Osteoporos Int (2015) 26:85–91
DOI 10.1007/s00198-014-2939-3

ORIGINAL ARTICLE

Ankylosing spondylitis confers substantially increased risk of clinical spine fractures: a nationwide case-control study

D. Prieto-Alhambra · J. Muñoz-Ortego · F. De Vries · D. Vosse · N. K. Arden · P. Bowness · C. Cooper · A. Diez-Perez · P. Vestergaard

Received: 15 May 2014 / Accepted: 14 October 2014 / Published online: 24 October 2014

Abstract
Summary Ankylosing spondylitis (AS) leads to osteopenia/osteoporosis and spine rigidity. We conducted a case-control study and found that AS-affected patients have a 5-fold and 50 % increased risk of clinical spine and all clinical fractures, respectively. Excess risk of both is highest in the first years and warrants an early bone health assessment after diagnosis.
Introduction Ankylosing spondylitis (AS) is related to spine rigidity and reduced bone mass, but data on its impact on fracture risk are scarce. We aimed to study the association between AS and clinical fractures using a case-control design.
Methods From the Danish Health Registries, we identified all subjects who sustained a fracture in the year 2000 (cases) and matched up to three controls by year of birth, gender and region. Clinically diagnosed AS was identified using International Classification of Diseases, 8th revision (ICD-8; 71249), and International Classification of Diseases, 10th revision (ICD-10; M45) codes. We also studied the impact of AS duration. Conditional logistic regression was used to estimate crude and adjusted odds ratios (ORs) for non-traumatic fractures (any site, clinical spine and non-vertebral) according to AS status and time since AS diagnosis. Multivariate models were adjusted for fracture history, socio-economic status, previous medical consultations, alcoholism and use of oral glucocorticoids.
Results We identified 139/124,655 (0.11 %) AS fracture cases, compared to 271/373,962 (0.07 %) AS controls. Unadjusted (age- and gender-matched) odds ratio (OR) were 1.54 [95 % confidence interval (95 %CI) 1.26–1.89] for any fracture, 5.42 [2.50–11.70] for spine and 1.39 [1.12–1.73] for non-vertebral fracture. The risk peaked in the first 2.5 years following AS diagnosis: OR 2.69 [1.84–3.92] for any fracture.
Conclusions Patients with AS have a 5-fold higher risk of clinical spine fracture and a 35 % increased risk of non-

D. Prieto-Alhambra · N. K. Arden · P. Bowness · C. Cooper
Oxford NIHR Musculoskeletal Biomedical Research Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford OX3 7LD, UK

D. Prieto-Alhambra · F. De Vries · N. K. Arden · C. Cooper
MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK

D. Prieto-Alhambra · A. Diez-Perez
URFOA-IMIM and RETICEF, Parc de Salut Mar and Instituto de Salud Carlos III, Barcelona, Spain

D. Prieto-Alhambra
GREMPAL Research Group, IDIAP Jordi Gol Primary Care Research Institute, Universitat Autònoma de Barcelona, Barcelona, Spain

J. Muñoz-Ortego
Rheumatology Department, Hospital Universitari Sagrat Cor, Barcelona, Spain

F. De Vries
Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre, Maastricht, The Netherlands

F. De Vries
Utrecht Institute for Pharmaceutical Sciences, Universiteit Utrecht, Utrecht, The Netherlands

D. Vosse
Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Centre, Maastricht, The Netherlands

P. Vestergaard
Aalborg University Hospital, Aalborg University, Aalborg, Denmark

P. Vestergaard (✉)
Department of Endocrinology, Aalborg Hospital, Medicinerhuset Mølleparkvej 4, 9000 Aalborg, Denmark
e-mail: p-vest@post4.tele.dk

vertebral fracture. This excess risk peaks early, in the first 2.5 years of AS disease. Patients should be assessed for fracture risk early after AS diagnosis.

