Severity of the Apnea-Hypopnea Sleep Syndrome in Patients with Rheumatoid Arthritis and Spondyloarthropathies. Modulation of the Sleep Apnea Index with Anti-TNF-α Inhibitors

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Abstract

Objective: To evaluate severity of the sleep apnea-hypopnea syndrome (SAHS) in patients with rheumatoid arthritis (RA) and spondyloarthropathies (SpA). To study the behavior of the apnea-hypopnea index (AHI) in patients treated with anti-TNF-α.

Materials and methods: An observational, retrospective study was conducted in patients with RA and SpA (study group) and with osteoarthritis (control group) who have SAHS symptoms. AHI (expressed in median and 25-75 percentiles), mean oxygen saturation (SaO2) and information on associated cardiovascular risk factors (CVRF) were collected. This information was also collected in the anti-TNF-α treated study group.

Results: The study group (75 patients [48 with RA and 27 with SpA], 36 men) were younger (53.1 ± 10.6 vs. 57.2 ± 9.6 years, p=0.022) compared to the control group (58 patients, 23 men). The study group had a higher incidence of hypercholesterolemia (82.7% vs. 17.2%, p<0.001) and ischemic heart disease (17.3% vs. 3.4%, p=0.013). Sixteen patients of the study group were treated with anti-TNF-α. Patients in the study group had higher AHI than the control group (median 37.4 vs. 27.8, p=0.025). Those treated had a similar value to the control group (29.1 vs. 27.8, NS) and a lower value compared to the non-treated (29.1 vs. 36.8, p=0.052). No differences in the SaO2 were observed.

Conclusions: Patients with SAHS and inflammatory arthritis are younger and have more CV risk factors than those who have non-inflammatory arthropathy. Patients with SAHS and inflammatory arthritis treated with TNF-α inhibitors have a lower AHI than those treated only with disease modifying drugs and one that is similar to patients with non-inflammatory arthropathy. This suggests improvement of the SAHS.

Keywords: Rheumatoid arthritis; Spondyloarthropathy; Sleep apnea-hypopnea Syndrome (SAHS); Apnea-hypopnea index (AHI); TNF inhibitors

Introduction

There is greater cardiovascular risk (CV) in those having chronic inflammatory diseases such as rheumatoid arthritis (RA) or spondyloarthropathies (SpA) than in the general population. This risk is not only explained by the association of the traditional risk factors of arterial hypertension (AHT), dyslipidemia, diabetes mellitus (DM) and smoking [1]. In this sense, early endothelial dysfunction and accelerated atherosclerotic process [2] have been described in these diseases and may be related to the same inflammatory process and be mediated by the tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) [3]. Sleep apnea-hypopnea syndrome (SAHS) has a 3-4% [4] prevalence in Western countries and is also associated to the metabolic syndrome and other CV risk factors [5]. SAHS per se constitutes an independent CV risk factor in male subjects and young subjects with this disease [6].

Sleep abnormalities are common in RA [7,8] and SAHS has been attributed as being a factor that contributes to CV mortality in patients with RA [9]. There seems to be a systemic inflammatory component in the etiopathogeny of SAHS, although the mechanism is little known. The repeated episodes of hypoxia and reoxygenation cause oxidative stress that may play an important role in the associated systemic inflammatory process [10]. This would entail an increase in the expression of TNF-α.

Association of inflammatory pathophysiology and an evolution occurring with more CV complications observed in RA as well as SpA and SAHS acquire greater conceptual support when we observe the response to the treatment. Thus, when SAHS is treated with continuing positive air pressure, a reduction is observed in blood pressure, triglycerides and glyceded hemoglobin [11]. Furthermore, it has been stated that treatment with anti-TNF-α in patients with RA and sleep disorders improves sleep quality [12]. However, at present, there are still few studies that evaluate the severity of SAHS in patients with RA or SpA, the increase of CV risk that this association implies and the possible modulation of the nighttime anoxia-hypoxia episodes with treatment with anti TNF-α drugs. This study has aimed to evaluate the severity of SAHS in patients with RA or SpA and to verify the behavior of the apnea-hypopnea index (AHI) in patients with and without anti-TNF-α treatment.

