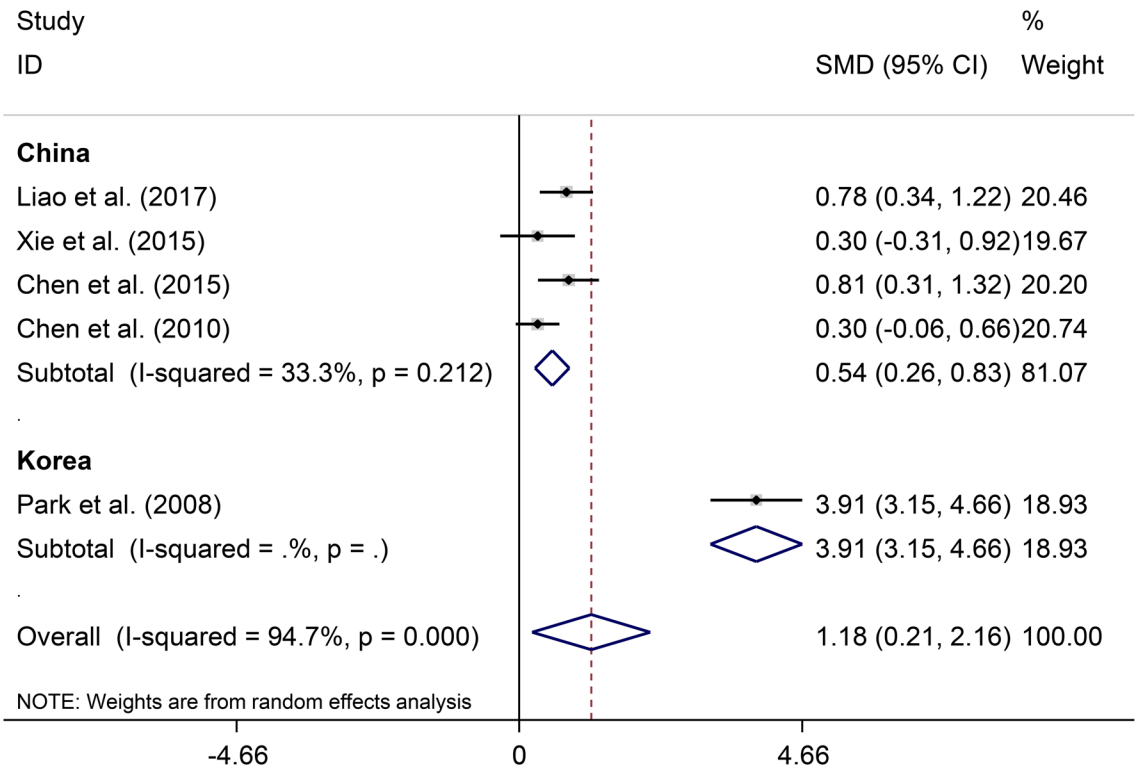

Fig. 5 Forest plot of subgroup analysis for AS patients versus healthy controls stratified by country for serum BMP-2 levels

impact the measuring values of serum sclerostin. Durozier et al. [59] indicated that in the same study, sclerostin levels were remarkably different according to the immunoassay kits used. Piec et al. [60] also observed that sclerostin levels in serum obtained from healthy subjects were significantly higher when using the Biomedica assay than R&D Systems and TECO*medical*, and TECO*medical* were more accurate than Biomedica assay and R&D Systems. In our study, we found that serum sclerostin levels were lower in AS patients than that in controls when using kits not only from TECO*medical* but also from AUROGENE srl, ICL Lab Inc, NovaTeinBio and from Rapidbio. However, no study has evaluated the accuracy of these four kits in measuring serum sclerostin levels. In addition, the number of studies using these kits to measure sclerostin levels is limited, further researches are therefore warranted.

Table 3 Meta-regression analysis coefficients for serum sclerostin levels in the examined group of studies

Variables	Coefficient (SE)	95% Confidence interval	*p*
Publication year	0.159 (0.180)	[− 0.222, 0.541]	0.389
Total sample size	0.002 (0.008)	[− 0.015, 0.018]	0.834
NOS score	0.338 (0.796)	[− 1.350, 2.027]	0.677

