‘Preclinical’ rheumatoid arthritis in patients with celiac disease: A cross-sectional study

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1. Introduction

Rheumatoid arthritis (RA) is a chronic immune-mediated disease leading to joint and synovial inflammation. Even with the advent of effective pharmacotherapy, RA is still associated with a high health-care burden due to the expensive medical treatment, management of comorbidities and increased premature mortality[1]. Studies done on RA patients have demonstrated that preceding the clinical manifestations of RA, there is a period of abnormal immune tolerance characterized by the presence of specific autoantibodies (Rheumatoid factor/anti-CCP antibodies)[2]. However, exactly when and how this process starts is still unknown as the autoantibodies may be detected 3–5 years prior to the initial joint symptoms. This disease period has been referred to as ‘preclinical’ or ‘latent’ RA in the medical literature although the proper term still remains undecided[3].

Identifying preclinical RA is important as it can help us understand the natural history of RA while developing effective screening and preventive strategies. For this purpose, research is being done to identify appropriate population group who are at high risk of developing RA in the future. The role of genetic and various environmental factors such as smoking and infections in triggering RA is well established[2]. In addition, the presence of another autoimmune disorder is also being investigated as a possible risk factor. This is because the joints/synovium are pathologically normal in preclinical RA leading to the hypothesis that previous immune dysfunction may cause initial RA-associated autoantibody production which then results in synovial inflammation characteristic of RA [2,4].

The above stated hypothesis is also strengthened by the medical literature documenting the co-occurrence of RA with various other autoimmune diseases—one of which is Celiac disease (CD)[5]. This RA-CD relationship is especially important because it has been postulated that immune dysfunction in RA arises from the intestinal mucosa and the increased intestinal permeability in CD leads to protein citrullination with subsequent autoantibody production in RA. Hallgren et al [6] demonstrated that CD patients exhibit increased levels of rheumatoid factor in the gut mucosa while another study showed clinical improvement in patients with RA when kept on a gluten-free diet (GFD)[7]. Celiac disease is phenotypically distinct from RA but recently, a possible symptomatic overlap has been described in both these diseases. Patients with CD...
may exhibit various rheumatological manifestations while RA patients can have some degree of intestinal symptoms. In addition, similar environmental and genetic features have been observed in both diseases\[8\]. However, detailed studies evaluating the presence of RA features or serology in CD patients are still lacking. Our study was thus performed to assess whether patients with CD should be considered as a high-risk population group based on the prevalence of positive RA serology.

2. Methodology

We conducted a cross-sectional study based on data obtained from patients being treated at Benazir Bhutto Hospital, Rawalpindi, Pakistan which is a tertiary care hospital. The duration of the study was 12 months extending from 1 January 2012 till 31 December 2012. The study method followed the principles of Declaration of Helsinki. Patients were enrolled from both the inpatient and clinic settings after initial case screening and data collection was performed by a resident physician.

Inclusion criteria included confirmed diagnosis of Celiac disease based on positive serology and/or small intestinal biopsy results.

Exclusion criteria included: 1) Age less than 16 years, 2) Positive serology for CD but diagnosis not confirmed with histopathology, 3) Positive serology for CD but histopathology was negative for CD.

Sixty patients were initially enrolled in the study, out of whom forty-five were included in the final study group based on the inclusion and exclusion criteria (Figure 1). Both verbal and written consent was taken from the patients.

In the first part of the study, we assessed each patient with the help of a questionnaire to gather the baseline data which included demographics and specific details about the Celiac disease. In addition, patients were evaluated for any current or previous joint symptoms (non-specific arthralgias, joint swelling, morning

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**Figure 1.** Flow chart of the study.
stiffness lasting for more than 2 hours) along with any radiological joint testing and abnormalities.

Then in the second part of the study, the standard RA serological testing was done which included Rheumatoid factor (RF) and anti-CCP (Citrullinated Cyclic Peptide) antibodies. Rheumatoid factor (IgM) levels were checked via Latex agglutination. Although the reference range for the test was 0–20 IU/ml, a cut-off value above 60 IU/ml was considered positive for this study. Anti-CCP antibodies were identified with the help of ELISA with a definite cut-off value of 8 IU/ml. Patients with positive serology were determined to have preclinical RA.

Mean and standard deviation was calculated for the quantitative variables which included age and time since diagnosis of Celiac disease. Frequency and percentage was calculated for all the qualitative variables such as gender, activity of Celiac disease and treatment modalities.

Prevalence was then measured for the following patient categories: 1) With positive antibodies (either RF or anti-CCP) 2) With positive RF titers 3) With positive anti-CCP antibodies and 4) With both positive RF and anti-CCP antibodies.