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Material and Methods

Between January 2008 and December 2009, patients aged 30 to 76 were recruited from the outpatient clinic of a Rheumatology Department. Patients fulfilling the following two enrolment criteria were selected: 1) having an established diagnosis of RA or SpA. 2) having symptoms of SAHS. The study was approved by the Ethics Committee of the Hospital Universitario de Fuenlabrada in September 2007. Each patient was verbally informed of the study objects and then signed the informed consent. Symptoms suggestive of SAHS were considered as daytime sleepiness, morning headache and snoring, as established in the National Consensus Document on sleep apneas-hyponeas [13]. RA diagnosis was established using the 1987 revised American College of Rheumatology criteria [14] because the current criteria for the year 2010 from the American College of Rheumatology/European League against Rheumatism had not been published when the registry was begun. The Dougados et al. diagnostic criteria of SpA were used [15]. These included the van der Linden et al. [16] criteria of ankylosing spondylitis.

Each patient underwent a polysomnography that collected the apnea-hypopnea index (AHI) and mean oxygen saturation (SaO₂). AHI was defined as the number of apneas and hypopneas divided by hours of sleep. A patient was considered to have SAHS when the AHI value was greater than 15 apneas/hour or when the AHI was greater than 5 and associated to symptoms. Three categories of SAHS severity were established: Mild SAHS, when the value of AHI was less than 15; moderate when the AHI value was between 15 and 30 and severe when the AHI was greater than 30 [17]. In the clinical history, data were collected regarding CV risk factors: obesity, HBP, dyslipidemia, DM, smoking, alcohol intake and data of established CV disease: stroke and ischemic heart disease.

HBP was defined as follows: systolic blood pressure levels equal or superior to 140 mmHg and/or diastolic BP 90 mmHg when measured in the doctor’s office (mean of 2 readings at rest with the patient in sitting position) or systolic levels of 130-135 mmHg and/or diastolic ones of 85 mmHg if the measurements were made by ambulatory monitoring (daytime mean of the readings), or when the patient measured their blood pressure at home (mean of all the recordings), or was receiving antihypertensive treatment, according to the European Society of Hypertension/European Society of Cardiology criteria [18]. HBP levels over 135/85 mmHg were considered if the patient had diabetes mellitus and/or chronic kidney disease. Obesity was considered when body mass index (weight in Kg/height in m²) was equal to or greater than 30 Kg/m², according to the Spanish Society for the Study of Obesity [19]. DM was defined as glucose levels with fasting equal to or greater than 126 mg/dL in 2 measurements on different days and/or casual glycaemia at any time of the day superior to 200 mg/dL and/or when the patient was receiving treatment with glucose-lowering drugs and/or insulin, in accordance with the criteria of the American Diabetes Association [20]. A patient was considered to be a smoker if he/she reported smoking (one or more cigarettes/week) at the time of the clinical questioning. Ex-smokers or non-smokers were not considered. Hypercholesterolemia was considered as total cholesterol concentration in blood equal to or greater than 200 mg/dL, or when the patient was being treated with statins [21]. Ischemic heart disease was considered to exist in those subjects who had suffered angina, an acute coronary syndrome episode, or who had received a coronary stent or coronary bypass. Stroke was recorded in the patients who had suffered ischemic or hemorrhagic cerebrovascular accident or transient ischemic attack.

Control group

A control group was established with patients who had osteoarthritis and SAHS diagnosed by polysomnography attended in the same Rheumatology Department. The same clinical and CV risk factors were collected in all the patients of the control group.

Statistical analysis

Mean and standard deviation (SD) were used in the continuous variables description. Median and quartiles were calculated for the principal continuous variables, that is, AHI and SaO₂, which did not have a normal distribution. Number and percentage of patients per response category were used to describe categoric variables. The Student’s T test and Pearson’s Chi-squared were used for the comparative analysis of the variables between groups (study vs. control, RA vs. SpA, treated vs. non-treated) for large samples. The Fisher test or correction of continuity was used for small samples. Comparison of the AHI and SaO₂ variables was performed using the non-parametric Mann-Whitney U Test.