Keywords Ankylosing · Bone · Electronic health records · Epidemiology · Fractures · Spondylitis

Introduction

Ankylosing spondylitis (AS) is one of the most common inflammatory arthritides, with a prevalence of 0.1 to 1.4 % in Caucasian populations [1, 2]. Unlike rheumatoid arthritis, which affects preferentially peripheral joints, AS is characterized by inflammation of the spinal joints. This has two consequences with a potential impact on vertebral fracture risk: firstly, inflammation-mediated reduction in bone mineral density [3] and secondly, a progressive bone formation and ankylosis leading, if no effective treatment is provided, to "bamboo spine" [4]. Such a risk is important to quantify, as spine fractures can have devastating consequences for these patients, including neurological sequelae [5, 6] and intra-abdominal injuries, which are more common in AS patients who suffer transversal fractures of the vertebral body (Chance fracture) [7]. In a previous study, we characterized 66 patients with AS who sustained clinical vertebral fractures, mainly after minor trauma [8]: 47 % of these patients reported neurological complications. However, data on the impact of AS on fracture risk is scarce, and fracture prevalence varies greatly in the literature, from as low as 0.4 % to as high as 32 % [9–13]. This large difference reflects in part the problems of recognition of vertebral fractures in patients with AS: back pain is often misinterpreted as a flare of disease and fractures can be missed on plain radiographs [14]. Previous studies have shown that bone resorption biomarkers are up-regulated in AS patients compared with healthy controls and may correlate with inflammatory activity [15, 16]. Loss of bone mass in both hips and vertebrae due to inflammation are well recognized in patients with severe and long-term AS [17]. Even more worrying, recent findings suggest that even patients with early AS have a low bone mineral density (BMD) and a high prevalence of spine fractures [18, 19].

In a recently reported retrospective cohort study by our group, we have reported an increased risk of clinical vertebral and non-vertebral fractures among patients with AS [20, 21].

The aim of the current study was to analyse the association between AS and the risk of non-traumatic fractures (all, clinical spine and non-vertebral) in a case-control study using data from the Danish Health Registries.

Methods

Data source

The extensive nature of registers in Denmark covering contacts to the health sector offers good possibilities for studies on the occurrence of fractures [22]. Using the unique 10-digit civil registry number that is assigned to all Danish citizens shortly after birth, a complete hospital discharge and prescription history can be established for each individual, and valid linkage between population-based registries can be obtained. The unique civil registry number is used in all registers, i.e. if a person buys a drug on prescription, the drug is registered as bought by this individual, and the same applies for admissions to hospitals and contacts to general practitioners for reimbursement purposes.

This case-control study was performed within the Danish population that constituted approximately 5.3 million individuals during the study period.

The study was subject to control by the National Board of Health and the Danish Data Protection Agency.

Study design

This study was designed as a classical case-control study. Cases were all subjects, both genders and all ages, who sustained a fracture during the year 2000. Controls were matched subjects without a fracture in the same year using the criteria below. Exposure was use of drugs and diseases before the date of fracture or a matched index date in the controls. Information on fractures and diseases prior to the fracture was based on hospital records of in- and outpatients.

Identification of fracture cases

In Denmark, the National Hospital Discharge Register covers all contacts (on in- or outpatient basis) to the hospitals [23, 24]. The register was founded in 1977, but outpatient records were first completely incorporated from 1995. The files of the National Hospital Discharge Register include information on the civil registry number of the patient, date of discharge and discharge diagnoses, assigned exclusively by the physician at discharge according to the Danish version of the International Classification of Diseases, 8th revision (ICD-8), until the end of 1993, and to the Danish version of the International Classification of Diseases, 10th revision (ICD-10). The register has nationwide coverage of public hospitals with an almost 100 % completeness of recordings and a high precision of diagnoses [23, 24], particularly for fracture diagnoses [25]. Using the National Hospital Discharge Register, we identified all subjects who had sustained a clinically apparent fracture between 1 January 2000 and 31 December 2000 (n=124,655). Clinical spine fractures were the primary outcome of interest.