To analyze the relationship of the different variables, the patients were stratified into two major groups: Patients with positive RA serology (preclinical RA) and those with negative RA serology. Group of patients with positive serology were further studied after being divided into sub-groups based on the type of positive serology (RF positive vs. anti-CCP positive).

Data analysis was done with the help of OpenEpi, version 3.01. The log-binomial regression (CI 95%) and chi-square test was performed. P-values <0.05 were considered statistically significant.

3. Results

The baseline characteristics of the patients are summarized in Table 1. Out of the forty-five patients enrolled in the study, forty were female (88%) and five were male, with a female-to-male ratio of 8:1. The mean age was 26.2 years (±5.84 SD) while the mean duration of CD since diagnosis was 6.4 months (± 6.26 SD). Eighteen patients had active CD symptoms (40%) while overall six patients required steroids in addition to gluten-free diet for disease management (13%).

Twenty-seven patients endorsed experiencing some degree of arthritic symptoms. However, only sixteen patients (36%) gave history of significant joint swelling associated with morning stiffness >2 hours. Twelve patients had undergone radiological imaging of the joints for the evaluation of these symptoms, out of whom six patients (13%) were documented to have joint abnormalities such as osteopenia and erosions.

Out of the forty-five CD patients, sixteen (35%) were found to have positive RA serology (Table 2). These included fifteen patients with positive RA factor (33%) and three with positive anti-CCP antibodies (6%). However, only two patients had both positive RA factor and anti-CCP antibodies.

Detailed analysis (Table 3) demonstrated that 87% of the patients with positive serology (n = 14) and 89% of patients with negative serology (n = 26) were females. The overall prevalence rate of positive RA serology in females was 35% as compared to 40% in males showing no statistical significance for gender (p-value 0.59). Duration of CD was also not statistically different between both groups of patients (p-value 0.25).

Patients with active celiac disease were found to have a higher prevalence rate of positive serology (61%) as compared to patients with controlled CD (18.5%). The prevalence ratio was statistically significant (p-value of 0.004) showing that the probability of positive RA serology in active CD is almost 3 times higher.

A similar trend (p-value of 0.01) was seen for CD patients being treated with steroids in addition to gluten-free diet who were subsequently found to have positive RA serology (83%) indicating that although GFD is a major component in management of CD, it might not be enough in CD patients who are at high-risk for other autoimmune diseases such as RA.

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**Table 1. Clinical characteristics of the patients.**

| Baseline Characteristics | Mean | Standard Deviation |
|-------------------------|------|--------------------|
| Age (years)             | 26.28| 5.84               |
| Duration of celiac disease (months) | 6.4  | 6.26               |

| Treatment modalities:          | Number (n) | Percentage (%) |
|-------------------------------|------------|----------------|
| Controlled                    | 27         | 60%            |
| Not controlled                | 18         | 40%            |

**Table 2. Prevalence of RA-associated serological markers in patients with Celiac disease.**

| Positive RA serology n (%) | Positive RF n (%) | Positive anti-CCP n (%) | Both RF and anti-CCP n (%) |
|----------------------------|-------------------|--------------------------|---------------------------|
| 16 (35%)                   | 15 (33%)          | 3 (6.6%)                 | 2 (4.4%)                  |
Based on prevalence ratio, the probability of preclinical RA was 3 times higher in patients with arthritic symptoms as compared to patients without such symptoms. However, no statistical difference was seen for the radiological abnormalities (p-value of 0.1).

Analysis of variables between patients with positive RA factor and patients with positive anti-CCP antibodies was also performed (Table 4). However, there was no statistical significance seen for any baseline characteristics between these two sub-groups.

4. Discussion

Through this study, the authors have tried to answer the following questions:

(1) Identifying pre-clinical RA in patients with CD to consider screening/early treatment interventions
(2) Predictive factors of preclinical/early RA in CD patients
(3) Preferred autoantibody test for preclinical RA in CD

Several studies have been performed reporting the presence of characteristic RA autoantibodies (Rheumatoid factor and anti-CCP antibodies) in up to 50% of the patients prior to the appearance of clinical manifestations indicating abnormal immune tolerance. In patients with early clinical RA, the frequency of RF is 50–66% and the prevalence of anti-CCP is 41–48%, compared to 7–13% and 2–3% respectively in normal. However, almost all of these have been retrospective studies as the major problem in conducting a prospective study of preclinical RA is that the number of such individuals is likely quite low, and it would be expensive to find them in general population. Therefore, identifying individuals that may be at particularly high risk for future RA such as with known autoimmune diseases can improve the yield of diagnosing preclinical phase of RA.