Results

A total of 133 subjects were enrolled. Of these 75 belonged to the study group and 58 to the control group. The study group was made up of two subgroups, one with 48 patients with RA and another with 27 with SpA. Of these, 16 had ankylosing spondylitis and 11 psoriatic arthritis (4 in axial form and 7 in mixed peripheral axial form). The control group was made up of osteoarthritis in different locations. The mean duration of illness in the group of patients with RA was greater of two years in the group of patients with RA. 80% of patients had inflammatory indices DAS 28 over 5. Sixteen patients from the study group were treated with anti TNF-α. Among the 8 patients with AR, 3 received adalimumab, 1 adalimumab with methotrexate, 1 etanercept, 1 etanercept with methotrexate and 2 infliximab with methotrexate. All patients with spondyloarthropathy BASDAI indexes showed greater than 50 mm. The mean duration of disease was 8 years since the onset of symptoms. Of the 8 patients with SpA, 3 received adalimumab with methotrexate, 3 adalimumab with methotrexate and leflunomide, 1 etanercept and methotrexate and 1 etanercept with methotrexate and leflunomide (Figure 1). The associated CV risk factors and SAHS characteristics of the study and control group are shown in Table 1. The exact duration of the symptoms of OSAS was not picked up by more than 40% of patients in the case group and more than 50% of control subjects. In other cases the average duration of symptoms was more than 5 years in both the control group and the case group. It stands out that compared to the control group, the study group patients were younger and greater prevalence of ischemic heart disease, hypercholesterolemia, HBP and stroke. The following stand out in the polysomnography: higher AHI in patients from the study group versus the control group (37.4 vs. 27.8, p=0.025), while no differences were observed in the SaO₂. Patients with RA and SpA compared to those with osteoarthritis had more severe (62.7% vs. 51.7%) and less mild forms of SAHS (9.3% vs. 20.7%). The clinical characteristics of the patients from the subgroups with RA and SpA are shown in Table 2. Patients with RA compared to patients with SpA were older, had a lower proportion of men and greater tendency to a higher incidence of HBP.

The clinical characteristics of the control group patients treated with anti-TNF-α agents and the untreated patients are shown in Table 3. It should be mentioned that in the treated patients compared to the untreated group, AHI was lower (38.61 vs. 29.1, p=0.059), this being similar to that of patients of the control group with osteoarthritis (27.8).
Distribution of the patients


Table 1: General data of the population (study and control group).

<table>
<thead>
<tr>
<th></th>
<th>Study group N 75</th>
<th>Control group N 58</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Age, years, X(SD)</td>
<td>53.1±10.6</td>
<td>57.2±9.6</td>
<td>0.022</td>
</tr>
<tr>
<td>Gender, men, n(%)</td>
<td>36(48.0)</td>
<td>23(39.7)</td>
<td>0.337</td>
</tr>
<tr>
<td>CV risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity, n(%)</td>
<td>63(84.0)</td>
<td>43(74.1)</td>
<td>0.161</td>
</tr>
<tr>
<td>Alcohol intake, n(%)</td>
<td>44(58.7)</td>
<td>29(50.0)</td>
<td>0.319</td>
</tr>
<tr>
<td>HBP, n(%)</td>
<td>10(13.3)</td>
<td>3(5.1)</td>
<td>0.116</td>
</tr>
<tr>
<td>Hypercholesterolemia, n(%)</td>
<td>49(65.3)</td>
<td>30(51.7)</td>
<td>0.113</td>
</tr>
<tr>
<td>DM, n(%)</td>
<td>17(22.7)</td>
<td>11(19.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic heart disease, n(%)</td>
<td>13(17.3)</td>
<td>2(3.4)</td>
<td>0.013</td>
</tr>
<tr>
<td>Stroke, n(%)</td>
<td>6(8.0)</td>
<td>1(1.7)</td>
<td>0.110</td>
</tr>
<tr>
<td>SAHS Evaluation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI, median (p25-p75)</td>
<td>37.4(25.5-56.2)</td>
<td>27.8(19.5-49.6)</td>
<td>0.025</td>
</tr>
<tr>
<td>Sat O₂, median (p25-p75)</td>
<td>93(91-94)</td>
<td>92(91-93)</td>
<td>0.125</td>
</tr>
<tr>
<td>OSAS severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild, n(%)</td>
<td>7(9.3)</td>
<td>12(20.7)</td>
<td>0.165</td>
</tr>
<tr>
<td>Moderate, n(%)</td>
<td>21(28.0)</td>
<td>16(27.6)</td>
<td></td>
</tr>
<tr>
<td>Severe, n(%)</td>
<td>47(62.7)</td>
<td>30(51.7)</td>
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Discussion

