



## Original article

## Anti-transglutaminase, antigliadin and ultra purified anti-gliadin antibodies in patients with a diagnosis of rheumatoid arthritis

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## ARTICLE INFO

## Article history:

Received January 12, 2010

Accepted March 8, 2010

## Keywords:

Rheumatoid arthritis

Celiac disease

Anti-tissue transglutaminase

Anti-gliadin and ultra purified anti-gliadin antibodies

## ABSTRACT

Celiac disease (CD) is an enteric disease caused by dietary gluten in individuals with genetic predisposition. One of the clinical manifestations of CD is peripheral arthritis that may simulate RA.

**Objective:** To determine the frequency of anti-gliadin (aGL), anti-tissue transglutaminase (aTGT) and ultra purified anti-gliadin (AGLU) antibodies in patients with RA.

**Methods:** Cross-sectional study. We included consecutive patients diagnosed as RA (ACR). Demographic and clinical data were registered by direct interview and serum levels of aGL, aTGT and aGLU were determined using ELISA.

**Results:** Eighty-five RA patients were included; 87% were women. Mean age was 44±12 years, mean disease duration 12±9 years. IgG aGL antibodies were positive in 16 patients, IgA aGL antibodies in 29 patients, aGLU in 14 patients and only one patient had aTGT.

**Conclusions:** It is possible that CD may be the correct diagnosis in a patient with polyarthritis, even if the patient meets the ACR criteria for RA. In other words, CD should be considered among the differential diagnoses in a patient with polyarthritis.

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### Anticuerpos anti-transglutaminasa, anti-gliadina y anti-gliadina ultra-purificada en pacientes con diagnóstico de artritis reumatoide del adulto

## RESUMEN

La enfermedad celiaca (EC) es una afección entérica ocasionada por la ingesta de granos que contienen gluten. Una manifestación clínica poco reconocida es la artritis periférica, que puede simular artritis reumatoide.

**Objetivo:** Determinar la frecuencia de anti-Gliadina (aGL), anti Transglutaminasa Tisular (aTGT) y anti-Gliadina Ultra-purificada (aGLU) en pacientes con diagnóstico de AR.

**Métodos:** Es un estudio transversal de pacientes con AR (criterios ACR). Se registraron variables demográficas y clínicas y se les realizaron determinaciones séricas de anticuerpos aGL, aGLU y aTGT por ELISA.

**Resultados:** Se incluyeron 85 pacientes con AR. El 87% de los pacientes fueron mujeres. El promedio de edad fue de 44 años ± 12, con una media de 12 ± 9 años de evolución. Los anticuerpos aGL IgG estuvieron positivos en 16 pacientes, los aGL IgA en 29 pacientes, la aGLU en 14 pacientes y solo un paciente fue positivo para aTGT.

**Conclusiones:** Es posible que pacientes con poliartrosis y que cumplan con los criterios de clasificación de AR puedan tener de hecho EC. De otra forma, la EC debe considerarse dentro del diagnóstico diferencial de poliartrosis.

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## Palabras clave:

Artritis reumatoide

Enfermedad celiaca

Anticuerpos anti-transglutaminasa tisular

Anti-gliadina y anti-Gliadina ultra-purificada

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## Introduction

The diagnosis of rheumatoid arthritis (RA) does not pose any major problem once the structural damage is well established; nonetheless, in the early stages it represents a challenge as there are multiple illnesses that may course with arthritis.<sup>1</sup>

One rarely encountered cause of polyarthritis in Mexico is coeliac disease (CD), characterized by intestinal alterations triggered by the intake of grain containing gluten in genetically predisposed individuals.<sup>2</sup> Recent populational studies have shown that CD occurs not only in Anglo-Saxon countries but also in others where it was believed not to exist; in fact, in countries in North America, Asia and Africa, the prevalence of CD reaches 1% of the general population.<sup>3-7</sup>

The determination of serum antibodies such as tissue anti-transglutaminase (aTGT), anti-endomysium (aEM), anti-gliadin (aGL) and ultrapurified anti-gliadin (aGLU) is useful for the diagnosis of CD.<sup>8</sup> aTGT antibodies have the greatest sensitivity (98%) and specificity (96%) for the diagnosis of CD, whereas aGL and aGLU show a sensitivity of 80% and a specificity of 80%-90%.<sup>9</sup>

There is some controversy in the literature regarding the interrelation between CD and RA. The information can be grouped along three axes: 1) where there is an increase in intestinal permeability in patients with RA secondary to the use of NSAIDs, with activation of auto-immunity and CD in genetically predisposed subjects<sup>10</sup>; 2) where both illnesses occur by chance in the same subject, without sharing pathogenic mechanisms,<sup>11</sup> and 3) where some patients diagnosed as having RA actually suffer from CD with joint manifestations.<sup>12</sup> The aim of the present study was to evaluate the frequency of aGL, aTGT and aGLU in a consecutive sample of patients diagnosed as having RA seen at the rheumatology clinic.

## Patients and methods

This is a transversal study assessing consecutive patients diagnosed as having RA according to the ACR classification criteria<sup>13</sup> and under treatment from a rheumatologist at an IMSS second-level hospital (HGR 45) over a period of 2 months.

Demographic and clinical variables were noted for each patient by means of a direct interview following a questionnaire specifically designed for the purpose and with a review of the case file. Each patient give consent for an additional 5 mL sample of peripheral venous blood to be taken for the determination of IgG and IgA aGL, aTGT and aGLU antibodies.

