The incidence of spondyloarthritis in Slovenia

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Abstract
Epidemiological studies of spondyloarthritis (SpA) are rare and data for our country are lacking. We aimed to determine the incidence of SpA in a well-defined region in Slovenia.

We performed a retrospective chart review of adults diagnosed with SpA between January 2014 and December 2016 at an integrated secondary/tertiary medical center, which provides rheumatology services to almost a half of the adult national population, that is, 700,000 adults. Potential cases were ascertained by searching the electronic medical records for ICD-10 codes M02\textsuperscript{*}, M07\textsuperscript{*}, M13\textsuperscript{*}, M45\textsuperscript{*}, M 46.1, K50\textsuperscript{*}, K51\textsuperscript{*}, and L40\textsuperscript{*}. SpA cases were stratified as axial and peripheral SpA and then the annual incidence rates of SpA overall and both subsets were estimated.

During the 3-year period we identified 302 SpA cases (55.0\% males, median [interquartile range] age 46.7 [35.0–57.5] years). 98 (32.5\%) of them had predominantly axial SpA and the remainder peripheral SpA. The estimated annual incidence rate per 100,000 adults in our region was 14.3 (95\% confidence interval [CI] 12.8–16.0) for SpA overall, 4.6 (95\% CI 3.8–5.6) for axial SpA, and 9.6 (95\% CI 8.4–11.1) for peripheral SpA.

The estimated annual incidence rate of 14.3 cases per 100,000 adults in SpA overall was comparable to that of rheumatoid arthritis in our population. The peripheral SpA was twice as common as axial SpA.

Abbreviations: ASAS = Assessment of spondyloarthritis international society, CI = confidence interval, IQR = interquartile range, SpA = spondyloarthritis, UMCL = University Medical Centre Ljubljana.

Keywords: axial spondyloarthritis, epidemiology, incidence, peripheral spondyloarthritis, spondyloarthritis

1. Introduction
Spondyloarthritides (SpA) are a heterogeneous group of diseases affecting the axial and peripheral skeleton. Traditionally, we considered spondyloarthritis as an umbrella term for ankylosing spondylitis, psoriatic arthritis, enteropathic arthritis, reactive arthritis, undifferentiated SpA and juvenile SpA.\textsuperscript{11} A decade ago, the Assessment of spondyloarthritides international society (ASAS) developed a classification criteria for axial and peripheral SpA that reflected the overlapping clinical manifestations, association with the human leukocyte antigen B27 (HLA B27) antigen, and the familial clustering of these diseases, and took advantage of the improved imaging modalities.\textsuperscript{[2–11]} The ASAS classification criteria facilitate the identification of patients with early forms of the disease, which may expedite the introduction of disease-modifying treatments, and thus influence the long-term prognosis of SpA patients. These classification criteria also revamp the epidemiology of the SpA. Thus far, 5 studies estimated the overall annual incidence rates of SpA at 0.48 to 62.5 cases per 100,000 persons.\textsuperscript{[4–8]} Significant variations of the SpA annual incidence rates per 100,000 persons among countries and regions have also been reported in the traditional SpA subsets: ankylosing spondylitis 0.44 to 7.3; psoriatic arthritis 0.1 to 23.1, and reactive arthritis 0.6 to 28.\textsuperscript{[4,5,9–13]}

Since the development of the ASAS criteria, particularly peripheral SpA as an entity has been poorly investigated. As the epidemiological data of SpA are lacking worldwide, we aimed to retrospectively determine the incidence rate of SpA in 2 well-defined Slovenian regions.

2. Methods
2.1. Setting
This retrospective study was conducted at the Department of Rheumatology, University Medical Centre Ljubljana (UMCL). UMCL is an integrated secondary/tertiary teaching hospital. Its Department of Rheumatology is the only rheumatology referral center providing services to the adult residents of the Ljubljana and Kranj health regions.

According to the data from the Department of Demographic and Social Statistics at the Statistical Office of the Republic of Slovenia, the Ljubljana and Kranj health regions had, at the time of the study, a pooled average adult (≥18 years) population of
704,342 citizens (342,694 males and 361,648 females). More than 95% of residents were Caucasian. The prevalence of HLA B27 antigen in Slovenian population was 11.4%.[14]

2.2. Patients

We retrospectively identified patients who were residents of the Ljubljana or Kranj health regions, diagnosed with SpA for the first time between 1 January 2014 and 31 December 2016 by searching the medical records for the International Classification of Diseases, 10th Revision codes M02, M07, M13, M45, M46.1, K50, K51, and L40, and then thoroughly reviewed the electronic and paper records of the potential cases. The clinical features consistent with SpA, for example, arthritis, dactylitis, enthesitis, uveitis, or inflammatory bowel disease, were only considered to be present at the time of presentation if they were objectified by a physician using the appropriate tests. We considered the results of sacroiliac joint radiographic and magnetic resonance (MRI) imaging studies.[2]