The finding of the study presented has the limitation of being collected in a retrospective manner. However the data show that the forms of SAHS in patients with RA and SpA are more severe and less mild than in patients with osteoarthritis. In addition, CV risk factors such as hypercholesterolemia or ischemic heart disease show a 3 to 5 times greater prevalence in patients with RA and SpA than in those with osteoarthritis. In patients treated with anti-TNF-α agents who had RA or SpA, the AHI levels were lower than in those not treated with these agents and were similar to patients suffering osteoarthritis and associated SAHS. This suggests a possible modulator role of anti-TNFα agents in the number of nighttime apneas-hypopneas in patients with SAHS. It is known that patients with RA generally have increased CV risk compared to the general population. However, it does not seem that this increase can be explained by traditional CV risk factors [1]. In this way, ischemic heart disease incidence is almost 5 times greater in the study group than in patients with osteoarthritis. In fact, early appearance of myocardial infarctions prior to the formal diagnosis of
as an independent factor [11]. Furthermore, patients with SAHS have a SAHS per se may contribute to the CV mortality of patients with RA to AHI, independently of obesity. Some authors have considered that an acute coronary episode [24]. SAHS is also generally associated to formation and instability of the atheromatous plaque and may trigger which may harm the endothelium [23]. IL-6 contributes to the of CV events, play a role in the pathogenesis of RA. These cytokines such as the TNF-α and IL-6, which also are independent predictors 

The spondyloarthropathy group was formed by ankylosing spondylitis (n=16) and by psoriatic arthritis (n=11) X (SD), mean (standard deviation). CV: cardiovascular. HBP, high blood pressure. DM, diabetes mellitus. SAHS, sleep apnea hypopnea syndrome, AHI, apnea-hypopnea index. Sat O2, oxygen saturation. OSAS: Obstructive Sleep Apnea Syndrome, RA: rheumatoid arthritis

<table>
<thead>
<tr>
<th>RA Group</th>
<th>Untreated N 59</th>
<th>Treated N 16</th>
<th>p</th>
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<tr>
<td>Age, years, X(SD)</td>
<td>55.8±4.9</td>
<td>48.2±10.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Gender, men, n(%)</td>
<td>19(39.6)</td>
<td>17(63.0)</td>
<td>0.052</td>
</tr>
</tbody>
</table>

The treated patients received adalimumab, or etanercept or infliximab, associated or not to methotrexate and/or leflunomide (see text) X (SD), mean (standard deviation). CV: cardiovascular. HBP: high blood pressure. DM: diabetes mellitus. SAHS, sleep apnea hypopnea syndrome, AHI, apnea-hypopnea index. Sat O2, oxygen saturation. OSAS: Obstructive Sleep Apnea Syndrome