While RA-related autoantibodies may be generated in the joints in individuals with established disease, medical data suggests that mucosal sites may be the initial site of production. One of the autoimmune disorders with similar pathology to that seen in RA is CD and several studies have shown co-occurrence of the two disorders [5,8]. In our study, 35% (16/45) of patients with CD were found to have positive RA serology which included fifteen patients with positive RF (33%) and three with positive anti-CCP antibodies (6.6%). This shows a higher prevalence of autoantibody positivity in CD as compared to the healthy individuals indicating that patients with CD might be a considered for RA screening.

Another study showed that unregulated immune dysfunction occurs in active celiac disease leading to enhanced mucosal RF antibody production[6]. Statistical significance was observed for active CD (p-value of 0.004) as a risk factor when comparing the CD patients with and without RA serology. Active CD was seen in 68% (n = 11) of seropositive vs 24% (n = 7) in seronegative patients while the overall prevalence of positive serology in active CD patients was 61%.

Rheumatological manifestations described in patients with CD include non-specific arthralgias, polyarthritis with morning stiffness, enthesopathy, subclinical synovitis and sacro-ilitis [8,9]. In our study, history

Table 3. Association of baseline characteristics and serology results.

| Variables                                  | Serology positive n (%) | Serology negative n (%) | Prevalence ratio (Confidence interval 95%) | p-value |
|--------------------------------------------|-------------------------|-------------------------|-------------------------------------------|---------|
| Gender                                     |                         |                         |                                           |         |
| • Females                                  | 14 (35%)                | 26 (65%)                | 0.87 (0.27–2.77)                          | 0.59    |
| • Males                                    | 2 (40%)                 | 3 (60%)                 | 1.14 (0.36–3.62)                          | 0.57    |
| Activity of celiac disease:                |                         |                         |                                           |         |
| • Not controlled                           | 11 (61%)                | 7 (38.8%)               | 3.3 (1.37–7.89)                           | 0.004   |
| • Controlled                               | 5 (18.5%)               | 22 (81.4%)              | 0.47 (0.17–1.26)                          | 0.12    |
| Treatment modalities:                      |                         |                         |                                           |         |
| (1) Diet alone                             | 11 (28.2%)              | 28 (71.7%)              | 0.33 (0.18–0.62)                          | 0.01    |
| (2) Diet plus steroids                     | 5 (83.3%)               | 1 (16.6%)               | 2.9 (1.59–5.46)                           | 0.01    |
| Arthritis with morning stiffness >2 hrs    | 10 (62.5%)              | 6 (37.5%)               | 3.02 (1.34–6.77)                          | 0.006   |
| Radiological joint abnormalities           | 4 (66.6%)               | 2 (33.3%)               | 2.16 (1.03–4.52)                          | 0.1     |

Table 4. Association of baseline characteristics based on type of positive serology.

| Variables                                  | RF positive n (%) | Anti-CCP positive n (%) | Prevalence ratio (Confidence interval 95%) | p-value |
|--------------------------------------------|-------------------|-------------------------|-------------------------------------------|---------|
| Gender                                     | MALE              | FEMALE                  |                                           |         |
| • Females                                  | 13 (86.6%)        | 2 (13.3%)               | 1.3 (0.57–2.96)                           | 0.44    |
| • Males                                    | 2 (66.6%)         | 1 (33.3%)               | 0.76 (0.33–1.75)                          | 0.32    |
| Activity of celiac disease:                |                    |                         |                                           |         |
| • Not controlled                           | 10 (90.9%)        | 1 (9%)                  | 1.27 (0.76–2.10)                          | 0.32    |
| • Controlled                               | 5 (71.4%)         | 2 (28.5%)               | 0.78 (0.47–1.30)                          | 0.32    |
| Treatment modalities:                      |                    |                         |                                           |         |
| (1) Diet alone                             | 11 (84.6%)        | 2 (15.3%)               | 1.05 (0.64–1.73)                          | 0.64    |
| (2) Diet plus steroids                     | 4 (80%)           | 1 (20%)                 | 0.94 (0.57–1.55)                          | 0.41    |
| Arthritis with morning stiffness >2 hrs    | 9 (90%)           | 1 (10%)                 | 1.2 (0.76–1.88)                           | 0.41    |
| Radiological joint abnormalities           | 3 (75%)           | 1 (25%)                 | 0.87 (0.47–1.60)                          | 0.55    |
of joint inflammation showed a significant association between the two groups of patients with and without RA serology (p-value 0.006) but no statistical difference was seen for presence of radiological abnormalities.