Any non-traumatic clinical fracture (any fracture not presenting with an accident mechanism code signalling a trauma of more than a fall at the same level or less as fracture energy) and non-vertebral clinical fractures were defined as secondary outcomes for this study.

Selection of population-based controls

Using the Civil Registration System, which has electronic records on all changes in vital status, including change of address and date of death for the entire Danish population since 1968, we randomly selected up to three controls for each case, matched by gender, year of birth and region. The controls were selected using the incidence-density sampling technique [26].

Data on ankylosing spondylitis

Patients with a diagnosis of 71249 (ICD-8) or M45.X (ICD-10) were identified from the National Hospital Discharge Register.

Data on baseline characteristics and potential confounders

Using the National Hospital Discharge Register [23], we gathered information on the number of days spent in hospital the year preceding fracture (year 1999) and history of a prior fracture in the period 1977–2000. Similarly, data from the National Bureau of Statistics was obtained for a more accurate patient characterization including income, social status, working status and educational status in 1999. The National Health Organisation Register information was then used to study number of contacts to general practitioners and practising specialists for the period 1996 to 2000.

Information on alcoholism was collected as appearance of a diagnosis of alcoholism in the National Hospital Discharge Register [23] or in the Psychiatric Central Register [27], or a prescription of disulfiram in the Prescription database.

Statistics

Data from the different registers were merged at the National Bureau of Statistics, and for each subject, the 10-digit civil registry number was substituted by a unique anonymous ID.

The analyses of the association between AS and fractures (clinical spine, any non-traumatic and non-vertebral) in the year 2000 (cases vs. controls) were carried out using crude and multivariable conditional logistic regression models. The latter were adjusted for fracture history, annual income, social status, working status, educational status (in the year 1999), number of consultations to general practitioners and practising specialists (in 1996–2000), alcoholism (as defined above) and use of oral NSAIDs and oral corticosteroids. In a sensitivity analysis, we also adjusted the association for use of bisphosphonates and hormone replacement therapy (HRT).

We further stratified the analyses by NSAID use, as previous studies have shown a discordant effect of AS on fracture risk according to NSAID utilization [12, 20, 21].

Finally, we studied the association between the duration of AS and any clinical fracture by categorizing time since AS clinical diagnosis in quartiles (up to 2.5, >2.5 to 5, >5 to 12.5 and >12.5 years) for the analyses of all fractures and in tertiles (up to 1, >1 to 10 and >10 years) for the analyses of clinical spine fractures. We plotted a smooth spline representation of this association.

All these analyses were performed using Stata 12.0 (StataCorp., College Station, TX) and SPSS 19.0 (SPSS Inc., Chicago Ill.). SPSS was used to generate the datasets from raw data and check the completeness of data, while Stata was used for the actual statistical analyses.

Results

Baseline characteristics for fracture cases and controls are shown in Table 1. Cases had lower annual income, were more likely to be alcoholic and to have a history of previous fracture, had more comorbidities (Charlson index), and used more drugs with a negative effect on bone metabolism and fracture risk (corticosteroids, antiepileptics, sedatives, etc.).

Among 124,655 cases, 139 (0.11 %) had a diagnosis of AS, while 271 (0.07 %) out of 373,962 controls had AS (crude odds ratio (OR) 1.54 [95 % confidence interval (95 %CI) 1.26–1.89]). Similarly, 18 (0.54 %) out of 3364 spine fracture cases compared to 10 (0.10 %) out of 10,079 matched controls had AS (age- and gender-matched OR 5.42 [2.50–11.70]). Finally, 121 (0.10 %) and 261 (0.07 %) AS participants were also identified among the 121,291 non-vertebral fracture cases and their corresponding 363,883 matched controls. In this group, the age- and gender-matched OR was 1.39 [1.12–1.73]. The observed associations were attenuated after multivariable adjustment, with the exception of clinical spine fractures: adjusted OR 4.21 [1.78–9.96] [Table 2]. None of the observed associations changed after further adjustment for use of bisphosphonates/HRT (data not shown).