SE standard error; *NOS* Newcastle–Ottawa scale

With regard to serum BMP-2 levels in AS, we observed that serum levels of BMP-2 in AS group were materially higher than that in control group. There is evidence that serum BMP-2 levels were closely associated with osteoarthritis and degenerative joint disease, and may act as an alternative biological indicator to estimate disease severity of primary osteoarthritis [61]. Results of subgroup analysis indicated that country may be a source of heterogeneity across the five studies. Both China and Korea subgroup showed a consistent result that serum BMP-2 levels were higher in AS patients when compared to controls. However, the SMD of Korea subgroup was dramatically higher than that of China subgroup, which meant that the serum BMP-2 difference between AS patients and healthy controls in Korea was greater than that in China. When interpreting this result, we took the following issues into consideration. First, although Chinese and Korean have little difference in appearance, their living habits, genetic and environmental background are different, which may explain why serum BMP-2 levels in Korean were different with that in Chinese population. Second, the Korean subgroup only contained one study in which AS patients had much higher disease activity (mean BASDAI = 7.3) than the patients in Chinese studies (all mean BASDAI no more than 4.5). Park et al. [36] observed a positive correlation between BMP-2 and BASDAI in AS patients. Therefore, it may be the discrepant

disease activity that accounts for the different result between the countries. Additionally, serum levels of BMP-2 were associated with CRP in AS patients, suggesting a probable role of BMP-2 in inflammation. Indeed, BMP-2 can inhibit the expression of interleukin-34, a proinflammatory cytokine involved in rheumatoid arthritis (RA), thereby contributing to restrain inflammation and bone erosions in RA [62].

As a recommended indicator of assessing the severity of radiographic damage in AS, mSASSS is good for reflect the degree of erosions, sclerosis and syndesmophytes of the cervical and lumbar spine in AS patients [63]. Sun et al. [21] and Chen et al. [37] held the view that sclerostin was negatively related to mSASSS. While Klingberg et al. [28] revealed a positive association between sclerostin and mSASSS. Meanwhile, several other studies did not find the correlation of sclerostin and mSASSS [3, 16]. In the present meta-analysis, the synthetical results showed no association between sclerostin and mSASSS. The reasons may be as follows. On the one hand, although Wnt signaling pathway plays a crucial role in syndesmophytes formation, sclerostin is one of many inhibitors of Wnt signal. The another Wnt antagonist–DKK-1 have been reported to be negatively related to mSASSS in a recent meta-analysis [47]. On the other hand, mSASSS of AS patients is influenced by many factors, such as sex [64], occupation [65] and smoking [66]. But due to the limited information, it was difficult to conduct further stratification analysis. Hence, further longitudinal studies with high-quality data are required to determine their real relationship. Nevertheless, it was clearer and more consistent for the association between BMP-2 and radiographic damage, despite that no subgroup analysis was performed due to the limited number of studies. Serum BMP-2 levels were reported to be elevated in AS patients with spinal fusion whose mSASSS and Bath Ankylosing Spondylitis Radiology Index (BASRI) were significantly higher than those of patients without spinal fusion [35]. The positive relationships of mSASSS and BASRI with BMP-2 were also observed by many researchers [35, 37], which suggesting that BMP-2 is likely to exert a significant impact on the pathogenesis of spinal ankylosis in AS patients. Therefore, the serum levels of BMP-2 may reflect radiographic progression of AS.

In this study, several limitations should be taken into account. First, we could not understand the true source of heterogeneity among the studies about sclerostin by analyzing the limited factors due to the lack of available data. Other factors, like sex, BMI and drug use, might influence serum sclerostin levels in AS and partially generate heterogeneity. Second, the association of serum levels of BMP-2 with AS needs to be further validated considering the limited number of researches.

In conclusion, serum sclerostin levels are not significantly different between AS patients and healthy controls, and serum sclerostin levels in AS are associated with region, age, ESR, CRP, BASFI and ELISA kit. Serum BMP-2 levels in AS patients are higher than that in healthy controls, and are influenced by CRP.

Acknowledgements This study was supported by Grants from the National Natural Science Foundation of China (30972530, 81273169, 81573218 and 81773514).

Author Contributions Corresponding author Faming Pan came up with the idea and he is guarantor. Authors #a and #b performed the literature search. Author #c was responsible for statistical analysis. Author Jiajia Yang wrote the first draft of the article. Author #d and #e modified the manuscript. All authors reviewed the paper and approved the final version. All authors agree to be accountable for the work and to ensure that any questions relating to the accuracy and integrity of the paper are investigated and properly resolved.

Funding This study was funded by grants from the National Natural Science Foundation of China (30972530, 81273169, 81573218 and 81773514).

Compliance with Ethical Standards

Conflict of interest Jiajia Yang, Shanshan Xu, Mengya Chen, Yaping Yuan, Xu Zhang, Yubo Ma, Meng Wu, Renfang Han, Xingxing Hu, Rui Liu, Jixiang Deng, Shiyang Guan, Xing Gao, Meijuan Pan, Shengqian Xu, Zongwen Shuai, Shanqun Jiang, Shihe Guan, Liwen Chen, and Faming Pan declare they have no conflicts of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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