Gluten-free diet (GFD) is postulated to confer some degree of protection from developing various auto-antibodies. Various studies have shown the deleterious effects of gluten on the immune-system[10]. Our study showed that only 28% of patients who were on GFD were positive for RF/anti-CCP. However, 83.3% of seropositive patients required additional steroids to achieve control of CD as compared to 16.6% in seronegative patients (p-value 0.01) indicating that although GFD is a major component in management of CD, it might not be enough in CD patients who are at high-risk for other autoimmune diseases such as RA.

The sensitivity of RF is 70–80% while specificity is 80–85%. On the other hand, anti-CCP antibodies have a sensitivity of 45–90% but higher specificity of 95–98%. A meta-analysis has shown that the pooled sensitivities of anti-CCP and RF are similar, but anti-CCP positivity is more specific for RA and especially early RA[11]. However, the specificity of RF increases to almost 95% if a higher cut-off value is used as suggested in 2010 EULAR criteria for classification of RA[12]. The authors thus considered patients with RF levels above 60 IU/ml as seropositive. During data comparison between patients with positive RF and those with anti-CCP antibodies, there was no statistical difference seen in the baseline characteristics. This indicates that although combined RF and anti-CCP positivity is needed to make a diagnosis of RA, RF testing alone might be enough for screening purposes in CD patients.

5. Conclusion

Increased prevalence of RF/anti-CCP positivity indicates that patients with CD might be at a higher risk of developing RA and should be considered for RA serology screening. Additional predictive factors which might help in identifying such individuals are presence of rheumatological manifestations, active CD and patients requiring steroids despite being managed with gluten-free diet. Although a combination of RF and anti-CCP testing is recommended for the definite diagnosis of RA, RF testing alone with a higher cut-off level might be adequate and more cost effective for RA screening in patients with CD.

6. Drawbacks

Although patients with CD can be screened for preclinical RA with autoantibody testing, this recommendation needs to be validated by further clinical studies and trials. In addition, the serology can be negative in almost 30% of patients with RA- a condition called ‘seronegative RA’. This necessitates a longer study duration in these patients to assess the actual development of clinical RA in the context of initial serology results.

The results may be limited as the sample size was small and study participants were not included from general population. Many of the patients declined to participate in the initial study or for further follow-up due to practical limitations such as frequent hospital visits. In addition, possible recall bias should be considered for the historical data provided by the patients.

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References

[1] Uhlig T, Moe RH, Kvien TK. The burden of disease in rheumatoid arthritis. Pharmacoeconomics. 2014;32 (9):841–851.
[2] Deane KD. Preclinical Rheumatoid Arthritis (Autoantibodies). An updated review. Curr Rheumatol Rep. 2014;16(5):419.
[3] Bos WH, Wolbink GJ, Boers M, et al. Arthritis development in patients with arthralgia is strongly associated with anti-citrullinated protein antibody status: a prospective cohort study. Ann Rheum Dis. 2010;69:490–494.
[4] Dorner T, Hansen A. Autoantibodies in normals – the value of predicting rheumatoid arthritis. Arthritis Res Ther. 2004;6(6):282–284.
[5] Warjri SB, Ete T, Beyong T, et al. Celiac disease with Rheumatoid arthritis: an unusual association. Gastroenterology Res. 2015;8(1):167–168.
[6] Hällgren J, Knutson F, Lavö B, et al. Increased mucosal synthesis of rheumatoid factor (RF) in celiac disease. Clin Exp Immunol. 1996;103 (1):94–98.
[7] Hafstrom I, Ringertz B, Spangberg A, et al. A vegan diet free of gluten improves the signs and symptoms in rheumatoid arthritis: the effects on arthritis correlate with a reduction in antibodies to food antigens. Rheumatology (Oxford). 2001;40:1175–1179.
[8] Lerner A, Matthías T. Rheumatoid arthritis-celiac disease relationship: joints get that gut feeling. Autoimmun Rev. 2015;14(11):1038–1047.
[9] Lubrano E, Ciacci C, Ames PR, et al. The arthritis of coeliac disease: prevalence and pattern in 200
adult patients. Br J Rheumatol. 1996;35(12):1314–1318.

[10] Lauret E, Rodrigo L. Celiac disease and autoimmune-associated conditions. Biomed Res Int. 2013;2013:127589.

[11] Bas S, Perneger TV, Seitz M, et al. Diagnostic tests for rheumatoid arthritis: comparison of anti-cyclic citrullinated peptide antibodies, anti-keratin antibodies and IgM rheumatoid factors. Rheumatology. 2002;41(7):809–814.

[12] Kay J, Upchurch KS, ACR/EULAR 2010. Rheumatoid arthritis classification criteria. Rheumatology. 2012;51 (Suppl.1):vi5–vi9.