The association between AS and any clinical fracture risk varied with AS disease duration: the excess risk was highest in patients with short-term AS of ≤2.5 years (age- and gender-matched OR 2.69 [1.84–3.92]), followed by those with a long-term disease >12.5 years (age- and gender-matched OR 1.48 [1.00–2.20]). No significant increase in any clinical fracture risk was seen for patients with >2.5 to ≤12.5 years since AS diagnosis. Figure 1 shows a smooth spline representation of this association that confirms this trend. Similarly, the

Table 1 Characteristics of fracture patients (cases—any fracture) and controls

Variable	Cases (n=124,655)	Controls (n=373,962)	p
Age (years)	43.44±27.39 (0–100)	43.44±27.39 (0–100)	–
Gender			–
Men	60,107 (48.2 %)	180,321 (48.2 %)	
Women	64,548 (51.8 %)	193,641 (51.8 %)	
Annual income (DKR)	161,036±138,789	172,322±193,704	<0.01
Marital status			<0.01
Widowed	18,365 (14.8 %)	52,550 (14.2 %)	
Divorced	10,423 (8.4 %)	23,239 (6.3 %)	
Married	35,859 (28.9 %)	123,719 (33.3 %)	
Unmarried	59,335 (47.8 %)	171,349 (46.2 %)	
Other[a]	90 (0.1 %)	264 (0.1 %)	
Occupational status			<0.01
Independent	3374 (3.3 %)	11,816 (3.9 %)	
Assisting wife	209 (0.2 %)	951 (0.3 %)	
Working	37,797 (36.9 %)	124,984 (40.8 %)	
Retired	40,201 (39.3 %)	109,447 (35.7 %)	
Other[b]	20,752 (20.3 %)	59,278 (19.3 %)	
Charlson index[c]			<0.01
0	97,256 (78.0 %)	314,099 (84.0 %)	
1–2	19,634 (16.8 %)	47,745 (12.8 %)	
3–4	5450 (4.4 %)	9132 (2.4 %)	
≥5	2315 (1.9 %)	2986 (0.8 %)	
Previous fracture	41,315 (33.1 %)	56,200 (15.0 %)	<0.01
Alcoholism	8863 (7.1 %)	9473 (2.5 %)	<0.01
Ever use of any corticosteroid	67,695 (54.3 %)	189,636 (50.7 %)	<0.01
Ever use of NSAIDS	59,690 (47.9 %)	142,274 (38.0 %)	<0.01
Ever diagnosed with ankylosing spondylitis	139 (0.1 %)	271 (0.07 %)	<0.01

The drugs are ever used from 1996 to 2000 and the diseases prior the occurrence of the disease in question between 1977 and 2000

[a] Registered partnership

[b] Not working (students, children, etc.)

[c] A composite index of 19 comorbid conditions (see text)

Table 2 Results for the association between fracture and AS status (conditional logistic regression)

Skeletal site	Age- and gender-matched OR (95 %CI)	Multivariable adjusted[a] OR (95 %CI)
Any non-traumatic fracture	1.54 (1.26–1.89)*	1.16 (0.93–1.44)
Clinical spine	5.42 (2.50–11.7)*	4.21 (1.78–9.96)*
Non-vertebral	1.39 (1.12–1.73)*	1.05 (0.84–1.32)

OR odds ratio, *95 %CI* 95 % confidence interval

*p<0.05

[a] Adjusted for fracture history, annual income, social status, working status, educational status, number of consultations to general practitioners and practising specialists, alcoholism and use of oral NSAIDs and oral corticosteroids

association between AS duration and clinical spine fractures was strongest in the first years of disease: age- and gender-matched ORs 8.03 [2.13–30.30] for short-term AS (≤1 year since diagnosis), 7.52 [1.46–38.8] for midterm duration AS (>1 to 10 years), and 3.01 [0.87–10.40] for long-term disease (>10 years since AS diagnosis).