Patients were considered cases if they could be classified as SpA by the ASAS classification criteria.[2,3] Based on the predominant clinical feature at presentation, patients were stratified into axial and peripheral SpA. For the purpose of comparison with older studies we classified the SpA patients into traditional categories: ankylosing spondylitis by the Modified New York classification criteria,[15] psoriatic arthritis by the 2006 CASPAR classification criteria for psoriatic arthritis,[16] enteropathic arthritis if the patients had proven inflammatory bowel disease, reactive arthritis if the SpA onset was preceded by a gastrointestinal or an urogenital infection caused by bacteria commonly associated with reactive arthritis, and undifferentiated SpA for those not fitting any of the other subsets including the patients with nonradiographic axial SpA.

2.3. Statistical analysis

The incidence rate for SpA was calculated by dividing the data of new disease onsets (numerator) and (average population size) × (duration of follow-up) as the denominator. A crude incidence was standardized to the 2016 population data in Slovenia. SpA patients were stratified into axial and peripheral groups and incidence rates based on gender and on different age groups were also calculated.

2.4. Ethics committee approval

The study was approved by the National Medical Ethics Committee. Patient consent was not obtained. The data used in this study were collected as a part of routine clinical care and is presented in an anonymized group level fashion.

3. Results

During the 3-year observation period we identified 302 SpA cases (166 [55.0%] males, and the male to female ratio was 1.2, 94/215 [43.7%] ever smokers). The median (interquartile range [IQR]) patient age was 46.7 (35.0–57.5) years, range 18 to 84 years, and the median (IQR) symptom duration 7.1 (1.9–24.7) months. At presentation 165 (54.6%) patients had arthritis, 90 (29.8%) inflammatory back pain, 55 (18.2%) dactylitis, 21 (7.0%) heel enthesitis, and 21 (7.0%) history of uveitis. The HLA B27 antigen was present in 162/269 (60.2%) screened patients. An X-ray of the sacroiliac joints was performed in 167 (55.3%) patients, and 73/167 (43.7%) of them had radiographic signs of sacroilitis. The MRI revealed active sacroilitis in an additional 1728 patients without radiographic sacroilitis. In 12 patients an MRI of the sacroiliac joints was the only imaging modality used, and was consistent with the active sacroilitis in 9 of them. The patients with active sacroilitis on the MRI were significantly younger compared to the patients with radiographic sacroilitis (33.6 [23.3–43.9] vs 43.5 [37.0–56.9] years, P=.003); however, the symptom duration before the diagnosis was comparable (24.5 [10.6–48.7] vs 36.5 [5.5–101.9] months, P=.367). Using the traditional SpA subsets, the cases were classified as ankylosing spondylitis, psoriatic arthritis, enteropathic arthritis, reactive arthritis, and an undifferentiated SpA in 62 (20.5%), 115 (38.1%), 12 (4.0%), 22 (7.3%), and 91 (30.1%) cases, respectively.

We allocated 98 (32.5%) patients of our cohort to an axial SpA, and 204 (67.5%) patients to a peripheral SpA subset. The characteristics of our SpA cohort and both subsets are presented in Table 1. The patients with the axial SpA were significantly younger compared to those with the peripheral SpA (P=.004) and had a significantly longer symptom duration (P<.001). The axial SpA group consisted of ankylosing spondylitis (57 cases; 58.2%), psoriatic arthritis (5 cases; 5.1%), enteropathic arthritis (5 cases 5.1%), and undifferentiated SpA (31 cases; 31.6%).

The peripheral SpA group consisted of psoriatic arthritis (110 cases, 53.9%), undifferentiated SpA (60 cases; 29.4%), reactive arthritis (22 cases; 10.8%), enteropathic arthritis (7 cases; 3.4%), and ankylosing spondylitis without a prominent inflammatory back pain but with predominant peripheral arthritis at presentation (5 cases; 2.5%).

Based on the adult population of the pooled Ljubljana and Kranj health regions, the estimated annual incidence rates per 100,000 adults in our region were 14.3 (95% confidence interval

| Table 1: Characteristics and incidence rates of spondyloarthritis. |
|---------------------------------|------------------|------------------|
| Characteristics                | All SpA (100)    | Peripheral SpA (67.5) | Axial SpA (32.5) |
| No. (%) of cases               | 302              | 204              | 98              |
| Males (%)                      | 166 (55.0%)      | 99 (48.5%)       | 67 (68.4%)      |
| Age, yr                        | 46.7 (35.0–57.5) | 49.8 (36.0–58.2) | 39.8 (33.1–55.4) |
| Symptom duration, mo*          | 6.8 (1.9–24.6)   | 3.5 (1.0–12.1)   | 31.1 (10.6–73.2) |
| HLA B27 + (%)                  | 162/269 (60.2)   | 84/174 (48.3)    | 78/86 (82.1)    |
| Incidence rate                 | 14.3 (12.8–16.0) | 9.6 (8.4–11.1)   | 4.6 (3.8–5.6)   |
| Incidence rate in females†     | 12.5 (10.6–14.8) | 9.7 (8.0–11.7)   | 2.9 (2.0–4.0)   |
| Incidence rate in males†       | 16.2 (13.8–18.8) | 9.6 (7.9–11.7)   | 6.5 (5.1–8.2)   |