<table>
<thead>
<tr>
<th>OSAS severity</th>
<th>Mild, n(%)</th>
<th>Moderate, n(%)</th>
<th>Severe, n(%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSAS Evaluation</td>
<td>AHI, median (p25-p75)</td>
<td>38.7(27.1-70.0)</td>
<td>34.8(22.6-44.6)</td>
<td>0.109</td>
</tr>
<tr>
<td></td>
<td>Sat O2, median (p25-p75)</td>
<td>93(91-94)</td>
<td>93(91-94)</td>
<td>0.716</td>
</tr>
</tbody>
</table>

The development of the biological agents that selectively block cytokines, especially the TNF-α inhibitors, has meant a fundamental advance in the treatment of inflammatory arthritis. TNF-α is elevated in RA, ankylosing spondylitis and in psoriatic arthritis. In the patients of this study who had this type of arthritis as well as associated SAHS, treatment with TNF-α inhibitors (adalimumab with or without methotrexate, etanercept with methotrexate and infliximab with methotrexate) improved the AHI. This suggests that the inflammatory condition common to both conditions shares a pathogenic mechanism that may improve with the same therapeutic target.

In addition, AHI in this study of patients with inflammatory arthritis was greater than in the patients with osteoarthritis. When these patients were treated with biological agents, their AHI decreased, resembling the levels of the osteoarthritis group. This would support the hypothesis that a chronic increase over time in inflammation could be the cause of the SAHS. In fact, it has been described that there is generally an association to SAHS in patients with an increased in TNF-α, and those that have a polymorphism of it (~308A) [27]. The earlier RA treatment is initiated, the greater is the likelihood that the inflammatory condition can be controlled, thus reducing the structural damage [28]. However, treatment is generally initiated with methotrexate when significant activity is already present and when rapid progression is to be expected, treatment is generally associated to a biological agent, such as an anti-TNF-α [3] that clearly contributes to the inflammatory condition of the RA [29]. On the other hand, the fact that there is greater CV risk in both inflammatory arthritis and in SAHS emphasizes the importance of considering TNF-α inhibitors as a therapeutic alternative. It has been demonstrated that these inhibitors improve endothelial function [30] and lead to a reduction in the incidence of CV events [31]. In this work, greater severity of the SAHS is observed in patients with inflammatory arthritis as well as its improvement, evaluated through the AHI, with treatment with anti-TNF-α. This corroborates some preliminary observation [12] and the importance that these drugs may have as modulators of the common etiopathogenic nexus of inflammatory arthropathies with associated SAHS.

This study has some limitations, such as the fact that it evaluates retrospective data, it lacks baseline comparator data of the patients treated and the two study groups have not been adjusted as this is a small sample. However, as far as we know, this is the first time that data are presented on the severity of SAHS in RA and SpA and the behavior of SAHS in patients treated with anti-TNF-α. In summary, the data of the present study show that patients with inflammatory arthropathies have greater severity of SAHS, greater prevalence of traditional CV risk factors and that treatment with TNF-α inhibitors improves the SAHS. This suggests that the inflammatory condition may contribute to the development of SAHS.

RA has been described [22]. A series of pro-inflammatory cytokines, such as the TNF-α and IL-6, which also are independent predictors of CV events, play a role in the pathogenesis of RA. These cytokines may be released into the circulation with important systemic effects, which may harm the endothelium [23]. IL-6 contributes to the formation and instability of the atheromatous plaque and may trigger an acute coronary episode [24]. SAHS is also generally associated to higher CV risk, especially in young subjects [8]. Patients with SAHS usually also have increased TNF-α and IL-6, [25] that is also related to AHI, independently of obesity. Some authors have considered that SAHS per se may contribute to the CV mortality of patients with RA as an independent factor [11]. Furthermore, patients with SAHS have a greater risk of developing certain autoimmune disease [26]. However, the excess CV risk that may be entailed in the combined appearance of inflammatory arthritis and SAHS in one same patient is something that has not been clarified. Given the high and growing prevalence of the latter condition in Western countries, these associations may represent an important health care problem. The data from the present study show that patients with inflammatory arthritis have less mild and more severe forms of SAHS than the control group with non-inflammatory arthropathies. This would corroborate the hypothesis that this syndrome may contribute to the development of the autoimmune disease.
References