After stratifying by NSAID use, the excess risk of any clinical fracture associated with AS appeared stronger in the group of NSAID users, although the interaction term was borderline significant (p for interaction= 0.095). Table 3 shows the OR for overall fracture risk and risk of clinical spine and non-vertebral fractures stratified by NSAID use.

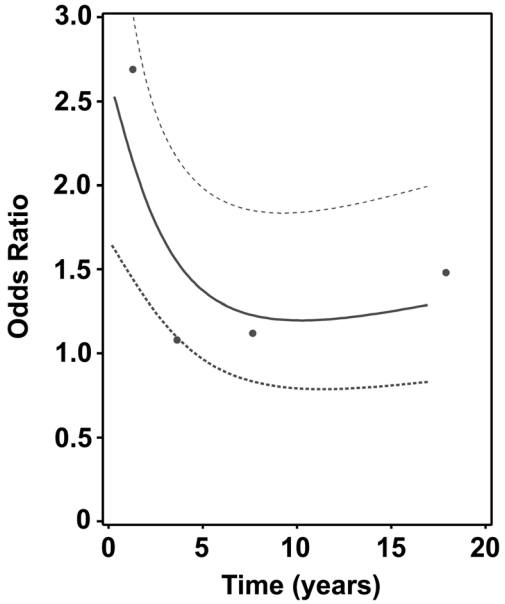

Fig. 1 Smooth spline analysis of fracture risk (odds ratio) plotted against AS disease duration (in years)

Discussion

Key findings

We report a strong association between AS and clinical spine fractures, with a 5-fold higher risk amongst AS patients when compared to age- and gender-matched peers. Similarly, AS participants appeared in our study to be at over 50 % increased risk of overall non-traumatic fractures, and non-vertebral fracture risk was almost 40 % higher in the AS patients. All these associations were attenuated and no longer significant after multivariable adjustment for further potential confounders, except for clinical spine fracture risk, that remained more than 4-fold higher in AS participants. Further adjustment for use of drugs with a proved anti-fracture efficacy did not change the observed associations.

We want to stress that it is the age- and gender-matched results that are of most interest, as all other confounders might be in the causal pathway, and adjustment for them does only demonstrate that, as expected, AS disease has an impact on patients' socio-economic status, health-care resource use and lifestyle, which might partially account for the observed increased risk of any fracture amongst these patients.

The excess risk of both overall and clinical spine fracture in AS patients peaked in the first 2.5 years following diagnosis and decreased subsequently. This supports the recent data of van der Weijden et al. [18], who reported an early increase in spine fractures even in early disease. Such results could, in our data, be due to chance findings of silent spine fractures during imaging for the diagnosis of AS, or to the effectiveness of available therapies, which might potentially reduce the deleterious effects of AS both on progressive ankylosis [28] and bone loss [29, 30]. The latter would suggest that fractures in AS are associated with acute flares rather than to long-standing low-grade inflammation, but more data are needed to explain these findings.

Interpretation

A significantly increased risk of clinical spine fractures has been previously reported by a number of authors: Vosse et al. [12] reported an almost 3-fold higher risk of clinical vertebral fractures in a population-based case-control study using data from the UK. And a recent parallel cohort study by our group has shown a doubled risk of spine fractures in AS patients when compared to disease-free matched peers [20, 21]. Our current data broadly support these results, and the finding of a higher excess risk in the Danish registries could be due to the nature of the data, study design or health-care differences between these three countries. Cooper et al. [10] conducted a retrospective cohort study including 158 AS patients and concluded that AS patients were at a more than 7-fold higher risk of radiological vertebral fractures, pointing towards an even stronger association, which might be underestimated in our data, where only clinical fractures were accounted for.