*HLA B27 = human leucocyte antigen B27, SpA = spondyloarthritis.
†Median (IQR).
†Incidence rate per 100,000 adults per yr and 95% confidence interval.
12.8 (95% CI 10.8–16.0) for SpA overall, 4.6 (95% CI 3.8–5.6) for axial SpA, and 9.6 (95% CI 8.4–11.1) for peripheral SpA. The age and gender-specific incidence rates of axial and peripheral SpA are presented in Figures 1 and 2, respectively. The estimated incidence rates for traditional SpA diagnoses are presented in Table 2.

4. Discussion

The epidemiology of SpA as an entity is not well studied. Most studies explored the epidemiology of individual diseases traditionally joined under the umbrella of SpA. The published data suggests that the incidence and prevalence rates vary among different populations. This may be explained, in part, by the
differences in the prevalence of the HLA B27 antigen in different geographical regions or ethnic groups, but also by the different criteria used for case definition. For example, a higher prevalence of psoriatic arthritis was observed in North America and northern Europe compared to southern Europe, and in studies that used self-report definitions of the disease compared to those that used classification criteria. In the present study we retrospectively determined the incidence rates of the entire spectrum of SpA as a single entity, the predominantly axial- or peripheral-SpA as defined by ASAS, and also of the traditional diagnoses of SpA: ankylosing spondylitis, psoriatic arthritis, enteropathic arthritis, reactive arthritis, and undifferentiated SpA in 2 well-defined regions of Slovenia. The Slovenian population of about 2 million is demographically homogenous, thus we assume that the incidence rates are representative of the entire country. Based on these data we estimated the annual incidence rate per 100,000 adults in Slovenia at 14.3 (males 16.2, females 12.5).

Based on these data we estimated the annual incidence rate per 100,000 adults makes SpA as common as rheumatoid arthritis in our population, with the peripheral SpA being 2 times more frequent than axial SpA.

Table 2
Characteristics and incidence rates of diseases of the spondyloarthritis spectrum.

| Characteristics          | Ankylosing spondylitis | Psoriatic arthritis | Enteropathic arthritis | Reactive arthritis | Undifferentiated spondyloarthritis |
|--------------------------|------------------------|---------------------|------------------------|--------------------|-----------------------------------|
| No. of cases             | 62                     | 115                 | 12                     | 22                 | 91                                |
| Males (%)                | 44 (71.0)              | 57 (49.6)           | 6 (50.0)               | 10 (45.5)          | 49 (53.8)                         |
| Age, yr[^1^]             | 41.1 (55.1–55.9)       | 51.1 (39.4–59.6)    | 52.0 (33.6–58.6)       | 39.7 (31.4–54.3)   | 44.3 (28.4–56.0)                  |
| HLA B27 + (%)            | 48/59 (81.4)           | 25/115 (21.7)       | 5/10 (50.0)            | 16/20 (80.0)       | 68/87 (78.2)                      |
| Incidence rate[^1^]      | 2.9 (2.3–3.7)          | 5.4 (4.5–6.5)       | 0.6 (0.3–1.0)          | 1.0 (0.7–1.6)      | 4.3 (3.5–5.3)                     |

[^1^] HLA B27 = human leukocyte antigen B 27.
[^2^] Median (IQR).
[^3^] Incidence rate per 100,000 adults per yr and 95% confidence interval.

[^1^] The prevalence of HLA B27 in our patients diagnosed with ankylosing spondylitis was over 80%, which was in line with the results found in the literature[^10,24].

[^2^] The main limitations of our study were the retrospective, single center design, and a short observation period. An HLA B27 status was determined in 88.8% cases, and imaging studies were not systematically performed. Systematic radiographic studies could change the proportions between the historical diagnoses in our cohort (eg, one might expect an increase in the frequency of ankylosing spondylitis with a concurrent decrease of undifferentiated SpA).

[^3^] On the other hand, it is unlikely that we significantly underestimated the overall SpA incidence rate, despite a retrospective study design, as our rheumatology department represents the only referral center for the entire population under study. Besides, other subspecialists – for example, dermatologists, gastroenterologists, infectious disease specialists regularly consult rheumatologists in cases of arthralgias in patients with psoriasis, genitourinary tract infections, or inflammatory bowel disease.

[^4^] In conclusion, the estimated annual incidence rate of 14 cases per 100,000 adults makes SpA as common as rheumatoid arthritis in our population[^23], with the peripheral SpA being 2 times more frequent than axial SpA.
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