The antibody concentrations were evaluated using the ELISA technique with commercial kits. The upper normal limits recommended by the manufacturer (EUROIMMUN®. Medizinische Labordiagnostika AG) were 20 UR/mL for aTGT and 25 UR/mL for aGL.

The differences between means were determined using the Student's *t*-test for independent samples, and with two tails. The differences between proportions were determined using the chi-square test with Fisher's correction when considered appropriate. Statistical significance was deemed to have been achieved if  $P < .05$ . The trial was approved by the Ethics Committee of the IMSS HGR 45.

All patients included in the study received sufficient information and gave informed consent in writing in order to take part in the same.

## Results

A total of 85 patients diagnosed as having RA were recruited; of these, 74 were female (87%). Table 1 presents the main demographic and clinical details of the patients. The age range was from 16 to 76 years. Of these patients, 25.8% had had the disease for less than 5 years, 25.8% for between 5 and 10 years and 48.4% for more than 10 years. Most of the patients were under treatment with methotrexate and 13% used some anti-TNF alpha.

**Table 1**

Demographic and clinical characteristics of the 85 patients studied

Variables	Results
Gender	n (%)
Females	74 (87%)
Males	11 (13%)
Age, mean in years ( $\pm$ SD)	49.1 $\pm$ 11.8
Years since diagnosis ( $\pm$ SD)	11.2 $\pm$ 9.3
Treatment, n (%):	
Methotrexate	73 (85)
Sulphasalazine	20 (23.5)
Chloroquine	25 (29.4)
Anti-TNF	11 (12.9)
Others	13 (15.2)
Anti-cyclic citrullinated peptide (%)	66 (77.6)
Rheumatoid Factor, n (%)	64 (75.2)

SD indicates standard deviation.

**Table 2**

Distribution of antibody frequencies in 85 patients with rheumatoid arthritis

	Anti-Gliadin antibodies*		
	IgG	IgA	Ultrapurified
FR+, n (%)	15 (94)	24 (83)	10 (71)
FR-, n (%)	1 (6)	5 (17)	4 (29)
Anti-CCP+, n (%)	13 (81.5)	22 (76)	10 (72)
Anti-CCP-, n (%)	3 (18.5)	7 (24)	4 (28)

\*All comparisons with  $P > .06$ .

IgG aGL antibodies were positive in 16 patients with an upper limit of 157 and a lower limit of 29.9 mg/dL. IgA aGL antibodies fueron positive in 29 patients with an upper limit of 163 and a lower limit of 31 mg/dL. aGLU was positive in 14 patients with upper and lower values of 129 and 28 mg/dL, respectively. Table 2 shows the frequency distribution of the serum antibodies studied sorted by groups: rheumatoid factor and anti-cyclic citrullinated peptide antibodies; the differences observed had no statistical significance. The frequency of IgG aGL antibodies was 18%, IgA aGL was 34% and aGLU was 16%. Only one patient was positive for both IgA and IgG aGL as well as for aTGT, the latter with a value of 92.5 mg/dL. No significant differences were determined between the clinical characteristics of the patients with and without these antibodies.

## Discussion

This study has found that between 16% and 34% of consecutive patients diagnosed as having RA and seen by a rheumatology specialist had serum antibodies related to antigenicity for gluten. Only one patient, representing 1% of the population studied, had 3 positive antibodies, including aTGT. This patient had a diagnosis of RA, was seropositive to rheumatoid factor and anti-CCP and had no evident erosions in the simple X-rays of her hands and feet. She was considered to have had a failed response to methotrexate and was therefore given rituximab, with a favourable response. Nonetheless, 13 months later, she once more presented polyarthritis and acceleration of globular erythro sedimentation. The patient started a gluten-free diet and total remission of the polyarthritis was achieved in 2 months without administration of rituximab or methotrexate. After twenty months, the patient continues in remission with a gluten-free diet.

These findings support 2 ideas. The first is that patients with RA may have gastrointestinal alterations entailing antigenicity for gluten. The clinical relevance of this is not known but it has been suggested that it may have therapeutic implications. For example,

Hafström et al<sup>11</sup> randomized 66 patients with active RA to receive either gluten-free diet (38 patients) or their normal diet but well-balanced (28 patients) over one year. Among the patients receiving the gluten-free diet, 40.5% met the ACR20 response criteria in comparison with 4% of the non-diet group; the aGL IgG also diminished.

The second concept has to do with the fact that the joint manifestations of CD, at least in some patients, may resemble RA. In our series, 1% of the patients had a final diagnosis of coeliac disease and not rheumatoid arthritis. The diagnosis of CD may go unnoticed in many cases as the systemic manifestations such as polyarthritis may predominate and the gastrointestinal ones may be mild or even absent; it has been called the “great impostor of the modern age”. CD may be a “silent” illness as the diarrhoea may not be prominent and could be diagnosed as irritable bowel syndrome, or it may present with polyarthritis, osteoporosis, anaemia, peripheral neuropathies, ataxia, epilepsy, recurrent pancreatitis, mouth ulcers, hyperamylasaemia or alterations in liver function tests; it may also be associated with such other diseases as auto-immune hepatitis, thyroid-related disorders, type I diabetes mellitus and psoriasis, among others.<sup>14</sup> For example, between 2% and 7% of patients with osteoporosis have been found to have CD.<sup>15</sup>

In conclusion, the presence of aGL, aGLU and aTGT antibodies is frequent in patients with RA and some of those diagnosed as having RA may in fact have CD. We suggest coeliac disease should be included within the differential diagnosis process for polyarthritis, particularly when patients show no improvement with DMARDs.

#### Conflict of interest

The authors have stated that there is no conflict of interest.

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