According to our results, the association between AS and fracture risk is much weaker in AS patients who do

Table 3 OR for fracture among AS patients compared to non-AS patients

Fracture site	No NSAID		NSAID	
	Crude	Adjusted[a]	Crude	Adjusted[a]
Any non-traumatic fracture	0.89 (0.49–1.64)	0.56 (0.28–1.11)	1.37 (1.10–1.71)*	1.27 (1.01–1.59)*
Clinical spine	4.12 (0.91–18.4)	2.79 (0.39–20.2)	5.27 (2.04–13.6)*	4.83 (1.79–13.0)*
Non-vertebral	0.74 (0.37–1.46)	0.48 (0.23–1.02)	1.25 (0.99–1.57)	1.15 (0.91–1.47)

*$p<0.05$

[a] Adjusted for age, gender, fracture history, annual income, social status, working status, educational status, number of consultations to general practitioners and practising specialists, alcoholism and use of oral NSAIDs and oral corticosteroids

not take NSAIDs. This might be due to either a higher excess risk amongst patients with severe symptomatic disease or to detrimental effects of NSAIDs on bone metabolism including negative effects on fracture healing, and a potential inhibition of syndesmophyte formation. Interestingly, the two other studies that have looked at this found the opposite: in the study by Vosse et al. [12], as well as in our recent report [20, 21], AS patients who took NSAIDs regularly did not have an increased fracture risk. A major difference between these two and our current study is that here we use data from 2000, when anti-TNFs were not yet in widespread clinical use. Therefore, it is likely that in our current dataset, a higher utilization of NSAIDs is a proxy for AS severity, which would explain the observed positive association between NSAID use and fractures. However, our analysis for an interaction with NSAID use was underpowered and borderline significant (p value for an interaction=0.095), and therefore these data should be interpreted with caution.

Extraarticular involvement of AS might also contribute to the increased fracture risk. Cardiovascular [31], pulmonary [32], neurological [33] or other comorbidities [34, 35] can increase bone loss and fractures. However, the early increase in fracture risk in our population makes this possibility unlikely.

Strengths and limitations

The main limitation of this study is the lack of validation of either the exposure (AS) or the outcome of interest (individual fractures). However, coding of fractures has been validated in the Danish Health Registries [36, 37] and shown to be highly accurate. As mentioned above, our methodology is likely to miss asymptomatic fractures (e.g. silent spine fractures), which could translate in a potential underestimation of the observed associations. Finally, we do not have data on AS disease severity (patient reported, imaging or biochemistry) or bone mineral density, which would help us explain the mechanisms underlying the increased risk of fractures in AS patients.

The principal strengths of our study are the large number of participants studied (more than 124,000 fracture cases matched to >373,000 controls) and the representativeness of the data, which was routinely collected in actual practice conditions.

Conclusions

We report that patients with AS are at a more than 5-fold increased risk of vertebral clinical fractures and at a 50 % higher risk of overall non-traumatic fractures, when compared to age- and gender-matched peers. According to our data, the excess risk peaks in the early stages of disease. Thus, AS patients should be assessed for fracture risk as close as possible to the time of diagnosis.

Acknowledgments Statistics Denmark is acknowledged for the help with the acquisition of the data.

Funding DPA, NKA and CC receive partial funding from the Oxford NIHR Musculoskeletal Biomedical Research Unit. DPA receives partial funding from the MRC Lifecourse Epidemiology Unit (Southampton), the IDIAP Jordi Gol Primary Care Research Institute and the URFOA (IMIM, Parc de Salut Mar, Barcelona). DPA receives funding from the NIHR Clinician Scientist Award scheme.

The data retrieval was sponsored by a grant from the Danish Medical Research Council (Grant number 22-04-0495).

Conflicts of interest None.

References

1. Braun J, Bollow M, Remlinger G, Eggens U, Rudwaleit M, Distler A, Sieper J (1998) Prevalence of spondylarthropathies in HLA-B27 positive and negative blood donors. Arthritis Rheum 41:58–67
2. van der Linden SM, Valkenburg HA, de Jongh BM, Cats A (1984) The risk of developing ankylosing spondylitis in HLA-B27 positive individuals. A comparison of relatives of spondylitis patients with the general population. Arthritis Rheum 27:241–249
3. Westerveld LA, Verlaan JJ, Oner FC (2009) Spinal fractures in patients with ankylosing spinal disorders: a systematic review of the literature on treatment, neurological status and complications. Eur Spine J 18:145–156
4. Sieper J, Appel H, Braun J, Rudwaleit M (2008) Critical appraisal of assessment of structural damage in ankylosing spondylitis: implications for treatment outcomes. Arthritis Rheum 58:649–656
5. Graham B, Van Peteghem PK (1989) Fractures of the spine in ankylosing spondylitis. Diagnosis, treatment, and complications. Spine (Phila Pa 1976) 14:803–807
6. Fox MW, Onofrio BM, Kilgore JE (1993) Neurological complications of ankylosing spondylitis. J Neurosurg 78:871–878
7. Tyroch AH, McGuire EL, McLean SF, Kozar RA, Gates KA, Kaups KL, Cook C, Cowgill SM, Griswold JA, Sue LA, Craun ML, Price J (2005) The association between Chance fractures and intra-abdominal injuries revisited: a multicenter review. Am Surg 71: 434–438
8. Vosse D, Feldtkeller E, Erlendsson J, Geusens P, van der Linden S (2004) Clinical vertebral fractures in patients with ankylosing spondylitis. J Rheumatol 31:1981–1985
9. Donnelly S, Doyle DV, Denton A, Rolfe I, McCloskey EV, Spector TD (1994) Bone mineral density and vertebral compression fracture rates in ankylosing spondylitis. Ann Rheum Dis 53:117–121
10. Cooper C, Carbone L, Michet CJ, Atkinson EJ, O'Fallon WM, Melton LJ 3rd (1994) Fracture risk in patients with ankylosing spondylitis: a population based study. J Rheumatol 21:1877–1882
11. Ralston SH, Urquhart GD, Brzeski M, Sturrock RD (1990) Prevalence of vertebral compression fractures due to osteoporosis in ankylosing spondylitis. BMJ 300:563–565
12. Vosse D, Landewe R, van der Heijde D, van der Linden S, van Staa TP, Geusens P (2009) Ankylosing spondylitis and the risk of fracture:

results from a large primary care-based nested case-control study. Ann Rheum Dis 68:1839–1842
13. Montala N, Juanola X, Collantes E, Munoz-Gomariz E, Gonzalez C, Gratacos J, Zarco P, Sueiro JL, Mulero J, Torre-Alonso JC, Batlle E, Carmona L (2011) Prevalence of vertebral fractures by semiautomated morphometry in patients with ankylosing spondylitis. J Rheumatol
14. Delmas PD, van de Langerijt L, Watts NB, Eastell R, Genant H, Grauer A, Cahall DL (2005) Underdiagnosis of vertebral fractures is a worldwide problem: the IMPACT study. J Bone Miner Res 20:557–563
15. Arends S, Spoorenberg A, Bruyn GA, Houtman PM, Leijsma MK, Kallenberg CG, Brouwer E, van der Veer E (2011) The relation between bone mineral density, bone turnover markers, and vitamin D status in ankylosing spondylitis patients with active disease: a cross-sectional analysis. Osteoporos Int 22:1431–1439
16. Franck H, Meurer T, Hofbauer LC (2004) Evaluation of bone mineral density, hormones, biochemical markers of bone metabolism, and osteoprotegerin serum levels in patients with ankylosing spondylitis. J Rheumatol 31:2236–2241
17. Will R, Palmer R, Bhalla AK, Ring F, Calin A (1989) Osteoporosis in early ankylosing spondylitis: a primary pathological event? Lancet 2: 1483–1485
18. van der Weijden MA, van der Horst-Bruinsma IE, van Denderen JC, Dijkmans BA, Heymans MW, Lems WF (2012) High frequency of vertebral fractures in early spondylarthropathies. Osteoporos Int 23: 1683–1690
19. van der Weijden MA, Claushuis TA, Nazari T, Lems WF, Dijkmans BA, van der Horst-Bruinsma IE (2012) High prevalence of low bone mineral density in patients within 10 years of onset of ankylosing spondylitis: a systematic review. Clin Rheumatol
20. Muñoz-Ortego J, Vestergaard P, Blanch J, Wordswoth P, Judge A, Kassim M, Arden N, Cooper C, Díez-Perez A, Prieto-Alhambra D (2012) Ankylosing spondylitis is associated with an increased risk of osteoporotic fractures: a population-based cohort study. Arthritis Rheum 64
21. Muñoz-Ortego J, Vestergaard P, Rubio JB, Wordsworth P, Judge A, Javaid MK, Arden NK, Cooper C, Diez-Perez A, Prieto-Alhambra D (2014) Ankylosing spondylitis is associated with an increased risk of vertebral and non-vertebral clinical fractures: a population-based cohort study. J Bone Miner Res 29(8):1770–1776
22. Frank L (2000) Epidemiology. When an entire country is a cohort. Science 287:2398–2399
23. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH (1999) The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 46:263–268
24. Mosbech J, Jorgensen J, Madsen M, Rostgaard K, Thornberg K, Poulsen TD (1995) The national patient registry. Evaluation of data quality. Ugeskr Laeger 157:3741–3745
25. Vestergaard P, Mosekilde L (2002) Fracture risk in patients with celiac disease, Crohn's disease, and ulcerative colitis: a nationwide follow-up study of 16,416 patients in Denmark. Am J Epidemiol 156: 1–10
26. Wacholder S, McLaughlin JK, Silverman DT, Mandel JS (1992) Selection of controls in case-control studies. I. Principles. Am J Epidemiol 135:1019–1028
27. Munk-Jorgensen P, Mortensen PB (1997) The Danish Psychiatric Central Register. Dan Med Bull 44:82–84
28. Wanders A, Heijde D, Landewe R, Behier JM, Calin A, Olivieri I, Zeidler H, Dougados M (2005) Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. Arthritis Rheum 52:1756–1765
29. Kang KY, Ju JH, Park SH, Kim HY (2013) The paradoxical effects of TNF inhibitors on bone mineral density and radiographic progression in patients with ankylosing spondylitis. Rheumatology (Oxford) 52: 718–726
30. Kang KY, Lee KY, Kwok SK, Ju JH, Park KS, Hong YS, Kim HY, Park SH (2011) The change of bone mineral density according to treatment agents in patients with ankylosing spondylitis. Joint Bone Spine 78:188–193
31. Mathieu S, Gossec L, Dougados M, Soubrier M (2011) Cardiovascular profile in ankylosing spondylitis: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 63: 557–563
32. Quismorio FP Jr (2006) Pulmonary involvement in ankylosing spondylitis. Curr Opin Pulm Med 12:342–345
33. Khedr EM, Rashad SM, Hamed SA, El-Zharaa F, Abdalla AK (2009) Neurological complications of ankylosing spondylitis: neurophysiological assessment. Rheumatol Int 29:1031–1040
34. Leirisalo-Repo M, Turunen U, Stenman S, Helenius P, Seppala K (1994) High frequency of silent inflammatory bowel disease in spondylarthropathy. Arthritis Rheum 37:23–31
35. Gratacos J, Collado A, Sanmarti R, Poch E, Torras A, Munoz-Gomez J (1993) Coincidental amyloid nephropathy and IgA glomerulonephritis in a patient with ankylosing spondylitis. J Rheumatol 20: 1613–1615
36. Andersen T, Madsen M, Jørgensen J, Mellemkjær L, Olsen J (1999) The Danish National Hospital Register. Dan Med Bull 46:263–268
37. Mosbech J, Jørgensen J, Madsen M, Rostgaard K, Thornberg K, Poulsen T (1995) The Danish National Patient Register: evaluation of data quality. Ugeskr Laeger 157:3741–3745